Fibromyalgia/Long Covid Wellness Clinic

Resources

Christine Stamatos DNP, ANP-C

WEBSITES:

The Arthritis Foundation
www.arthritis.org

The American College of Rheumatology
www.rheumatology.org

University of Michigan
www.painguide.com

Calm
www.calm.com

NIH
www.nih.gov/health-information

National Fibromyalgia Association
www.fmaware.org

Google: 60 Beats per Minute

BOOKS:

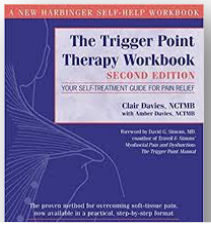
- **Trigger Point Therapy Workbook by** *Davies & Davies*
- **Pain Survival Guide by** *Turk & Winter*
- **Chronic Pain Reset by** *Afton Hassett*

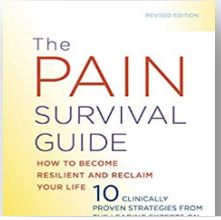
APPS:

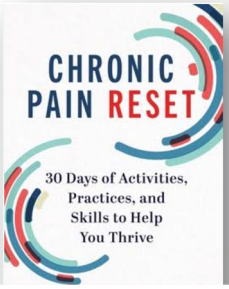
- **Calm**
- **Insight**
- Happify
- **10% Happier**
- Autogenic Training
- Gratitude
- Sleep cycle
- MyFitnessPal

SM Tools:

- Activity Tracker
- Mechanical Massage
- Massage Stick
- Foam Roller
- Back Knobber







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Genetic Risk Assessments in Individuals at High Risk for Inherited Breast Cancer in the Breast Oncology Care Setting

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Abstract

Background—It has become increasingly common to consider BRCA mutation status when determining optimal cancer risk management and treatment options in order to improve patient outcomes. Knowledge about the risk for hereditary cancer at or as close as possible to the time of diagnosis allows patients access to the most risk reduction options available.

Methods—This paper illustrates the role of genetic risk assessment for hereditary breast cancer, using hereditary breast and ovarian cancer (HBOC) syndrome as a model due to germline mutations in the BRCA1 and BRCA2. Specifically, the value of genetic counseling and testing for HBOC across the cancer prevention and control continuum is outlined as it pertains to breast cancer.

Results—In recognition of the importance of risk assessment for hereditary breast cancer, leading health professional organizations have developed specific guidelines and recommendations to providers for identification of women at increased risk for carrying a BRCA mutation.

Conclusions—Institutional efforts specific to genetic counseling and testing have resulted in the implementation of a model driven by physician recommendation as a referral system for high-risk breast cancer patients. Establishing an infrastructure to support research, education, and outreach initiatives focused on BRCA genetic counseling and testing will provide information that can improve the delivery of cancer genetics services.

Overview of Genetic Counseling and Testing Using *BRCA* as a Model

The majority of inherited breast cancers are attributed to hereditary breast and ovarian cancer (HBOC) syndrome due to mutations in the *BRCA1* and *BRCA2 (BRCA)* genes. Although there are several other genes that also lead to hereditary breast cancer predisposition (eg, *PTEN, P53, STK11*), they are much rarer. Furthermore, for the purposes of this review, we will not specifically consider individuals at high risk by virtue of a

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striking family history, in whom a germline *BRCA* mutation is not identified (recognizing that in the clinical setting, it may be appropriate to offer these individuals many of the risk management options recommended for *BRCA* mutation carriers). Consequently, we use HBOC as a model for outlining the importance of genetic counseling and testing services across the cancer prevention and control continuum (Figure).

The *BRCA* genes were discovered approximately 15 years ago,[1,2] representing a tremendous opportunity to identify individuals at greatly elevated risk for HBOC.[1–3] Mutations in these genes account for approximately 5% of all breast cancers[4] and 10% to 15% of all ovarian cancers.[2,5,6] Lifetime cancer risks to age 70 in *BRCA* mutation carriers are approximately 60% to 70% for breast cancer[7–11] and 40% or lower for ovarian cancer.[7,9] Moreover, the risk of a second primary breast cancer in *BRCA* mutation carriers, particularly those diagnosed with breast cancer at a younger age, is much higher (upwards of 50%) than in non-carriers.[12,13] It is becoming exceedingly important to identify women who carry *BRCA* mutations so that they may utilize the latest medical advances in prevention, early detection, and treatment.[3,14–19] To facilitate identification and referral of patients most likely to benefit from these advances, the National Comprehensive Cancer Network (NCCN) publishes annual guidelines that outline referral criteria for genetic counseling and testing in the oncology care setting.[20] NCCN criteria for appropriate referrals in those with a personal and family history of breast cancer include, but are not limited to, early age of diagnosis of breast cancer (ie, ≤ age 50), number of relatives with breast cancer, two breast cancer primaries, triple-negative disease, male breast cancer, and previously identified *BRCA* mutation in the family (Table 1). Other considerations for referral include ethnic background, limited family size/structure, and presence of other *BRCA*-associated cancers in the family.

Several models have been developed that predict the probability of a *BRCA* mutation in individuals or families, including those based on Bayesian approaches and statistical models[21] or empiric observations (such as those based on Myriad prevalence tables).[22] Overall, the use of prediction models has been shown to improve the ability of clinicians as to which patients are most likely to harbor a *BRCA* mutation.[23] Studies that compared the different models suggest that no single model is consistently superior to others.[24,25] Additional means shown to better improve the performance of prediction models and discriminate between *BRCA1* and *BRCA2* are inclusion of breast tumor markers such the estrogen receptor, progesterone receptor, and Her-2/neu status.[26–28]

Prevention

A number of studies have evaluated medical and surgical options for breast cancer prevention in *BRCA* mutation carriers. Tamoxifen has been the primary agent evaluated in the medical context. However, its role for primary prevention in *BRCA* carriers remains unclear. Specifically, a single small study of 8 *BRCA1* carriers and 11 *BRCA2* carriers showed a 62% reduction in breast cancer incidence in *BRCA2* carriers who used tamoxifen, but no similar risk reduction was observed in *BRCA1* carriers. To date, no larger studies have been conducted to examine the efficacy of tamoxifen for primary prevention of breast cancer. Additionally, there has been speculation that poly ADP-ribose polymerase (PARP)

inhibitors may someday be considered as targeted chemoprevention agents for primary prevention of breast cancers in *BRCA* mutation carriers,[29] and future efficacy studies are expected. For women with a prior breast cancer diagnosis, several studies have demonstrated a 50% to 70% reduction in risk for contralateral disease with use of tamoxifen.[30–32] While promising, each of these studies have limitations such as retrospective design and lack of histopathological data (especially estrogen and progesterone receptor status) of the primary tumor.

In terms of surgical options, bilateral prophylactic mastectomy represents the highest level of risk reduction in *BRCA* mutation carriers. Multiple studies demonstrate a greater than 90% reduction in breast cancer risk.[33–39] (For an overview of bilateral mastectomy in the context of a breast cancer diagnosis, refer to the Treatment section.) Another surgical option for breast cancer prevention is prophylactic bilateral salpingo-oophorectomy, which reduces ovarian cancer risk by approximately 80%[40,41] and also confers a 50% reduction in breast cancer risk when performed premenopausally in *BRCA* carriers.[41–43] It is unclear whether the magnitude of breast cancer risk reduction depends on time since oophorectomy, particularly when it is performed premenopausally, although available data suggest prophylactic oophorectomy performed after the age of 50 likely does not lower breast cancer risk.[44] In terms of survival, prophylactic bilateral salpingo-oophorectomy has been reported to lead to a reduction in breast and ovarian cancer-specific mortality as well as overall mortality.[39] Finally, there are data to suggest that prophylactic oophorectomy may also reduce contralateral breast cancer risk.[45] A recent computer-simulated survival analysis examined the impact of screening and prophylactic surgeries in *BRCA* mutation carriers[46] and developed an online tool for guiding management in patients.[47] Recognizing the numerous assumptions on which modeling studies are based, these studies may nevertheless provide additional information for both patients and providers when making challenging management decisions.

Early Detection and Diagnosis

Several studies in *BRCA* mutation carriers have evaluated the impact of various breast cancer screening modalities on early cancer detection. For women with a *BRCA* mutation, the NCCN has issued recommendations for breast cancer surveillance,[48] including monthly breast self-examination, semiannual clinical breast examination, annual mammogram, and annual breast magnetic resonance imaging (MRI), as illustrated in Table 2. Although yearly mammograms starting as early as 25 years of age are recommended as part of the screening strategy in *BRCA* mutation carriers, one potential concern is that *BRCA* carriers may be more prone to radiation-induced breast cancers than nonmutation carriers due to the role of the *BRCA* genes in DNA repair.[49] However, there is currently insufficient evidence to indicate that radiation exposure from mammograms increases breast cancer risk.[50–52]

Studies have consistently shown that MRI is more sensitive than mammography and/or breast ultrasound in detection of early-stage breast cancers in *BRCA* mutation carriers.[53–58] Furthermore, a prospective study of *BRCA* mutation carriers annually screened by MRI reported a significant reduction in the incidence of advanced breast cancer compared with those not screened by MRI.[59] The optimal benefit of MRI appears to be achieved through

annual screening between the ages of 25 to 65 years. The benefits of screening in this age group likely do not persist much beyond 2 years after the date of the last MRI; moreover, the long-term health implications of 40 doses of gadolinium in *BRCA* carriers have not been evaluated.[44] Although trials indicate that MRI is superior to mammography in the detection of breast cancer, mammography identifies some cancers not detected by MRI, particularly ductal carcinoma in situ with microcalcifications.[60,61] As a consequence, current evidence supports the benefits of both mammography and breast MRI annually in *BRCA* mutation carriers.[3,46,62–64] Despite the proven benefits of MRI for breast cancer detection[53–58] and recent data which suggest that it reduces the risk of advanced breast cancer,[59] it is currently unknown if MRI results in a survival benefit.

Treatment

Several treatment considerations should be addressed for women with breast cancer who carry a *BRCA* mutation, including the high risks for contralateral disease and ovarian cancer, as well as the emergence of targeted treatment approaches currently offered in the context of clinical trials. Contralateral breast cancer rates in *BRCA* carriers are higher than that of non-carriers, with 10-year rates reported as 25% to 27% for carriers and 1% to 9% for non-carriers.[65] Furthermore, recent studies indicate that contralateral breast cancer risk depends of age at first breast cancer diagnosis (with substantially elevated risks in those diagnosed at an early age) as well as affected *BRCA* gene (with higher risks for those with *BRCA1* mutations).[12,13] In fact, the lifetime contralateral breast cancer risk was reported to be over 60% in those with *BRCA1* mutations diagnosed below the age of 40 after 25 years of follow-up.[12] Because the presence of a germline *BRCA* mutation diagnosed at the time of a breast cancer diagnosis raises an individual's risk of a synchronous and metachronous tumor, surgical treatment decision is often influenced by this knowledge. Due to this increased risk of a second primary breast cancer, approximately half of North American women with a *BRCA* mutation who are diagnosed with unilateral breast cancer select bilateral mastectomy for surgical treatment.[66] This finding is supported by two US-based studies of newly diagnosed high-risk breast cancer patients who underwent *BRCA* testing at or near the time of diagnosis. In both studies, women who tested positive for a *BRCA* mutation chose bilateral mastectomy more often than women who received negative or uninformative results.[67,68]

A number of organizations provide guidelines to identify, refer, and counsel newly diagnosed high-risk breast cancer patients for genetic counseling, including those from the American Society of Clinical Oncology (originally published in 2003)[69–71] and the American Society of Breast Surgeons (issued in 2009).[72] However, a 2011 study of administrative data from a sample of 14.4 million commercially insured patients over a 3-year period found that of approximately 1,500 women with early-onset breast cancer ≤ age 40, only 30% had genetic testing, with even lower rates among black and Hispanic patients.[73] Importantly, this study found that even among those who had testing (and presumably pretest genetic counseling), less than 20% did so within a month of diagnosis, suggesting that testing (and presumably pretest genetic counseling) generally occurred after definitive surgical treatment.

When considering ipsilateral breast cancer risk, a number of studies support breast conservation therapy (ie, lumpectomy and radiation) for treatment of the primary tumor, based on similar ipsilateral recurrence rates in carriers and non-carriers at 10 years of follow-up.[12,74–76] However, at 15 years of follow-up, the risk of ipsilateral events (including second primary cancer and recurrence of initial cancer) has been reported to be as high as 24%.[74,76] Ultimately, there is no documented difference in overall survival of *BRCA* carriers choosing breast conservation therapy vs mastectomy at 15 years following treatment.[74] However, some data suggest it may take 20 years or more of follow-up to definitively determine whether bilateral mastectomy results in a mortality reduction.[44,77] Another consideration for *BRCA* mutation carriers who select lumpectomy and radiation therapy but who may consider bilateral mastectomy in the future is the potential impact of radiation on breast reconstruction options. Changes to the skin caused by radiation have been well documented,[78] and several reports have substantiated that implant reconstructions subsequent to radiation therapy have a significantly higher complication rate.[79] Given the possibility of fewer options, *BRCA* mutation carriers should be fully informed about the impact of radiation therapy on future breast reconstruction.

While the influence of *BRCA* mutation carrier status on surgical decisions has become more widely considered in treatment planning,[80] options to inform medical treatment strategies based on *BRCA* mutation carrier status are imminent in the era of personalized medicine. For example, preclinical models suggest *BRCA1*-associated breast cancers are resistant to taxanes and sensitive to DNA damaging agents such as mitomycin C and cisplatin.[44] Subsequently, data have emerged to suggest that taxanes may not be useful in neoadjuvant treatment of *BRCA1*-associated breast cancers,[81–84] whereas these cancers may be particularly sensitive to platinum agents.[85,86] Currently, it remains unclear whether responsiveness to platinum-based agents in *BRCA1*-related breast cancers relates to the triple-negative phenotype or specifically to the *BRCA* mutation status itself. Interestingly, in a study of 28 women with stage II/III triple-negative breast cancer treated with cisplatin, 6 patients achieved complete clinical response, which included 2 women with *BRCA1* mutations in the entire sample.[87] However, more data are needed regarding the use of cisplatin in the clinical setting before clinical recommendations can be made.

Among the many tailored treatments currently under investigation,[88] much interest has focused on the PARP inhibitors, which may be particularly effective in *BRCA*-associated cancers.[89–92] This is the first treatment regimen to be based on a synthetic lethality approach, as inhibiting PARP-mediated pathways selectively affects only those cells that have lost *BRCA*-associated homologous recombination function (ie, tumor cells), whereas normal cells are unaffected. Consequently, this approach is associated with minimal systemic toxicity.[18] Several international trials are underway to test the effectiveness of PARP inhibitors in *BRCA* mutation carriers,[17–19,91,93–95] and many have reported promising preliminary results.[17–19] Notably, single-agent PARP (olaparib) has shown effectiveness in treating metastatic breast cancer.[18,96]

In individuals with a new diagnosis of breast cancer and determined to have a *BRCA* mutation, another concern is the high risk of metachronous ovarian cancer, which is a common cause of mortality in those *BRCA* mutation carriers who were successfully treated

for early-stage breast cancers.[97] Specifically, patients with a *BRCA* mutation also have a 7% to 13% chance of developing ovarian cancer within 10 years after diagnosis.[97] As surveillance has not been shown to be effective in detecting early-stage ovarian cancers, the benefits of bilateral salpingo-oophorectomy (in addition to lowering the risk of breast cancer) are related to their effect on survival from ovarian cancer.[97] Further discussion of bilateral salpingo-oophorectomy is included below (related to the management of symptoms associated with menopause) and in the Prevention section (related to breast cancer risk reduction).

Quality of Life and Survivorship

Several important considerations regarding quality of life and survivorship are unique to women who carry a *BRCA* mutation, including the impact of risk-reducing surgery, fertility and reproductive health concerns, communication of genetic test results, and concerns about insurability and discrimination. Overall, the published literature indicates high levels of satisfaction (80% to 100%) with prophylactic mastectomy over time.[98–102] One of the first studies of psychosocial outcomes of prophylactic mastectomy to include only women who were genetically susceptible to breast cancer was published in 2006.[103] Among the 114 Dutch women who underwent prophylactic mastectomy and breast reconstruction, after a median follow-up of 3 years, 60% of participants were satisfied with the results of the surgery. The sample included 63 women with *BRCA* mutations and 14 at high risk for breast cancer by virtue of their strong family history. Those who perceived a lack of information, experienced complications, had ongoing feelings that the reconstructed breasts did not feel like their own, and stated they would not choose this type of reconstruction again were least likely to be satisfied and to report adverse effects on their sexual relationship. Additionally, negative impacts on the patient's sexual relationship were also associated with altered feelings of femininity, discrepant expectations, and perceptions that the partner had a negative perception of femininity and sexuality. The level of satisfaction reported in this study is lower than what has previously been reported in women who were not specifically identified as *BRCA* mutation carriers. Since this study was conducted in the Netherlands, there may be some variation specific to the healthcare system; however, it is also possible that there are psychosocial issues specific to *BRCA* mutation-positive women undergoing prophylactic mastectomy that warrant further exploration.

For women who undergo bilateral prophylactic oophorectomy, evidence suggests an improvement in psychosocial functioning after surgery. Among 846 Dutch women at high risk for HBOC, 44% selected prophylactic bilateral salpingo oophorectomy and 56% selected surveillance.[104] Women who selected oophorectomy had fewer breast and ovarian cancer worries compared with those selecting surveillance. However, those who selected surgery were also significantly more likely to report menopausal symptoms and worse sexual functioning (eg, less pleasure during sexual activities). The use of hormone replacement therapy (HRT) to mitigate the symptoms associated with surgical menopause in young women who undergo bilateral prophylactic oophorectomy has been an issue of debate. A concern about HRT in *BRCA* carriers is its potential to raise the risk of breast cancer, as seen in the general population.[105–107] However, two studies in *BRCA* mutation carriers reported that HRT did not increase the subsequent risk of breast cancer, nor did it

appear to reduce the protective effect of oophorectomy on breast cancer risk.[108,109] Recent results from the Women's Health Initiative in the general population also provide reassurance as to estrogen use for about 5 years in terms of breast cancer risk and mortality.[110] Ultimately, HRT mitigates many of the symptoms associated with menopause. However, studies have suggested that quality of life does not return to presurgical levels.[104,111]

Fertility has been identified as a leading quality of life concern among breast cancer patients diagnosed during their reproductive years.[112] Estimated infertility risks for women treated with adjuvant breast cancer therapy for 6 weeks with the most commonly used chemotherapy regimens are > 80% for premenopausal women aged 40 and above, 20% to 80% for women aged 30 to 39, and < 20% for women under age 30.[113] In recognition of the immediacy of fertility concerns, professional guidelines have been released by both the American Society for Reproductive Medicine (ASRM) in 2005 and the American Society of Clinical Oncology (ASCO) in 2006 that highlight the role of oncologists to initiate discussion of fertility so their patients can make family-building decisions that are right for them.[113,114] Despite these guidelines, research suggests a lack of patient knowledge and a need for improved communication about fertility between cancer patients and their providers. A survey of cancer survivors found that only 57% of patients report receiving information about fertility from healthcare providers.[115] Another study of young female cancer survivors reported a higher discussion rate of 72%.[116] However, only 51% of these women felt their concerns were addressed adequately, suggesting that even if this communication is occurring, patients may not receive sufficient information regarding fertility risk and fertility preservation options. Finally, a national study of US oncologists found that 47% of respondents reported routinely referring cancer patients of childbearing age to a reproductive endocrinologist.[117]

The possibility of transmitting a mutation to a child may also pose a concern to families with a *BRCA* mutation,[118] perhaps to the extent that some carriers may avoid childbearing.[119,120] These concerns may prompt women to consider using a preimplantation genetic diagnosis (PGD), a newer technique used to test fertilized embryos for genetic disorders prior to uterine implantation.[121–124] PGD involves the use of in vitro fertilization, in which an egg is fertilized and develops for 3 days until it reaches the 8-cell stage, at which time 1 cell is removed and examined using polymerase chain reaction (PCR) or fluorescence in situ hybridization (FISH).[122] Using the information obtained from the genetic testing, potential parents can decide whether or not to implant embryos. A review by Offit et al[125] indicated that PGD has been used in the context of several hereditary cancer syndromes, including HBOC. Given the immediate and long-term issues related to reproductive health based on medical and surgical treatment and risk reduction options for *BRCA* mutation carriers, the optimal time for oncology care providers to discuss fertility-related concerns is prior to the initiation of chemotherapy.[126]

A primary motivation for many breast cancer patients to undergo *BRCA* testing is to provide information to their at-risk relatives.[127–130] In clinical practice, healthcare providers give test results directly to patients and encourage them to share the results with at-risk family members.[131] Several studies to date have documented that women generally share *BRCA*

test results with their at-risk relatives.[132] However, some studies indicate that females who have been tested may choose less frequently to share results with their relatives who are male, with those they do not feel emotionally close to, or with those whose emotional or psychological well being is a concern.[133–137] Although likely uncommon, a recent case report documented deliberate disclosure of incorrect test results by a patient to her at-risk family member.[138] There is also recent literature suggesting that parents are disclosing test results to minor children.[139–141] While there is no specific clinical guidelines about the appropriate age to disclose a parent's test results to children, there are clear guidelines against testing minor children for *BRCA* mutations. Consensus guidelines from experts consistently emphasize that genetic testing for adult onset conditions should be deferred until legal adulthood (age 18), when individuals can decide for themselves whether they would like to pursue testing.[70,142–144] This guideline reflects concerns regarding autonomy, potential discrimination, and possible psychological effects.[142,144,145] Therefore, in HBOC, where there is no risk of malignancy in childhood and no risk reduction strategies are recommended in minors, testing should not be offered. Even after 18 years of age, testing is generally not strongly recommended due to potential implications to future insurability in the absence of any medical interventions implemented at this age. The age at which screening strategies are initiated is in the mid 20s (Table 2), which is typically the time at which many clinicians recommend testing for at risk women.

Other concerns expressed by women considering *BRCA* testing are those related to genetic discrimination and insurability. Specifically, when embarking on genetic testing for inherited cancer susceptibility, particularly in the context of a family member who does not have a cancer diagnosis, potential implications regarding future insurability are an important aspect of discussion during the genetic counseling session. At the federal level, the Genetic Information Non-Discrimination Act (GINA) was passed in 2008, which imparts protections for individual and group health insurance policies as well as in the workplace.[146] Note that GINA does not cover life insurance, disability insurance, or other supplemental insurances. In addition, those in the military are not covered under GINA. However, other protections against discrimination are in place.[147]

As patients move from treatment to survivorship, it is important to consider their transition back to primary care providers. Given the strict laws in some states with regard to confidentiality of genetic test results, some centers limit documentation of *BRCA* mutation results in the medical record and/or implement additional safety guards to house and release this information within the medical record. Consequently, patients may share some responsibility to inform their healthcare providers of their mutation results, particularly as they are transitioning back to primary care settings. This information will be useful for providers to not only make cancer screening recommendations based on mutation status, but also ensure that patients follow recommended screening and behavioral guidelines for prevention and early detection of non–*BRCA*-related cancers.[148]

These quality of life and survivorship issues in conjunction with the difficulty some patients may have to accurately recall their test results[149–151] underscore the importance of pre- and posttest genetic counseling that is provided by a knowledgeable genetics professional. In addition to expertise in cancer risk assessment and medical management of individuals with

hereditary cancer predisposition, these individuals are also trained to identify potential psychosocial and educational needs of patients.[152] They are critical members of the healthcare team and can help ensure that patients understand the medical and psychosocial implications of results for themselves and at-risk family members and serve as a resource for patients to develop strategies for effective communication.

Considerations for Delivery of *BRCA* Counseling and Testing in the Breast Oncology Care Setting

Several health and professional organizations strongly encourage referral to a certified/credentialed cancer genetics professional for pretest counseling, prior to genetic testing.[20,70,143,152–156] There are three main groups of healthcare professionals with advanced degrees and experience in genetics. (1) A Certified Genetic Counselor (CGC) has at least a Master's degree in genetic counseling and has passed a national board examination, (2) a Diplomate, American Board of Medical Genetics (DABMG), or Fellow, American College of Medical Genetics (FACMG) is a physician who has completed residency or fellowship training in medical genetics and passed the board examination, and (3) an Advanced Practice Nurse in Genetics (APNG) has completed both a graduate nursing program and professional portfolio review process.[157] As outlined in a recent publication,[158] the traditional model of delivering genetic counseling and testing services involve five steps: patient identification, genetic consultation, genetic testing if appropriate, posttest counseling, and cancer risk management.

Patients are referred by healthcare providers or family members, or they are self-referred. The model for providing comprehensive *BRCA* testing begins with an in-person pretest genetic counseling session during which time informed consent for genetic testing is obtained followed by a results disclosure session.[16] During this session, the patient typically meets with a genetics professional with the training described above. The professional obtains personal and family cancer history and provides the patient with a risk assessment, including which, if any, genetic tests may be appropriate to perform. Given the complexities of delivering high-quality genetics services, ASCO provides key points that should be discussed with any patient during a pretest genetic counseling session (Table 3).[70,143] This initial appointment typically lasts 60 to 90 minutes. One of the primary goals of the initial session is to determine whether genetic testing is appropriate for a given patient and then proceed accordingly.[152] For those who proceed with testing, the patient returns for in-person disclosure of test results and discussion of medical management options. However, over the last decade, the delivery of genetics services (including who provides these services) has evolved, resulting in new models to optimize development of and access to these services.[158–160] Increasingly, comprehensive services for hereditary breast cancer are delivered by a multidisciplinary team that includes genetic counselors working in conjunction with oncologists, medical geneticists, other medical specialists, and often a mental health professional.[161] This interdisciplinary approach can help avoid problems such as inappropriate or incomplete testing, misinterpretation of test results by both patients and clinicians, inappropriate cancer screening and prevention recommendations, and psychological issues.[71,162,163]

Compared with most other clinical services, provision of genetic counseling involves significant amounts of provider time.[160,164–167] However, low reimbursement rates relative to the time required to provide adequate services impedes the provision of adequate risk counseling, particularly for providers outside of an academic setting.[168] One study found that only one-third of the time needed to deliver genetic counseling services involves face-to-face patient care that can be billed.[169] Specifically, most genetic counseling programs cost more than the direct revenue they generate.[77] However, another crucial consideration to illustrate institutional value of genetic counseling programs must incorporate "downstream revenue analysis," which includes reimbursement from surveillance, prophylactic surgeries, or cancer treatments for individuals with *BRCA* mutations.[170] Thus, the inclusion of this income is essential in any cost-benefit calculation of genetic counseling services, and additional research regarding this revenue is needed. Ultimately, public and private healthcare policy reform is needed to address the gap in insurance coverage for adequate risk counseling and genetic analyses as a component of preventive care.

Institutional Efforts Specific to Genetic Counseling and Testing

At our institute, a model driven by physician recommendation has been implemented as a referral system for recently diagnosed high-risk breast cancer patients. The available personal and family history records for newly diagnosed breast cancer patient are reviewed by a genetic counselor during the weekly Breast Program tumor board meetings to assess if the patient meets NCCN guidelines for referral to the Cancer Genetic Counseling and Testing Service, as illustrated in Table 1.[20] Each patient who is discussed and meets these criteria is noted by the genetic counselor. A letter is generated by the Cancer Genetic Counseling and Testing Service and sent to the surgeon for his or her signature. In addition to a surgeon discussing genetic counseling and testing during the initial consultation, a referral letter signed by the patient's physician (often a surgeon) is sent to a breast cancer patient who has been identified as meeting NCCN criteria. This brief letter is addressed directly to the patient, signed by his or her surgeon, and recommends that the patient make an appointment for genetic counseling.[171] In an effort to continually improve our delivery of clinical services, our team evaluates important outcomes such as patient uptake of and satisfaction with genetics services.[172,173] These data are in turn used to generate additional research opportunities. For example, we were recently awarded peer-reviewed funding to develop and test an educational intervention specific to postsurgical breast cancer patients at risk for HBOC who are transitioning to survivorship care.

While the physician referral model works well in settings with access to trained genetics professionals, there are many rural areas or certain states where such professionals are not readily available.[174,175] This shortage is compounded by the paucity of education and training opportunities in clinical cancer genetics,[176] despite priorities set forth by key stakeholders emphasizing the need for cancer genetics education.[177–185] Thus, integrating genetic counseling and testing for HBOC into clinical care remains an ongoing challenge. However, several innovative approaches to delivering quality genetics services to an increasing number of patients in community settings have been developed. For example, successful strategies for delivering comprehensive genetic counseling and testing services include academic-community partnerships that focus on collaboration with nongenetics

providers to offer genetic testing for hereditary cancers.[158,159] This approach can leverage the expertise of an academic center for challenging cases as well as allow patients to remain in their community and provide better access to resources for long-term follow-up care. Other innovative approaches to successfully identify high-risk patients, particularly in the primary care and community setting, include automated family collection tools through which risk assessment is performed at a hospital or practice-wide level and appropriate patients are identified and referred for genetic counseling and testing.[186–188] These software tools are particularly of interest as many hospitals and practices transition to electronic health records, and they have the potential to enhance the identification of patients at risk for inherited cancers at a system-wide level.

At our institute, we secured peer-reviewed funding to develop an infrastructure (called the Inherited Cancer Research [ICARE] Initiative) to support research, education, and outreach initiatives focused on *BRCA* genetic counseling and testing. The ICARE Initiative leverages a state mandate to reach the citizens of Florida and provide access to high-quality cancer care. Moffitt works with its partners (referred to as “affiliates”) to offer clinical expertise and research trials found at an NCI-designated Comprehensive Cancer Center. The Moffitt Affiliate Network (MAN) Program represents strategic affiliations with 15 Florida hospitals, 1 Georgia hospital, and more than 400 community oncologists, through which Moffitt reaches approximately 20% of Florida cancer patients. Through networking with our MAN sites, providing access to a genetic counselor for general questions, and utilizing other directed learning opportunities and educational resources/materials over the last year, 12 of the 15 sites have actively participated in our bimonthly case conferences. Furthermore, an additional 2 sites have requested and received in-person presentations from the ICARE team on the topic of inherited cancer susceptibility. In addition to our educational and outreach efforts, MAN practitioners refer high-risk patients to our research registry to provide the research link, which has in turn contributed to the tremendous growth of our registry since initiation of the grant in the summer of 2010. This provides unprecedented opportunities to understand cancer risk management practices and recommendations in *BRCA* mutation carriers at the patient and practitioner level. These efforts will provide information that can improve the delivery of cancer genetics services in the state of Florida and serve as a model for other states.

Conclusions

Over the last several years, it has become increasingly common to consider *BRCA* mutation status when determining optimal cancer risk management and treatment options in order to improve patient outcomes. Knowledge about the risk for hereditary cancer at or as close as possible to the time of diagnosis allows patients access to options that may improve their outcome and reduce treatment-associated risks. Thus it has become important for providers in the breast oncology care setting to identify at-risk patients and offer testing, either by themselves or through referral to a cancer genetic counseling and testing service. As such, leading health professional organizations such as the National Comprehensive Cancer Network,[20] the American Society of Breast Surgeons,[72] and the American Society of Clinical Oncology[189] provide specific guidelines and recommendations to providers for identification of women at increased risk for carrying a *BRCA* mutation. For those providers

without in-house clinical cancer genetics providers, several promising collaborative models across the United States are successfully bringing the expertise of these providers to breast oncology care for patients in community settings.[158,159]

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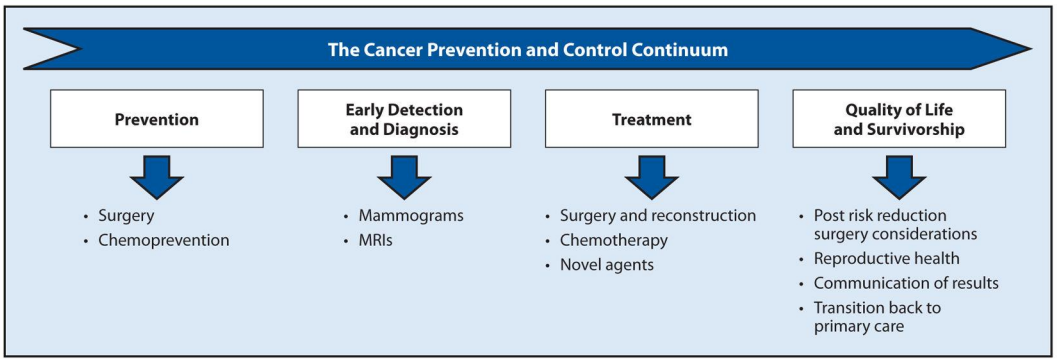

Figure.

Management of inherited breast cancer across the cancer prevention and control continuum.

Table 1

NCCN Referral Criteria for Further Genetic Risk Evaluation for HBOC

An affected individual with one or more of the following:

- Early-age-onset breast cancer
- Triple negative (ER−, PR−, HER2−) breast cancer
- Two breast cancer primaries in a single individual
- Breast cancer at any age, and
  - ≥ 1 close blood relative with breast cancer ≤ 50 y old, or
  - ≥ 1 close blood relative with epithelial ovarian/fallopian tube/primary peritoneal cancer at any age, or
  - ≥ 2 close blood relatives with breast cancer and/or pancreatic cancer at any age
  - From a population at increased risk
- A combination of breast cancer with one or more of the following: thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumors, diffuse gastric cancer, dermatologic manifestations or leukemia/lymphoma on the same side of the family (especially if early onset)
- Ovarian/fallopian tube/primary peritoneal cancer
- Male breast cancer

An unaffected individual with a family history of one or more of the following:

- ≥ 2 breast primaries, either in 1 individual or 2 different individuals from the same side of the family (maternal or paternal)
- ≥ 1 ovarian primary from the same side of the family (maternal or paternal)
- First- or second-degree relative with breast cancer ≤45 y
- A combination of breast cancer with one or more of the following: thyroid cancer, sarcoma, adrenocortical carcinoma, endometrial cancer, pancreatic cancer, brain tumors, diffuse gastric cancer, dermatologic manifestations or leukemia/lymphoma on the same side of the family (especially if early onset)
- A known mutation in a breast cancer susceptibility gene within the family
- Male breast cancer

Table 2

NCCN Management Recommendations for HBOC Syndrome Management

Women

- Breast self-examination training and education starting at age 18 y
- Clinical breast examination, every 6–12 months, starting at age 25 y
- Annual mammogram and breast MRI screening starting at age 25 y, or individualized based on earliest age of onset in family
- Discuss option of risk-reducing mastectomy on case-by-case basis and counsel regarding degree of protection, reconstruction options, and risks
- Recommend risk-reducing salpingo-oophorectomy, ideally between 35 and 40 y, and upon completion of child bearing, or individualized based on earliest age of onset of ovarian cancer in the family. Counseling includes a discussion of reproductive desires, extent of cancer risk, degree of protection for breast and ovarian cancer, management of menopausal symptoms, possible short-term hormone replacement therapy (HRT) to a recommended maximum age of natural menopause, and related medical issues
- For those patients who have not elected risk-reducing salpingo-oophorectomy, consider concurrent transvaginal ultrasound (preferably day 1–10 of menstrual cycle in premenopausal women) + CA-125 (preferably after day 5 of menstrual cycle in premenopausal women), every 6 months starting at age 30 y or 5–10 y before the earliest age of first diagnosis of ovarian cancer in the family
- Consider chemoprevention options for breast and ovarian cancer, including discussing risks and benefits
- Consider investigational imaging and screening studies, when available (eg, novel imaging technologies and more frequent screening intervals) in the context of a clinical trial

Risk to Relatives

- Advise about possible inherited cancer risk to relatives, options for risk assessment, and management
- Recommend genetic counseling and consideration of genetic testing for atrisk relatives

Reproductive Options

- For couples expressing the desire that their offspring not carry a familial *BRCA* mutation, advise about options for prenatal diagnosis and assisted reproduction, including pre-implementation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies
- For *BRCA2* mutations carriers, risk of a rare (recessive) Fanconi anemia/brain tumor phenotype in offspring if both partners carry a *BRCA2* mutation should be discussed.

Table 3

Basic Elements of Informed Consent for Cancer Susceptibility Testing

1	Information on the specific test being performed
2	Implications of a positive and negative result
3	Possibility that the test will not be informative
4	Options for risk estimation without genetic testing
5	Risk of passing a mutation to children
6	Technical accuracy of the test
7	Fees involved in testing and counseling
8	Psychological implications of tests results (benefits and risks)
9	Risks and protections against genetic discrimination by employers or insurers
10	Confidentiality issues
11	Options and limitations of medical surveillance and strategies for prevention following testing
12	Importance of sharing genetic test results with at-risk relatives so that they may benefit from this information

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JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Risk Assessment, Genetic Counseling, and Genetic Testing for *BRCA*-Related Cancer

US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

IMPORTANCE Potentially harmful mutations of the breast cancer susceptibility 1 and 2 genes (*BRCA1/2*) are associated with increased risk for breast, ovarian, fallopian tube, and peritoneal cancer. For women in the United States, breast cancer is the most common cancer after nonmelanoma skin cancer and the second leading cause of cancer death. In the general population, *BRCA1/2* mutations occur in an estimated 1 in 300 to 500 women and account for 5% to 10% of breast cancer cases and 15% of ovarian cancer cases.

OBJECTIVE To update the 2013 US Preventive Services Task Force (USPSTF) recommendation on risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer.

EVIDENCE REVIEW The USPSTF reviewed the evidence on risk assessment, genetic counseling, and genetic testing for potentially harmful *BRCA1/2* mutations in asymptomatic women who have never been diagnosed with *BRCA*-related cancer, as well as those with a previous diagnosis of breast, ovarian, tubal, or peritoneal cancer who have completed treatment and are considered cancer free. In addition, the USPSTF reviewed interventions to reduce the risk for breast, ovarian, tubal, or peritoneal cancer in women with potentially harmful *BRCA1/2* mutations, including intensive cancer screening, medications, and risk-reducing surgery.

FINDINGS For women whose family or personal history is associated with an increased risk for harmful mutations in the *BRCA1/2* genes, or who have an ancestry associated with *BRCA1/2* gene mutations, there is adequate evidence that the benefits of risk assessment, genetic counseling, genetic testing, and interventions are moderate. For women whose personal or family history or ancestry is not associated with an increased risk for harmful mutations in the *BRCA1/2* genes, there is adequate evidence that the benefits of risk assessment, genetic counseling, genetic testing, and interventions are small to none. Regardless of family or personal history, the USPSTF found adequate evidence that the overall harms of risk assessment, genetic counseling, genetic testing, and interventions are small to moderate.

CONCLUSIONS AND RECOMMENDATION The USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with *BRCA1/2* gene mutations with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing. (B recommendation) The USPSTF recommends against routine risk assessment, genetic counseling, or genetic testing for women whose personal or family history or ancestry is not associated with potentially harmful *BRCA1/2* gene mutations. (D recommendation)

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The US Preventive Services Task Force (USPSTF) makes recommendations about the effectiveness of specific preventive care services for patients without obvious related signs or symptoms.

It bases its recommendations on the evidence of both the benefits and harms of the service and an assessment of the balance. The USPSTF does not consider the costs of providing a service in this assessment.

The USPSTF recognizes that clinical decisions involve more considerations than evidence alone. Clinicians should understand the evidence but individualize decision-making to the specific patient or situation. Similarly, the USPSTF notes that policy and coverage decisions involve considerations in addition to the evidence of clinical benefits and harms.

Summary of Recommendations and Evidence

The USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with breast cancer susceptibility 1 and 2 (*BRCA1/2*) gene mutations with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing (B recommendation) (**Figure 1**).

The USPSTF recommends against routine risk assessment, genetic counseling, or genetic testing for women whose personal or family history or ancestry is not associated with potentially harmful *BRCA1/2* gene mutations. (D recommendation)

Rationale

Importance

Potentially harmful mutations of the *BRCA1/2* genes are associated with increased risk for breast, ovarian, fallopian tube, and peritoneal cancer.[1-6] For women in the United States, breast cancer is the most common cancer after nonmelanoma skin cancer and the second leading cause of cancer death.[7] In the general population, *BRCA1/2* mutations occur in an estimated 1 in 300 to 500 women and account for 5% to 10% of breast cancer cases and 15% of ovarian cancer cases.[8-11] A woman's risk for breast cancer increases if she has clinically significant mutations in the *BRCA1/2* genes.[12,13] Mutations in the *BRCA1/2* genes increase breast cancer risk to 45% to 65% by age 70 years. Risk of ovarian, fallopian tube, or peritoneal cancer increases to 39% for *BRCA1* mutations and 10% to 17% for *BRCA2* mutations.[12,13]

Detection

Genetic risk assessment and *BRCA1/2* mutation testing is a multistep process that begins with identifying patients with family or personal histories of breast, ovarian, tubal, or peritoneal cancer; family members with known harmful *BRCA1/2* mutations; or ancestry associated with harmful *BRCA1/2* mutations. Risk for clinically significant *BRCA1/2* mutations can be further evaluated with genetic counseling by suitably trained health care clinicians, followed by genetic testing of selected high-risk individuals and posttest counseling about results. The USPSTF found adequate evidence that familial risk assessment tools are accurate in identifying women with increased likelihood of *BRCA1/2* mutations. These tools can be used by primary care clinicians to guide referrals to genetic counseling.

The USPSTF has previously established that there is adequate evidence that current genetic tests can accurately detect known *BRCA1/2* mutations.[14]

Benefits of Screening, Genetic Counseling, and Genetic Testing

The USPSTF found adequate evidence that the benefits of risk assessment, genetic counseling, and genetic testing are moderate in women whose family history is associated with an increased risk for harmful mutations in the *BRCA1/2* genes.

The USPSTF found adequate evidence that the benefits of risk assessment, genetic counseling, and genetic testing are small to none in women whose family history is not associated with an increased risk for harmful mutations in the *BRCA1/2* genes.

Harms of Screening, Genetic Counseling, and Genetic Testing

The USPSTF found adequate evidence that the harms associated with risk assessment, genetic counseling, genetic testing, and interventions are small to moderate.

USPSTF Assessment

The USPSTF concludes with moderate certainty that the net benefit of risk assessment for increased risk of *BRCA1/2* mutations, testing for *BRCA1/2* mutations, and use of risk-reducing interventions outweighs the harms in women whose family or personal history is associated with an increased risk for potentially harmful mutations in the *BRCA1/2* genes.

The USPSTF concludes with moderate certainty that the harms of risk assessment for increased risk of *BRCA1/2* mutations, testing for *BRCA1/2* mutations, and use of risk-reducing interventions outweigh the benefits in women whose family or personal history is not associated with an increased risk for potentially harmful mutations in the *BRCA1/2* genes.

Clinical Considerations

Patient Population Under Consideration

This recommendation applies to women who are asymptomatic for *BRCA*-related cancer and have unknown *BRCA* mutation status (**Figure 2**). It includes women who have never been diagnosed with *BRCA*-related cancer, as well as those with a previous breast, ovarian, tubal, or peritoneal cancer diagnosis who have completed treatment and are considered cancer free but have not been previously tested. While this recommendation applies to women, the net benefit estimates are driven by biological sex (ie, male/female) rather than gender identity. Persons should consider their sex at birth to determine which recommendation best applies to them.

Assessment of Risk

Mutations in the *BRCA1/2* genes cluster in families, showing an autosomal dominant pattern of inheritance in either the mother's or father's family. When taking medical and family history information from patients, primary care clinicians should ask about specific types of cancer, primary cancer sites, which family members were

Figure 1. USPSTF Grades and Levels of Evidence

What the USPSTF Grades Mean and Suggestions for Practice

Grade	Definition	Suggestions for Practice
A	The USPSTF recommends the service. There is high certainty that the net benefit is substantial.	Offer or provide this service.
B	The USPSTF recommends the service. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.	Offer or provide this service.
C	The USPSTF recommends selectively offering or providing this service to individual patients based on professional judgment and patient preferences. There is at least moderate certainty that the net benefit is small.	Offer or provide this service for selected patients depending on individual circumstances.
D	The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits.	Discourage the use of this service.
I statement	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.	Read the Clinical Considerations section of the USPSTF Recommendation Statement. If the service is offered, patients should understand the uncertainty about the balance of benefits and harms.

USPSTF Levels of Certainty Regarding Net Benefit

Level of Certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative primary care populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as the number, size, or quality of individual studies. inconsistency of findings across individual studies. limited generalizability of findings to routine primary care practice. lack of coherence in the chain of evidence. As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess effects on health outcomes. Evidence is insufficient because of the limited number or size of studies. important flaws in study design or methods. inconsistency of findings across individual studies. gaps in the chain of evidence. findings not generalizable to routine primary care practice. lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.
The USPSTF defines certainty as "likelihood that the USPSTF assessment of the net benefit of a preventive service is correct." The net benefit is defined as benefit minus harm of the preventive service as implemented in a general, primary care population. The USPSTF assigns a certainty level based on the nature of the overall evidence available to assess the net benefit of a preventive service.	

USPSTF indicates US Preventive Services Task Force.

affected, and whether relatives had multiple types of primary cancer. Clinicians should also inquire about the age at diagnosis, age at death, and sex of affected family members, both immediate (ie, parents and siblings) as well as more distant (ie, aunts, uncles, grandparents, and cousins).

For women who have family members with breast, ovarian, tubal, or peritoneal cancer or have a personal history of these types of cancer, primary care clinicians may use appropriate brief familial risk assessment tools to determine the need for in-depth genetic counseling. Tools evaluated by the USPSTF include the Ontario Family History Assessment Tool (**Table 1**), Manchester Scoring System (**Table 2**), Referral Screening Tool (**Table 3**), Pedigree Assessment Tool (**Table 4**), 7-Question Family History Screening Tool (**Table 5**), International Breast Cancer Intervention Study instrument (Tyrer-Cuzick) (**Table 6**), and brief versions of BRCAPRO. Each of these tools has been validated and accurately estimate the likelihood of carrying a harmful *BRCA1/2* mutation. They can be used to guide referrals to genetic counseling for more definitive risk assessment.[28] General breast cancer risk assessment models (eg, the National Cancer Institute Breast Cancer Risk Assessment Tool, which is based on the Gail model) are not designed to identify *BRCA*-related cancer risk and should not be used for this purpose.

In general, these brief familial risk assessment tools include factors associated with increased likelihood of potentially harmful

Figure 2. Clinical Summary: Risk Assessment, Genetic Counseling, and Genetic Testing for *BRCA*-Related Cancer

Population	Women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with *BRCA1/2* gene mutations	Women whose personal or family history or ancestry is not associated with potentially harmful *BRCA1/2* gene mutations
Recommendation	Assess with an appropriate brief familial risk assessment tool. Grade: B	Do not perform routine risk assessment, genetic counseling, or genetic testing. Grade: D

Risk Assessment	Patients with family or personal histories of breast, ovarian, tubal, or peritoneal cancer or ancestry associated with harmful *BRCA1/2* mutations should be assessed using a familial risk assessment tool. The USPSTF found adequate evidence that these tools are accurate in identifying women with increased likelihood of *BRCA1/2* mutations. Tools evaluated by the USPSTF include the Ontario Family History Assessment Tool, Manchester Scoring System, Referral Screening Tool, Pedigree Assessment Tool, 7-Question Family History Screening Tool, International Breast Cancer Intervention Study instrument (Tyrer-Cuzick), and brief versions of BRCAPRO. These tools should be used to guide referrals to genetic counseling.
Genetic Counseling	Genetic counseling about *BRCA1/2* mutation testing should be performed by trained health professionals, including suitably trained primary care providers. The process of genetic counseling includes detailed kindred analysis and risk assessment for potentially harmful *BRCA1/2* mutations. It also includes identification of candidates for testing, patient education, discussion of the benefits and harms of genetic testing, interpretation of results after testing, and discussion of management options.
Genetic Testing	Tests for *BRCA1/2* mutations are highly sensitive and specific for known mutations. Testing for *BRCA1/2* mutations should be performed when an individual has personal or family history that suggests an inherited cancer susceptibility, when an individual is willing to see a health professional who is suitably trained to provide genetic counseling and interpret test results, and when test results will aid in decision making.
Treatment and Interventions	In general, the care of women with harmful *BRCA1/2* mutations is managed with a variety of interventions to lower future cancer risk. This includes intensive screening, risk-reducing medications, and risk-reducing mastectomy and salpingo-oophorectomy.
Relevant USPSTF Recommendations	The USPSTF recommends that clinicians offer to prescribe risk-reducing medications such as tamoxifen, raloxifene, or aromatase inhibitors to women at increased risk for breast cancer and at low risk for adverse medication effects. It recommends against the routine use of medications for risk reduction of primary breast cancer in women not at increased risk for breast cancer. The USPSTF recommends against screening for ovarian cancer in women. This recommendation does not apply to women with known genetic mutations that increase their risk for ovarian cancer (eg, *BRCA1/2* mutations). The USPSTF found insufficient evidence to assess the balance of benefits and harms of performing screening pelvic examinations in asymptomatic women for the early detection and treatment of a range of gynecologic conditions.

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to https://www.uspreventiveservicestaskforce.org.

U.S. Preventive Services TASK FORCE

JAMA

BRCA indicates breast cancer susceptibility gene; USPSTF, US Preventive Services Task Force.

BRCA1/2 mutations. These include breast cancer diagnosis before age 50 years, bilateral breast cancer, presence of both breast and ovarian cancer in one individual, male family members with breast cancer, multiple cases of breast cancer in the family, 1 or more family members with 2 primary types of *BRCA*-related cancer (such as ovarian cancer), and Ashkenazi Jewish ancestry. The USPSTF recognizes that each risk assessment tool has advantages and limitations and found insufficient evidence to recommend one over another.

Genetic Counseling

The process of genetic counseling includes detailed kindred analysis and risk assessment for potentially harmful *BRCA1/2* mutations. It also includes identification of candidates for testing, patient education, discussion of the benefits and harms of genetic testing, interpretation of results after testing, and discussion of management options. Genetic counseling about *BRCA1/2* mutation testing should be performed by trained health professionals, including suitably trained primary care clinicians. Several professional organizations describe the skills and training necessary to provide comprehensive genetic counseling.

Genetic Testing

Testing for *BRCA1/2* mutations should be performed only when an individual has personal or family history that suggests an inherited cancer susceptibility, when an individual is willing to talk with a health professional who is suitably trained to provide genetic counseling and interpret test results, and when test results will aid in decision-making. Clinical practice guidelines recommend that *BRCA1/2* mutation testing begin with a relative with known *BRCA*-related cancer, including male relatives, to determine if a clinically significant mutation is detected in the family before testing individuals without cancer.[29] If an affected family member with a *BRCA*-related cancer is not available, then the relative with the highest probability of

Table 1. Ontario Family History Assessment Tool[a]

Risk Factor	Points
Breast and ovarian cancer	
Mother	10
Sibling	7
Second-/third-degree relative	5
Breast cancer relatives	
Parent	4
Sibling	3
Second-/third-degree relative	2
Male relative (add to above)	2
Breast cancer characteristics	
Onset age, y	
20-29	6
30-39	4
40-49	2
Premenopausal/perimenopausal	2
Bilateral/multifocal	3
Ovarian cancer relatives	
Mother	7
Sibling	4
Second-/third-degree relative	3
Ovarian cancer onset age, y	
<40	6
40-60	4
>60	2
Prostate cancer onset	
Age <50 y	1
Colon cancer onset	
Age <50 y	1
Family total	
Referral[b]	≥10

[a] See Gilpin et al,[15] Oros et al,[16] Panchal et al,[17] Parmigiani et al.[18]

[b] Referral with score of 10 or greater corresponds to doubling of lifetime risk for breast cancer (22%).

Table 2. Manchester Scoring System[a,b]

Risk Factor (Age at Onset for Relative in Direct Lineage)	*BRCA1* Score	*BRCA2* Score
Female breast cancer, y		
<30	6	5
30-39	4	4
40-49	3	3
50-59	2	2
≥60	1	1
Male breast cancer, y		
<60	5[c]	8[d]
≥60	5[c]	5[d]
Ovarian cancer, y		
<60	8	5
≥60	5	5
Pancreatic cancer		
Any age	0	1
Prostate cancer, y		
<60	0	2
≥60	0	1
Total individual genes	10	10
Total for combined = 15		

Abbreviation: *BRCA*, breast cancer susceptibility gene.

[a] See Oros et al,[16] Parmigiani et al,[18] Antoniou et al,[19] Barcenas et al,[20] Evans et al.[21]

[b] A score of 10 in either column or a combined score of 15 for both columns would be equivalent to a 10% chance of identifying a *BRCA1* or *BRCA2* mutation.

[c] If testing for *BRCA2*.

[d] If testing for *BRCA1*.

mutation should be tested. The type of mutation analysis required depends on family history. Individuals from families with known mutations or from ancestry groups in which certain mutations are more common (eg, Ashkenazi Jewish founder mutations) can be tested for these specific mutations. Because risk assessment is primarily based on family history, it is unclear how women with a limited or unknown family history should be assessed for *BRCA1/2* mutation risk and potential referral to counseling or genetic testing.

Tests for *BRCA1/2* mutations are highly sensitive and specific for known mutations. The availability of testing options has changed since the 2013 US Supreme Court ruling that determined human genes are not patentable (*Association for Molecular Pathology et al v Myriad Genetics Inc et al*).[30] Previously, *BRCA1/2* mutation testing in the United States was mainly conducted by 1 laboratory. Since the ruling, the number of testing options has significantly increased, with more than 80 multigene panels that include *BRCA1/2*, as well as tests marketed directly to consumers.[31]

Guidelines from the American College of Medical Genetics and Genomics, which were updated in 2015, recommend new standard terminology for reporting *BRCA1/2* mutations identified by genetic tests. These include a 5-tier terminology system using the terms "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign."[32]

Treatment and Interventions

Management of increased cancer risk related to *BRCA1/2* mutations is beyond the scope of this Recommendation Statement. In general, care for women with harmful *BRCA1/2* mutations consists of a variety of interventions to lower future cancer risk. This includes intensive screening, risk-reducing medications, and risk-reducing mastectomy and salpingo-oophorectomy.

Additional Tools and Resources

The National Cancer Institute Cancer Genetics Services Directory provides a list of professionals who offer services related to cancer genetics, including cancer risk assessment, genetic counseling, and genetic testing.[33]

Other Related USPSTF Recommendations

The USPSTF recommends that clinicians offer to prescribe risk-reducing medications such as tamoxifen, raloxifene, or aromatase inhibitors to women at increased risk for breast cancer and at low

risk for adverse medication effects (B recommendation). It recommends against the routine use of medications for risk reduction of primary breast cancer in women not at increased risk for breast cancer (D recommendation).[34]

The USPSTF recommends against screening for ovarian cancer in women (D recommendation). This recommendation does not apply to women with known genetic mutations that increase their risk for ovarian cancer (eg, *BRCA1/2* mutations).[35] The USPSTF found insufficient evidence to assess the balance of benefits and harms of performing screening pelvic examinations in asymptomatic women for the early detection and treatment of a range of gynecologic conditions (I statement).[36]

Other Considerations

Research Needs and Gaps

Research on risk assessment and testing for *BRCA1/2* mutations has focused on short-term outcomes for highly selected women in referral centers. To determine the best approaches for population-based risk assessment and testing, more research is needed about mutation prevalence and effects on the general population as well as ethnicities or ancestries associated with *BRCA1/2* mutations. Because risk assessment is primarily based on family history, more research is needed to better understand how women with an unknown family history should be assessed for *BRCA1/2* mutation risk. Additional studies are needed, including comparative effectiveness trials, of approaches to risk screening and strategies to improve access to genetic counseling, as well as *BRCA1/2* testing for high-risk individuals.

It would be helpful to understand which methods of delivery of genetic counseling are most effective, including those that can increase access to genetic counseling in rural or other settings with limited access. Trials comparing types of clinicians and protocols could address these questions. The consequences of genetic testing for individuals and their relatives require more study. Well-designed investigations using standardized measures and diverse study populations are needed.

An expanded database or registry of patients receiving genetic counseling for inherited breast and ovarian cancer susceptibility or who are tested for *BRCA1/2* mutations would provide useful information about predictors of cancer and response to interventions. Additional data are needed from women of varying socioeconomic and racial/ethnic groups.

For women who are *BRCA1/2* mutation carriers, studies about the effectiveness of intensive cancer screening and risk-reducing medications and the effects of age at intervention on improving long-term outcomes are needed. This research would increase knowledge of the relative benefits and harms of interventions that are provided on the basis of genetic risk information.

Discussion

Burden of Disease

For women, breast cancer is the most common cancer in the United States after nonmelanoma skin cancer and the second leading cause of cancer death.[37] In 2017, an estimated 252 710 women were diagnosed with breast cancer in the United States and 40 610 died of the disease.[37] Ovarian cancer is the fifth leading cause of cancer death in women in the United States.[37] In 2017, an estimated 22 440 women were diagnosed with ovarian cancer and 14 080 died of the disease.[37] Mutations of the *BRCA1/2* genes are estimated to occur in 1 in 300 to 500 women in the general population[8-11] and account for 5% to 10% of breast cancer cases and 15% of ovarian cancer cases.[9,11,38]

Estimates of the prevalence of potentially harmful *BRCA1/2* mutations vary by population. The estimated prevalence is 0.2% to 0.3% in the general population of women, 6.0% in women with cancer onset before age 40 years, and 2.1% in the general population of Ashkenazi Jewish women.[39] In a meta-analysis of studies in which recruitment was based on family history of breast or ovarian cancer, *BRCA1* mutation prevalence was 13.6%, *BRCA2* mutation prevalence was 7.9%, and prevalence of either mutation was 19.8%.[39]

Scope of Review

To update its 2013 recommendation, the USPSTF commissioned a systematic review[28,40] on risk assessment, genetic counseling, and genetic testing for potentially harmful *BRCA1/2* mutations in

Table 3. Referral Screening Tool[a,b]

History of Breast or Ovarian Cancer in the Family? If Yes, Complete Checklist		
Risk Factor	Breast Cancer at Age ≤50 y	Ovarian Cancer at any Age
Yourself		
Mother		
Sister		
Daughter		
Mother's side		
Grandmother		
Aunt		
Father's side		
Grandmother		
Aunt		
≥2 cases of breast cancer after age 50 y on same side of family		
Male breast cancer at any age in any relative		
Jewish ancestry		

[a] See Bellcross et al.[22]

[b] Referral if 2 or more checks in table.

Table 4. Pedigree Assessment Tool[a,b]

Risk Factor	Score for Every Family Member With Breast or Ovarian Cancer Diagnosis, Including Second-/Third-Degree Relatives
Breast cancer at age ≥50 y	3
Breast cancer at age <50 y	4
Ovarian cancer at any age	5
Male breast cancer at any age	8
Ashkenazi Jewish heritage	4
Total	

[a] See Hoskins et al,[23] Teller et al.[24]

[b] Score 8 or greater is the optimal referral threshold.

Table 5. Seven-Question Family History Screening[a,b]

No.	Questions
1	Did any of your first-degree relatives have breast *or* ovarian cancer?
2	Did any of your relatives have bilateral breast cancer?
3	Did any man in your family have breast cancer?
4	Did any woman in your family have breast *and* ovarian cancer?
5	Did any woman in your family have breast cancer before age 50 y?
6	Do you have 2 or more relatives with breast *and/or* ovarian cancer?
7	Do you have 2 or more relatives with breast *and/or* bowel cancer?

[a] See Ashton-Prolla et al,[25] Fischer et al.[26]

[b] One positive response initiates referral.

Table 6. International Breast Cancer Intervention Study Model[a,b]

No.	Risk Factor
1	Personal history: current age, age at menopause, age at menarche, childbirth history, menopausal status, use of menopausal hormone therapy
2	Personal breast history, breast density (optional), prior breast biopsy, history of cancer (breast or ovarian), genetic testing
3	Ashkenazi Jewish inheritance
4	Family history (genetic risk)—relatives with breast or ovarian cancer, age at diagnosis, genetic testing

[a] See Fischer et al,[26] Cuzick.[27]

[b] Referral for genetic testing if the personal risk level for a mutation in breast cancer susceptibility gene 1 or 2 is 10% or greater.

asymptomatic women who have never been diagnosed with *BRCA*-related cancer, as well as those with a previous breast, ovarian, tubal, or peritoneal cancer diagnosis who have completed treatment and are considered cancer free. The USPSTF reviewed interventions to reduce the risk for breast, ovarian, tubal, or peritoneal cancer in women with potentially harmful *BRCA1/2* mutations, including intensive cancer screening (eg, earlier and more frequent mammography or magnetic resonance imaging [MRI] of the breast), medications (eg, tamoxifen, raloxifene, or aromatase inhibitors), and risk-reducing surgery (eg, mastectomy or salpingo-oophorectomy). Although male breast cancer, pancreatic cancer, prostate cancer, and melanoma are associated with *BRCA1/2* mutations, discussion of these types of cancer is outside the scope of this recommendation.

Accuracy of Familial Risk Assessment

The USPSTF reviewed studies of familial risk stratification tools that could be used in primary care settings to determine the likelihood of potentially harmful *BRCA1/2* mutations. These tools are primarily intended for use by health care clinicians untrained in genetic cancer risk assessment to guide referral to genetic counselors for more definitive evaluation. In general, these tools elicit information about factors associated with increased likelihood of *BRCA1/2* mutations, including family and personal history of cancer (including types of cancer and age of diagnosis) and ancestry (Ashkenazi Jewish). Because risk assessment is primarily based on family history, it is unclear how women with an unknown family history should be assessed for *BRCA1/2* mutation risk.

Models that have been validated in studies include the Ontario Family History Assessment Tool (Table 1),[15-18] Manchester Scoring System (Table 2),[16-21,41] Referral Screening Tool (Table 3),[22] Pedigree Assessment Tool (Table 4),[23,24] 7-Question Family History Screening Tool (Table 5),[25] and the International Breast Cancer Intervention Study instrument (also known as Tyrer-Cuzick) (Table 6), and their variations.[26] The USPSTF found that these tools are clinically useful predictors of which individuals should be referred for genetic counseling. Compared with results of other models or genetic testing in studies, these tools all have sensitivity estimates between 77% and 100% and areas under the receiver operating characteristic curve between 0.68 and 0.96,[28] although some models have been evaluated in only 1 study.[22,25,26] The USPSTF reviewed a study of brief versions of BRCAPRO (eg, BRCAPRO-LYTE), designed for primary care clinicians, followed by the full BRCAPRO (used by genetic counselors) and found that the sequential testing scheme identified a similar number of *BRCA* mutation carriers as the full BRCAPRO.[42] The USPSTF recognizes that each risk assessment tool has advantages and limitations and found insufficient evidence to recommend one tool over another.

Effectiveness of Genetic Counseling, Genetic Testing, and Interventions

To understand the full benefits and harms of genetic counseling, the USPSTF reviewed studies on pretest and posttest counseling, *BRCA1/2* mutation testing, and interventions.

Pretest and Posttest Counseling

The USPSTF reviewed 28 studies on pretest counseling.[43-72] Studies reported measures of distress associated with genetic counseling for *BRCA*-related cancer, including cancer worry (17 studies), anxiety (13 studies), and depression (7 studies). In general, pretest genetic counseling either decreased or had no effect on breast cancer worry, anxiety, and depression.[28] Twenty-two studies examined understanding of risk, with most reporting either improved understanding (14 studies)[45,48,53,55-58,61,64,65,67-69,72,73] or no association (6 studies),[43,52,59,62,70,71] 1 study reporting decreased understanding,[60] and 1 study reporting mixed results.[46] Five studies that evaluated the effects of genetic counseling on *BRCA1/2* mutation testing intention found decreased intent to test in 4 studies[45,53,58,67] and increased intent in 1 study.[74]

Although several studies included discussion of management options as part of the pretest counseling process, none evaluated benefits or harms of counseling conducted after receiving test results.

BRCA1/2 Mutation Testing

One good-quality trial (n = 1034) of women and men of Ashkenazi Jewish ancestry evaluated population-based *BRCA1/2* mutation testing vs family history–based testing.[75] Results showed that a strategy of population-based testing for founder mutations detected more *BRCA1/2* mutation carriers than testing persons who met family history criteria. However, no clinical outcomes were reported and, because not all participants had *BRCA1/2* mutation testing, the accuracy of this strategy could not be determined. Genetic testing generally improved risk perception, with increased perceived risk of breast and ovarian cancer risk in *BRCA1/2* mutation carriers and decreased perceived risk in persons testing negative.[76,77]

Interventions

Studied interventions to reduce risk for cancer in women who are *BRCA1/2* mutation carriers include earlier, more frequent, or more intensive cancer screening (eg, breast MRI or mammography); use of risk-reducing medications (eg, selective estrogen receptor modulators or aromatase inhibitors); and risk-reducing surgery (eg, mastectomy or salpingo-oophorectomy).

The USPSTF reviewed 11 randomized clinical trials of selective estrogen receptor modulators and aromatase inhibitors, although none were conducted specifically in women who were *BRCA1/2* mutation carriers. Results of meta-analysis[78] indicated clinically significant reductions in invasive breast cancer with the use of tamoxifen, raloxifene, and aromatase inhibitors, with 7 fewer events per 1000 women for tamoxifen (4 trials),[79-82] 9 fewer events per 1000 women for raloxifene (2 trials),[83,84] and 16 fewer events per 1000 women for aromatase inhibitors (2 trials),[85-89] assuming 5 years of treatment. Tamoxifen reduced invasive breast cancer more than raloxifene in the head-to-head trial (relative risk, 1.24 [95% CI, 1.05-1.47]).[90] Risk reduction persisted at least 8 years after discontinuation in the 2 tamoxifen trials providing long-term follow-up data. All medications reduced estrogen receptor–positive, but not estrogen receptor–negative, invasive breast cancer. Breast cancer–specific and all-cause mortality were not reduced.[78]

In cohort studies of high-risk women and women who were *BRCA1/2* mutation carriers, risk-reducing surgery such as mastectomy (6 studies),[91-97] oophorectomy (7 studies),[98-104] or salpingo-oophorectomy (2 studies)[91,105] were associated with reduced risk for breast or ovarian cancer. Bilateral mastectomy was associated with a 90% to 100% reduced breast cancer incidence and 81% to 100% reduced breast cancer mortality. Oophorectomy was associated with 81% to 100% reduced ovarian cancer incidence. In general, there was no association between oophorectomy or salpingo-oophorectomy and reduced breast cancer risk, although some studies showed reduced risk in younger women (age <50 years).[78,98,99]

The USPSTF found no studies on the benefits of intensive screening for *BRCA*-related cancer on clinical outcomes in women who are *BRCA1/2* mutation carriers.

Harms of Genetic Counseling, Genetic Testing, and Interventions

The USPSTF reviewed the psychological effects of test results. Nine studies evaluated breast cancer worry or distress after genetic testing. Increased worry was found in 7 studies,[77,106-111] particularly in women who are *BRCA1/2* mutation carriers, and 2 studies reported decreased worry.[112,113] Studies reporting anxiety related to genetic testing were mixed, with 4 reporting increased anxiety,[106,109,113,114] 2 reporting decreased anxiety,[111,115] and 6 reporting no association.[75,108,112,116-118] Two studies noted higher anxiety in women who were not tested compared with those who were tested.[111,119] Of the 8 studies evaluating depression, none reported increases in anxiety after genetic testing.[75,108,111,112,115,117,118,120]

Intensive screening for breast and ovarian cancer is associated with false-positive results, additional imaging tests, and surgery for women without cancer. In a retrospective analysis of a cohort of women with potentially harmful *BRCA1/2* mutations or first-degree relatives with *BRCA1/2* mutations, women screened with mammography were more likely to have additional imaging tests than those screened with MRI.[121] In 2 studies comparing mammography with MRI for breast cancer screening in which 18% to 100% of study participants were *BRCA1/2* mutation carriers, MRI was associated with higher false-positive rates (14% vs 5.5% in the first round of screening; $P < .001$[122]; 15% vs 11% in another study[121]). Intensive screening for ovarian cancer using transvaginal ultrasound demonstrated high false-positive rates (3.4%).[123] A second study in women who were *BRCA1/2* mutation carriers reported a diagnostic surgery rate of 55% after annual screening with transvaginal ultrasound and serum tumor marker cancer antigen 125 measurements for women without cancer.[124] Most women did not experience anxiety after screening with MRI, mammography, or clinical breast examination, although women recalled for additional testing reported transient anxiety.[125]

Eight placebo-controlled trials and 1 head-to-head trial of tamoxifen and raloxifene reported harms of risk-reducing medications. Raloxifene and tamoxifen increased risk for thromboembolic events compared with placebo, and raloxifene caused fewer events than tamoxifen in the head-to-head trial.[78,126,127] An increased risk of endometrial cancer was seen with tamoxifen (4 cases per 1000 women) but not with raloxifene or aromatase inhibitors. Women using tamoxifen had more cataract procedures compared with placebo or raloxifene.[79,90] The most common adverse effects were vasomotor symptoms and vaginal discharge, itching, or dryness for tamoxifen and vasomotor symptoms and leg cramps for raloxifene.[28]

Thirteen studies of mastectomy[128-140] and 9 studies of oophorectomy or salpingo-oophorectomy[141-145] reported harms associated with surgical interventions, although most were small in size and had mixed outcomes. For mastectomy, complication rates ranged from 49% to 69%.[28] Complications included numbness, pain, tingling, infection, swelling, breast hardness, bleeding, organizing hematoma, failed reconstruction, breathing problems, thrombosis, and pulmonary embolism.[28] Postsurgical complications associated with oophorectomy/salpingo-oophorectomy included bleeding, pain, infection, and hematoma formation, with 1% to 3% of women in 1 study reporting such complications.[142] In another small study of women who were *BRCA1/2* mutation carriers, most women reported worsening vasomotor symptoms and decreased sexual function.[146] Seven studies reported psychological outcomes in women receiving risk-reducing mastectomy[132-140] and 3 studies in those receiving risk-reducing oophorectomy/salpingo-oophorectomy.[143-145] Commonly reported symptoms included reductions in body image, sexual activity/satisfaction, and general mental health (anxiety/depression symptoms); however, many of these symptoms were transient.[28]

Estimate of Magnitude of Net Benefit

For women whose family or personal history is associated with an increased risk for harmful mutations in the *BRCA1/2* genes, there is adequate evidence that the benefits of risk assessment, genetic counseling, genetic testing, and interventions are moderate. For women whose family history is not associated with an increased risk for harmful mutations in the *BRCA1/2* genes, there is adequate evidence that the benefits of risk assessment, genetic counseling, genetic testing, and interventions are small to none.

The USPSTF found adequate evidence that the overall harms of risk assessment, genetic counseling, genetic testing, and interventions are small to moderate.

For women whose family history is associated with an increased risk for harmful mutations in the *BRCA1/2* genes, the USPSTF concludes with moderate certainty that the net benefit outweighs the harm of risk assessment and referral to genetic counseling for consideration of testing, detection, and intervention is moderate. For women whose family history is not associated with an increased risk for harmful mutations in the *BRCA1/2* genes, the USPSTF concludes with moderate certainty that the harms of risk assessment and referral to genetic counseling for consideration of testing, detection, and intervention outweigh the benefits.

How Does the Evidence Fit With Biological Understanding?

The *BRCA1* and *BRCA2* genes are tumor suppressor genes. Harmful mutations of these genes have been linked to hereditary breast and ovarian cancer. Risks for breast, ovarian, and other types of *BRCA*-related cancer are greatly increased in patients who have inherited potentially harmful *BRCA1/2* mutations. Genetic testing may identify these mutations. Several options are available to reduce cancer risk in patients found to be mutation carriers.

Response to Public Comment

A draft version of this Recommendation Statement was posted for public comment on the USPSTF website from February 19 through March 18, 2019. In response to public comments, the USPSTF clarified language regarding risk assessment and included additional information on the risk assessment tools referenced in the recommendation. It also incorporated language clarifying that the recommendation includes women with a personal history of *BRCA*-related cancer who have completed treatment and are considered cured.

Comments requested that the population under consideration be expanded to include other *BRCA*-associated cancers such as pancreatic cancer, melanoma, and prostate cancer, as well as men with breast or prostate cancer. The USPSTF recognizes the association of *BRCA1/2* mutations with cancers such as pancreatic, prostate, and melanoma. However, the scope of the recommendation is limited to the prevention of breast, ovarian, tubal, and peritoneal cancer because the net benefit demonstrated was in the prevention of these cancers. The USPSTF did not review evidence on the benefits or harms of risk assessment, genetic counseling, and genetic testing in men.

Several comments requested changes to the recommendation related to newer genetic testing options. This includes the use of multigene panels, expanding the recommendation to include other gene mutations linked to increased risk of cancer (eg, *TP53, ATM, PALB2*), and the use of direct-to-consumer testing. The USPSTF acknowledges that there is increasing access to multigene panels; however, the clinical significance of identifying pathogenic variants in multigene panels requires further investigation. The evidence is currently limited on other moderate penetrance genes, given their relatively low incidence in the population. The USPSTF's recommendation focuses on *BRCA1/2* mutations because they are more prevalent and the findings are clinically actionable. The USPSTF found no evidence on the benefits or harms associated with the use of direct-to-consumer testing. Current National Comprehensive Cancer Network guidelines recommend that multigene testing be offered in the context of professional genetic expertise for pretest and posttest.[29] The USPSTF added language emphasizing that the net benefit relies on genetic counseling to accompany testing results, including results from direct-to-consumer testing.

Update of Previous USPSTF Recommendation

In 2005 and 2013, the USPSTF recommended that women whose family history is associated with an increased risk for potentially harmful mutations in the *BRCA1/2* genes be referred for genetic counseling and evaluation for *BRCA1/2* testing. It also recommended against routine referral for genetic counseling or routine *BRCA1/2* mutation testing for women whose family history is not associated with an increased risk for potentially harmful mutations in the *BRCA1/2* genes.[14,147] This Recommendation Statement is consistent with the USPSTF's previous recommendation.

Since 2013, the validity of genetic testing for *BRCA1/2* mutations has been established and the potential benefits and harms of previously reviewed interventions, such as risk-reducing medications and surgery, have been studied for longer follow-up periods. In addition, there have been more studies of newer imaging techniques (breast MRI), surgical procedures (salpingo-oophorectomy rather than oophorectomy alone), and medications (aromatase inhibitors). The updated recommendation expands the population eligible for screening to include women with a previous breast, ovarian, tubal, or peritoneal cancer diagnosis who have completed treatment and are considered cancer free and more explicitly includes ancestry associated with *BRCA1/2* mutations (ie, founder mutations) as a risk factor.

Recommendations of Others

The National Comprehensive Cancer Network provides specific criteria for genetic counseling and testing.[29] The American College of Medical Genetics and the American Society of Clinical Oncology recommend testing for *BRCA1/2* mutations only when an individual has personal or family cancer history suggestive of inherited cancer susceptibility, the test can be adequately interpreted, and the results will aid in management.[148,149] The American College of Obstetricians and Gynecologists recommends performing a hereditary cancer risk assessment and subsequent referral to a specialist in cancer genetics if necessary.[150] The Society for Gynecologic Oncology recommends that individuals with a likelihood of inherited predisposition to cancer based on personal or family history should be offered genetic counseling.[151] The American Society of Breast Surgeons recommends that genetic testing be made available to all patients with a personal history of breast cancer.[152] The National Institute for Health and Care Excellence recommends that health care professionals respond to a patient who presents with concerns but should not, in most instances, actively seek to identify persons with a family history of breast cancer.[153] It recommends that in some circumstances, including when a patient has concerns about relatives with breast cancer, a first- and second-degree family history be taken in primary care to assess risk. Referral to secondary care is recommended if risk factors are identified in family history taking.[153] The European Society for Medical Oncology follows the recommendations of the National Institute for Health and Care Excellence for initial risk assessment and the decision when to perform genetic counseling and testing.[154]

ARTICLE INFORMATION

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Update in women's health

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Update in Women's Health

Pamela Charney, MD; Judith Walsh, MD, MPH; and Ann B. Nattinger, MD, MPH

Many important articles on a variety of women's health topics were published in 1998. We chose the articles for this Update because of their implications for clinical practice in four areas: gynecology, risk factors for coronary artery disease, risk factors for and prevention of breast cancer, and osteoporosis. Some of the articles—such as Burgio and colleagues' study of incontinence—offer observations and practical advice, whereas others—such as Jick and colleagues' study of the association between use of obesity drugs and occurrence of heart disease—send a warning signal. Each article presents interesting and useful information for the internist. Although some of the articles have already been described in other Updates in this year's series, this Update concentrates on aspects of each published study that are of particular importance in the care of women.

Gynecology

A comparison of drug versus behavioral treatment for incontinence in older women, an examination of the risk factors for chlamydial infection, and an evaluation of the use of emergency contraception provide the internist insight into the special needs of women.

Behavioral Biofeedback Is a Well-Tolerated and Successful Strategy for Treatment of Incontinence in Older Women

Burgio KL, Locher JL, Goode PS, et al. Behavioral vs drug treatment for urge urinary incontinence in older women: a randomized controlled trial. JAMA. 1998;280:1995-2000.

As described in the Update in General Internal Medicine (1), Burgio and colleagues conducted an 8-week randomized, placebo-controlled trial to compare the effectiveness of biofeedback-assisted behavioral therapy with that of oxybutynin for treatment of urge incontinence. The behavioral interventions, described in **Table 1**, were more effective (80.7%) than oxybutynin (68.5%) or placebo (39%) by self-described improvement in symptoms. Furthermore, participants greatly preferred behavioral interventions. Seventy-four percent of participants required only one session, in which pelvic contraction without abdominal relaxation was taught by using biofeedback with a rectal manometer. Even the controls, who completed a bladder diary and frequently saw the nurse practitioner, achieved a 40% reduction in incontinence episodes. The message for internists is that behavioral interventions are effective and are preferred by patients with urge incontinence, which is common in older women.

Ligase Chain Reaction Screening for Chlamydial Infection Yielded a High Prevalence of This Infection in Female Military Recruits

Gaydos CA, Howell MR, Pare B, et al. *Chlamydia trachomatis* infections in female military recruits. N Engl J Med. 1998;339:739-44.

Gaydos and colleagues conducted a prospective cohort study to determine the prevalence of chlamydial infection, to assess the feasibility of screening urine specimens for *Chlamydia trachomatis* with

Table 1. Behavioral Interventions for Urge Incontinence

All participants
Daily bladder diary (time of voiding, incontinence, and large or small volume of urine loss)
Four visits with a nurse practitioner every 2 weeks
Behavioral intervention group only
Instructed with biofeedback (anorectal manometer) to contract and relax pelvic muscles without abdominal contractions (pelvic exercise)
Pelvic exercise to be repeated 15 times three times daily in different positions, working to sustain each contraction up to 10 seconds
Urge sensation response strategies, including the following: pausing, relaxing, and even sitting when possible, then pelvic exercises before walking to bathroom
If there is difficulty learning pelvic exercises, combined bladder–rectal feedback

Ann Intern Med. 1999;131:952-958.

For author affiliations and current addresses, see end of text.

Table 2. Sexual Risk Factors for Chlamydial Infection in Female Military Recruits (Multivariate Analysis)

Risk Factor	Odds Ratio (95% CI)
Vaginal sex	5.9 (2.9–10.6)
More than one sex partner in past 90 days	1.4 (1.2–1.7)
New sex partner in past 90 days	1.3 (1.1–1.6)
Inconsistent condom use in past 90 days	1.4 (1.1–1.6)
Ever had sexually transmitted disease	1.2 (1.0–1.4)

ligase chain reaction, and to determine factors predictive of infection. Female military recruits who presented for physical examination were invited to participate in the study, which involved urine screening for *C. trachomatis*; 13 223 of 16 593 women (79.7%) agreed to participate. The study participants completed a questionnaire about demographic characteristics and sexual history. Their urine specimens were tested for chlamydial DNA by ligase chain reaction, which has a reported sensitivity of 88.6% and specificity of 99.7%.

Results showed that the overall prevalence of *C. trachomatis* infection was 9.2%. The average participant age was 21 years (range, 17 to 39 years), and 87.9% of women with *C. trachomatis* infection were 25 years of age or younger. The highest prevalence of infection was among 17-year-old participants (12.2%), and infection rates declined with increasing age. The prevalence was 1.4% in female recruits who reported that they had not had vaginal sex.

The identification of young age as a risk factor for chlamydial infection confirms the results of previous studies. However, even if all women younger than 25 years of age in this population were screened, 4.7% of the infections would still be missed.

Because chlamydial infection can have serious consequences (for example, increased subsequent risk for ectopic pregnancy and infertility) but still be asymptomatic, a screening strategy is appropriate. Screening for chlamydial infection is especially important in the presence of such risk factors as age younger than 25 years, more than one sex partner, and a history of vaginal sex (**Table 2**).

In a Swedish cervical screening program, the prevalence of chlamydial infections varied from 6.5% in women 20 to 24 years of age to 2.2% in women 35 to 39 years of age (2). Screening for chlamydia in women older than 25 years of age, despite the lower prevalence, might be considered if future fertility is an issue. In populations with a disease prevalence similar to or greater than that in this population (for example, the sexual contacts of those with chlamydial infection), screening with urine ligase chain reaction is simple and probably cost-effective.

Self-Administered Emergency Contraception Is Safe in Women without Contraindications

Glasier A, Baird D. The effects of self-administered emergency contraception. N Engl J Med. 1998;339: 1-4.

Glasier and colleagues conducted this prospective cohort study to assess the safety and efficacy of providing self-administered emergency contraception to women 16 to 44 years of age. The researchers recruited 1083 women (553 in the treatment group and 530 in the control group) who had no history of arterial disease, venous thromboembolism, or severe migraine headaches. Recruitment took place at a follow-up visit for contraception after emergency contraception or a therapeutic abortion.

Women randomly assigned to the treatment group received an emergency contraceptive packet consisting of four birth control pills to keep at home. Verbal and written instructions advised taking two pills (50 μg of ethinyl estradiol and 0.25 μg of levonorgestrel) within 72 hours of intercourse and taking a repeated dose at 24 hours. If pills were taken, the participants were to send a notification card to the clinic and then report for evaluation within 1 week after the date of the next expected menstrual cycle. If the woman was not pregnant and she wished to continue to participate, another package of pills was distributed. Women in the control group were advised that emergency contraceptive pills were available through the clinic and that a notification card should be mailed to the study if this birth control method was used. Substantial effort was made to identify all pregnancies that occurred within 1 year.

Analysis after 1 year revealed that women who received an emergency contraception packet were more likely to use emergency contraception once (36% compared with 14% of controls; $P < 0.001$) but not use it more than once (12% compared with 13%; $P > 0.2$). By self-report, participants had used the pills correctly. Overall, contraceptive failure rate was 3%, with similar rates of pregnancy in both groups. However, 18 pregnancies in the treatment group and 25 in the control group were unintended (relative risk, 0.7 [95% CI, 0.4 to 1.2]). No complications of therapy were seen, and, if pregnancy prevention was unsuccessful, the fetus was not harmed.

The study shows that self-administered emergency contraception is safe in women without contraindications. However, pregnancy rates were similar to those for women who take oral contraceptives regularly. If this method is to be used more widely, providing education in the proper use of emergency contraception and oral contraceptives is essential and should include written as well as verbal instruction.

Risk Factors for Coronary Artery Disease

Coronary artery disease is the leading cause of death in the United States, and half of all deaths from this disease occur in women. Two questions often considered are 1) Can we reduce the rates of heart disease in women? and 2) what are the data for risk factor modification in women? The following articles help to answer these questions.

Evidence suggests that the modification of some risk factors, including smoking cessation, treatment of hypertension, diet, exercise, and maintenance of ideal body weight, is important in women as well as in men. In 1998, literature focused on other potential treatments, such as the use of hormone replacement therapy (HRT) as secondary prevention, lipid-lowering agents for primary prevention, and use of vitamin B_6.

Prescribing Hormone Replacement Therapy To Prevent Recurrence in Women with Coronary Artery Disease Is Not Recommended

Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA. 1998; 280:605-13.

This much-cited study conducted by the Heart and Estrogen/progestin Replacement Study (HERS) Research Group studied 2763 postmenopausal women with established coronary artery disease to determine whether estrogen plus progestin therapy alters the risk for cardiac events in this population. As detailed in the Update in General Internal Medicine (1), the results indicated that women receiving HRT had a statistically significantly increased risk for thromboembolic events and gallbladder disease and that HRT did not decrease the overall risk for coronary artery disease–related events in postmenopausal patients with established coronary artery disease during 4 years of follow-up.

Although recurrence of coronary artery disease was increased in HRT users during the first 2 years, rates of coronary artery disease were lower in HRT users during years 3 and 4. Because of the finding of an early increase in coronary artery disease events in women receiving HRT, prescribing HRT to prevent recurrent coronary artery disease is not recommended. Receiving HRT for several years was associated with a reduction in coronary artery disease events; thus, it may be appropriate for women already receiving HRT to continue this therapy. Previously, observational studies had shown that women who take postmenopausal hormones have a lower rate of heart disease, but these results may be related in part to a "healthy user bias" as well as to differences in the study samples and treatments. The increased risk for thromboembolic events in women who take estrogen and progestin must be considered in the decision to prescribe HRT. The extent to which the results of this study apply to women without established coronary artery disease and to women who take unopposed estrogen or other estrogen–progestin formulations are unknown. Future research (including the Women's Health Initiative) will investigate the effects of estrogen–progestin as primary prevention for coronary artery disease.

Further Studies Are Needed for Primary Prevention of Acute Coronary Events with Lovastatin in Women

Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998;179:1615-22.

This randomized, placebo-controlled trial has received substantial attention and was also described in the Update in General Internal Medicine (1). Downs and colleagues studied the effect of long-term lipid-lowering therapy on coronary events, with a mean follow-up of 5.2 years. The results indicate a trend toward more benefit in patients with diabetes or hypertension. Overall, participants treated with lovastatin had a 37% lower incidence of first major acute coronary events. For women, the difference in coronary artery disease events between lovastatin and placebo recipients was not statistically significant (1.4% and 2.6%, respectively).

However, too few women were included to allow the authors to find a statistically significant reduction in coronary artery disease events in women (only 997 women among 6605 participants). Because the coronary artery disease event rate in women is lower than that in men at any given age, many more women than men must be treated to prevent one such event. Although the increase in breast cancer cases among lovastatin-treated women was not statistically significant, the trend is in the same direction as that seen in the Cholesterol and Recurrent Events (CARE) Study (3).

No data are available on the long-term risks of lovastatin use in women. Until further data are available, the possible association between lipid-lowering medications and breast cancer should be considered in the risk–benefit analysis. Clinicians should consider a woman's cholesterol levels in the context of her other risk factors for coronary artery disease when deciding whether to treat hyperlipid-

emia. Further studies are needed before the results of the Air Force/Texas Coronary Atherosclerosis Prevention Study can be generalized to low-risk women.

Higher Intake of Folate and Vitamin B_6 Is Associated with Lower Rates of Coronary Artery Disease in Women

Rimm EB, Willett WC, Hu FB, et al. Folate and vitamin B_6 from diet and supplements in relation to the risk of coronary heart disease among women. JAMA. 1998;279:359-64.

As part of the Nurses' Health Study, Rimm and colleagues evaluated the relation between the intake of folate and vitamin B_6 and the occurrence of heart disease in women. For 14 years, this prospective observational cohort study followed 80 062 women who were initially free of cardiovascular disease, cancer, hypercholesterolemia, and diabetes. In 1980, the women completed a detailed food-frequency questionnaire, which included questions about their use of vitamin supplements. They were resurveyed in 1984, 1986, and 1990. Reported intake of vitamin B_6 and folate was divided into quintiles. The rate of coronary artery disease events (nonfatal myocardial infarction or death from coronary artery disease) in each quintile was compared with that in the lowest quintile of intake. Multivariate analysis was performed to correct for the confounders of age, time period, smoking status, body mass index, postmenopausal hormones, aspirin, vitamin E supplements, exercise, hypertension, parental history of coronary artery disease, and fat and alcohol intake.

Intake of folate and intake of vitamin B_6 were highly correlated, thereby limiting the researchers' ability to assess their independent contributions. During 14 years of follow-up, 658 nonfatal myocardial infarctions and 281 deaths from coronary artery disease were recorded. Women in the highest quintile of folate intake had an age-adjusted multivariate relative risk for coronary artery disease of 0.69 (95% CI, 0.55 to 0.87) compared with women in the lowest quintile. In addition, a dose–response effect was noted. Women in the highest quintile of vitamin B_6 intake had an age-adjusted multivariate relative risk that was 0.67 (CI, 0.53 to 0.85) times that of women in the lowest quintile; again, a dose–response effect was noted.

Multivitamins were found to be the major source of folate and vitamin B_6 in the study, and the results indicated that risk for coronary artery disease was reduced in women who regularly took multivitamins (relative risk, 0.76 [CI, 0.65 to 0.90]) compared with women who did not. Similar associations with coronary artery disease were seen regardless of whether the folate came from supplements or dietary sources. Women in the highest quintile for reported intake of both folate and vitamin B_6 had a relative risk for coronary artery disease that was 0.55 (CI, 0.41 to 0.74) times that of women in the lowest quintile of intake of both nutrients. The inverse association between folate and coronary artery disease was stronger among women who consumed up to one alcoholic drink per day (relative risk, 0.69 [CI, 0.49 to 0.97]) or more than one drink per day (relative risk, 0.27 [CI, 0.13 to 0.58]) than in nondrinkers. High folate intake seems to be protective, particularly in women who drink alcohol. [*Editor's note:* Folate may be more protective in persons who consume less methionine (from protein) in the diet, which may be true for persons who drink more; in addition, the metabolism of alcohol can inactivate folate.]

Although observational evidence suggests a strong association between elevated homocysteine levels and cardiovascular disease, and experimental evidence indicates that higher folate and vitamin B_6 intake is associated with lower homocysteine levels, no evidence from randomized, controlled trials indicates that increased folate and vitamin B_6 intake is associated with a reduction in risk for coronary artery disease. Given the existing evidence, increasing the intake of folate to 400 μg/d and vitamin B_6 to 3 mg/d is likely to result in favorable coronary artery disease outcomes and is unlikely to have significant negative effects. Future research must address whether supplementation with folate and vitamin B_6 is appropriate for women in the general population.

Aortic and Mital Regurgitation Were the Abnormalities Most Often Seen in a Study of Obesity Drugs and Heart Disease

Jick H, Vasilakis C, Weinrauch LA, et al. A population-based study of appetite-suppressant drugs and the risk of cardiac-valve regurgitation. N Engl J Med. 1998;339:719-24.

Jick and colleagues conducted a case–control study nested within a United Kingdom population-based study to determine the risk for cardiac valvular regurgitation after more than 3 months' exposure to appetite-suppressant drugs. The persons studied were generally healthy users of appetite-suppressant drugs who were younger than 70 years of age at recruitment and had no previously documented cardiovascular disease or substance abuse.

The analysis compared 9765 persons who used appetite-suppressant drugs (6532 had previously used dexfenfluramine, 2371 had previously used fenfluramine, and 862 had previously used phentermine) with 9281 obese persons who had not taken these drugs; the two groups were matched for age,

sex, and weight. Computerized records were reviewed to identify new diagnoses of valvular heart disease after prescription of appetite-suppressant drugs, and echocardiograms were reviewed by a senior cardiologist who was not aware of any drug exposure. Average follow-up was 4 years.

New-onset valvular regurgitation (6 cases of aortic regurgitation, 2 cases of mitral regurgitation, 3 cases of both) was identified in 11 persons after the development of symptoms or a new murmur. Six women had received fenfluramine and 5 had received dexfenfluramine. No new valvular abnormalities were noted among the controls. The 5-year cumulative incidence of cardiac valve abnormalities increased with greater duration of exposure. After 1 to 3 months of dexfenfluramine or fenfluramine therapy, there were 7.1 valve abnormalities per 10 000 persons (CI, 3.6 to 17.8 abnormalities); with therapy lasting longer than 4 months, there were 35 abnormalities per 10 000 persons (CI, 16.4 to 76.2 abnormalities).

Because persons with more than 3 months of exposure to appetite-suppressant drugs are at slightly increased risk for the development of valvular abnormalities (most often aortic or mitral regurgitation), screening of patients exposed to these drugs for even a brief time should include at least auscultation and a careful assessment for cardiac symptoms. Echocardiography should be ordered for persons with a positive result on screening or those with more than 4 months' exposure to appetite-suppressant drugs.

Risk Factors for and Prevention of Breast Cancer

Identifying risk factors and finding methods for prevention of breast cancer are of great importance. The need for research on the former is demonstrated by the fact that the current known risk factors for breast cancer account for fewer than half of the breast cancer cases. The need for research on the latter point is clear because breast cancer remains the most common cancer diagnosis among U.S. women. The following articles show some promise for addressing each of these needs.

Alcohol Consumption Increases the Risk for Breast Cancer

Smith-Warner SA, Spiegelman D, Yaun S, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA. 1998;279:535-40.

Even though more than 50 epidemiologic studies have examined the relation between alcohol consumption and breast cancer, the association has remained controversial. Smith-Warner and colleagues performed a pooled analysis of primary data from six prospective cohort studies conducted in Canada, the Netherlands, Sweden, and the United States to examine the association between alcohol consumption and risk for breast cancer. The studies included a total of 322 647 women followed for 5 to 11 years, of whom 4335 developed invasive breast cancer.

Table 3. Alcohol Intake Conversions

Type of Alcohol	Conversion
Wine	10.8 g/glass
Beer	13.2 g/can or bottle
Liquor	15.1 g/shot

Women who drank 30 to 60 g of alcohol per day (approximately 2 to 5 drinks per day; see **Table 3** for conversions) had a statistically significant 40% increase in the risk for developing breast cancer. Only 1% of the cohort drank more than 60 g of alcohol per day. Such women had a 30% increased risk for breast cancer. The association was not affected by type of alcohol consumed (wine, beer, or liquor) or by other known risk factors for breast cancer.

Assessing the overall risk-to-benefit ratio of alcohol consumption for any given patient is difficult. Although this study shows that there is a 30% to 40% increase in breast cancer among women who drink at least 30 g of alcohol per day, studies also have shown that moderate alcohol consumption may be associated with a lower risk for cardiovascular disease and total mortality. However, recognition of alcohol as a risk factor for breast cancer is important because alcohol intake is potentially modifiable, unlike many other breast cancer risk factors.

Tamoxifen Therapy Shows Both Benefits and Risks

Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998;90:1371-88.

Yet another much-cited study, this randomized, double-blind, placebo-controlled trial was designed to determine whether therapy with tamoxifen—the antiestrogen chemoprophylactic agent—prevents breast cancer in women at relatively high risk for the disease. As described in the Update in General Internal Medicine and other Updates in this series, this study was important because it provided the first direct evidence that chemoprophylaxis against breast cancer is possible. Fisher and colleagues' 4-year multicenter randomized, placebo-controlled trial of 13 388 women at increased risk for breast cancer showed that tamoxifen reduced the incidence of invasive breast cancer, with a 5-year risk reduc-

Table 4. Outcomes of Prophylactic Tamoxifen Compared with Placebo

Outcome	Events in Placebo Group	Events in Tamoxifen Group	Relative Risk (95% CI)
	n		
Breast cancer	175	89	0.51 (0.39–0.66)
Carcinoma in situ	69	35	0.50 (0.33–0.77)
Fractures	137	111	0.81 (0.63–1.05)
Ischemic heart disease	62	71	1.15 (0.81–1.64)
Endometrial cancer	15	36	2.53 (1.35–4.97)
Deep venous thrombosis	22	35	1.60 (0.91–2.86)
Pulmonary embolism	6	18	3.01 (1.15–9.27)
Stroke	24	38	1.59 (0.93–2.77)
Death	71	57	0.81 (0.56–1.16)

tion of 0.51 and an absolute risk reduction of 1.7% (number needed to treat for benefit for 5 years, 60). As can be seen in **Table 4**, the tamoxifen group had an elevated risk for several adverse events, including endometrial carcinoma and thromboembolism. Total mortality did not differ between the two groups. Whether this intervention decreases the risk for death from breast cancer or simply postpones death has not been demonstrated. However, the study did demonstrate 17 fewer cases of invasive breast cancer and 7 fewer cases of ductal carcinoma in situ, but also 5 additional episodes of deep venous thrombosis or pulmonary embolism and 7 additional cases of endometrial cancer.

One concern is that two European trials of tamoxifen for prevention of breast cancer published in July l998 failed to show any benefit of tamoxifen (3, 4). However, there were major differences between these trials and the U.S. trial. The two European trials together reported only 119 cases of breast cancer or carcinoma in situ, compared with 368 cases in the U.S. trial. The European trials had substantial rates of noncompliance. Many participants in these trials received HRT (41% of women in the British trial [4] and 14% in the Italian trial [5]) in addition to tamoxifen. Overall, the U.S. trial seems more credible because of its larger size and stronger study design.

As a result of the large number of adverse events in the tamoxifen group and the lack of a confirmatory trial, it seems prudent to offer tamoxifen mainly to women with a substantially elevated risk for breast cancer. Appropriate candidates are those with lobular or ductal carcinoma in situ or atypical hyperplasia and possibly those with a *BRCA1* or *BRCA2* mutation. Other candidates may include premenopausal women with elevated breast cancer risk (younger women in the U.S. trial had fewer adverse events while receiving tamoxifen) and high-risk postmenopausal women who have undergone hysterectomy. Newer selective estrogen-receptor modulators may provide prophylaxis against breast cancer with fewer adverse effects. A trial is being undertaken to compare raloxifene with tamoxifen for this purpose.

Osteoporosis

Prevention of osteoporosis is still an important topic. The following study evaluated the use of alendronate compared with HRT in a specific patient population—women younger than 60 years of age.

Both Alendronate and Estrogen–Progestin Therapies Prevent Postmenopausal Bone Loss

Hosking D, Chilvers CE, Christiansen C, et al. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. N Engl J Med. 1998;338:485-92.

This study randomly assigned 1174 postmenopausal women aged 45 to 59 years to 2.5 or 5.0 mg of alendronate or to placebo and randomly assigned an additional 435 women to 2.5 or 5.0 mg of alendronate, HRT, or placebo. At 2 years of follow-up, bone mineral density at the lumbar spine and hip was increased for HRT users and for women who received either alendronate dose compared with placebo recipients. At each site, density was greatest for HRT, followed by 5 mg of alendronate and then 2.5 mg of alendronate. At the distal forearm, only HRT prevented a loss of bone density.

Given this information, HRT remains the most effective agent for prevention of postmenopausal bone loss. However, 5 mg of alendronate is a reasonable alternative for women who cannot or do not wish to take HRT.

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Risk Factors for and Prevention of Breast Cancer

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THE AMERICAN SOCIETY OF Breast Surgeons - Official Statement -

Consensus Guideline on Genetic Testing for Hereditary Breast Cancer

Purpose

To outline recommendations for genetic testing that medical professionals can use to assess hereditary risk for breast cancer in their patients.

Methods

Literature review included large datasets, basic science publications, and recent updated national guidelines. This is not an exhaustive systematic review, but a comprehensive review of the most impactful evidence in the modern literature on this subject. Genetic testing to assess hereditary risk of cancer is a broad and dynamic area of medical research. The dominant focus of this guideline is limited in scope to breast cancer. Similar guidelines have been previously put forth from this body in 2006, 2012, 2016, and 2017.

Approval

Please see list of Authors and Disclosures at the end of the statement. This consensus statement was developed under the direction of and approved by the ASBrS Board of Directors.

Recommendations

1. **Breast surgeons, genetic counselors, and other medical professionals knowledgeable in genetic testing can provide patient education and counseling and make recommendations to their patients regarding genetic testing and arrange testing.** When the patient's history and/or test results are complex, referral to a certified genetic counselor or genetics professional may be useful. Genetic testing is increasingly provided through multi-gene panels. There are a wide variety of panels available, with different genes on different panels. There is a lack of consensus among experts regarding which genes should be tested in different clinical scenarios. There is also variation in the degree of consensus regarding the understanding of risk and appropriate clinical management of mutations in some genes.

2. **Genetic testing should be made available to all patients with a personal history of breast cancer.** Recent data support that genetic testing should be offered to each patient with breast cancer (newly diagnosed or with a personal history). If genetic testing is performed, such testing should include BRCA1/BRCA2 and PALB2, with other genes as appropriate for the clinical scenario and family history. For patients with newly diagnosed breast cancer, identification of a mutation may impact local treatment

recommendations (surgery and potentially radiation) and systemic therapy. Additionally, family members may subsequently be offered testing and tailored risk reduction strategies.

3. **Patients who had genetic testing previously may benefit from updated testing.** Every patient being seen by a breast surgeon, who had genetic testing in the past and no pathogenic variant was identified, should be re-evaluated and updated testing considered. In particular, a patient who had negative germline BRCA1 and 2 testing, who is from a family with no pathogenic variants, should be considered for additional testing.[1] Genetic testing performed prior to 2014 most likely would not have had PALB2 or other potentially relevant genes included and may not have included testing for large genomic rearrangements in BRCA1 or BRCA2.

4. **Genetic testing should be made available to patients without a history of breast cancer who meet NCCN guidelines.** Unaffected patients should be informed that testing an affected relative first, whenever possible, is more informative than undergoing testing themselves. When it is not feasible to test the affected relative first, then the unaffected family member should be considered for testing if they are interested, with careful pre-test counseling to explain the limited value of "uninformative negative" results. It is also reasonable to order a multi-gene panel if the family history is incomplete (i.e., a case of adoption, patient is uncertain of exact type of cancer affecting family members, among others) or other cancers are found in the family history, as described above.

5. **Variants of uncertain significance are DNA sequences that are NOT clinically actionable.** This type of result needs to be considered as inconclusive, and the patient should be managed based on their risk factors and not influenced by this result.

Summary of Data Reviewed

The National Cancer Institute estimates for 2018 were that more than 266,000 new cases of invasive breast cancer would be diagnosed in the United States, and more than 40,000 patients would die from the disease.[2] Approximately 10% of breast cancers are associated with a pathogenic germline variant in one of several different genes.[3] More than 50% of pathogenic germline variants are mutations in the BRCA1 and BRCA2 genes.[4-9] Using genetic testing to identify patients who are at increased risk to develop breast cancer enables patients to take steps to reduce this risk. There are several risk management strategies available for individuals at increased risk (e.g., chemoprevention along with enhanced screening; risk reducing surgeries).[10-18] **Unfortunately, in the current state of medical practice, a significant number of pathogenic mutation carriers remain undetected and undiagnosed. These are largely women with "moderate penetrance" mutations, but even women with BRCA1 or 2 mutations may not be identified.**[19-20] There is an unmet challenge to improve our identification and diagnosis of patients who have an inherited increased lifetime risk of breast cancer.

Access to Genetic Counseling and Testing

There are fewer barriers to genetic testing now than previously, and testing is less costly and being offered by more labs. The indications for who should be offered testing are ever increasing - each guideline update casting a wider net, and there is more public awareness. However, some barriers remain - one of which is the limited availability of genetic counseling nationwide for patients and their family members.[19-20]

Increased access to testing would likely lead to more patients pursuing testing and improving rates of identification of gene carriers. Breast surgeons are well positioned to be a resource for patients who may benefit from testing. Breast surgeons can identify individuals who are suitable for testing, inform patients of the risks and benefits, provide access to genetic testing, and also discuss risk management strategies for those patients who test positive. For patients with less common mutations, strong consideration should be given to consultation with cancer genetics specialists.[21-23]

Hereditary Breast Cancer Syndromes

Hereditary mutations to be considered include BRCA 1&2, PALB2, and other hereditary breast cancer syndromes, which include but are not limited to Li-Fraumeni syndrome (TP53 pathogenic variant), Cowden syndrome (PTEN pathogenic variant), Hereditary diffuse gastric cancer syndrome (CDH1 pathogenic variant), and Peutz-Jegher syndrome (STK11 pathogenic variant).

Impact of genetic testing results on management recommendations

Identification of patients with pathogenic variants in these genes can influence patient management in terms of high-risk screening and risk reduction as well as therapeutic options related to surgery, radiation, and systemic therapies.[24-26] For example, identifying that a breast cancer patient has a BRCA1 pathogenic variant provides that patient the opportunity to learn of her elevated risk for contralateral breast cancer as well as of ovarian cancer and to make educated decisions to reduce those risks.[26] Studies are underway to determine whether these patients also might benefit from PARP inhibitors being included in their adjuvant therapy regimen. Another example is that radiation is relatively contraindicated in patients with TP53 pathogenic variants (associated with Li-Fraumeni Syndrome) due to their increased risk of developing radiation-induced secondary malignancies.

Identifying a patient who has a pathogenic variant that indicates high hereditary breast cancer risk can have a profound impact on that patient's health and management. Additionally, it has potential impact on that patient's family members who should be counselled to consider testing for the mutation identified in the family, the result of which can guide their risk of breast cancer development and consideration of risk management strategies.

The genetic testing information should be considered together with the details of each patient's case including age, family history, medical history, and contributing risk factors, as

well as careful review of existing management guidelines. It is important to understand that risk of development of breast and other cancers and risk management guidelines vary both by the mutated gene and the penetrance of the specific genetic mutation. Additionally, not all pathogenic variants identified are medically actionable.

Just because a hereditary pathogenic mutation that predisposes to breast cancer is identified does not mean that the risk-reducing mastectomy is indicated. Risk-reducing mastectomy can be considered in BRCA1, BRCA 2, PTEN, and TP53. Consideration may also be appropriate for patients with mutations in other genes when combined with a significant family history of breast cancer.

Patients with BRCA1 or BRCA2 pathogenic variants should consider risk-reducing bilateral salpingo-oophorectomy after child-bearing or between the ages of 35-40 to reduce ovarian and fallopian tube cancer risk. Women with BRCA1 should consider oophorectomy between ages 35-40, while BRCA2 carriers should consider it between ages 40-45.

Prophylactic oophorectomy in premenopausal women with BRCA2 pathogenic variants has also been shown to reduce the risk of breast cancer by about 50%. There is also breast cancer risk reduction from RRSO in BRCA1 patients but to a lesser degree.[10,11,17]

For patients with mutations in ATM, CDH1, CHEK2, NBN, NF1, PALB2, and STK11, enhanced screening is recommended; however, currently the data are not sufficient to support risk-reducing mastectomy in the absence of other factors such as a strong family history. There are substantial gaps in our ability to predict individual risks associated with mutations in some of these genes. Risk is modulated by age, family history, and in some cases, the specific mutation in a particular gene. For the aforementioned syndromes, the guidelines broadly support considering mammography with tomosynthesis and breast MRI with and without contrast for annual screening due to the elevated risk for breast cancer.

For BARD1, MSH2, MLH1, MSH6, PMS2, EPCAM, BRIP1, RAD51C, RAD51D, there are some data suggesting an elevated lifetime risk of breast cancer; however, there is insufficient evidence to support change in breast cancer risk management based on the presence of a mutation alone. Mutations in these genes may be associated with an increased risk of gynecological cancers, which may warrant specific management. MSH2, MLH1, MSH6, and PMS2 are associated with the Lynch Syndrome, a multi-organ predisposition syndrome that requires multidisciplinary management.

The list of actionable genes and recommendations for screening and risk management continually evolves as additional information becomes available. We refer the readers to the NCCN guidelines, available online at www.nccn.org under the title Familial High-Risk Assessment: Breast and Ovarian Cancer (most recently updated in early 2019). The All Syndromes Known to Man Evaluator (https://ask2me.org/) is another tool available with information on the spectrum and estimated penetrance for pathologic variants.[27]

Limitations of genetic testing

Health care providers and patients need to know that genetic testing is one of several tools for assessing breast cancer risk. Not every genetic test yields a straightforward answer with clear guidance on how to proceed for optimal care. Patients should be made aware that negative test results do not necessarily mean they are not at increased risk for developing breast cancer.

Many factors contribute to a patient's lifetime risk of breast cancer, and genetic testing is an effort to better define one of these elements (the measurable inherited risk). When counseling patients about their lifetime risk of breast cancer, it is critical to look broadly at the patients' other contributing factors, some of which are: age, medical history, lifestyle, exposures, and family history. For patients who test positive for a pathogenic variant, it is important to gain detailed understanding of that variant when advising on risk management strategies – details such as the penetrance of the cancer risk among carriers (how likely is the patient to actually develop breast cancer). Penetrance varies among the identified hereditary cancer syndromes. In other words, not all carriers of pathogenic genetic variants will develop breast cancer, and the level of risk varies with the gene affected and likely the variant as well.[6,28,29]

For example, some types of CHEK2 and ATM variants have low penetrance while other types are more highly penetrant.[30,31] Just because a patient tests positive for a hereditary breast cancer syndrome does not mean that patient will develop breast cancer. ask2me.org can be useful in understanding the penetrance and the management for most cancer-causing genes, and the BRCA Decision Tool, http://brcatool.stanford.edu/brca.html, can be useful in known BRCA pathogenic variant carriers to predict likelihood of developing breast or ovarian cancer and likelihood of dying from either disease based on patient age and a variety of interventions chosen for screening and prophylaxis. It is important to note that these calculators are constrained by the limitations of the studies that provide the underlying odds ratios used to generate the absolute risk estimates and do not account for modification of those odds ratios by age, mutation position, family history, or polygenic background risk.[32]

Pre-and Post-test Counseling

Before testing, patients need to be made aware of the implications that the test result can have (pre-test counseling); and when results become available, patients should be reminded of these implications and be provided the appropriate clinical context for the results to make informed decisions (post-test counseling). All genetic testing should be performed in the setting of informed consent. The American College of Surgeons Commission on Cancer accreditation program mandates that cancer risk assessment, counseling, and genetic testing services be provided to patients by a physician who does risk assessment regularly and/or is qualified to do testing or a qualified genetic professional either on site or by referral.[33] A systematic review of the literature indicates that pre-test counseling, whether by a geneticist, breast surgeon, oncology nurse, or other medical professional with expertise and experience in cancer genetics reduces distress, improves risk perception accuracy, and improves follow through for testing.[34] Breast surgeons who are knowledgeable in cancer genetics can initiate and guide genetic testing for their patients. Pre-test counseling should include discussion of

the types of results (true positive = pathogenic, true negative = benign (although without a known positive in a family, it may also be inconclusive as well), and inconclusive = variant of uncertain significance (VUS)). Other potential issues of testing should also be reviewed, such as inconclusive results, misperception of true risk, and discrimination. As noted above, patients need to know there are limitations to this testing including non-informative results or negative tests as well as the reality of the evolving science. It is important to educate patients on the benefits of testing as a vehicle to knowing better their individual risk and empowerment to consider interventions to manage or reduce that risk. It can be helpful to set expectations for when the test results will be available.

Post-test counseling is important regardless of the actual result. The current best practice is for all patients who undergo genetic testing to have some form of post-test counseling. By NCCN guidelines, this can occur in person or remotely. This allows for patients' questions to be answered and for a thorough debriefing. If a result is negative or non-informative (such as a variant of uncertain significance – VUS) then the patient's other risk factors for breast cancer (age, medical history, family history, etc.) need to be evaluated to formulate the appropriate risk management plan. Depending on the level of risk for breast cancer, strategies to manage that risk can be discussed, including enhanced screening imaging (annual mammogram and breast MRI); chemoprevention (endocrine therapy to lower risk); lifestyle modification with respect to obesity, tobacco use, and alcohol consumption; and exogenous hormone use among others.

For patients who test positive for a pathogenic variant, a clear review of the state of evidence for that specific syndrome is imperative. To make educated decisions, patients need to know about the spectrum of risk management strategies. Ultimately, a customized plan for the patient is the goal with their informed consent. In this discussion, a frank statement of the level of risk reduction for each intervention is needed. For example, risk-reducing mastectomy and reconstruction in a BRCA1-positive 35-year-old patient leads to much greater risk reduction for breast cancer mortality than that same intervention in a 65-year-old patient.[21,35,36] The surgeon should discuss these issues and refer to other specialists (such as gynecologic oncologists, gastroenterologists, etc.) for other organs at risk as appropriate. For complex scenarios, referral to a genetics professional is recommended.

Multi-gene Panel Testing

Genetic testing has expanded in scope and availability since 2013 when the U.S. Supreme Court ruling in Association for Molecular Pathology v. Myriad Genetics, Inc. increased the testing options. Increased competition has helped to lower the cost. Improvements in technology, like next-generation sequencing, has made testing for more than one gene at a time a reality.[37-41] which can improve the cost-effectiveness and efficiency of testing. While BRCA1 and BRCA2 remain the most likely genes to be mutated in a family with high breast and ovarian cancer risk, panel testing can allow for more comprehensive coverage of less common syndromes that can also confer hereditary cancer risk.[4,7,21,42-45] Numerous recent studies have shown that panel testing can significantly increase the rate of detection of pathogenic variants, with the most frequently identified pathogenic variants (outside of BRCA1 and BRCA2) being in PALB2, CHEK2, and ATM.[4,21,44] As noted above, there is a

comparatively limited understanding of individual breast cancer risk associated with mutations in genes other than BRCA1 and BRCA2. However, the presence of mutations in PALB2, ATM, truncating mutations in CHEK2, and possibly other genes are likely to be associated with lifetime breast cancer risks of greater than 20% and therefore, in the United States, at least support a decision for enhanced surveillance with annual mammography with tomosynthesis and breast MRI with contrast. Mutations in other genes may also reach this threshold, although the rarity of such mutations and the possibility of subtype-specific predisposition make risk estimation more challenging. A multi-gene panel may include genes with varying degrees of evidentiary support and "actionability." This testing method is optimal when the individual genes included are clinically valid and comprehensively address the details of each patient's case.

Panel testing can be considered for patients who qualify for hereditary breast cancer testing to more efficiently and cost-effectively evaluate genes that confer risk and impact management recommendations. When genetic testing is being recommended based on phenotypic syndromes (for example three or more close family members affected by breast cancer at any age) then multi-gene panel testing is likely to be more efficient in evaluating patients. In fact, the most recent NCCN guidelines allow that panel testing will largely replace sequential gene sequencing (i.e., the older approach of evaluating BRCA pathogenic variants first, then selecting additional genes if BRCA tests are negative).[20,28,41] Insurance companies are urged to incorporate the advantages of panel testing into their algorithms to allow hereditary cancer syndrome testing for patients at high risk. Surgeons, genetic counselors, and other health care professionals who order panel testing for breast cancer patients or their family members should at a minimum test the breast cancer genes that are clinically actionable given the current state of medical evidence. Testing of additional genes can also be performed at the discretion of the ordering physician or as directed by the family history.

Variant of uncertain significance (VUS)

Variants of uncertain significance are DNA sequences that are NOT clinically actionable. This type of result needs to be considered as inconclusive. For example, a patient who receives a genetic testing result of "BRCA1 variant of uncertain significance" should NOT be recommended for a change in management based on that test result alone. No clinical treatment plan or risk management plan should be influenced by a VUS. These are DNA sequences about which the lab is still accruing data for definitive classification as to benign or pathogenic. The vast majority are re-classified as benign when enough data are collected. Usually it takes several years for the reclassification to take place.[42,46]

The American College of Medical Genetics has published guidelines for reporting DNA sequence variations.[47] The rate of identifying VUSs can be high when new syndromes are identified but that rate decreases as data regarding those genes and the VUSs are accrued. Current rates of identifying a VUS with newer multi-gene panel testing is reported to be between 6.7-41.7%.[21,42-44] There are still VUSs identified with BRCA1/2 testing. However, the rates are generally much lower, ranging from 2-5%, now that testing of these two syndromes has been available for more than 20 years. In general, patients with VUSs should be managed

based on their family history, medical history, age, and other factors that influence breast cancer risk. No weight should be given to the VUS found, and co-segregation among affected family members is not conclusive evidence of pathogenicity.

This statement was developed by the panel members listed below, and on February 10, 2019, was approved by the Board of Directors.

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Kevin Hughes- Honoraria from Focal Therapeutics (Surgical implant for radiation planning with breast conservation), 23andMe, and is a founder of and has a financial interest in CRA Health (Formerly Hughes RiskApps). Dr. Hughes's interests were reviewed and are managed by Massachusetts General Hospital and Partners Health Care in accordance with their conflict of interest policies.

Mark Robson- Honoraria (Advisory): AstraZeneca,
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THE AMERICAN SOCIETY OF Breast Surgeons - Official Statement -

Consensus Guideline on Genetic Testing for Hereditary Breast Cancer

Purpose

To outline recommendations for genetic testing that medical professionals can use to assess hereditary risk for breast cancer in their patients.

Methods

Literature review included large datasets, basic science publications, and recent updated national guidelines. This is not an exhaustive systematic review, but a comprehensive review of the most impactful evidence in the modern literature on this subject. Genetic testing to assess hereditary risk of cancer is a broad and dynamic area of medical research. The dominant focus of this guideline is limited in scope to breast cancer. Similar guidelines have been previously put forth from this body in 2006, 2012, 2016, and 2017.

Approval

Please see list of Authors and Disclosures at the end of the statement. This consensus statement was developed under the direction of and approved by the ASBrS Board of Directors.

Recommendations

1. **Breast surgeons, genetic counselors, and other medical professionals knowledgeable in genetic testing can provide patient education and counseling and make recommendations to their patients regarding genetic testing and arrange testing.** When the patient's history and/or test results are complex, referral to a certified genetic counselor or genetics professional may be useful. Genetic testing is increasingly provided through multi-gene panels. There are a wide variety of panels available, with different genes on different panels. There is a lack of consensus among experts regarding which genes should be tested in different clinical scenarios. There is also variation in the degree of consensus regarding the understanding of risk and appropriate clinical management of mutations in some genes.

2. **Genetic testing should be made available to all patients with a personal history of breast cancer.** Recent data support that genetic testing should be offered to each patient with breast cancer (newly diagnosed or with a personal history). If genetic testing is performed, such testing should include BRCA1/BRCA2 and PALB2, with other genes as appropriate for the clinical scenario and family history. For patients with newly diagnosed breast cancer, identification of a mutation may impact local treatment

recommendations (surgery and potentially radiation) and systemic therapy. Additionally, family members may subsequently be offered testing and tailored risk reduction strategies.

3. **Patients who had genetic testing previously may benefit from updated testing.** Every patient being seen by a breast surgeon, who had genetic testing in the past and no pathogenic variant was identified, should be re-evaluated and updated testing considered. In particular, a patient who had negative germline BRCA1 and 2 testing, who is from a family with no pathogenic variants, should be considered for additional testing.[1] Genetic testing performed prior to 2014 most likely would not have had PALB2 or other potentially relevant genes included and may not have included testing for large genomic rearrangements in BRCA1 or BRCA2.

4. **Genetic testing should be made available to patients without a history of breast cancer who meet NCCN guidelines.** Unaffected patients should be informed that testing an affected relative first, whenever possible, is more informative than undergoing testing themselves. When it is not feasible to test the affected relative first, then the unaffected family member should be considered for testing if they are interested, with careful pre-test counseling to explain the limited value of "uninformative negative" results. It is also reasonable to order a multi-gene panel if the family history is incomplete (i.e., a case of adoption, patient is uncertain of exact type of cancer affecting family members, among others) or other cancers are found in the family history, as described above.

5. **Variants of uncertain significance are DNA sequences that are NOT clinically actionable.** This type of result needs to be considered as inconclusive, and the patient should be managed based on their risk factors and not influenced by this result.

Summary of Data Reviewed

The National Cancer Institute estimates for 2018 were that more than 266,000 new cases of invasive breast cancer would be diagnosed in the United States, and more than 40,000 patients would die from the disease.[2] Approximately 10% of breast cancers are associated with a pathogenic germline variant in one of several different genes.[3] More than 50% of pathogenic germline variants are mutations in the BRCA1 and BRCA2 genes.[4-9] Using genetic testing to identify patients who are at increased risk to develop breast cancer enables patients to take steps to reduce this risk. There are several risk management strategies available for individuals at increased risk (e.g., chemoprevention along with enhanced screening; risk reducing surgeries).[10-18] **Unfortunately, in the current state of medical practice, a significant number of pathogenic mutation carriers remain undetected and undiagnosed. These are largely women with "moderate penetrance" mutations, but even women with BRCA1 or 2 mutations may not be identified.**[19-20] There is an unmet challenge to improve our identification and diagnosis of patients who have an inherited increased lifetime risk of breast cancer.

Access to Genetic Counseling and Testing

There are fewer barriers to genetic testing now than previously, and testing is less costly and being offered by more labs. The indications for who should be offered testing are ever increasing - each guideline update casting a wider net, and there is more public awareness. However, some barriers remain - one of which is the limited availability of genetic counseling nationwide for patients and their family members.[19-20]

Increased access to testing would likely lead to more patients pursuing testing and improving rates of identification of gene carriers. Breast surgeons are well positioned to be a resource for patients who may benefit from testing. Breast surgeons can identify individuals who are suitable for testing, inform patients of the risks and benefits, provide access to genetic testing, and also discuss risk management strategies for those patients who test positive. For patients with less common mutations, strong consideration should be given to consultation with cancer genetics specialists.[21-23]

Hereditary Breast Cancer Syndromes

Hereditary mutations to be considered include BRCA 1&2, PALB2, and other hereditary breast cancer syndromes, which include but are not limited to Li-Fraumeni syndrome (TP53 pathogenic variant), Cowden syndrome (PTEN pathogenic variant), Hereditary diffuse gastric cancer syndrome (CDH1 pathogenic variant), and Peutz-Jegher syndrome (STK11 pathogenic variant).

Impact of genetic testing results on management recommendations

Identification of patients with pathogenic variants in these genes can influence patient management in terms of high-risk screening and risk reduction as well as therapeutic options related to surgery, radiation, and systemic therapies.[24-26] For example, identifying that a breast cancer patient has a BRCA1 pathogenic variant provides that patient the opportunity to learn of her elevated risk for contralateral breast cancer as well as of ovarian cancer and to make educated decisions to reduce those risks.[26] Studies are underway to determine whether these patients also might benefit from PARP inhibitors being included in their adjuvant therapy regimen. Another example is that radiation is relatively contraindicated in patients with TP53 pathogenic variants (associated with Li-Fraumeni Syndrome) due to their increased risk of developing radiation-induced secondary malignancies.

Identifying a patient who has a pathogenic variant that indicates high hereditary breast cancer risk can have a profound impact on that patient's health and management. Additionally, it has potential impact on that patient's family members who should be counselled to consider testing for the mutation identified in the family, the result of which can guide their risk of breast cancer development and consideration of risk management strategies.

The genetic testing information should be considered together with the details of each patient's case including age, family history, medical history, and contributing risk factors, as

well as careful review of existing management guidelines. It is important to understand that risk of development of breast and other cancers and risk management guidelines vary both by the mutated gene and the penetrance of the specific genetic mutation. Additionally, not all pathogenic variants identified are medically actionable.

Just because a hereditary pathogenic mutation that predisposes to breast cancer is identified does not mean that the risk-reducing mastectomy is indicated. Risk-reducing mastectomy can be considered in BRCA1, BRCA 2, PTEN, and TP53. Consideration may also be appropriate for patients with mutations in other genes when combined with a significant family history of breast cancer.

Patients with BRCA1 or BRCA2 pathogenic variants should consider risk-reducing bilateral salpingo-oophorectomy after child-bearing or between the ages of 35-40 to reduce ovarian and fallopian tube cancer risk. Women with BRCA1 should consider oophorectomy between ages 35-40, while BRCA2 carriers should consider it between ages 40-45.

Prophylactic oophorectomy in premenopausal women with BRCA2 pathogenic variants has also been shown to reduce the risk of breast cancer by about 50%. There is also breast cancer risk reduction from RRSO in BRCA1 patients but to a lesser degree.[10,11,17]

For patients with mutations in ATM, CDH1, CHEK2, NBN, NF1, PALB2, and STK11, enhanced screening is recommended; however, currently the data are not sufficient to support risk-reducing mastectomy in the absence of other factors such as a strong family history. There are substantial gaps in our ability to predict individual risks associated with mutations in some of these genes. Risk is modulated by age, family history, and in some cases, the specific mutation in a particular gene. For the aforementioned syndromes, the guidelines broadly support considering mammography with tomosynthesis and breast MRI with and without contrast for annual screening due to the elevated risk for breast cancer.

For BARD1, MSH2, MLH1, MSH6, PMS2, EPCAM, BRIP1, RAD51C, RAD51D, there are some data suggesting an elevated lifetime risk of breast cancer; however, there is insufficient evidence to support change in breast cancer risk management based on the presence of a mutation alone. Mutations in these genes may be associated with an increased risk of gynecological cancers, which may warrant specific management. MSH2, MLH1, MSH6, and PMS2 are associated with the Lynch Syndrome, a multi-organ predisposition syndrome that requires multidisciplinary management.

The list of actionable genes and recommendations for screening and risk management continually evolves as additional information becomes available. We refer the readers to the NCCN guidelines, available online at www.nccn.org under the title Familial High-Risk Assessment: Breast and Ovarian Cancer (most recently updated in early 2019). The All Syndromes Known to Man Evaluator (https://ask2me.org/) is another tool available with information on the spectrum and estimated penetrance for pathologic variants.[27]

Limitations of genetic testing

Health care providers and patients need to know that genetic testing is one of several tools for assessing breast cancer risk. Not every genetic test yields a straightforward answer with clear guidance on how to proceed for optimal care. Patients should be made aware that negative test results do not necessarily mean they are not at increased risk for developing breast cancer.

Many factors contribute to a patient's lifetime risk of breast cancer, and genetic testing is an effort to better define one of these elements (the measurable inherited risk). When counseling patients about their lifetime risk of breast cancer, it is critical to look broadly at the patients' other contributing factors, some of which are: age, medical history, lifestyle, exposures, and family history. For patients who test positive for a pathogenic variant, it is important to gain detailed understanding of that variant when advising on risk management strategies – details such as the penetrance of the cancer risk among carriers (how likely is the patient to actually develop breast cancer). Penetrance varies among the identified hereditary cancer syndromes. In other words, not all carriers of pathogenic genetic variants will develop breast cancer, and the level of risk varies with the gene affected and likely the variant as well.[6,28,29]

For example, some types of CHEK2 and ATM variants have low penetrance while other types are more highly penetrant.[30,31] Just because a patient tests positive for a hereditary breast cancer syndrome does not mean that patient will develop breast cancer. ask2me.org can be useful in understanding the penetrance and the management for most cancer-causing genes, and the BRCA Decision Tool, http://brcatool.stanford.edu/brca.html, can be useful in known BRCA pathogenic variant carriers to predict likelihood of developing breast or ovarian cancer and likelihood of dying from either disease based on patient age and a variety of interventions chosen for screening and prophylaxis. It is important to note that these calculators are constrained by the limitations of the studies that provide the underlying odds ratios used to generate the absolute risk estimates and do not account for modification of those odds ratios by age, mutation position, family history, or polygenic background risk.[32]

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Before testing, patients need to be made aware of the implications that the test result can have (pre-test counseling); and when results become available, patients should be reminded of these implications and be provided the appropriate clinical context for the results to make informed decisions (post-test counseling). All genetic testing should be performed in the setting of informed consent. The American College of Surgeons Commission on Cancer accreditation program mandates that cancer risk assessment, counseling, and genetic testing services be provided to patients by a physician who does risk assessment regularly and/or is qualified to do testing or a qualified genetic professional either on site or by referral.[33] A systematic review of the literature indicates that pre-test counseling, whether by a geneticist, breast surgeon, oncology nurse, or other medical professional with expertise and experience in cancer genetics reduces distress, improves risk perception accuracy, and improves follow through for testing.[34] Breast surgeons who are knowledgeable in cancer genetics can initiate and guide genetic testing for their patients. Pre-test counseling should include discussion of

the types of results (true positive = pathogenic, true negative = benign (although without a known positive in a family, it may also be inconclusive as well), and inconclusive = variant of uncertain significance (VUS)). Other potential issues of testing should also be reviewed, such as inconclusive results, misperception of true risk, and discrimination. As noted above, patients need to know there are limitations to this testing including non-informative results or negative tests as well as the reality of the evolving science. It is important to educate patients on the benefits of testing as a vehicle to knowing better their individual risk and empowerment to consider interventions to manage or reduce that risk. It can be helpful to set expectations for when the test results will be available.

Post-test counseling is important regardless of the actual result. The current best practice is for all patients who undergo genetic testing to have some form of post-test counseling. By NCCN guidelines, this can occur in person or remotely. This allows for patients' questions to be answered and for a thorough debriefing. If a result is negative or non-informative (such as a variant of uncertain significance – VUS) then the patient's other risk factors for breast cancer (age, medical history, family history, etc.) need to be evaluated to formulate the appropriate risk management plan. Depending on the level of risk for breast cancer, strategies to manage that risk can be discussed, including enhanced screening imaging (annual mammogram and breast MRI); chemoprevention (endocrine therapy to lower risk); lifestyle modification with respect to obesity, tobacco use, and alcohol consumption; and exogenous hormone use among others.

For patients who test positive for a pathogenic variant, a clear review of the state of evidence for that specific syndrome is imperative. To make educated decisions, patients need to know about the spectrum of risk management strategies. Ultimately, a customized plan for the patient is the goal with their informed consent. In this discussion, a frank statement of the level of risk reduction for each intervention is needed. For example, risk-reducing mastectomy and reconstruction in a BRCA1-positive 35-year-old patient leads to much greater risk reduction for breast cancer mortality than that same intervention in a 65-year-old patient.[21,35,36] The surgeon should discuss these issues and refer to other specialists (such as gynecologic oncologists, gastroenterologists, etc.) for other organs at risk as appropriate. For complex scenarios, referral to a genetics professional is recommended.

Multi-gene Panel Testing

Genetic testing has expanded in scope and availability since 2013 when the U.S. Supreme Court ruling in Association for Molecular Pathology v. Myriad Genetics, Inc. increased the testing options. Increased competition has helped to lower the cost. Improvements in technology, like next-generation sequencing, has made testing for more than one gene at a time a reality.[37-41] which can improve the cost-effectiveness and efficiency of testing. While BRCA1 and BRCA2 remain the most likely genes to be mutated in a family with high breast and ovarian cancer risk, panel testing can allow for more comprehensive coverage of less common syndromes that can also confer hereditary cancer risk.[4,7,21,42-45] Numerous recent studies have shown that panel testing can significantly increase the rate of detection of pathogenic variants, with the most frequently identified pathogenic variants (outside of BRCA1 and BRCA2) being in PALB2, CHEK2, and ATM.[4,21,44] As noted above, there is a

comparatively limited understanding of individual breast cancer risk associated with mutations in genes other than BRCA1 and BRCA2. However, the presence of mutations in PALB2, ATM, truncating mutations in CHEK2, and possibly other genes are likely to be associated with lifetime breast cancer risks of greater than 20% and therefore, in the United States, at least support a decision for enhanced surveillance with annual mammography with tomosynthesis and breast MRI with contrast. Mutations in other genes may also reach this threshold, although the rarity of such mutations and the possibility of subtype-specific predisposition make risk estimation more challenging. A multi-gene panel may include genes with varying degrees of evidentiary support and "actionability." This testing method is optimal when the individual genes included are clinically valid and comprehensively address the details of each patient's case.

Panel testing can be considered for patients who qualify for hereditary breast cancer testing to more efficiently and cost-effectively evaluate genes that confer risk and impact management recommendations. When genetic testing is being recommended based on phenotypic syndromes (for example three or more close family members affected by breast cancer at any age) then multi-gene panel testing is likely to be more efficient in evaluating patients. In fact, the most recent NCCN guidelines allow that panel testing will largely replace sequential gene sequencing (i.e., the older approach of evaluating BRCA pathogenic variants first, then selecting additional genes if BRCA tests are negative).[20,28,41] Insurance companies are urged to incorporate the advantages of panel testing into their algorithms to allow hereditary cancer syndrome testing for patients at high risk. Surgeons, genetic counselors, and other health care professionals who order panel testing for breast cancer patients or their family members should at a minimum test the breast cancer genes that are clinically actionable given the current state of medical evidence. Testing of additional genes can also be performed at the discretion of the ordering physician or as directed by the family history.

Variant of uncertain significance (VUS)

Variants of uncertain significance are DNA sequences that are NOT clinically actionable. This type of result needs to be considered as inconclusive. For example, a patient who receives a genetic testing result of "BRCA1 variant of uncertain significance" should NOT be recommended for a change in management based on that test result alone. No clinical treatment plan or risk management plan should be influenced by a VUS. These are DNA sequences about which the lab is still accruing data for definitive classification as to benign or pathogenic. The vast majority are re-classified as benign when enough data are collected. Usually it takes several years for the reclassification to take place.[42,46]

The American College of Medical Genetics has published guidelines for reporting DNA sequence variations.[47] The rate of identifying VUSs can be high when new syndromes are identified but that rate decreases as data regarding those genes and the VUSs are accrued. Current rates of identifying a VUS with newer multi-gene panel testing is reported to be between 6.7-41.7%.[21,42-44] There are still VUSs identified with BRCA1/2 testing. However, the rates are generally much lower, ranging from 2-5%, now that testing of these two syndromes has been available for more than 20 years. In general, patients with VUSs should be managed

based on their family history, medical history, age, and other factors that influence breast cancer risk. No weight should be given to the VUS found, and co-segregation among affected family members is not conclusive evidence of pathogenicity.

This statement was developed by the panel members listed below, and on February 10, 2019, was approved by the Board of Directors.

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Relevant Author Disclosures

Kevin Hughes- Honoraria from Focal Therapeutics (Surgical implant for radiation planning with breast conservation), 23andMe, and is a founder of and has a financial interest in CRA Health (Formerly Hughes RiskApps). Dr. Hughes's interests were reviewed and are managed by Massachusetts General Hospital and Partners Health Care in accordance with their conflict of interest policies.

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Article

Should Genetic Testing for Cancer Predisposition Be Standard-of-Care for Women with Invasive Breast Cancer? The Murtha Cancer Center Experience

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Abstract: Currently, genetic testing is offered only to women diagnosed with breast cancer who meet a defined set of criteria and is not included as standard-of-care treatment at the time of diagnosis. Thus, a significant number of women diagnosed with breast cancer may miss the opportunity for precision medical treatment and risk management. The effects of eligibility, timing, and uptake of genetic testing were evaluated in a cohort of women with invasive breast cancer diagnosed between 2001–2018. Risk status was estimated using NCCN *BRCA1/2* testing criteria and panel testing was performed for all women who had genomic DNA available. Of the 1231 women, 57.8% were eligible for genetic testing. Uptake of testing within high-risk women was 42.7% of which 6.6% pursued clinical testing only after a second tumor event. Mutation frequencies were 15.8%, 5.5%, and 4.0% in high-risk women with clinical testing, high-risk women without clinical testing, and low-risk women, respectively. More than 4% of all patients harbored pathogenic or likely pathogenic mutations detected only in the research setting. Inclusion of panel testing at the time of diagnosis would allow for appropriate surveillance and treatment strategies to be employed to reduce the risk of secondary tumors and improve patient outcome.

Keywords: breast cancer; genetic testing; BRCA1/BRCA2; standard-of-care

1. Introduction

Discovery of the breast cancer 1 (*BRCA1*) and breast cancer 2 (*BRCA2*) genes [1,2] led to the development of genetic tests to identify individuals at risk for hereditary breast and ovarian cancer (HBOC). Early genetic testing involved costly and time consuming sequencing of each gene in a largely sequential manner. Two decades after the BRCA genes were identified, technical advances in next generation sequencing allowed for the simultaneous assessment of multiple genes, decreasing cost and time to return of test results. In conjunction, the Supreme Court of the United States overturned Myriad Genetics' patent on the *BRCA1* and *BRCA2* genes, which allowed for the development of multi-gene cancer predisposition panels that today are offered by multiple commercial companies [3].

As technologies to identify mutations in cancer predisposition genes have evolved, the utility for identifying patients with hereditary cancers has expanded from personal or family risk assessment to

personalized treatment strategies. For example, women with *BRCA1* or *BRCA2* mutations may benefit from double mastectomy to reduce risk of contralateral disease [4] and demonstrate improved response to platinum agents and poly(ADP-ribose) polymerase (PARP) inhibitors [5–8]. For patients with germline mutations in *ATM*, *CHEK2*, *NBN*, *NF1*, and *PALB2*, enhanced surveillance through addition of MRI may be warranted while breast cancer patients with mutations in *BRIP1* or mismatch repair genes may benefit from risk-reducing salpingo-oophorectomy (RRSO), endoscopy, or colonoscopy.

Despite the clinical benefits of identifying germline mutations in cancer predisposition genes, genetic testing is not currently offered to all women with breast cancer. When first offered in 1996, clinical testing was reserved for women diagnosed at an early age or with a significant family history of breast and ovarian cancer [9,10]. Guidelines from the National Comprehensive Cancer Network (NCCN) have evolved to include an expanded family history of cancers of the prostate and pancreas as well as breast and ovarian, and a diagnosis of triple negative breast cancer at <60 years of age, with or without a family history (https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf). After over 20 years of restricting genetic testing to those women who meet a certain set of criteria, in February 2019, the American Society of Breast Surgeons (ASBS), recognizing that a significant number of test-ineligible women in fact harbor germline mutations in cancer predisposition genes, recommended that all women newly diagnosed or with a personal history of breast cancer should be offered genetic testing to improve patient treatment and provide personal and family risk management strategies (https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Genetic-Testing-for-Hereditary-Breast-Cancer.pdf).

If implemented, these recommendations would afford all breast cancer patients the opportunity for genetic testing; however, testing has not been standardized and the uptake and timing of testing and choice of genes to evaluate may differ significantly between patients. Incorporating panel testing into standard-of-care at the time of diagnosis may improve the identification of ostensibly low-risk patients who harbor germline mutations in cancer predisposition genes, as well as to prevent additional breast tumors or cancers at secondary sites in the patient or family members. To explore the utility of panel testing in all breast cancer patients at the time of diagnosis, a panel of cancer predisposition genes was sequenced in women diagnosed at the Murtha Cancer Center, Walter Reed National Military Medical Center (MCC/WRNMMC) representing three groups: (1) Those who met NCCN guidelines and underwent clinical testing; (2) those who met NCCN guidelines but did not pursue clinical testing; and (3) patients who were ineligible for genetic testing using NCCN criteria.

2. Results

Between 2001 and 2018, 1231 females diagnosed with invasive breast cancer at the MCC/WRNMMC enrolled in the Clinical Breast Care Project (CBCP). Seventy-six (6.2%) women were diagnosed with non-breast cancers before their breast cancer diagnosis. One thousand (81.2%) women had at least one first or second degree relative diagnosed with a cancer other than basal cell or squamous cell carcinoma of the skin.

Based on guidelines at the time of their diagnosis, 542 (44.0%) patients were eligible for genetic testing. An additional 170 (13.8%) women would be eligible for testing using version 1.2018 guidelines. Using the NCCN version 1.2018 criteria, high-risk patients were significantly ($p < 0.001$) younger at diagnosis (52.5 years of age), more likely to have a family history of cancer (91.6%), and more likely to have triple negative breast cancer (TNBC) (19.8%) than low-risk women (63.8 years of age, 67.1%, and 6.4%, respectively; Table 1).

Uptake of genetic testing within the high-risk group was 42.7% and was significantly higher ($p < 0.001$) among women eligible for testing at diagnosis (281/542, 51.8%) compared to those whose status changed from low to high-risk through changes in NCCN criteria or additional cancer events within the family (23/170, 13.5%). Demographic and clinical data from high-risk women are shown in Table 2. Those who pursued genetic testing were significantly ($p < 0.001$) younger and more likely to be college educated.

Table 1. Demographic and clinical information for all patients classified as high-risk or low-risk using the National Comprehensive Cancer Network (NCCN) version 1.2018 criteria.

Classification	High-Risk (n = 712)		Low-Risk (n = 519)		p-Value
Age at Diagnosis	52.5 years		63.8 years		<0.001
	N	%	N	%	
Ethnicity					0.167
African American	212	29.8	132	25.4	
Asian American	29	4.1	32	6.2	
Hispanic American	26	3.6	13	2.5	
European American	432	60.7	332	64.0	
Other/unknown	13	1.8	10	1.9	
Personal (non-breast) cancer history					0.478
Yes	41	5.8	35	6.7	
No	671	94.2	484	93.3	
Family history of cancer					<0.001
Yes	652	91.6	348	67.1	
No	60	8.4	171	32.9	
Triple Negative Breast Cancer					<0.001
Yes	141	19.8	33	6.4	
No	553	77.7	479	92.3	
Unknown	18	2.5	7	1.3	

Table 2. Demographic and clinical information for patients classified as high-risk at the time of diagnosis.

Classification	Tested (n = 304)		Not Tested (n = 408)		p-Value
Age at Diagnosis	46.8 years		56.3 years		<0.001
	N	%	N	%	
Ethnicity					0.575
African American	87	28.6	125	30.6	
Asian American	14	4.6	15	3.7	
Hispanic American	12	3.9	14	3.4	
European American	188	61.9	244	59.8	
Other/unknown	3	1.0	10	2.5	
Marital status					0.891
Married	235	77.3	321	78.7	
Not married	67	22.0	84	20.6	
Unknown	2	0.7	3	0.7	
Education					<0.001
<College degree	89	29.3	168	41.2	
≥College degree	171	56.3	165	40.4	
Unknown	44	14.4	75	18.4	
Family History					0.990
Yes	229	75.3	308	75.5	
No	73	24.0	97	23.8	
Unknown	2	0.7	3	0.7	
TNBC					0.672
Yes	74	24.3	97	23.8	
No	224	73.7	299	73.3	
Unknown	6	2.0	12	2.9	

Time-to-testing ranged from time of diagnosis to 15.3 years post-diagnosis. The mean time-to-testing was significantly ($p < 0.001$) shorter in women who were eligible for testing at diagnosis

(0.72 years) compared to those women whose status changed from low to high-risk (5.38 years). Twenty (6.6%) women had testing only after a second tumor event (19 breast, one ovary).

Clinical testing (n = 304) was performed using the Ashkenazi 3-site mutation panel (n = 5), *BRCA1/2* sequencing (n = 142), Lynch syndrome testing (n = 1), and multi-gene panel testing (n = 156). Of the patients who had their original testing limited to *BRCA1* and/or *BRCA2*, eight BRCA negative patients later underwent additional panel testing. One woman was diagnosed with a pathogenic *TP53* mutation after an ipsilateral recurrence, two years after her original breast cancer diagnosis.

Forty-eight (15.8%) of the women with clinical testing carried a pathogenic or likely pathogenic mutation (Table 3). Within the 111 women with limited (*BRCA1* and/or *BRCA2* only) testing who later had panel testing performed in the research setting, 10 had pathogenic/likely pathogenic mutations in non-BRCA genes. Among 346 high-risk women who did not pursue clinical testing, 19 (5.5%) harbored pathogenic or likely pathogenic mutations detected in the research laboratory. Likewise, in 429 women classified as low-risk, 17 (4.0%) had pathogenic/likely pathogenic mutations, including three women with *BRCA2* mutations. Overall, the frequency of pathogenic or likely pathogenic mutations was 11.8% in high-risk compared to 4.0% in low-risk patients.

Table 3. Frequency of pathogenic or likely pathogenic mutations in cancer predisposition genes by risk and testing groups.

Gene	High-Risk Clinical Testing (n = 304)		High-Risk BRCA Negative with Panel Testing (n = 111)		High-Risk Research Results (n = 346)		Low-Risk Research Results (n = 429)	
	N	%	N	%	N	%	N	%
BRCA1/2 genes								
BRCA1	17	5.6%	0	0.0%	6	1.7%	0	0.0%
BRCA2	16	5.3%	0	0.0%	4	1.2%	3	0.7%
Other breast cancer genes								
ATM	5	1.6%	1	0.9%	0	0.0%	2	0.5%
CHEK2	1	0.3%	0	0.0%	3	0.9%	1	0.2%
NBN	2	0.7%	1	0.9%	0	0.0%	1	0.2%
PALB2	1	0.3%	1	0.9%	0	0.0%	0	0.0%
TP53	4	1.3%	0	0.0%	1	0.3%	0	0.0%
Lynch syndrome genes								
MSH2	1	0.3%	0	0.0%	0	0.0%	0	0.0%
Other cancer genes								
BLM	0	0.0%	2	1.8%	2	0.6%	2	0.5%
CDKN2A	1	0.3%	0	0.0%	0	0.0%	0	0.0%
FH	0	0.0%	0	0.0%	0	0.0%	2	0.5%
MUTYH	0	0.0%	4	3.6%	3	0.9%	4	0.9%
NF1	0	0.0%	1	0.9%	0	0.0%	0	0.0%
RET	0	0.0%	0	0.0%	0	0.0%	1	0.2%
SDHB	0	0.0%	0	0.0%	0	0.0%	1	0.2%

Because prophylactic mastectomy has long been recommended for women with BRCA1 and BRCA2 mutations, the effects of delayed or lack of testing were evaluated (Table 4). Patients were classified by time-to-testing of <1 year from diagnosis (n = 24), >1 year from diagnosis (n = 8) or no clinical testing (n = 13). One woman did not have a reported date of testing and was excluded from analysis. The frequency of prophylactic mastectomy was 86% in women who had testing within one year, 63% in those with delayed testing, and 45% in women without clinical results. Breast cancer recurrence or distant metastasis were significantly more likely ($p < 0.05$) in those with delayed testing (50%) or no clinical testing (37%) compared to one (4%) woman who had testing <1 year. In addition, breast cancer survival was significantly lower ($p = 0.011$) in women with delayed testing (25%) compared to those with testing within one year (0%). The breast cancer mortality rate was not significantly higher ($p = 0.168$) in the group of women with only research test results (8%) compared to those who had testing within one year.

Table 4. Effects on surgical decision making and outcome in 45 women with BRCA1 or BRCA2 mutations by time-to-testing.

Time to BRCA Testing	RRPM [a]	Time to RRM (Years)	Second Cancer Event	Time to Second Cancer (Years)	Patient Status [c] (Years)
Clinical testing <1 year from diagnosis					
	Yes	0.0			NED (0.5)
	Yes	0.0			NED (9.6)
	Yes	0.0			NED (5.2)
	Yes	0.0			NED (4.2)
	Yes	0.0			NED (5.0)
	No				NED (1.9)
	Yes	0.0	DM [d]	1.9	NED (1.9)
	Yes	0.0			NED (0.1)
	Yes	0.0			NED (2.0)
	NA [b]				NED (4.8)
	Yes	0.0			NED (1.1)
	Yes	0.0			NED (1.9)
	No				NED (10.0)
	Yes	0.9			NED (2.4)
	Yes	0.0			NED (3.2)
	NA				NED (6.4)
	Yes	1.4			NED (4.4)
	Yes	0.0			NED (3.8)
	Yes	0.0			NED (6.6)
	Yes	0.0			NED (9.4)
	Yes	0.4			NED (14.5)
	Yes	0.0			NED (0.5)
	Yes	0.0			NED (5.1)
	No				NED (9.8)
Clinical testing ≤1 year from diagnosis					
	Yes	1.5			NED (1.5)
	No		Contralateral	5.8	DOD (7.5)
	Yes	2.6			NED (1.4)
	Yes	0.0			NED (3.8)
	No		Contralateral	4.2	DOD (6.41)
	No				NED (8.2)
	Yes	7.9	Ipsilateral	8.2	NED (12.9)
	Yes	10.9	Ipsilateral	10.9	NED (10.9)
Research testing only					
	Yes	0.0	Ipsilateral	3.2	NED (4.9)
	No		Contralateral	11.2	NED (11.7)
	No				NED (8.2)
	Yes	8.9			NED (13.6)
	NA				NED (10.5)
	No		Contralateral	2.8	NED (2.9)
	No				NED (8.7)
	Yes	0.0			NED (8.0)
	No				NED (8.6)
	Yes	0.0			NED (10.6)
	No				DOC (1.1)
	Yes	0.00	DM	1.8	DOD (2.5)
	NA				NED (8.5)

[a] Risk-reducing prophylactic mastectomy. [b] Patient had synchronous bilateral breast cancer and a double mastectomy at the time of diagnosis. [c] NED = no evidence of disease, DOC = dead other causes, DOD = dead of disease. [d] DM = distant metastasis.

In addition to mutations associated with risk of hereditary cancer, pathogenic/likely pathogenic mutations were detected in *ERCC2* (n = 1), *FANCA* (n = 1), *FANCC* (n = 1), *HNF1A* (n = 1), *PRF1* (n = 1) *RECQL4* (n = 2), *WRN* (n = 1), and *XPA* (n = 1). Associated conditions, such as Xeroderma pigmentosum, Fanconi anemia and Werner Syndrome are all inherited in an autosomal recessive fashion, and each of the individuals in this study carried a single mutant allele. In addition, 49 (17.2%) women who underwent clinical testing harbored at least one variant of uncertain significance VUS, including 12 women with *BRCA1* (n = 2) or *BRCA2* (n = 10) variants whose pathogenicity has not yet

been resolved. Within the patients who had panel testing in the research laboratory, 28.2% harbored at least one VUS, including twelve women with previously unreported variants in *ATM*, *BLM*, *BRCA1*, *BRCA2*, *BRIP1*, and *PALB2*.

3. Discussion

During the 25 year period since the *BRCA1* and *BRCA2* genes were identified, a number of additional breast cancer genes have been identified [11]. Management of breast cancer patients who harbor germline mutations in cancer predisposition genes may differ from those patients with sporadic breast cancer. Management ranges from altered surgical and adjuvant approaches for women with *BRCA1* and *BRCA2* mutations, to enhanced surveillance for women with mutations in moderate-penetrance breast cancer genes or in genes associated with risk of other types of cancer [12]. Although criteria have been developed to identify women most likely to harbor germline mutations in cancer predisposition genes, restriction of testing to high-risk patients may exclude a significant number of women who carry pathogenic mutations. For example, application of the NCCN version 2.2017 criteria to a cohort of 1371 newly diagnosed breast cancer patients from Norway who were tested for *BRCA1* and *BRCA2* mutations, revealed that 32 of 38 (88.9%) mutation carriers would have been classified as high-risk [13]. More recently, evaluation of 165,000 high-risk patients found that 5.8% of patients with *BRCA1/2* mutations did not meet NCCN version 1.2018 guidelines [14]. Within our study, 6.5% of patients with *BRCA1/2* mutations were classified as low-risk. These data suggest that stratifying patients into risk groups may miss 5–10% of patients who harbor BRCA mutations.

Expanded testing through multigene panels may be important for identifying significantly more women with hereditary cancers. Our results show that the mutation frequency was 4.1% in *BRCA1* and *BRCA2* and 5.4% in other cancer genes. Similarly, when 35,000 women with breast cancer were tested using a 25 gene panel, approximately 5.2% of the 9.3% of women with pathogenic variants carried mutations in non-BRCA genes [15]. Two large studies have shown that factors associated with mutations in *BRCA1* and *BRCA2*, such as young age, Ashkenazi heritage, family history of breast or ovarian cancer, or having TNBC, were not associated with mutations in non-BRCA genes [15,16]. This suggests that guidelines such as NCCN may exclude from testing a significant number of women with mutations in cancer predisposition genes other than *BRCA1* and *BRCA2*.

The 2019 ASBS statement recommends that all patients with invasive breast cancer be offered genetic testing. Despite these recommendations, testing is not incorporated into standard-of-care. Genetic testing in the United States, even within high-risk women, is underutilized. Recent data from the National Health Interview Survey demonstrated that only 15.3% of high-risk women underwent genetic testing [17]. Uptake of testing was higher within the CBCP/MCC/WRNMMC where 42.7% of test-eligible women pursued genetic testing; however, over half of the eligible patients did not pursue testing. Within the untested high-risk population, 5.5% of women harbored germline mutations in cancer predisposition genes, many of which (>70%) have management guidelines recommended by NCCN. Inclusion of genetic testing into routine patient care may improve the treatment of those with hereditary forms of breast cancer.

Including genetic testing as standard-of-care may also prevent delays in time-to-testing and improve patient treatment by avoiding radiation before later electing for prophylactic mastectomy or utilizing platinum agents or PARP inhibitors for treatment of the primary tumor [18]. Within the nine patients with pathogenic or likely pathogenic mutations who underwent clinical testing more than one year post-diagnosis, one originally had breast conserving surgery with radiation followed by delayed bilateral mastectomy, while five underwent prophylactic mastectomy of the contralateral breast 1–5 years after diagnosis. In addition, four patients recurred before undergoing testing and survival was significantly worse in women with delayed testing. Delays in testing may thus represent a lost opportunity for prevention in these patients.

While incorporating multigene testing into standard-of-care for breast cancer patients may enhance the identification of patients with hereditary forms of breast cancer, universal testing is not without

considerations. Although costs for gene sequencing have decreased significantly in recent years, the estimated cost to provide genetic testing to the >260,000 women diagnosed with invasive breast cancer in the United States each year is upwards of $80,000,000 [19]. This figure covers only the cost of sequencing and does not include costs for pre and post-test counseling. In addition, ~60,000 women diagnosed with ductal carcinoma in situ DCIS each year in the United States would also be eligible for testing, further adding to the cost of including germline testing as standard-of-care. In conjunction, there is a shortage of genetic counselors in the United States, thus universal testing would require development of new strategies for delivering test results [20]. In addition to the costs involved, not all mutations detected will be useful in patient management or risk assessment. For example, 0.6% of the patients in this study had pathogenic mutations in *BLM*, which to date, has not been clearly associated with increased risk of breast cancer and no strategies for risk reduction have been developed. Procedures for disclosure of secondary findings, especially those derived from large panel tests, must be determined. Finally, use of multigene panels is associated with increased detection of VUS. The ASBS Consensus Guidelines on Genetic Testing for Hereditary Breast Cancer state that VUS are not clinically actionable and any patient with a VUS should be counseled based on factors such as family history and age at diagnosis [21]. Most importantly is the concept of patient autonomy [22]. If genetic testing were to be incorporated into routine clinical practice, mechanisms must be developed so that the patient may forgo genetic testing.

There are several limitations to this study. Unlike the general population of the United States, all patients in this study had access to comprehensive breast care. Genetic testing services were covered by TriCare insurance, which may account for higher uptake of testing within this cohort (42.7%) as compared to that measured by the National Health Interview Survey (15.3%), as cost has been identified as a significant barrier to genetic testing [23]. This study includes women who voluntarily enrolled in the CBCP, not all women treated within the MCC/WRNMMC system. The high rate of testing in this study may reflect a selection bias of women who were emotionally, mentally, or physically willing to join a research protocol and thus may also be more likely to pursue genetic testing. In addition, rates at which eligible patients declined testing were not available. Offering genetic testing to all patients with invasive breast cancer may reduce physician burdens in identifying and referring eligible patients for testing; however, patient anxiety, education, and cost may diminish test rates and reduce overall impact of democratization of testing. At the variant level, we used a stringent classification system, not including variants with conflicting interpretations or with single submitters. This eliminated 130 additional patients who had variants with weaker levels of classification support, 19 of which harbored variants that had at least one pathogenic or likely pathogenic interpretation. Therefore, the true mutation frequencies may be higher than those reported here. Finally, data was not available for RRSO, chemotherapy, or post-diagnostic mammography and/or MRI. Inclusion of these data in future studies may be useful for determining whether costs associated with expansion of testing at the time of diagnosis alters treatment regimens and surveillance for secondary cancers and whether these measures improve patient outcomes.

4. Materials and Methods

4.1. Patient Eligibility and Consent

Eligibility criteria for this study required patients to be: (1) At least 18 years of age; (2) mentally competent and willing to sign informed consent documents; and (3) diagnosed with invasive breast cancer at MCC/WRNMMC. All subjects voluntarily agreed to participate in the CBCP and gave written informed consent. Blood samples were collected with approval from the WRNMMC Human Use Committee and Institutional Review Board (protocol WRNMMC IRB #20704).

4.2. Clincopathological Data

Individuals with a previous history of stage 0–IV breast cancer were excluded from this study. Family cancer histories through third degree relatives were collected and genetic risk determined using the NCCN *BRCA1/2* testing criteria published from the year of diagnosis as well as version 1.2018 criteria. Genetic test results and date of testing were extracted from the CBCP database for all patients who underwent clinical testing. Triple negative tumors were classified using ASCO/CAP guidelines for determining estrogen receptor, progesterone receptor and HER2 status [24,25].

4.3. Multi-Gene Sequencing and Analysis

Genomic DNA was isolated from all patients (n = 1043) who had available blood samples using the Gentra Clotspin and Puregene DNA purification kits (Qiagen, Valencia, CA, USA) and quantitated by fluorometry. Libraries were created from 50 ng of DNA using the TruSight Rapid Capture kit and TruSight cancer panel and sequenced on a MiSeq (Illumina, Inc., San Diego, CA, USA) according to manufacturer's protocols. Data were analyzed using Variant Interpreter (Illumina, Inc., San Diego, CA, USA) and filtered for missense or frameshift mutations, stop gains or losses, initiator codons, in-frame insertions or deletions, and splice site alterations with a minor allele frequency of ≥0.25. The predicted effect of variants was evaluated using the ClinVar database (http://www.clinvar.com/) and classified as pathogenic, likely pathogenic, VUS, likely benign, or benign. Only variants from multiple submitters with no conflicts or that were reviewed by an expert panel were considered pathogenic or likely pathogenic.

5. Conclusions

Provision of multigene genetic testing to all breast cancer patients identified an additional 46/1079 (4.3%) women with hereditary cancer beyond the 48 (4.4%) detected through clinical testing. As recommended by ASBS, offering testing to all patients would identify an additional 1.6% of women carrying pathogenic or likely pathogenic mutations currently classified as low-risk. Lifting restrictions on eligibility for genetic testing, however, may not be sufficient to identify the majority of patients with germline mutations in cancer predisposition genes as genetic testing rates—even within an insured system with access to genetic counseling such as MCC/WRNMMC—are below 50%. Within the cohort of high-risk women who did not undergo genetic testing, 2.9% harbored germline mutations. Including testing as standard-of-care at the time of diagnosis may encourage testing among all patients, optimizing the care of and improving outcomes for patients with hereditary cancers.

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Hormone Therapy for Women…Do Not Be Afraid

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Common Conditions Associated With Chronic Pelvic Pain

Visceral

- Gynecologic
  - Adenomyosis
  - Adnexal mass
  - Chronic pelvic inflammatory disease/chronic endometritis
  - Endometriosis
  - Leiomyoma
  - Ovarian remnant syndrome
  - Pelvic adhesions
  - Vestibulitis
  - Vulvodynia
- Gastrointestinal
  - Celiac disease
  - Colorectal cancer and cancer therapy
  - Diverticular colitis
  - Inflammatory bowel disease
  - Irritable bowel syndrome
- Urologic
  - Bladder cancer and cancer therapy
  - Chronic or complicated urinary tract infection
  - Interstitial cystitis
  - Painful bladder syndrome
  - Urethral diverticulum

Neuromusculoskeletal

- Fibromyalgia
- Myofascial syndromes
  - Coccydynia
  - Musculus levator ani syndrome
- Postural syndrome
- Abdominal wall syndromes
  - Muscular injury
  - Trigger point
- Neurologic

    - Abdominal epilepsy
    - Abdominal migraine
    - Neuralgia
    - Neuropathic pain

Psychosocial

- Abuse
    - Physical, emotional, sexual
- Depressive disorders
    - Major depressive disorder
    - Persistent depressive disorder (dysthymia)
    - Substance-induced or medication-induced depressive disorder
- Anxiety disorders
    - Generalized anxiety disorder
    - Panic disorder
    - Social anxiety disorder
    - Substance-induced or medication-induced anxiety disorder
- Somatic symptom disorders
    - Somatic symptom disorder with pain features
    - Somatic symptom disorder with somatic characteristics
- Substance use disorder
    - Substance abuse
    - Substance dependence

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2015 Consensus Terminology and Classification of Persistent Vulvar Pain

A. Vulvar pain caused by a specific disorder*

- Infectious (eg, recurrent candidiasis, herpes)
- Inflammatory (eg, lichen sclerosus, lichen planus, immunobullous disorders)
- Neoplastic (eg, Paget disease, squamous cell carcinoma)
- Neurologic (eg, postherpetic neuralgia, nerve compression or injury, neuroma)
- Trauma (eg, female genital cutting, obstetric)
- Iatrogenic (eg, postoperative, chemotherapy, radiation)
- Hormonal deficiencies (eg, genitourinary syndrome of menopause [vulvovaginal atrophy], lactational amenorrhea)

B. Vulvodynia—Vulvar pain of at least 3 months' duration, without clear identifiable cause, which may have potential associated factors

The following are the descriptors:

- Localized (eg, vestibulodynia, clitorodynia), generalized, or mixed (localized and generalized)
- Provoked (eg, insertional, contact), spontaneous, or mixed (provoked and spontaneous)
- Onset (primary or secondary)
- Temporal pattern (intermittent, persistent, constant, immediate, delayed)

*Women may have a specific disorder (eg, lichen sclerosus) and vulvodynia

Reprinted from Bornstein J, Goldstein AT, Stockdale CK, Bergeron S, Pukall C, Zolnoun D, et al. 2015 ISSVD, ISSWSH, and IPPS Consensus Terminology and Classification of Persistent Vulvar Pain and Vulvodynia. Consensus Vulvar Pain terminology Committee of the International Society for the Study ofVulvovaginal Disease, the International Society for the Study of Women's Sexual Health, and the International Pelvic Pain Society; Obstet Gynecol 2016;127:745–51.

BMC Medicine

RESEARCH ARTICLE

Open Access

A roadmap for sex- and gender-disaggregated health research

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Abstract

Sex and gender are fundamental aspects of health and wellbeing. Yet many research studies fail to consider sex or gender differences, and even when they do this is often limited to merely cataloguing such differences in the makeup of study populations. The evidence on sex and gender differences is thus incomplete in most areas of medicine. This article presents a roadmap for the systematic conduct of sex- and gender-disaggregated health research. We distinguish three phases: the exploration of sex and gender differences in disease risk, presentation, diagnosis, treatment, and outcomes; explaining any found differences by revealing the underlying mechanisms; and translation of the implications of such differences to policy and practice. For each phase, we provide critical methodological considerations and practical examples are provided, taken primarily from the field of cardiovascular disease. We also discuss key overarching themes and terminology that are at the essence of any study evaluating the relevance of sex and gender in health. Here, we limit ourselves to binary sex and gender in order to produce a coherent, succinct narrative. Further disaggregation by sex and gender separately and which recognises intersex, non-binary, and gender-diverse identities, as well as other aspects of intersectionality, can build on this basic minimum level of disaggregation. We envision that uptake of this roadmap, together with wider policy and educational activities, will aid researchers to systematically explore and explain relevant sex and gender differences in health and will aid educators, clinicians, and policymakers to translate the outcomes of research in the most effective and meaningful way, for the benefit of all.

Keywords Sex, Gender, Research methods, Epidemiology, Health research

Background

Sex and gender are fundamental drivers of virtually all major causes of death and disease [1]. Despite this, evidence informing today's health care policies and practices is still largely obtained from predominantly male study populations. It is assumed that the evidence from these 'male studies' is equally applicable to women. However, this is not necessarily true, and sex- and gender-inclusive health research is vital to improve health outcomes for both women and men.

The importance of sex and gender as a routine part of research has led to policy changes at major funding agencies, worldwide [2, 3]. Despite significant uptake and growing awareness for sex- and gender-inclusive research and reporting, critical barriers remain. Indeed, women continue to be underrepresented in clinical trials in various domains and sex- and gender-disaggregated analyses and reporting, including on gender-diverse participants, are still frequently omitted, often without justification [4–10].

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While guidelines and policies are one way to change research practices, it should not end up being a checkbox exercise. Where sex- and gender-disaggregated analyses are conducted, they are frequently mainly descriptive in nature. Whilst knowing where sex and gender differences exist (and where not) is important, it is only a necessary first step in the research and translation cycle. Equipping the research community with the necessary skills and knowledge to embed sex and gender considerations as a routine part of their work should lead to a more systemic change at the grassroot level.

In this article, we present a roadmap for the conduct of sex- and gender-disaggregated research with the aim to further increase their uptake, scope, and quality. We explain the roadmap with examples, mainly drawn from the field of cardiovascular disease (CVD), and provide practical recommendations on how to improve sex- and gender-disaggregated health research.

Main text

Defining sex and gender

Sex and gender are integrally related and influence health in different ways [11]. According to the World Health Organization, sex refers to 'the different biological and physiological characteristics of females, males and intersex persons, such as chromosomes, hormones and reproductive organs', whilst gender refers to 'the socially constructed characteristics of women, men, girls and boys'. This includes norms, behaviours and roles associated with being a woman, man, girl or boy, as well as relationships with each other. These can vary from society to society and can change over time. The gender construct can be described in three related dimensions; gender norms, gender identity, and gender relations that together encompass the socially constructed roles, relationships, behaviours, relative power, and other traits that societies routinely ascribe to women and men [12]. A more comprehensive definition, also inclusive of diverse genders, refers to gender as follows: 'depending on the context, gender may reference gender identity, gender expression, and/or social gender role, including understandings and expectations culturally tied to people who were assigned male or female at birth'. Gender identities other than those of men and women (who can be either cisgender or transgender) include transgender, nonbinary, genderqueer, gender neutral, agender, gender fluid, and 'third' gender, among others; many other genders are recognized around the world' [13].

Decision trees for the steps involved in analysing and reporting sex versus gender have been described before [14]. In this article, we will speak of women and men throughout, instead of females and males, as we feel this is more holistic and reflective of the complex interplay of sex and gender factors on human beings. We acknowledge that this is a simplification of the reality as sex and gender are often intertwined, especially when studying behavioural or societal factors. We also acknowledge that the dichotomy of women and men does not cover the true non-binary nature of both sex and gender and that this approach might not be sufficient for research across different gender identities [12, 15, 16]. However, this choice does not affect the roadmap presented here, as the principles remain the same. Since studies typically do not separate between sex and gender, and few studies have considered sex (or gender) beyond binary variables (although numbers are rightly increasing) [17], our approach is consistent with the majority of medical and health research. Taking such an approach does not affect the essence of our roadmap, as the phases that we present later remain the same. However, the methodologies within each phase need minor adaptations when a holistic approach is taken to account for sex and gender diversity.

Intersectionality

We limit this article to sex and gender differences, acknowledging that not all women are the same, and neither are all men. Ideally, research should explore differences in an intersectional perspective, including combinations of socio-demographic features [18]. For instance, women's risk for coronary heart disease (CHD) is one third of that of men overall, but this statement hides the fact that the sex ratio decreases with increasing age and differs across regions [19]. However, in human populations, sex or gender is generally split in roughly equal numbers, or at least data are more equally distributed by sex and gender than by other socio-demographic factors. So, we argue that disaggregation by sex or gender, or both, is a minimum requirement for health research. Researchers should determine themselves whether sex, gender, or both, are most relevant to their research and disaggregate the research accordingly. We leave it to others to make similar arguments to those expressed here for other important aspects of intersectionality.

What is meant by sex- and gender-disaggregated research

Health and medical studies often include a diverse group of people, including people that differ by sex and gender. The published article may well report differences in the study population by sex or gender, typically in a table with baseline characteristics (i.e. what is often called 'Table 1'). They may also go on to adjust, or 'control', their study outcome results for sex or gender, either by fitting multivariable regression models or weighting sex/gender results equally or according to their distribution in the parent population. Neither analysis can be claimed

Table 1 Using the other sex as the comparator to put finding into a perspective and disentangle mechanisms

Example 1: Finding that a large percentage of women do not receive guideline-based care may be headline grabbing, but if men have a similarly low prevalence, the most crucial finding is that better care is required per se. This was the case in a survey of care given to people living with CHD that found only 6% of women were treated to target, for a cluster of risk factors [20]. This is an extremely poor result, which is worthy of attention, but cannot be used to show that women are disadvantaged since the equivalent result for men was 8%. The message here is to, whenever possible, include the other sex, perhaps only to serve as a comparator group, to produce meaningful findings even if the interest of the research is on a single sex
Example 2: As an example of where including men as comparator group led to a different interpretation, consider the effect of increasing family size on cardiometabolic risk. Several studies showed that women with a higher number of pregnancies were at a higher risk of cardiometabolic diseases [21–23]. While there are biological reasons to support this, even when ruling out the role of adverse pregnancy outcomes, having large families might also impose a burden on the cardiovascular system. Men cannot get pregnant, but they do get children. Men can therefore be used as a control group in determining whether it is childbearing or childrearing that explains the associations between the number of pregnancies and cardiovascular risk seen in women. In analyses in the UK Biobank and China Kadoorie Biobank, we demonstrated that the association between number of children and the risk of cardiometabolic diseases was similar in women and men [23–25]. Hence, it may be mainly childrearing, and not childbearing, that underpins the association between the number of pregnancies and cardiovascular risk in women. Interestingly, in the UK Biobank, those with the lowest risk of CVD, had two children whereas having one child was associated with the lowest risk in the China Kadoorie Biobank. This might suggest that societal norms, structures, and policies on preferred family size might explain why those deviating from that preferred standard are at a higher risk of CVD

as 'taking account of sex and gender'. Sex- and gender-disaggregated research requires the outcomes, not the inputs, to be reported and interpreted by sex and/or gender and thus, rather than remove the effects of sex and gender on outcomes, show what differences there are in such effects. Only in this way can important questions, such as whether a new drug is equally effective in women and men, be resolved.

Sex- and gender-disaggregated research is not only about women

Another common misperception is that sex- and gender-disaggregated research only benefits women. Sex- and gender-disaggregated research initially aimed to address the lack of research on women in many disease areas and the assumption that men's patterns of disease apply to women. The primary group expected to benefit are indeed women. However, sex- and gender-disaggregated research also benefits men, boys, and girls. Men, for example, have been largely neglected in osteoporosis or rheumatoid arthritis, as it is considered a disease of older women. Changing the name of organisations and initiatives for sex- and gender-specific research and medicine to include 'women and men' rather than just 'women' in their name would help dispel this notion. Also, a greater representation of male researchers in this research area would help to redress this misperception. Ultimately, this kind of research is not only about women—it is about getting the science right for the benefit of all.

Using the other sex as a comparator group

Studies that only involve one sex are clearly appropriate when the exposure (i.e. risk factor) of interest can only apply to that single sex. However, many studies are carried out only in women, or only in men. Whilst these certainly can provide useful evidence of effects for that sex, their interpretation is inevitably limited, whilst reports of findings may be misleading (Table 1). Using the other sex as a comparator group can also help to disentangle mechanisms, for example involving reproductive processes that only affect one sex.

Elements of sex and gender-disaggregated research methods

Sex and gender differences in health arise at many points in the lifespan, often identifiable at episodes of engagement with health systems. Figure 1 illustrates our proposed roadmap for sex-and gender-disaggregated research. Table 2 summarises the key recommendations and Table 3 highlights the strengths and limitations. The roadmap consists of three distinct phases: exploration of sex and gender differences; explanation of sex and gender differences; and translation of sex and gender differences to policy and practice. Adhering to the steps for integrating sex and gender in the design, analysis, and reporting of research as described in Fig. 2 is essential in using the roadmap.

Phase 1: Exploration of sex and gender differences

A critical first step in sex- and gender-disaggregated research is to explore where sex differences occur – as an agent for change towards improved health outcomes. Such exploration leads to the identification of areas where sex and gender differences do, or do not, exist. While there is often a tendency to mainly describe areas where differences are found, identifying and reporting where there are no differences is just as important. Routine conduct and reporting of sex-, and where possible, gender-stratified analyses, even when there is no specific hypothesis, allows researchers and users of research to interpret sex and gender differences in the context of the similarities. Areas in which sex and gender differences

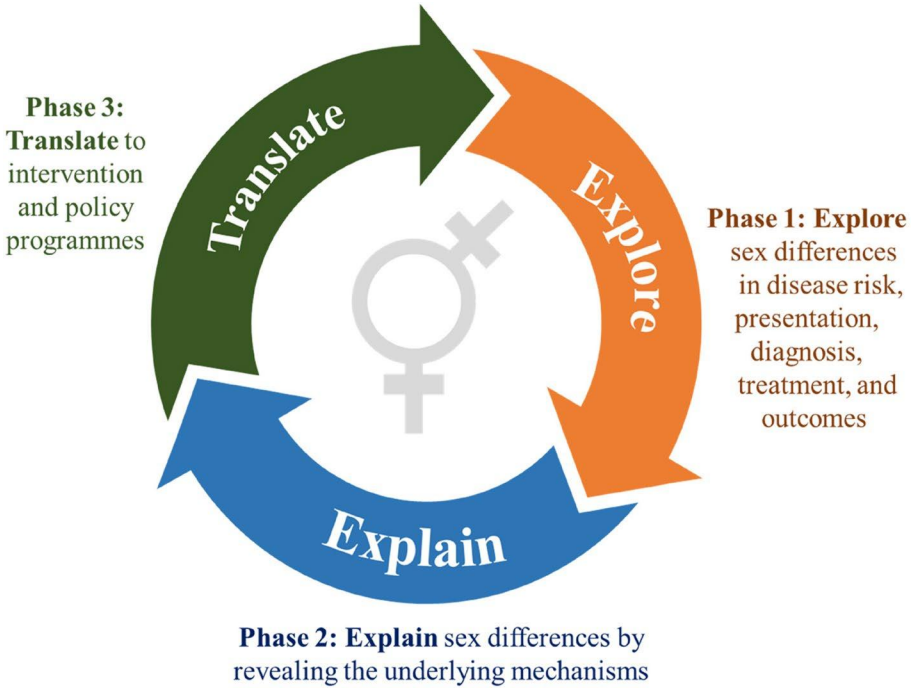

Fig. 1 Roadmap for sex and gender-disaggregated research. The three phases in the roadmap for sex- and gender-disaggregated research. The design, analysis, and reporting aspects from Fig. 1 are an integral part of phases 1 and 2, and, in some instances, also of phase 3

Table 2 Key recommendations of the roadmap for sex- and gender-disaggregated health research

Phase 1: Exploration of sex and gender differences
- Identify where sex and gender differences do (and do not) exist;
- Always report sex-specific findings (with measure of variability);
- Do not make conclusions on the presence (or absence) of sex differences based only on the sex-specific findings;
- Quantify sex differences using a full interaction model that accounts for the possibility of sex-specific confounding
Phase 2: Explanation of sex and gender differences
- Exclude the artefactual explanation;
- When evaluating sex differences in the associations of risk factors, consider both the absolute (risk difference) and relative (risk ratio) scales
- Assess to what extent any sex or gender differences are due to differences in biology or due to different interactions with the healthcare system;
- Use sex-specific Mendelian randomisation to strengthen sex-differentiated causal inferences;
- Broaden the scope of research on the role of sex hormones
Phase 3: Translation to policy and practice
- Embed sex- and gender-inclusive medicine in the curriculum of health professionals;
- Consider including sex-specific recommendations in guidelines;
Systemic factors
- Ensure that the participation of women and men in clinical trials, and medical research more broadly, is commensurate with the prevalence of the disease of interest in the population;
- Funders and publishers of medical research should make the integration of sex and gender a requirement for funding or publishing;
- Enhance the diversity in teams in research, policy, and practice, and address implicit biases against women

are commonly explored are plentiful, and include, but are not limited to, the identification of differences (and similarities) in the following categories.

Disease risk and prognosis

The leading causes of death are similar in women and men, which include cardiovascular disease, cancers, and lung diseases [26]. These figures, however, mask sex differences in disease risk across the life span. For example, in adolescence and young to middle-aged adulthood, self-harm and violence and road injuries, respectively, are the number two and three leading causes of death in men whereas HIV/AIDS and sexually transmitted infections are the number three leading cause of death in women. Cardiovascular diseases (number one in men and number two in women) and neoplasms (number one in women) complete these figures for people aged 15–49 years. Women have a longer life expectancy than

Table 3 Strengths and limitations of the roadmap

Strengths	*Limitations*
The roadmap: - In three distinct phases, allows for a systematic evaluation of sex and gender differences in health and disease; - Provides practical guidance for researchers, policy makers, clinicians, and educators on how to explore and explain sex and gender differences in health and how to translate such findings to policy and practice; - Is generic and can be applied to a broad range health research areas; - Can be adopted to assess other aspects of intersectionality and gender identities	The roadmap: - Underscores that sex and gender exist along a continuum and are often intertwined, yet presents sex and gender as binary variables, to enhance coherence and accessibility; - Does not address the issue of how research into sex might differ from research into gender, or how the two might be researched together; - Has a quantitative focus without discussing the complex cultural and psychosocial concepts underpinning sex and gender; - Is a guiding document, which needs to be adapted to the research question and setting, or translational aim, at hand

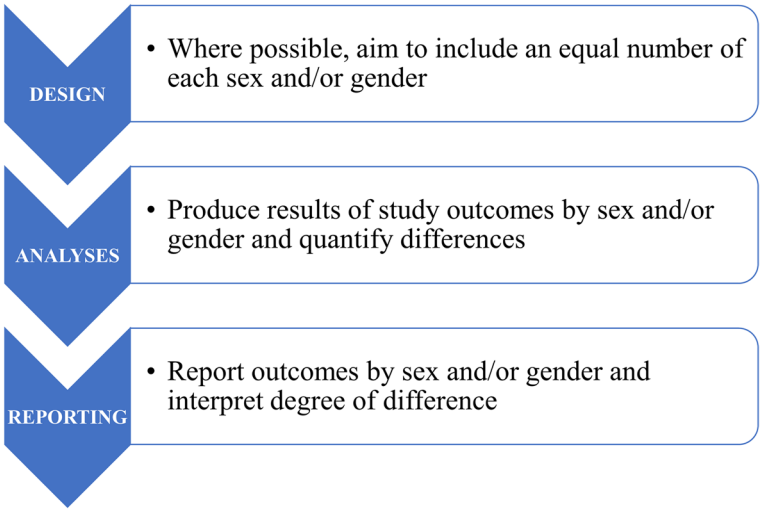

Fig. 2 Sex and gender considerations in the design, analysis, and reporting of research. Where the nature of the target population, or the funding mechanism, does not allow for equal numbers some attempt should still be made to recruit a substantial number in each sex and gender group. Where differences in outcomes are unimportant, or space limitations preclude detail when publishing, this should be commented upon, and stratified results included in a web supplement to inform potential future meta-analyses

men, but spend more time in ill-health. For example, women constitute the majority of the residents of nursing homes and two-thirds of individuals living with dementia are women.

Disease presentation and diagnosis

Timely and adequate diagnosis is the cornerstone for optimal treatment and management. A study in patients with an acute myocardial infarction showed that women were considerably more likely than men to receive another initial diagnosis, which was associated with lower use of guideline-recommended care and worse outcomes [27]. Such diagnostic delay might be explained by sex differences in symptom presentation. Recent meta-analyses have shown that symptoms at presentation of CHD and stroke can be different between women and men [28, 29]. However, campaigns to raise awareness of heart disease and stroke symptoms are typically based on the male pattern of disease. Lack of awareness of the risk of cardiovascular disease in women [30], including related warning signs, in both patients and care givers, as well as differences in disease aetiology, might also explain the diagnostic delay and misdiagnosis of cardiovascular disease in women.

Risk factor prevalence and associations

Sex differences in risk factors essentially manifest at two levels; differences in prevalence and differences in magnitude of the risk factor association. Sex differences in risk factor prevalence relate to the portion of women or men exposed to a risk factor, which can differ over time, between settings, and by age. Female-specific risk factors, such as pregnancy-related factors and factors related to the reproductive lifespan, affect virtually all women. On the other hand, prostate cancer affects only a proportion of all men, and even then, typically in older age groups.

Table 4 Sex differences in the association between diabetes and myocardial infarction

Diabetes is an important risk factor for a range of CVDs, regardless of sex. However, studies have consistently shown that the magnitude of that association in stronger in women [33]. Specifically, analyses in the UK Biobank showed that the adjusted hazard ratio for myocardial infarction associated with type 2 diabetes was 1.96 (1.60; 1.83) in women and 1.33 (1.18; 1.51) in men [34]. The corresponding women-to-men ratio of hazard ratios, as a measure of sex differences, was 1.47 (1.16; 1.87). In other words, the myocardial infarction conferred by diabetes is 47% greater in women than men. However, in absolute terms, the rates of myocardial infarction at a given age are lower in women than men, also in the presence of diabetes. Women lose some of their advantage, in terms of the risk of myocardial infarction, but do not surpass men

Other risk factors are male- or female-dominated. For example, in some parts of the world, large portions of men are smokers or consume alcohol whereas women largely abstain from these unhealthy habits [31]. Yet, women are more often exposed than men to abuse and intimate partner violence and have lower levels of health literacy. There is also a range of shared risk factors, such as hypertension, dyslipidaemia, diabetes, obesity, unhealthy diet, or a sedentary lifestyle, that are common in both women and men.

Sex differences in risk factor associations relate to differences in the strength of the association between the risk (or protective) factor and a disease outcome (Table 4). A detailed tutorial on how to assess sex differences in risk factor associations is provided elsewhere [32].

Safety and efficacy of interventions

Between 1997 and 2000, ten drugs were withdrawn from the US market because of serious side effects; eight posed greater risks for women than for men [35]. The fact that these data date back to over 25 years ago, and we are unaware of updates, typifies the dearth of evidence regarding sex differences in the safety and efficacy of interventions. Randomised controlled trials are typically not designed to assess sex-specific drug effects, neither in terms of efficacy nor safety. Meta-analyses of previous trials have addressed this issue of power to some extent [36, 37], but issues of limited representativeness and the evaluation of only a selection of outcomes remain. Nevertheless, recent studies using observational data suggest that women might achieve their maximum treatment benefit at a lower drug dosage than men [38, 39]. These sex differences in optimal treatment or treatment intensity could be explained by sex differences in pharmacokinetics or pharmacodynamics, amongst others [40]. For example, given that women generally have a lower bodyweight, higher proportion of body fat, and lower plasma volume, the duration of action of lipophilic (i.e. fat-soluble) drugs may be longer and the peak plasma concentrations of hydrophilic (i.e. water-soluble) drugs may be higher in women. The sedative Ambien is the only drug on the market for which the FDA has different suggested doses based on sex, even though many other drugs are also metabolised differently by men and women.

Provision and utilisation of healthcare services

In general, individuals at high risk of a disease and those with established disease require intensive risk factor control. For CHD, there is overwhelming evidence for the effectiveness of drug therapy and lifestyle modification, and hence such measures are universally recommended in clinical guidelines [41]. However, such evidence is often not sex-specific, which can lead to decisions based on personal beliefs or preferences and variation in treatment between the sexes that is not underpinned by guideline recommendations.

Quantification of sex differences

The phase of exploring sex and gender differences leads to the identification of areas where sex differences do or do not exist. This phase should also include a formal quantification of the sex-specific results, as well as their corresponding differences. Sex-specific subgroup analyses should be pre-defined and performed, whenever possible and appropriate. The methods for quantifying sex differences, as with any study, depend on the research question at hand. However, some general principles apply, as listed below, and discussed elsewhere [32].

1. Sex-specific results should always be reported. Studies may find no important sex differences or may be powered insufficiently to reliably quantify the presence, or absence, of sex differences. Null results are equally informative and should be reported to avoid publication bias and to be available for inclusion in future meta-analyses.
2. A statistically significant result in one sex but not the other is no evidence for a sex difference. Such a scenario can occur even when the effect estimates are identical between the sexes, but the level of precision of the estimate in one sex is much greater than that in the other (i.e. a wider vs. narrower confidence interval). Such a scenario is likely in several medical disciplines, because women tend to be underrepresented in clinical trials, the gold standard for establishing causality.

3. Always avoid sex-specific conclusions without statistical evidence of an interaction. Event rates can be different between women and men. As statistical power to find an effect, and the corresponding width of the confidence interval for the effect size, increases with an increasing number of events, there is a greater chance of finding an effect in the group with the higher event rate [42]. Many studies have tended to exaggerate the evidence for sex differences by ignoring this fundamental principle.
4. Assessing the sex interaction should not only be based on a *p*-value. It is more meaningful to estimate the sex interaction, together with an accompanying measure of uncertainty, such as a 95% confidence interval. Interaction terms between sex and any potential confounders should also be added to the model for sex differences in the impact of potential confounders on the association under study (i.e. sex-specific confounding).

Phase 2: Explanation of sex and gender differences

To date, most studies on sex and gender differences have focussed on phase 1; the exploration of the presence or absence of such differences. While critical in identifying and quantifying differences and similarities, studies in phase 1 do not provide explanations for such differences. As such, it often remains unclear what mechanisms, biological or otherwise, underpin the sex differences. Such knowledge is critical to know what could be done about them. Some differences might be an inherent consequence of nature, whereas others represent a sex bias that can, and should, be avoided. Categories that should be considered in explaining any identified sex differences are the artefactual explanation, the accessibility explanation, the biological explanation, and their combination.

The artefactual explanation

By artefactual explanations, we mean results that are merely a result of the way studies were designed or analyses have conducted. For example, interview questions might be routinely interpreted in a different way by women and men or a study in which questions are designed by men might be answered less accurately by women.

One might also think that sex differences in the association between some risk factors and disease outcomes, to women's disadvantage, are a mathematical artefact, explained by the lower 'background' risk in women for many diseases (Table 5). But such discordance is not inevitable. For example, recent analyses in the UK Biobank showed that diabetes, smoking, and high blood pressure, but not BMI and blood lipids, were associated with a greater relative risk of CHD in women than men [34, 43]. Hence, sex differences in relative risks are not a mathematical artefact inevitably caused by the lower baseline risk in women. This illustrates that, when evaluating sex differences in the associations of risk factors, it is important to consider both the absolute (risk difference) and relative (risk ratio) scales [32, 44].

The accessibility explanation

By the accessibility explanation, we mean that women and men may experience diseases differently because their interaction and experience with the health care system are different. Sex differences in disease prevention, treatment, and diagnosis might therefore explain the sex differences in disease risk and outcomes. The sex and gender of the health care provider have also been shown to influence processes and outcomes of care [45–47].

Before we describe some areas where differences exist, it is important to note that, for both women and men, substantial gaps exist between guideline-recommended care and care delivered. In CVD, for example, a large proportion of individuals do not receive the guideline-recommended treatments and do not meet the treatment targets, both in the primary and secondary prevention [20, 48]. This leads to a substantial disease burden, in both women and men, potentially avoidable through more timely diagnosis and better treatment. Several studies have found that women are even less likely than men to be screened regularly, to receive an adequate diagnosis, to be treated according to the clinical guidelines, and to achieve risk factor control [48–53], leading to worse outcomes [54, 55].

Sex differences in treatment: appropriate or inappropriate? Clinical guidelines rarely provide sex-specific treatment recommendations. Differences in treatment in clinical practice are therefore often seen as suboptimal

Table 5 The artefactual explanation

Suppose that the 10-year disease risk in the absence of a risk factor (i.e. the reference group) is 1% in women and 3% in men. In other words, women have a third the risk of men, which — as mentioned already — broadly is the case for CVD (although attenuating with age). When the risk in those with the risk factor is 1% higher in both sexes, this results in a relative risk of 2/1 = 2 in women and of 4/3 = 1.33 in men. That is, women have a 2/1.33 = 1.5 times higher excess risk compared to men when they have the risk factor, even though the risk factor increases the risk by the same amount in both sexes. Thus, some would conclude that this implies that a finding of a higher relative risk in women is purely an artificial finding due to the lower background risk in women and the mathematical (statistical) metric used to compare the sexes

treatment, However, inherent sex differences in the safety and efficacy of medications, or differences in comorbidities and polypharmacy, may be other (appropriate) reasons to treat women and men differently. The question on as to whether women and men might benefit from different treatments has yet to be answered.

Randomised controlled trials (RCTs) are the gold-standard design to study treatment effects. However, they are also conducted in highly selected populations, often with great underrepresentation of women and gender-diverse groups, and are not powered to uncover sex or gender differences [10]. As such, it remains uncertain whether some of the sex differences in treatment, as seen in clinical practice, are explained by inherent differences in drug safety and efficacy. Research in heart failure patients, for example, showed that women reach their maximum treatment effect at a lower dose than men [38, 39]. This sex difference in optimal treatment dosage may be attributable to sex differences in pharmacokinetics, for example, driven by the notable sex differences in body size and composition [40]. Sex differences in treatment may also be justified if the effects of risk factors, as described above [34], are causally different between the sexes. Hence, although there may be avoidable excess treatment gaps in women, some sex differences in treatment may be medically justifiable, yet, not reflected in clinical guidelines. Further research using different study designs with different strengths and limitations is needed to investigate whether women and men achieve better health outcomes if they receive different treatments. Where possible, this should also include investigation of drug effects within subgroups of women and men with, for example, different body sizes.

This issue is not only relevant for drug treatments. For instance, a recent study showed that the accuracy of non-invasive blood pressure measurements, which were lower than invasive measurements, was considerably lower in women than men [56], which might lead to underdiagnosis of hypertension and unrecognised undertreatment. Unless an appropriately large number of both women and men are included in studies, compelling evidence of a sex difference will never be available. On the reverse side, it is equally true that lack of appropriate sex-stratified data, in the cases where a drug has both a similar efficacy and risk in both sexes, can lead to loss of healthy life or death when cautious physicians, with good intentions, deny guideline-based care to those they perceive as more vulnerable. This may explain the lower uptake of guideline-based high-intensity statins after a myocardial infarction in women, compared to men, in the USA [51].

The biological explanation

By the biological explanation, we mean that sex differences in health may be explained by inherent biological differences. Women and men are biologically different in terms of genetics, body features, genitalia, and hormones. In addition to differences on the sex chromosome (XX in women and XY in men), women and men also differ considerably on the twenty-two autosomal chromosomes. Indeed, a study in 450,000 individuals of European ancestry in the UK Biobank showed that whilst widespread sex differences exist in genetic architecture for health-related traits, most were modest in magnitude [57]. Other studies found that gene expression and genetic co-expression are influenced by sex in about 30% of tissues [58, 59], thereby providing a biological basis for explaining any sex differences when found.

Most notable are the sex differences in the effects of genetic variants related to body anthropometry. Women and men, on average, have a different body composition and body fat distribution, with women having a higher fat mass and more subcutaneous fat, which results in the characteristic pear-like body shape. Several genome-wide association studies (GWAS) have shown that genetic associations of measures of adiposity strongly differ between the sexes [60–62]; including waist-to-hip circumference, where genetic variants are primarily identified in females.

While the number of sex-stratified GWAS is rising, many still use sex-combined models. This approach could mask potentially relevant genetic variants when these have a differentially signed genetic effect in each sex. That is, a genetic variant could have a positive effect in one sex and a negative effect in the other sex. Combined GWAS analyses could result in a weighted average genetic of near zero, leading to the conclusion of no effect. Masking could also happen when a genetic variant has a large effect in one of the sexes and a small or no effect in the other. In both cases, the weighted average is clearly misleading for both women and men.

Sex-specific Mendelian randomisation to strengthen sex-differentiated causal inferences Mendelian randomisation (MR) is a powerful method to strengthen causal inferences on sex differences in risk factor associations [63]. MR studies exploit the random assortment and independent inheritance of genetic variants in the population, which removes bias due to reverse causation and greatly reduces bias from residual or unmeasured confounding. In MR, single-nucleotide polymorphisms (SNPs) are used as proxies, i.e. instruments, for the exposure of interest. The SNPs that influence the exposure are randomly allocated at meiosis, thus producing

Table 6 Sex-specific Mendelian randomisation to strengthen causal inferences

A sex-specific Mendelian randomisation study based on data from the UK Biobank found no sex difference for the strength of the causal effect of genetic liability to type 2 diabetes on the risk of CHD [66]. This was in contrast with strong evidence from observational studies that consistently found evidence for a stronger association in women than men [34]. Another sex-specific Mendelian randomisation study showed that the genetically determined effect of BMI on the risk of type 2 diabetes was stronger in women than men [64]. It may therefore be that the sex differences in the association between diabetes and cardiovascular disease risk seen in observational studies actually occur before the actual diagnosis of diabetes. However, whether causal or otherwise, the higher excess risk seen in women with diabetes suggests a closer eye needs to be kept on them, and shows the importance of sex-specific risk scores

a population genotype distribution which is unrelated to the potential confounders an individual is exposed to throughout life. In this regard, MR is comparable to a RCT, where instead of random assortment of genetic variants, individuals are randomly assigned to different therapeutic arms.

By far most MR studies conduct sex-combined analyses, thereby ignoring reported sex differences in the effects of genetic variants on disease phenotypes. A main barrier for sex-specific MR is the limited public availability of sex-specific GWAS results. However, sex-specific MR studies have provided novel insights in the sex-specific effects of certain risk factors on disease outcomes (Table 6) [64–66]. MR can also be used to assess sex differences in the efficacy and safety of drug treatments [67]. Virtually all drug targets are proteins. GWAS have corroborated known effects of licensed drugs through associations at the loci of the genes coding for their corresponding target proteins [68]. By using the genes encoding drug target proteins as instrumental variable for the drug of interest, sex-specific drug-target MR can investigate the sex-specific efficacy and safety of existing drugs, as well as for the identification of new drug targets.

Broaden the scope of research on the role of sex hormones The sex hormones, oestrogen and testosterone, play an important role in both reproductive and non-reproductive systems. The contribution of hormones to understanding sex differences in health and disease, however, remains debated. To date, most research has focused on the role of oestrogen, which is thought to have an important role in the cardiovascular system, as it has vasodilator effects and reduces or prevents platelet activation [69]. In addition, it improves the profile of circulating lipoproteins, modulates blood pressure, and may underpin the observed sex differences in arterial blood pressure and differences in blood pressure between premenopausal versus postmenopausal women.

Studying the role of sex hormones in women is challenging, given the complexity of accurately measuring natural levels during women's monthly cycle. A recent study in the UK Biobank showed that the presumed cardioprotective effects of oestradiol seem to be largely confounded by age [70]. Early menopause in women, as a marker of accelerated reproductive ageing, has been associated with a higher risk of CHD and stroke in observational studies. However, the presumed adverse effects of an early menopause on cardiovascular risk have also been brought into question by new evidence from a MR study, which showed that genetically determined early age at natural menopause is not causally associated with either CHD risk or with CHD risk factors [71]. Postmenopausal hormone therapy alleviates menopausal symptoms and results from observational studies consistently showed that the use of hormone therapy was associated with a lower risk of CHD and stroke [72, 73]. However, findings from RCTs on the effects of hormone therapy have been null or showed adverse effects on stroke risk. It now seems that timing is critical, and the benefits only seem to be present when the therapy is initiated temporally close to menopause and not when initiated later [74].

The effects of testosterone on health outcomes, in both women and men, are considerably less well-studied. A recent study in postmenopausal women, however, showed that the balance between testosterone and estrogens, as expressed by the testosterone/estradiol ratio, as well as testosterone levels per se, were associated with the risk of CVD [75]. Studies on the role of sex hormones in men's health, although scarce, imply that higher levels of testosterone might be associated with a higher risk of CVD [76]. Also, sex hormone binding globulin (SHBG), which lowers circulating testosterone, might protect against CHD in men [65]. Future studies are needed to simultaneously assess the effects of multiple sex hormones, and their combinations, on a range of health outcomes in both women and men.

Phase 3: Translation to policy and practice

In the first two phases of the roadmap for sex- and gender-disaggregated research, sex and gender differences are systematically identified and explained. The third phase focusses on the translation of the evidence obtained into policy and practice. Once those changes have been made, the actual uptake of policy and practice

recommendations also needs to be evaluated. This is where implementation science plays a critical role. The field of implementation science seeks to systematically close the gap between what we know and what we do (often referred to as the know-do gap) by identifying and addressing the barriers that slow or halt the uptake of proven health interventions and evidence-based practices. As in all aspects of medical research, evidence for the efficacy (and potential disadvantages) of implementation is required. For example, cluster randomised trials can judge the merits of, for instance, training for awareness of unconscious sex bias or novel procedures designed to improve sex-specific diagnoses of stroke by ambulance crews. In the remainder of this section, we will discuss how evidence on sex and gender differences could be translated to policy and practice through education and clinical guidelines.

Education

Key to improving clinical practice will be to ensure that knowledge on known sex and gender differences, and the need to be sensitive to as yet unknown differences, is embedded into medical curricula, including for non-physician healthcare professionals. At present, however, most of the teaching around the impact of sex and gender on health focusses on the traditional aspects of women's health; that is, sexual and reproductive health, and a broader view of how sex and gender as fundamental drivers of health and wellbeing is typically lacking. Even so, successful examples of implementing sex- and gender-inclusive medicine in medical curricula have emerged in several (mostly Western) countries, most notably Canada, Germany, and the USA [77]. Other countries, like Sweden, the Netherlands, and Korea, now also offer some form of sex- and gender-inclusive medicine in their curricula [78]. However, a shared characteristic of these initiatives is that they are often self-designated and driven by the vision and passion of a select group of individuals. As such, embedding of sex- and gender-inclusive medicine in education is still the exception, not the norm, in most parts of the world, and evaluations have yet to be done. To ensure the wide adoption of sex and gender in medical curricula, structural financial resources and commitment from the highest level of governmental or institutional leadership are essential [79].

Clinical guidelines

The results from sex- and gender-disaggregated research provide critical information to inform changes in clinical guidelines, which is the most direct way to change clinical practice. This could involve accounting for differences in prognosis between women and men and sex differences in access to, and uptake or effectiveness of medical interventions or health services. In the United States, women-specific guidelines for the primary prevention of cardiovascular disease were first released in 2003, with the latest update in 2019 [80]. These guidelines highlight the importance of female-specific risk factors, such as reproductive- and pregnancy-associated conditions in the future risk of CVD, as well as differences in manifestations and response to treatments. A review of 118 Canadian clinical practice guidelines published between 2013 and 2015 revealed that 35% contained sex-related diagnostic or management recommendations, 7% contained recommendations for sex-specific laboratory reference values, and 41% referred to differences in epidemiologic features or risk factors only [81]. A study in the Netherlands showed that guidelines on osteoporosis had the highest percentage of sex-specific recommendations (19%), whereas guidelines on depression had the lowest (none) [82].

In many fields, evidence may be insufficient to have sex-specific recommendations. In such cases, guideline committees should specify this upfront, as it informs practitioners about the scope of the guidelines and calls on the research community to provide the evidence required. Ensuring that guideline committees include an individual who is tasked to appraise the literature for evidence on relevant sex differences is key. Using a previously published framework for generating sex-specific guidelines [83], such an individual, with the support of the full writing committee, should systematically determine whether sex is relevant to the guideline and, if so, conduct a systematic appraisal of the included literature to determine whether sex-specific assessments of the quality of the evidence or the recommendations should be made. In clinical practice, the application of sex-specific recommendations, once available, will involve routinely asking whether the presentation, diagnostic workup, or management might change for each patient if they were the opposite sex. This might require a different cognitive mindset of clinicians, as many may not be familiar with this process. However, precision (or personalised) medicine is routine practice for many and thinking of the relevance of sex at different stages of preventative, diagnostic, and management process should just be part of it. Implicit bias assessment amongst the health care profession and research community would be one way of learning more about the problems [84].

Systemic factors underpinning sex- and gender-disaggregated research

In order to systematically improve the uptake and quality of sex- and gender-inclusive research, women need to be

better represented in clinical trials, funding and publishing successes need to depend on it, and academic leadership needs to be more diverse.

Representation of women in trials

Women remain underrepresented in RCTs [4, 5, 8, 10]. For example, while women account for nearly 50% of all CHD patients, they only account for about 25% of all participants in CHD trials [5]. The reasons underpinning this underrepresentation are unclear, but it may be that women are less likely than men to consider and/or to be considered for participation in trials. Data to support this assertion, however, are scarce and it is important to record, and publish, the reasons for non-participation in trials by sex, gender and other key socio-demographic variables, for example by conducting 'studies within a trial' [85].

Despite evidence to show the opposite, it is still frequently assumed that the evidence from these studies in (predominantly) male populations is equally applicable to women. For example, the Danish Cardiovascular screening trial (DANCAVAS) included an impressive number of 46,611 participants, but, disappointingly, all of them were male [86]. The assumption that the findings of a male-only trial can be directly translated to women is simply flawed and, in the case of pharmaceutical interventions, ignores fundamental differences between women and men in the pharmacokinetics and pharmacodynamics. Also, even when trials include women, they are often underpowered to reliably assess women-specific drug effectiveness, let alone sex differences in drug effects.

Academic funding and publishing

Routine conduct of sex- and gender-disaggregated research maximises the benefits of research for both women and men. However, such analyses are still often lacking in many medical disciplines, often without justification. Furthermore, women's health journals should give better coverage of diseases that affect women's health during the life course, including those that affect both sexes [87].

A range of interventions is likely to be needed to increase the uptake of sex- and gender-disaggregated research. Funders and publishers of medical research should make the integration of sex and gender a requirement for funding or publishing. If research not fulfilling this requirement simply does not get funded and/or published, this would rapidly change academic practices and would be a quick fix to the system. An excellent framework for evaluating the uptake of policies for integrating sex and gender, as well as other intersectional characteristics, into research design, has recently been published [2]. A growing number of funding agencies and academic journals already mandate that sex and gender are taken into consideration in research [2, 3, 88–90]. The Sex And Gender Equity in Research (SAGER) guidelines provide sound guidance on how sex and gender can be integrated in the design, analyses, and reporting of research [91] While these guidelines are increasingly being used, barriers to the uptake and implementation include concerns about mandating, and limited time, capacity, and resources, as well as their resistance or lack of awareness [92, 93]. A particular challenge is to assess adherence and to avoid this becoming a checkbox exercise. However, as with other editorial policies and research checklists, adherence to the SAGER guidelines should be an integral part of the publishing process. Improving knowledge about the importance of sex and gender in medical research within the research community is also likely to increase the uptake of such analyses. Excellent courses are available online and could increase awareness to such level to enable systemic change [94]. Including sex and gender champions in research teams would ensure that sex and gender are an integral part of research initiatives and would strengthen subsequent design, analyses, and reporting strategies. Over the past decade, the Canadian Institutes of Health Research has implemented multicomponent interventions to increase the uptake of sex and gender in applications for research funding. These interventions included mandatory reporting of sex and gender integration on applicant forms, development of resources for applicants and evaluators, and grant review requirements. A 10-year evaluation of these interventions not only showed a rise in the number of applications that integrated sex and gender, but also showed that applications that included sex and gender were also more likely to be funded [95]. An important next step would be to also assess whether these awarded projects genuinely conducted the sex and gender-disaggregated considerations they set out to do.

Diverse teams

A very pervasive factor, reaching far beyond the persistent lack of sex-and gender-disaggregated research alone, is implicit bias against women and the lack of women in leadership positions. Indeed, mounting evidence exists to show that a lack of gender balance can have wide-reaching negative consequences, including decreasing productivity, less innovation, and worse decision-making. The field of medicine is not an exception. Women are not only underrepresented as research participants, but also as producers and planners of research and in senior clinical roles [96–100] Research in the field of cardiovascular disease has shown that women attend conferences less frequently than their

male colleagues, and if they attend, are less likely to speak or to attend as faculty. [97]. Gender bias is further exacerbated by the so-called child penalty, which, despite extension policies from funders, is a harsh reality for many, mostly, female academics. There is a wealth of data, however, showing that more women in different settings of academic research results in better science and more attention for sex and gender aspects in research. For example, greater representation of women in editorial boards is linked to a greater representation of women in key (i.e. first and last) authorship positions in various medical disciplines [101, 102], which in turn, is linked to a higher uptake of sex- and gender-based analyses [103]. Enhancing the diversity of teams reaches further than increasing sex and gender diversity alone. People from minority races and ethnicities, or from sexual minorities, also continue to be underrepresented or excluded. Men of minority races and ethnicities have also often been excluded.

Research benefits from including people from outside the academic community. Involving patients and the public throughout the research, from priority setting and planning to co-delivery and communication, allows for the inclusion of a broad range of voices and can enhance the quality and societal relevance of the research.

More diverse guideline committees are another critical component to ensure that the outcomes from sex- and gender-disaggregated research are translated into guideline recommendations and clinical practice [81, 83]. In doing so, ensuring that sex and gender are considered in guideline development becomes less of a task of a sex and gender champion alone. Indeed, diversification in both the clinical and scientific workforce and in the scientific studies is essential to produce the most rigorous and effective medical research. While the scale of the challenges may seem gigantic, a series of small steps made by individuals and institutions can lead to structural change and a more equitable world.

Conclusions

Sex- and gender-disaggregated research and implementation are essential to ensure that women and men benefit equally from scientific progress. The field of sex- and gender-inclusive-based research is evolving and improving. Yet, the roadmap for sex- and gender-disaggregated health research presented here should remain relevant and outlines three basic phases that can aid researchers to systematically identify and explain relevant sex and gender differences, where they exist, and can aid educators, clinicians, and policymakers to translate the outcomes of research in the most effective and meaningful way.

Abbreviations

CHD	Coronary heart disease
CVD	Cardiovascular disease
GWAS	Genome-wide association study
MR	Mendelian randomisation
RCT	Randomised controlled trial
SAGER	Sex and gender equity in research
SHBG	Sex hormone binding globulin
SNP	Single-nucleotide polymorphisms

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Authors' contributions

SP and MW conceived the idea for the manuscript. SP wrote the first draft. MW provided intellectual input. SP and MW read, reviewed, and approved the final manuscript.

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Publisher's Note

Carpal Tunnel Syndrome

Carpal tunnel syndrome is essentially a pinched nerve in the wrist. There is a space in the wrist called the carpal tunnel where the median nerve and nine tendons pass from the forearm into the hand **(Figure 1)**. Carpal tunnel syndrome happens when pressure builds up from swelling in this tunnel and puts pressure on the nerve.

Causes

Pressure on the nerve can happen several ways, including:

- Swelling of the lining of the flexor tendons, called tenosynovitis
- Joint dislocations
- Fractures
- Arthritis
- Fluid retention during pregnancy

The situations listed above can narrow the carpal tunnel or cause swelling in the tunnel. Thyroid conditions, rheumatoid arthritis and diabetes can also be associated with carpal tunnel syndrome. Ultimately, there can be many causes of this condition.

Signs and Symptoms

Symptoms of this condition can include:

- Pain
- Numbness
- Tingling
- Weak grip
- Occasional clumsiness
- Tendency to drop things

The numbness or tingling most often takes place in the thumb, index, middle and ring fingers. The symptoms usually are felt during the night but may also be noticed during daily activities such as driving or reading a newspaper. In severe cases, sensation and strength may be permanently lost.

Diagnosis

A detailed history including medical conditions, how the hands have been used, and any prior injuries is important in diagnosing carpal tunnel syndrome. An x-ray may be taken to check for arthritis or a fracture. In some cases, laboratory tests may be done. Electrodiagnostic studies are also a possibility to confirm the diagnosis and check for other possible nerve problems.

Treatment

Symptoms may often be relieved without surgery. Some treatment options are:

- Changing patterns of hand use (helps reduce pressure on the nerve)
- Keeping the wrist splinted in a straight position (helps reduce pressure on the nerve)
- Wearing wrist splints at night (helps relieve symptoms that interfere with sleep)
- Steroid injections into the carpal tunnel (helps reduce swelling around the nerve)

When symptoms are severe or do not improve, surgery may be needed to make more room for the nerve. Pressure on the nerve is decreased by cutting the ligament that forms the top of the tunnel on the palm side of the hand **(Figure 2)**. Following surgery, soreness around the cut area may last for several weeks or months. The numbness and tingling may disappear quickly or slowly. Recovery may take several months. Carpal tunnel symptoms may not completely go away after surgery, especially in severe cases.

Figure 1. The carpal tunnel

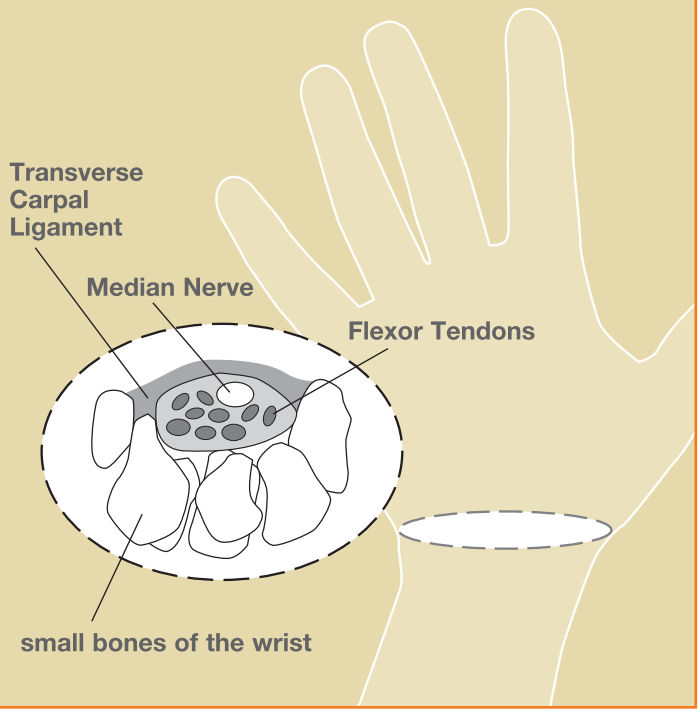
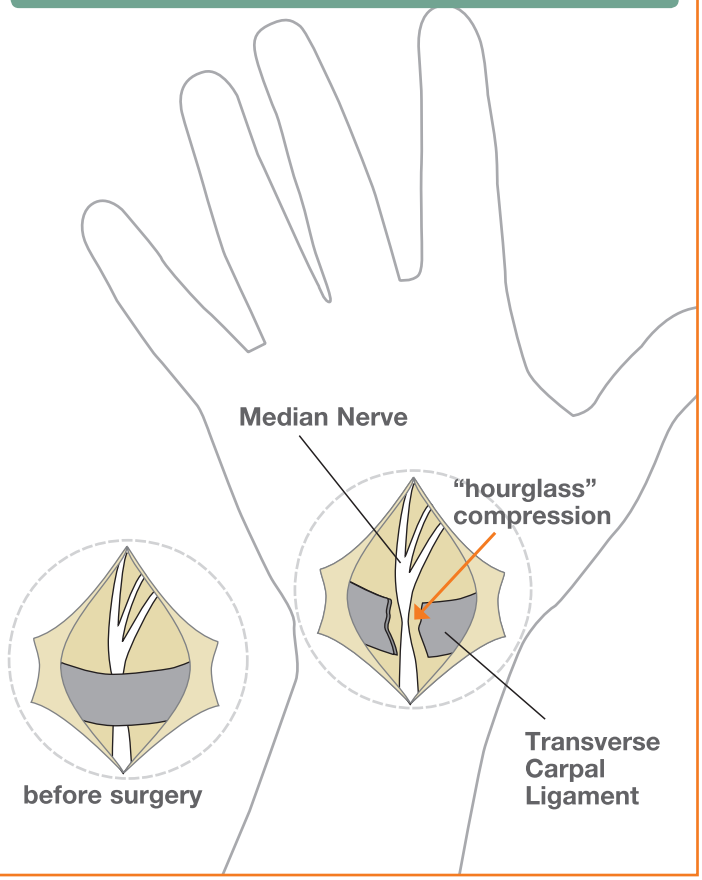


Figure 2. Carpal tunnel surgery



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NAMS Position Statement

The 2023 nonhormone therapy position statement of The North American Menopause Society

Abstract

Objective: To update the evidence-based Nonhormonal Management of Menopause-Associated Vasomotor Symptoms: 2015 Position Statement of The North American Menopause Society.

Methods: An advisory panel of clinicians and research experts in women's health were selected to review and evaluate the literature published since the Nonhormonal Management of Menopause-Associated Vasomotor Symptoms: 2015 Position Statement of The North American Menopause Society. Topics were divided into five sections for ease of review: lifestyle; mind-body techniques; prescription therapies; dietary supplements; and acupuncture, other treatments, and technologies. The panel assessed the most current and available literature to determine whether to recommend or not recommend use based on these levels of evidence: Level I, good and consistent scientific evidence; Level II, limited or inconsistent scientific evidence, and Level III, consensus and expert opinion.

Results: Evidence-based review of the literature resulted in several nonhormone options for the treatment of vasomotor symptoms. **Recommended**: Cognitive-behavioral therapy, clinical hypnosis, selective serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors, gabapentin, fezolinetant (Level I); oxybutynin (Levels I-II); weight loss, stellate ganglion block (Levels II-III). **Not recommended**: Paced respiration (Level I); supplements/herbal remedies (Levels I-II); cooling techniques, avoiding triggers, exercise, yoga, mindfulness-based intervention, relaxation, suvorexant, soy foods and soy extracts, soy metabolite equol, cannabinoids, acupuncture, calibration of neural oscillations (Level II); chiropractic interventions, clonidine; (Levels I-III); dietary modification and pregabalin (Level III).

Conclusion: Hormone therapy remains the most effective treatment for vasomotor symptoms and should be considered in menopausal women within 10 years of their final menstrual periods. For women who are not good candidates for hormone therapy because of contraindications (eg, estrogen-dependent cancers or cardiovascular disease) or personal preference, it is important for healthcare professionals to be well informed about nonhormone treatment options for reducing vasomotor symptoms that are supported by the evidence.

Key Words: Clinical hypnosis – Cognitive-behavioral therapy – Gabapentin – Hormone therapy – Menopause – Nonhormone therapy – Selective serotonin reuptake inhibitors – Serotonin-norepinephrine reuptake inhibitors – Stellate ganglion block – Vasomotor symptoms.

Hot flashes and night sweats (vasomotor symptoms [VMS]) are the most common symptoms of menopause and occur in up to 80% of menopausal women.[1] Vasomotor symptoms can be bothersome, lasting a mean duration of 7 to 9 years, and in one-third of women, can last more than 10 years.[2] Hormone therapy (HT) remains the most effective treatment and should be considered in menopausal women aged younger than 60 years, within 10 years of their final menstrual periods, and without contraindications. Despite this, the use of HT has declined substantially after the publication of the Women's Health Initiative (WHI).[3-5] Evidence suggests that contrary to guideline recommendations, younger women and those with more VMS were less likely to receive HT after the WHI than before.[6] Additionally, rates of continuation of HT have declined in women with more frequent VMS after the WHI, largely because of media reports and provider advice.

Despite the underuse of HT in symptomatic women, some may choose not to use HT or have contraindications to its use, such as a history of an estrogen-sensitive cancer (including breast cancer), coronary heart disease, myocardial infarction,

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stroke, venous thromboembolism, or inherited high risk of thromboembolic disease.[7] Nonhormone options are important considerations for women who are not good candidates for HT.

This Position Statement updates and expands information on the nonhormone management of VMS from the 2015 NAMS Position Statement on nonhormone therapies and is intended to provide direction to guide evidence-based nonhormone management of VMS.

METHODS

An advisory panel of clinicians and research experts in the field of women's health was selected to review and evaluate the literature published after the Nonhormonal Management of Menopause-Associated Vasomotor Symptoms: 2015 Position Statement of The North American Menopause Society.

Topics were divided into five sections for ease of review: lifestyle; mind-body techniques; prescription therapies; dietary supplements; and acupuncture, other treatments, and technologies. Individual panel members reviewed and evaluated the evidence on the different therapies for which they had special expertise, with the knowledge that trials of nonhormone treatments of VMS have a placebo improvement rate of 20% to 66%, and women with more anxiety show higher response to placebo.[8]

The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society was written after an extensive review of the pertinent literature and includes key points identified during the review process. The resulting manuscript was submitted to and approved by the NAMS Board of Trustees.

The panel assessed the most current and available literature to recommend or not recommend use with the level of evidence assigned on the basis of these categories:

- Level I: Good and consistent scientific evidence.
- Level II: Limited or inconsistent scientific evidence.
- Level III: Consensus and expert opinion.

This Position Statement uses gender-specific language as reflected in the referenced publications. However, NAMS recognizes that some persons experiencing menopause may identify differently than with the gender and pronouns used in this statement.

LIFESTYLE

Cooling techniques

Hot flashes can be triggered by small, core-body-temperature elevations[9-11]; therefore, it is feasible that changing lifestyle practices that control core body temperature may decrease VMS frequency. These include clothing adjustments (ie, dressing in layers; wearing sleeveless blouses; using breathable clothing materials; avoiding pullover sweaters, tops, and scarves) and environmental controls (hand or electric fans; cold packs under the pillow; turning the pillow when feeling warm; dual control electric blankets or a bed fan; lower room temperature). One small (N = 20), uncontrolled trial of postmenopausal women showed benefits with the use of a forehead cooling device and sleep hygiene instructions for reduction in self-reports of sleep problems and VMS over a 4-week period.[12] Another small trial (N = 39) of a nighttime thermal comfort intervention was studied in a 4-week randomized, crossover trial.[13] Women reported no objective changes in the number or duration of nighttime VMS with this device, despite some self-reported improvements in sleep compared with baseline (ie, no device). Overall, cooling interventions must be tested in larger randomized, placebo-/sham-controlled clinical trials for the treatment of VMS. (Level II; not recommended)

Avoiding triggers

Women are often told to avoid "triggers" such as alcohol, caffeine, spicy foods, or hot foods or liquids. One cross-sectional study of 4,595 Chinese women found a positive association between alcohol intake and VMS[14]; however, this has not been reported in other studies (such as the Melbourne Women's Midlife Health Project).[15] There are no clinical trials assessing the effects of avoiding triggers for the alleviation of VMS. (Level II; not recommended)

Exercise and yoga

Observational studies revealed that women who exercise regularly report fewer VMS.[16-18] However, others have found no relationship between level of physical activity or exercise and VMS,[19] and exercise may trigger VMS in symptomatic women.[10] Several *Cochrane* reviews concluded that there was insufficient or poor evidence to consider exercise as a treatment for VMS.[20-22] Among the challenges, methods and exercise interventions varied widely across studies. They included, for example, supervised walking versus yoga versus no intervention[23] and supervised aerobic exercise versus yoga versus usual activity plus omega-3 or placebo pills.[24] No difference was found between yoga and exercise. When study results comparing exercise to no exercise were pooled, exercise had no effect on VMS frequency.[22] One study in the *Cochrane* review comparing exercise and HT found that HT was far more effective than exercise in reducing VMS.

A pooled analysis of individual data from four MsFLASH trials (N = 1,005) assessed various interventions compared with placebo for the treatment of VMS, including estradiol, antidepressants, omega-3, cognitive-behavioral therapy (CBT) for insomnia, and yoga or aerobic exercise.[25] Women with more bothersome VMS benefited the most from estradiol, whereas those with VMS and insomnia improved with CBT for insomnia. Those with VMS and psychosocial complaints reported improvement with antidepressants or CBT for insomnia. Overall, exercise and yoga led to smaller improvements and were not recommended as single interventions for VMS.

A systematic review and meta-analysis of 12 randomized, controlled trials (RCTs; N = 1,306) assessed yoga against no treatment, health education, exercise, and auricular acupressure for the treatment of VMS.[26] Given that all outcomes were self-reported and that there was insufficient blinding of participants, there was a high risk for reporting and detection bias among the studies. Additionally, there was significant heterogeneity in yoga styles, intensity, and frequency, limiting the interpretability of the findings. Yoga had limited benefits compared

with exercise for the treatment of VMS, and there were no benefits compared with no treatment.

Although there are other health benefits associated with exercise or yoga, the evidence of those interventions for the treatment of VMS is sparse. (Level II; not recommended)

Dietary modification

Research evaluating the relationship of diet and VMS is limited. A study in postmenopausal women with more than two VMS per day (N = 84) randomized to a low-fat, plant-based diet and a half-cup of cooked soybeans per day versus no dietary changes found an 88% reduction in moderate to severe VMS compared with a 34% reduction in those with no dietary changes after 12 weeks.[27] In surveys, more vegetable and fruit consumption was associated with fewer menopause symptoms,[28] and women who followed a vegan diet reported fewer bothersome VMS than those who ate meat. For both, increased vegetable consumption was associated with fewer bothersome symptoms.[29] One longitudinal cohort study showed high-fat and -sugar diets were associated with an increased risk of VMS.[30] One study found that women who had higher soy milk and vegetable consumption had fewer menopause symptoms, whereas those who ate poultry and skimmed dairy products had worse menopause symptoms overall, including more VMS.[31] There is limited evidence from clinical trials to support the use of dietary modification for improving VMS. (Level III; not recommended)

Weight loss

Studies have found that women who are obese are more likely to report more frequent and severe hot flashes than women of normal weight.[32] Randomized, controlled trials have found that weight loss from behavioral interventions are associated with a decrease in VMS.[33,34] Additionally, reducing hot flashes was a major motivator for losing weight.[33] Evidence suggests that the role of adiposity and weight loss in VMS may vary depending on age or menopause stage and specifically that adiposity acts as a risk factor for VMS earlier in the transition (perimenopause and early postmenopause)[35] but not when women are older or later in the transition.[36] Weight loss may have greater effects in reducing VMS when women are earlier in the transition.[33] In an open-label single-arm pilot study of a weight-loss medication (selective serotonin 2C [5-HT2C] receptor agonist) tested in 20 women, after 12-weeks there were both a decrease in weight and significant improvement in VMS (decline, 5.4 hot flashes/d) from baseline to week 12.[37] The study also found that after the weight-loss medication was stopped, there was a rapid increase in VMS with a return to baseline weight, further supporting the notion that weight loss improved VMS. However, these studies are either small pilot studies, nonrandomized trials, or post hoc analyses of studies designed for a different purpose. Larger, rigorously designed RCTs are needed. The limited available evidence suggests that weight loss may be used to improve VMS for some women. (Levels II-III; recommended)

Key points

- There is no strong evidence that lifestyle changes such as cooling techniques and avoiding triggers improve VMS.
- There is insufficient or poor evidence to consider exercise or yoga as a treatment for VMS.
- A healthy diet is important for health promotion and chronic disease prevention; however, there is limited evidence to support dietary modifications as a tool for improving VMS.
- Weight loss may be considered for improving VMS.

MIND-BODY TECHNIQUES

Cognitive-behavioral therapy

Cognitive-behavioral therapy (CBT) has been shown to reduce the degree to which VMS are rated as a problem. Initial evidence came from two double-blind RCTs: MENOS 1, which showed that group CBT compared with usual care reduced VMS problem ratings in 96 survivors of breast cancer,[38] and MENOS 2, which showed self-guided and group CBT compared with usual care reduced VMS problem ratings in 140 perimenopausal and postmenopausal women without a history of breast cancer.[39]

A clinical psychologist administered the group CBT intervention, which involved psychoeducation (physiology of VMS; how thoughts and emotions affect the perception of physical sensations), training in relaxation and paced breathing, and cognitive and behavioral strategies to manage VMS (identifying and challenging negative beliefs about VMS; monitoring and modifying triggers of VMS; relaxation exercises). The content of the self-guided CBT was identical to that of the group CBT and included a self-help book completed during a 4-week period, two contacts with a clinical psychologist, weekly homework, and a compact disc for daily practice of relaxation and paced breathing.

The usual-care group received information about VMS, advice on treatment options and symptom management, and instructions for paced breathing and relaxation. In both studies, improvements in VMS problem ratings were maintained at 26 weeks, and more women in the CBT group (65%-78% across studies) reached a clinically significant threshold for improvement in VMS that are rated as a problem than in the usual-care group. Beliefs about coping and control over VMS and beliefs about sleep and night sweats mediated the effect of CBT on VMS problem ratings.[40]

Since these initial trials, several studies have extended this intervention to other modes of delivery and in other populations. Two studies in survivors of breast cancer showed that CBT reduced 1) VMS rated as a problem, hot flash interference, and self-reported VMS frequency when delivered by trained nurses in MENOS 4 (N = 130),[41] or 2) VMS rated as a problem and self-reported VMS frequency when delivered via the internet (with or without therapist support; N = 254).[42]

A workplace study of 124 menopausal women with problematic VMS found that women who received CBT for VMS using a self-help book had significant reductions in their VMS problem ratings compared with a waitlist control.[43] Another study examined CBT in combination with physical exercise in

422 survivors of breast cancer, showing that CBT (with or without exercise), but not physical exercise alone, reduced VMS problem ratings but not VMS frequency compared with a waitlist control.[44]

Finally, a study of 72 perimenopausal and postmenopausal women with VMS and depressed mood found that women randomized to a 12-week group-based CBT intervention had greater reductions in VMS bother and interference[45] as well as improvements in depressive symptoms than women randomized to a waitlist control. A caveat to this body of work is that the studies largely employ waitlist or usual-care controls, which are less rigorous controls than active controls matched on time and attention. However, the body of literature as a whole supports that CBT alleviates bothersome VMS for both survivors of breast cancer and menopausal women. (Level I; recommended)

Mindfulness-based interventions

Evidence is limited for mindfulness-based interventions (MBI) for the management of VMS. Common features of MBI include instruction in meditation practices and how to approach thoughts, feelings, and bodily sensations in an accepting, nonjudgmental manner. A widely disseminated MBI is mindfulness-based stress reduction (MBSR), a multicomponent intervention that includes mindfulness meditation, body awareness, and yoga.[46] An RCT of MBSR versus waitlist control was conducted in 110 women who had five or more moderate to severe hot flashes per day. The MBSR intervention was a standardized, widely used, 8-week program involving weekly 2.5-hour group classes, at-home practice (45 min, 6 d/wk), and an 8-hour in-person group retreat. Vasomotor symptoms were assessed via a diary. After 20 weeks, the MBSR group showed greater reductions in hot flash bother (21.62% vs 10.50%; $P = .07$) and intensity (44.56% vs 26.97%; $P = .057$) than waitlist controls; these differences were marginally significant, reflecting the pilot nature of the study, variability in the outcome, and pronounced placebo effect.

Several additional studies have examined MBSR or other MBI for a constellation of menopause symptoms (eg, VMS, anxiety, depressive symptoms, sleep disturbance) in women transitioning through menopause[47,48] who were survivors of breast cancer[49] or who had undergone early bilateral oophorectomy.[50] A meta-analysis similarly examined MBI for quality of life or general menopause symptoms.[51] These studies have generally shown positive effects in reducing menopause symptoms broadly, with mixed effects for VMS specifically. Given that these studies were limited by their small sizes or limited control groups and that they were not designed to consider VMS (eg, women with VMS were not specifically enrolled), there are not enough data to recommend MBSR for the management of VMS. Future rigorously designed trials are needed to test the efficacy of MBI for VMS. (Level II; not recommended)

Clinical hypnosis

Clinical hypnosis is a mind-body therapy that involves a deeply relaxed state and individualized mental imagery and suggestion. It has been widely used to manage other chronic symptoms such as pain and anxiety. Hypnosis has been studied for the treatment of hot flashes in two trials—one randomized trial in survivors of breast cancer[52] and one RCT in women with at least seven hot flashes per day.[53] In both trials, clinical hypnosis involved 5 weekly in-person sessions of hypnotherapy with at-home self-hypnosis practice. In a study of 60 women with a history of breast cancer, clinical hypnosis was significantly better at reducing hot flashes and improving mood and sleep than no treatment.[52]

A 2013 single-blind RCT of 187 postmenopausal women reporting at least 50 hot flashes a week at baseline evaluated clinical hypnosis over 12 weeks against an active structured-attention control.[53] Both clinical hypnosis and structured-attention control included 5 weekly sessions that included discussion of symptoms, attentive listening, interpersonal exchange, avoidance of negative suggestions, monitoring, measurement, and encouragement provided in a therapeutic environment with a trained clinician. The hypnosis group additionally received hypnotic inductions and cooling suggestions. Participants in the clinical-hypnosis arm reported significantly lower hot flash frequency (74% vs 17%; $P < .001$) and hot flash scores (frequency times severity, 80% vs 15%; $P < .001$) than controls. In addition, physiologically monitored hot flashes were reduced significantly more in the hypnosis group than in the attention-control group (57% vs 10%; $P < .001$), indicating a clinically significant improvement. A follow-up analysis showed that effects were not related to women's expectations about whether hypnosis would work.[54] The program can be delivered via a trained provider or accessed via a smartphone application. (Level I; recommended)

Paced respiration

Paced respiration is unlikely to provide any benefit for hot flashes. Paced respiration involves taking six to eight slow, deep breaths per minute while inhaling through the nose and exhaling through the mouth. Paced respiration was shown to reduce hot flashes in several small studies that were done in a behavioral laboratory.[55-57] Two larger studies did not show any benefits over other forms of breathing. In a randomized trial of 208 women, paced respiration was no better than shallow breathing or usual care for reducing hot flash frequency, severity, bother, or interference.[58] Similarly, in a randomized trial of 92 women, paced respiration practiced once or twice per day was no better than usual breathing for reducing hot flash scores (frequency times severity).[59] A third study showed that women who used a chest device to guide their slow, deep breathing practice at home for at least 15 minutes per day had significantly less benefit than a control group assigned to music listening.[60] (Level I; not recommended)

Relaxation

Evidence is limited and inconsistent on relaxation for hot flashes. A 2014 *Cochrane* review[61] and a 2008 systematic review[62] both concluded that evidence from RCTs of relaxation was insufficient. There are two studies that were not included in either review. The first was a nonblinded, randomized trial showing a reduction in hot flash frequency with applied relaxation (n = 33) compared with a waitlist control group (n = 27).[63,64]

The second was a randomized trial comparing a nine-module, internet-delivered, applied relaxation program to an untreated control group. Of 46 women randomized in a 1:1 fashion, 66% dropped out early (no reasons provided), and the study had to be terminated. Limitations across studies included small sample sizes or lack of an appropriate attention-control group.[55,56,63,65-68] (Level II; not recommended)

Key points

- CBT has been shown to reduce the bother and interference associated with VMS.
- Clinical hypnosis has been shown to reduce VMS frequency and severity.
- MBSR interventions for the management of VMS are limited by sample size and lack of control groups and are not designed to consider VMS; therefore, there are not enough data to recommend treatment.
- Paced breathing and relaxation techniques do not alleviate VMS and are not recommended.

PRESCRIPTION THERAPIES

Many nonhormone prescription therapies have been evaluated and found to significantly reduce VMS in symptomatic menopausal women. However, there are only two FDA approved for this indication: paroxetine mesylate 7.5 mg daily and fezolinetant 45 mg daily. Other medications that reduce VMS include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), gabapentin, and oxybutynin. Typically, the onset of action is within 2 weeks. There are limited trials comparing nonhormone prescription therapies head-to-head with hormone therapy.

Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors

Evidence exists that SSRIs and SNRIs are associated with mild to moderate improvements in VMS, regardless of whether menopause is natural or surgical, as supported by meta-analyses,[69-71] a pooled analysis,[72] a *Cochrane* review,[73] and a review focused on evidence in survivors of cancer.[74] Limitations to these reviews include heterogeneity of the populations and variations in inclusion criteria, as well as variability in the population that was tested, dosing, length of treatment, and outcomes evaluated.

Paroxetine,[75] escitalopram,[76] citalopram,[77] venlafaxine,[78,79] and desvenlafaxine[80] have been shown to significantly reduce VMS in large, double-blind RCTs of symptomatic women. Duloxetine has been found to reduce VMS in smaller studies.[81,82] Hot flash reductions vary from 25% to 69% with these treatments, with improvements in composite hot flash severity and frequency from 27% to 61%. Trends toward improvement have been seen with sertraline and fluoxetine, but these were statistically insignificant; therefore, they are not recommended.[69,79,83-86]

A pooled analysis from three RCTs showed that 10 mg to 20 mg of escitalopram, 0.5 mg of oral 17β-estradiol, and 75 mg of venlafaxine daily resulted in comparable reductions in VMS frequency. A trial reported that 75 mg per day of venlafaxine was similar to low-dose oral estradiol 0.5 mg per day.[79,87] Oral estradiol reduced the frequency of hot flashes by 2.3 more per day than placebo ($P < .001$), whereas venlafaxine reduced the frequency of hot flashes by 1.8 more per day than placebo ($P = .005$). However, neither of these trials allowed dose escalation, in which case estradiol would be expected to provide 77% improvement in hot flashes on average.[88]

A low-dose paroxetine salt (7.5 mg/d) was the first nonhormone pharmaceutical FDA approved for the treatment of moderate to severe VMS, with improvements found in VMS severity and frequency for up to 24 months, along with improvements in sleep disruption, without weight gain or negative effects on libido.[89,90]

Prior neuroleptic syndrome, serotonin syndrome, and concurrent use of monoamine oxidase inhibitors are contraindications to SSRIs and SNRIs. Caution should be taken in prescribing in patients with uncontrolled seizures, bipolar disorder, kidney or liver insufficiency, uncontrolled hyponatremia, and poorly controlled hypertension, as well as concurrent use of other SSRIs or SNRIs and pertinent polymorphisms in cytochrome P450 enzyme pathways. Black box warnings include uncommon suicidal thoughts in adolescents and children within the first few months.

Coadministration of SSRIs may lead to inhibition of CYP2D6 (the enzyme that converts tamoxifen to its most active metabolite, endoxifen) in women using tamoxifen, particularly with paroxetine and fluoxetine. Safer choices for those on tamoxifen include venlafaxine, desvenlafaxine, escitalopram, or citalopram because they have less of an effect on the CYP2D6 enzyme. There is a possible reported risk of bone fracture with SSRIs because serotonin alters signaling on bone metabolism,[91,92] although this has not been seen with short-term use.[93] They may produce nausea or dizziness, which typically improves after 1 to 2 weeks. (Level I; recommended)

Gabapentinoids

Gabapentin is FDA approved as an antiepileptic drug that is commonly used to treat diabetic neuropathy and postherpetic neuralgia. However, several trials studying the dose of 900 mg (300 mg three times/d) show that this has improved the frequency and severity of VMS.[94-96] Possible adverse events (AEs) include dizziness, unsteadiness, and drowsiness, typically seen during the first week, with improvement during the second week and resolution by week 4. In a placebo-controlled trial, higher doses of gabapentin (titrated to 2,400 mg/d) were as beneficial as estrogen (conjugated equine estrogens 0.625 mg/d) in reducing hot flash severity scores.[97] Adverse events of gabapentin at this dose included dizziness, headache, and disorientation, which limited its potential benefits. Because drowsiness is an AE, and the half-life is short, bedtime dosing of gabapentin may be a good choice for women with disruptive sleep from VMS. Black box warnings for all antiepileptic agents, including gabapentin, include uncommon suicidal thoughts or behaviors. Adverse events include drowsiness, dizziness, and impaired balance or coordination. The suggested dosing (Table 1) for gabapentin is 900 mg to 2,400 mg per day in divided doses. (Level I; recommended)

TABLE 1. *Suggested dosing ranges for nonhormone prescription therapies*

SSRIs		
Paroxetine salt	7.5 mg	Single dose, no titration needed
Paroxetine	10-25 mg/d	Start with 10 mg/d
Citalopram	10-20 mg/d	Start with 10 mg/d
Escitalopram	10-20 mg/d	Start with 10 mg/d (for sensitive or older women, start with 5 mg/d for titration, but this dose has not been evaluated for efficacy)
SNRIs		
Desvenlafaxine	100-150 mg/d	Start with 25-50 mg/d and titrate up by that amount each day
Venlafaxine	37.5-150 mg/d	Start with 37.5 mg/d
Gabapentinoids		
Gabapentin	900-2,400 mg/d	Start with 100-300 mg at night, then add 300 mg at night, then a separate dose of 300 mg in the morning (start 100 mg if concerned about sensitivity)
Neurokinin B antagonists		
Fezolinetant	45 mg/d	Single dose, no titration needed

SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

Pregabalin

Pregabalin is a gamma-aminobutyric acid analog structurally related to gabapentin FDA approved for the management of neuropathic pain and seizures. There has been one phase 3 RCT in 163 women (40% with a history of cancer) evaluating pregabalin for VMS.[98] After 6 weeks of treatment, pregabalin at a dose of 75 mg twice a day or 150 mg twice a day decreased VMS frequency by 59% and 61%, respectively, whereas placebo decreased symptoms by 35%. There were more dizziness and cognitive difficulties reported in those taking pregabalin. Because of limited studies, AEs, including weight gain, and because pregabalin is listed as a Schedule V controlled substance (because of the potential for abuse), pregabalin is not recommended. (Level III; not recommended)

Clonidine

Clonidine is a centrally active α-2 adrenergic agonist that has been shown to be modestly more beneficial than placebo[69] but less beneficial than SSRIs, SNRIs, and gabapentin in reducing VMS.[69,73] It is used infrequently because of AEs, including hypotension, lightheadedness, headache, dry mouth, dizziness, sedation, and constipation. Sudden cessation can lead to significant elevations in blood pressure. Because there are other more effective therapies with fewer AEs, clonidine is not recommended. (Levels I-III, not recommended)

Oxybutynin

Oxybutynin is an antimuscarinic, anticholinergic therapy that is used for the treatment of overactive bladder and urinary urge incontinence. One prospective study[99] and two randomized, double-blind studies[100,101] in postmenopausal women demonstrated that oxybutynin at doses ranging from 2.5 mg or 5 mg twice daily up to 15 mg extended-release daily significantly improved moderate to severe VMS. Adverse events of oxybutynin are usually dose-dependent and most commonly include a dry mouth and urinary difficulties. Long-term use of anticholinergics may be associated with cognitive decline, particularly in older persons.[102-104] (Levels I-II; recommended)

Suvorexant

Suvorexant is a dual orexin-receptor antagonist that blocks the effects of the hypothalamic neuropeptide orexin-A, which promotes wakefulness and may be involved in the occurrences of hot flashes. Postmenopausal women have plasma levels that are three times higher than premenopausal women, which may contribute to sleep disruption and impaired thermoregulation.[105] Suvorexant has been shown to reduce insomnia severity,[106-108] and findings in a small study of menopausal women showed that it led to reductions in nighttime VMS frequency compared with placebo and was well tolerated.[109] Suvorexant did not improve daytime VMS. Given limited data to support its use, suvorexant is not recommended. (Level II; not recommended)

Neurokinin B antagonists

New nonhormone therapies, only one of which (fezolinetant) is FDA approved, are important because their development was founded on the burgeoning understanding of VMS physiology. It is recognized that pulsatile gonadotrophin-releasing hormone (GnRH) secretion is itself driven by an ensemble of pacemaker cells that produce kisspeptin, neurokinin B, and dynorphin, leading to the coined acronym *KNDy* (pronounced *candy*) to describe this unique subset of hypothalamic neurons. These KNDy neurons are surrounded by a dense plexus of interconnected fibers to ensure that all KNDy neurons fire in concert and together constitute the GnRH pulse generator.[110]

Neurokinin B stimulates and dynorphin inhibits sustained pulsatile kisspeptin secretion. In turn, kisspeptin acts directly on GnRH neurons to stimulate GnRH secretion, thereby driving luteinizing hormone (LH) and follicle-stimulating hormone (FSH) release. In parallel with the effect of KNDy neurons on GnRH in the hypothalamus, the KNDy neuronal plexus has direct effects on the adjacent hypothalamic thermoregulatory center.[111] After declines in circulating levels of estradiol across the menopause transition, VMS are triggered by hyperactivity of the KNDy neuron plexus, resulting in hypersecretion of neurokinin B.[112] Hypersecretion of neurokinin B from the KNDy neurons onto the adjacent thermoregulatory center in the hypothalamus[111] causes disruption of temperature control and the occurrence of VMS.[112,113]

Therapeutic development of neurokinin B antagonists was initiated as a novel strategy to target VMS. This nonhormone approach directly targets the neural mechanism underlying VMS. Published results of RCTs are available for three distinct agents, with fezolinetant, which is FDA approved, and elinzanetant[114-116] in development. A third agent, antagonist (MLE4901),[117,118,121] is no longer being pursued as a VMS treatment.

Published trial results include demonstration of efficacy of fezolinetant[116,119,120] and elinzanetant[116,121] relative to placebo. Fezolinetant is a selective neurokinin B receptor-3 antagonist found to be more beneficial than placebo within and up to 12 weeks of use. Elinzanetant is a dual neurokinin B receptor-3 and receptor-1 antagonist found to be more beneficial than placebo within 2 weeks of use. Phase 3 trials have demonstrated safety, with headache as the most common AE.[120] Elevation of hepatic enzymes was rare and resolved either during continued treatment or with treatment discontinuation.

The effect of neurokinin B antagonists on other symptoms that commonly co-occur with VMS or are frequently experienced during the menopause transition has received less attention. Early evidence suggests benefit for quality of life- and VMS-related distress, nocturnal awakenings, and sleep quality.[114-116,119,121-123] Further effect on VMS-related mood and genitourinary, sexual, cardiovascular, metabolic, and bone health are lacking. Higher doses appear to suppress LH but not estradiol in postmenopausal women with VMS.[114] However, potentially advantageous and detrimental effects on other physiologic processes have yet to be fully investigated in larger populations.

Key points

- SSRIs and SNRIs are associated with mild to moderate improvements in VMS.
- Gabapentin is associated with improvements in the frequency and severity of VMS.
- Pregabalin is not recommended for VMS because of AEs and controlled-substance prescribing restrictions.
- Because of significant AEs and no recent studies showing greater benefit than placebo, clonidine is not recommended.
- Oxybutynin has been shown to reduce moderate to severe VMS, although in older adults, long-term use may be associated with cognitive decline.
- Given limited data, suvorexant is not recommended.
- Fezolinetant is a first-in-class neurokinin B antagonist that is FDA approved for management of vasomotor symptoms.

DIETARY SUPPLEMENTS

Managing VMS with dietary supplements is complex and challenging because there are limited rigorous randomized, clinical trial data from which to evaluate supplements and a lack of government regulation to ensure their purity and safety. These over-the-counter products remain widely marketed through direct-to-consumer marketing. They are permitted to market toward specific claims of alleviating symptoms despite limited evidence as long as there is no claim to provide disease benefit.

Dietary supplements with limited or inconsistent evidence of benefit

Soy foods and soy extracts

Soy is the most widely used isoflavone-containing food. Isoflavones are a class of phytochemicals, a broad group of nonsteroidal compounds of diverse structure that bind to estrogen receptors (ERs) in animals and human beings. Isoflavones have a greater affinity for ER-β than for ER-α and possess both estrogen-agonist and estrogen-antagonist properties.[124] Soy is among the eight most common food allergens,[125] and reactions can range from mild (eg, bloating, flatulence, loose stools) to severe (eg, anaphylaxis).

"The Nonhormonal Management of Menopause-Associated Vasomotor Symptoms: 2015 Position Statement of The North American Menopause Society" noted mixed evidence for use of soy for VMS.[126] Soy trials published since 2015 are difficult to summarize because of the wide variation in interventions tested (eg, soy-based drinks,[127,128] soy isoflavone derivatives in tablets only[129] or combined with exercise,[130] or mixed with other supplements [herbals, vitamins, or minerals]), with widely varying dosages tested.[131-135] These studies also have significant limitations, including small sample sizes,[129-131,133,134] use of symptom checklists[126-131,133,135] rather than VMS diaries,[134] and relatively short-term assessment of outcomes. For example, most participants reported VMS after 12 weeks of treatment,[127-129,131,133-135] yet meta-analyses suggest more than 13 weeks are needed to demonstrate half of the expected maximal effects,[136] and more than 16 weeks are needed for optimal effects.[137] As a result of these study differences and limitations, the findings are mixed, with some studies showing soy to be beneficial for reducing VMS or severity,[131,132,135] and others showing no benefit of soy over placebo[127,128,130,133] or finding soy to be less beneficial than other treatments.[129] (Level II; not recommended)

Soy metabolite equol

Equol is a nonsteroidal estrogen that binds to ER-α and ER-β, but because of its high affinity for ER-β, it is often designated as an ER-β agonist. Few studies have considered whether study participants can metabolize soy, which is critical for soy's potential estrogenic effects. Only 35% of North American women can metabolize the soy isoflavone daidzein to equol.[138] Women who are able to metabolize soy into equol would be expected to experience relief from VMS with soy products or equol. Women who cannot produce equol after ingesting soy do not benefit from soy but would be expected to benefit from equol. Tests to ascertain whether women are equol producers are not commercially available to the public or healthcare professionals.

A 2019 systematic review and meta-analysis found positive effects of equol supplementation over placebo for reducing VMS frequency in three of five trials.[139] Null findings in the remaining two trials were hypothesized to have been because of large differences in VMS at baseline in one trial and inclusion of only equol-producing women in the largest trial. A limitation in most studies (4 of the 6) was inclusion of fewer than 50 participants per group.

There is currently mixed evidence for soy foods, soy extracts, and the soy metabolite equol from widely diverse studies, with some significant limitations. (Level II; not recommended)

Pollen extract

A proprietary extract made from flower pollen has been available under the brand names Relizen, Serelys, Femal, and Femalen. One RCT (N = 53) found that women randomized to receive pollen extract showed significant reductions in VMS on the Menopause

Rating Scale (MRS; 65% VMS reduction with pollen extract vs 38% with placebo, $P < .006$) and daily diaries (27% greater reduction with treatment than placebo, $P < .026$) after 3 months of use.[140] A single-arm multicenter study (N = 104) found a significant decrease in menopause symptoms after 12 weeks' use of pollen extract.[141] An additional observational, single-arm study (N = 108) that included perimenopausal and menopausal women found reduction in hot flashes after 3 months' use of pollen extract.[142] However, based on expert opinion and limited scientific research for the management of VMS, pollen extract is not recommended. (Level III; not recommended)

Ammonium succinate

An ammonium succinate-based supplement (Amberen) was studied for the management of menopause symptoms in a manufacturer-sponsored clinical trial, with an initial study published in 2016,[143] and later a pooled analysis including this study and a second additional study was published in 2019.[144] The studies were identical multicenter, double-blind, 90-day RCTs including women aged 42 to 60 years with mild to moderate menopause symptoms (n = 227). Both studies showed improvement in menopause symptoms such as sleep, fatigue, loss of interest in sex, joint and muscle pain, VMS, and a decrease in anxiety compared with the placebo group. Women in the ammonium succinate-supplement group also showed an increase in serum estradiol levels and a decrease in leptin. The authors concluded that the pooled analysis of the two studies found that the ammonium succinate-based supplement improved menopause symptoms, including VMS, compared with placebo. Because of limited studies and the results being based on manufacturer-sponsored clinical trials, ammonium succinate is not recommended. (Level II; not recommended)

Lactobacillus acidophilus

Lactobacillus acidophilus YT1 was studied for managing menopause symptoms.[145] One 12-week, multicenter, double blind, RCT! (N = 67) involved women with menopause symptoms including VMS. After 12 weeks, total Kupperman Index (KI) scores decreased, and quality of life was improved (Menopause-Specific Quality of Life [MSQOL] questionnaire) in all four symptom domains (physical, psychological, vasomotor, and sexual). There were no reported changes in hormone levels or endometrial lining. Given that this data is limited to one small study, based on global menopause symptom ratings, and has not been replicated, it is not recommended at this time. (Level II; not recommended)

Rhubarb

Siberian rhubarb (*Rheum rhaponticum*) is used as a food and as a medicinal plant for constipation, diarrhea, and other gastrointestinal complaints. A single commercial preparation of rhubarb extract, which has been used in Germany for more than 20 years, was introduced in the United States (Estrovera). The product contains a proprietary extract called *rhaponticin* or extract ERr 731 and contains estrogenic properties but is not estrogen. One study randomized 109 symptomatic perimenopausal women to ERr 731 (n = 54) or placebo (n = 55) daily for 12 weeks.[146] Only 7 of 55 women randomized to placebo completed the trial (12.7% retention rate), and 39 of 54 women randomized to active treatment completed the trial. The researchers reported that at 12 weeks, the MRS total score and each symptom within the scale (including VMS) significantly improved in the active-treatment group versus placebo. Human safety data were drawn from a group of 23 women followed for 48 weeks, 20 of whom completed a 96-week observation period. Few AEs were reported.[147] Another open-label, single-arm study in Indian perimenopausal women over 12 weeks reported improved menopause symptoms.[148] Given the extremely low retention rate in clinical trials and the open-label study design in one study, the conclusions are limited. (Level II; not recommended)

Dietary supplements without demonstrated evidence of benefit

Black cohosh

Black cohosh, scientific name *Actaea racemosa L.* (previously *Cimicifugae racemosae*), is the most purchased botanical for menopause symptoms. The active ingredients in black cohosh extract are unknown, and its mechanism of action is unclear. At one time it was thought to be estrogenic, with in vitro and in vivo assays indicating estrogen-like activity.[149] Other studies indicate activity similar to selective estrogen-receptor modulators[150] or modulation of serotonergic pathways, as well as antioxidant and anti-inflammatory effects.

Reports of possible hepatotoxicity started to appear after 2000. After examining all reported cases, the US Pharmacopeial Convention Dietary Supplements-Botanicals Expert Committee found 30 reports possibly related to black cohosh. The committee issued a directive that black cohosh products carry a warning statement: "Discontinue use and consult a healthcare practitioner if you have a liver disorder or develop symptoms of liver trouble, such as abdominal pain, dark urine, or jaundice."[151]

A 2012 *Cochrane* review[152] analyzed 16 RCTs of 2,027 perimenopausal or postmenopausal women treated with black cohosh using a median daily dose of 40 mg for a mean duration of 23 weeks. There was no significant difference between black cohosh and placebo in the frequency of VMS. Data on safety were inconclusive. Other literature compared black cohosh to HT in a randomized trial of three groups: group A, 1 mg estradiol plus cyclic 4 mg medroxyprogesterone acetate; group B, 1 mg estradiol daily plus cyclic 100 mg micronized progesterone; and group C, 100 mg *Cimicifuga foetida* extract daily.[153] The study was limited by sample size because only 81 women (84%) completed the study, and although the KI scores were reduced in each group, there were no significant differences between groups. Despite this, the authors concluded that C foetida extract could alleviate VMS after 12 weeks. Another large systematic review (35 studies and one meta-analysis) noted that the effects of C foetida was possibly dose-dependent as well as augmented when combined with other products such as St. John's wort.[154] At this time, there is insufficient evidence to support the use of black cohosh for VMS. (Level I; not recommended)

Other supplements

Wild yam. *Dioscorea barbasco, D mexicana,* and *D villosa* are the varieties of wild yam most commonly used. *D villosa,* also known as Mexican yam or wild yam root, contains diosgenin, a steroid precursor used in the manufacture of synthetic steroids. Diosgenin is converted in vitro to progesterone, but there is no biochemical pathway for this conversion in vivo. Evidence for *Dioscorea* for VMS is limited. One clinical trial employing a yam cream to treat VMS reported no significant benefit.[155] Tested yam creams often do not contain any yam extract, and many have been adulterated with undisclosed steroids, including estrogens, progesterone, and medroxyprogesterone acetate. Because of the potential harm that may result from adulterants and lack of efficacy data, yam creams are not recommended for VMS. (Level II; not recommended)

Dong quai, also known as *Angelica sinensis*, dang gui, and tang kuei, is the root of the *Angelica polymorpha* Maxim var *sinensis* (Oliv). Researchers enrolled 71 women in an RCT of 4.5 g dong quai per day or placebo.[156] After 24 weeks, there were no differences in VMS frequency; KI scores; levels of FSH, LH, or estradiol; vaginal maturation index; or endometrial thickness. Dong quai does not appear to alleviate VMS, and there are a number of safety concerns, including possible photosensitization, anticoagulation, and carcinogenicity. (Level II; not recommended)

Evening primrose, *Oenothera biennis* L, is a flowering plant rich in linolenic acid and γ-linolenic acid. There is a single trial of evening primrose oil for menopause symptoms in which 56 women were randomized to evening primrose oil 500 mg per day or placebo for 6 months.[157] Evening primrose oil did not show benefit over placebo, with VMS declining by 1.0 per day with evening primrose oil and by 2.6 per day with placebo. (Level II; not recommended)

Maca (*Lepidium Meyennii* Walp, *Lepidium peruvianum* Chacon), a traditional foodstuff from South America, contains a weak phytosterol (β-sitosterol) also found in several other botanicals such as saw palmetto. Both methanolic and aqueous extracts of maca exhibit estrogenic activity in vitro, but studies have found no in vivo estrogenic effects. In a systematic review, four studies showed improvements in Greene Climacteric Scale or KI scores. However, because of quality, design, sample sizes, or limited reporting of study data,[158] existing evidence is not strong enough to support the use of maca for VMS. (Level II; not recommended)

Ginseng. There are two distinct true ginsengs in common use; *Panax ginseng* and *Panax quinquefolius,* as well as a third substance, Siberian ginseng (*Acanthopanax senticosus* or *Eleutherococcus senticosus*), a member of a closely related family of plants (Araliacea). In a study of a specific proprietary product, G115 (Ginsana in the United States), 384 postmenopausal women were randomized to G115 or placebo.[159] After 16 weeks, women taking G115 did not show greater VMS reductions than with placebo. Similarly, researchers found no significant effect of Korean red ginseng on VMS frequency versus placebo.[160] A second study similarly found that ginseng failed to affect VMS when measured by the KI and the MRS.[161] Thus, ginseng does not appear to be beneficial for VMS. (Level I; not recommended)

Labisia pumila/Eurycoma longifolia was studied in a double-blind, 24-week RCT of women aged 41 to 55 years (N = 119) experiencing menopause symptoms (MRS and MSQOL questionnaire used for assessment of symptoms).[162] At week 12, the group randomized to active treatment experienced improvement in symptoms (65%) compared with placebo (60%; $P < .01$). However, at weeks 12 to 24, significant improvement in the MRS and MSQOL questionnaire scores were noted in both treatment and placebo groups ($P < .001$). Overall, the authors concluded that there were no significant differences in menopause symptoms between treatment and placebo groups. (Level I; not recommended)

Chasteberry. Vitex species have estrogenic properties, and compounds such as apigenin and penduletin are their ER-β-selective compounds, whereas rotundifuran and agnuside activate ER-α-dependent responses.[163] Four double-blind RCTs have tested supplements containing varying amounts of Vitex agnus-castus (an amount equivalent to 1,000 mg dried vitex fruit,[164,165] 50 mg of vitex fruit extract,[166] or 125 mg vitex fruit[167]) in combination with various other supplements[165-167] or combined with *Nigella satvia* and citalopram 20 mg per day.[164] All trials included perimenopausal or postmenopausal women with VMS and included methods to assess compliance. The largest and most rigorous trial (n = 100) compared a mixed supplement to placebo and found no group differences in daily diary VMS frequency or questionnaire VMS intensity after 16 weeks of treatment.[165] The remaining three smaller (<50 women/group) trials used less rigorous questionnaire-only measures of VMS (rather than diaries) and found significant reductions in VMS frequency, bother, or intensity ratings after 8 to 12 weeks of treatment.[164,166,167] Few AEs were reported in any of the trials. Because of differences in the compounds that were tested, it is not possible to conclude that Vitex alone improves VMS. (Level II; not recommended)

Milk thistle is a member of the Asteracease family, a therapeutic herb used for fever and kidney and spleen disease. One previous study evaluated its effect in polyherbal formulations that included black cohosh, dong quai, and other herbs. It has been evaluated in a small RCT of 40 women receiving *Silybum marianum* extract and 40 women receiving placebo over a 12-week period and reported improvement in hot flashes and night sweats severity over placebo.[168] Because of the limitations of one study, there is not enough evidence to make a recommendation. (Level II; not recommended)

Omega-3 fatty acid supplements contain polyunsaturated fatty acids, including eicosapentaenoic acid, docosahexaenoic acid, and α-linolenic acid. Phospholipids, a major component of neuronal cells, contain a high prevalence of fatty acids. Two trials have evaluated omega-3s for VMS: In an 8-week trial of 91 women randomized to placebo or omega-3 supplement (total daily dose, 1,100 mg eicosapentaenoic acid plus 50 mg docosahexaenoic acid), VMS frequency and intensity were significantly improved with omega-3 compared with placebo.[169] In a 12-week trial, women were randomized in a 1:1 ratio to

omega-3s (n = 177) or placebo (n = 178) and simultaneously in a 3:3:4 ratio to yoga (n = 107), aerobic exercise (n = 106), or their usual physical activity (n = 142). There were no significant differences in VMS frequency or bother with omega-3s or placebo.[170] Therefore, there is mixed and inconclusive evidence for the use of omega-3s for the management of VMS. (Levels I-II; not recommended)

Vitamin E. Previous studies investigating the effects of vitamin E for VMS treatment included two crossover trials (N = 120; N = 50) that showed limited reduction in VMS frequency with vitamin E compared with placebo.[171,172] There is very little evidence for vitamin E having significant benefit in reducing VMS. A study from Iran with a total of 93 participants evaluated the use of curcumin alone and vitamin E alone in reducing VMS as well as other symptoms of menopause versus placebo (30 women/group).[173] There was some improvement seen at 4 weeks for curcumin and at 8 weeks for vitamin E compared with placebo. Results were significant at 4 weeks for curcumin and at 8 weeks for vitamin E, but sample sizes were small, limiting conclusions. Therefore, vitamin E is not recommended for the management of VMS. (Level I; not recommended)

Cannabinoids

The data evaluating the relationship between cannabinoids and menopause symptoms is very limited. This lack of evidence is particularly notable because more than one-quarter of women have used or are using marijuana to treat their menopause symptoms.[174] A systematic review found only three small studies that evaluated cannabis use and its associations with menopause symptoms, including VMS, insomnia, mood, and depression/anxiety.[175] Based on the lack of available evidence, cannabinoids cannot be recommended for the treatment of VMS. (Level II; not recommended)

Key points

- Given mixed evidence of benefit for VMS, soy foods, soy extracts, and the soy metabolite equol are not recommended.
- Given the lack of rigorous, evidence-based scientific research supporting the use of any over-the-counter supplements and herbal therapies for the management of VMS, these remedies are not recommended.
- Cannabinoids are not recommended for the treatment of VMS.

ACUPUNCTURE, OTHER TREATMENTS, AND TECHNOLOGIES

Acupuncture

Acupuncture is a component of the ancient practice of traditional Chinese medicine in which thin needles are inserted into the skin at key points in the body and activated through specific movements (manual acupuncture) or with electrical stimulation (electroacupuncture) to create an energy flow, or *Qi*, which is believed to improve overall health. Sham acupuncture is a placebo-equivalent treatment involving needles inserted at unrelated points or needles that do not pierce the skin.

Over the last decade, several systematic reviews and meta-analyses examined acupuncture versus no treatment or sham intervention for the treatment of VMS. In most systematic reviews,[176-178] as well as in RCTs,[179] acupuncture was deemed to alleviate some menopause-related symptoms (eg, mood, sleep, pain) as reflected in the reduction in menopause-related total scores (eg, KI, Greene Climacteric Scale) or the improvement in quality-of-life measurements (eg, MSQOL questionnaire); it had, however, little to no clinical benefit for the improvement of VMS compared with sham interventions, either for symptomatic midlife women or for survivors of breast cancer.

Consistent with this conclusion, a 2018 study (umbrella meta-analysis) that included three systematic reviews and four RCTs found modest benefits of acupuncture for the alleviation of menopause-related symptoms, quality of life, and VMS severity or frequency when treatments were compared with no treatment.[180] Results, however, were no longer clinically significant when acupuncture was compared with sham intervention.

There has been a considerable debate regarding the use of appropriate comparisons or control groups in acupuncture studies; some have argued, for example, that sham interventions may not be physiologically inert and therefore would not be the most appropriate comparison for studies or trials that aim to inform clinical practice. It is important to note that although most studies that compared traditional acupuncture with sham interventions found no significant difference in VMS frequency or severity, trials with electroacupuncture showed some benefits with this intervention and even stronger results for electroacupuncture when compared with manual acupuncture.[181]

In a 2021 model-based meta-analysis, Li and colleagues assessed 17 studies (1,123 participants), including manual acupuncture, electroacupuncture, and sham acupuncture.[178] The authors found that after 8 weeks of treatment, both electroacupuncture and a combination of both acupuncture modalities (traditional acupuncture and electroacupuncture) led to significant reduction of VMS per day compared with sham intervention. Moreover, the benefits of electroacupuncture for VMS were comparable to those reported in previous studies using nonhormone, pharmacologic treatments such as SSRIs, SNRIs, gabapentin, and escitalopram.

Existing evidence does not support the use of traditional acupuncture for the treatment of VMS, neither for midlife women nor for VMS in survivors of breast cancer. (Level I; not recommended). The use of electroacupuncture, although more promising, still warrants further investigation. (Level II; not recommended)

Stellate ganglion block

Stellate ganglion blockade is a widely used treatment for pain management, including for migraine and complex regional pain syndrome. The treatment is accomplished through the injection of an anesthetic agent at the lower cervical or upper thoracic region because the stellate ganglion is located bilaterally in the C6-T2 region of the anterior cervical spine. Adverse events, such as transient seizures or a bleeding complication, are extremely rare and minimized using imaging guidance during the procedure.[182]

Stellate ganglion blockade has emerged as a potential treatment option for VMS in both midlife women and those with breast cancer, although the exact mechanism of action of stellate ganglion blockade on VMS remains unclear.

One randomized, sham-controlled trial assessed active stellate ganglion blockade with bupivacaine versus a sham procedure (subcutaneous saline injection) for VMS in women with natural or surgical menopause (N = 40).[183] Over a 6-month follow-up, there was a reduction in subjectively reported VMS intensity and frequency (moderate to very severe) in the stellate ganglion blockade group compared with the sham-control group. Moreover, there was a reduction (21%, $P < .05$) of physiologic VMS measured with ambulatory skin conductance monitors from baseline to 3 months in the stellate ganglion blockade group, whereas the sham-control group showed no reduction. Four uncontrolled, open-label studies showed that stellate ganglion blockade reduced VMS, with effects ranging from a 45% to a 90% reduction 6 weeks to several months after blockade.[184-187]

In a study of patients with breast cancer (N = 40), stellate ganglion blockade (10 mL 0.5% bupivacaine injected bilaterally) was compared with paroxetine 7.5 mg per day over a 6-week period.[188] Both treatments had a positive effect on an index comprising both VMS frequency and severity, with no significant differences between treatments.

Overall, stellate ganglion blockade might help alleviate moderate to very severe VMS in select women. Results from ongoing larger RCTs are needed to provide more definitive evidence. Given that stellate ganglion blockade is a procedure that involves potential risks and AEs, its potential use for VMS should be carefully evaluated. (Levels II-III; recommended)

Calibration of neural oscillations

High-resolution, relational, resonance-based electroencephalic mirroring is a closed-loop acoustic stimulation neurotechnology based on the principle of allostasis. Essentially, scalp sensors and software algorithms translate specific brain frequencies into audible tones of varying pitch in real time, and these tones are immediately mirrored back via ear buds, allowing the brain to "listen to itself" in an acoustic mirror. High-resolution, relational, resonance-based electroencephalic mirroring has shown some preliminary benefits for the management of insomnia[189] and for military-related stress.[190]

In an uncontrolled study, 14 women showed a significant reduction in VMS frequency and severity after administration with high-resolution, relational, resonance-based electroencephalic mirroring aimed at autocalibration of neural oscillations.[191] Given the lack of controlled trials, high-resolution, relational, resonance-based electroencephalic mirroring is not recommended for treatment of VMS. (Level II; not recommended)

Chiropractic intervention

There have been no clinical trials of chiropractic interventions for VMS, and epidemiologic survey data show no association between use of such interventions and VMS.[192] Chiropractic interventions are not recommended for treatment of VMS. (Level II; not recommended)

Key points

- Existing evidence does not support the use of traditional acupuncture for the treatment of VMS; electroacupuncture requires more rigorous study before it can be recommended.
- Stellate ganglion blockade might alleviate moderate to very severe VMS in select women but is associated with potential risk.
- Calibration of neural oscillations and chiropractic interventions are not recommended for treatment of VMS.

RECOMMENDATIONS

Vasomotor symptoms are common in midlife women and remain undertreated. These symptoms can disrupt a women's overall quality of life and last a mean duration of 7 to 9 years, longer in some women. Hormone therapy remains the first-line recommended treatment to ameliorate VMS in healthy women at or around the time of menopause. However, it is important to recognize that not all women are candidates for HT because of contraindications or personal preference. This Position Statement supports the use of and recommends CBT, clinical hypnosis, SSRIs, SNRIs, gabapentin, fezolinetant (Level I); oxybutynin (Levels I-II); weight loss, stellate ganglion block (Levels II-III). There is negative or insufficient evidence for these, so they are not recommended: paced respiration (Level I); supplements/herbal remedies (Levels I-II); cooling techniques, avoiding triggers, exercise, yoga, MBI, relaxation, suvorexant, soy foods and soy extracts, soy metabolite equol, cannabinoids, acupuncture, calibration of neural oscillations (Level II), chiropractic interventions, clonidine; (Levels I-III); dietary modification and pregabalin (Level III). Clinicians should be knowledgeable of the nonhormone options supported by evidence that are available to offer to women (Table 2).

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TABLE 2. *Treatment recommendations for nonhormone therapies for vasomotor symptoms with levels of evidence*

Category	Treatment	Recommended	Not recommended
Lifestyle			
	Cooling techniques		Level II
	Avoiding triggers		Level II
	Exercise		Level II
	Yoga		Level II
	Dietary modifications		Level III
	Weight loss	Levels II-III	
Mind-body techniques			
	Cognitive-behavioral therapy	Level I	
	Mindfulness-based interventions		Level II
	Clinical hypnosis	Level I	
	Paced respiration		Level I
	Relaxation		Level II
Prescription therapies			
	SSRIs/SNRIs	Level I	
	Gabapentin	Level I	
	Pregabalin		Level III
	Clonidine		Levels I-III
	Oxybutynin	Levels I-II	
	Suvorexant		Level II
	Fezolinetant	Level I	
Dietary supplements			
	Soy foods and soy extracts		Level II
	Soy metabolites equol		Level II
	Supplements/Herbal remedies[a]		Levels I-III
	Cannabinoids		Level II
Acupuncture, other treatments, and technologies			
	Acupuncture		Level II
	Stellate ganglion block	Levels II-III	
	Calibration of neural oscillations		Level II
	Chiropractic intervention		Level II

Level I, good and consistent scientific evidence; Level II, limited or inconsistent scientific evidence; Level III, consensus and expert opinion.
SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.
[a]Pollen extract, ammonium succinate, *Lactobacillus acidophilus*, rhubarb, black cohosh, wild yam, dong quai, evening primrose oil, maca, ginseng, *labisia pumila/eurycoma longifolia*, chasteberry, milk thistle, omega-3 fatty acids, vitamin E.

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The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society has been designated a CME activity for all NAMS members. NAMS members should log in to the NAMS website, www.menopause.org, and then select Online CME in the Member Center. CME credit will be available from June 1, 2023, to June 1, 2024.

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NAMS Position Statement

The 2022 hormone therapy position statement of The North American Menopause Society

Abstract

"The 2022 Hormone Therapy Position Statement of The North American Menopause Society" (NAMS) updates "The 2017 Hormone Therapy Position Statement of The North American Menopause Society" and identifies future research needs. An Advisory Panel of clinicians and researchers expert in the field of women's health and menopause was recruited by NAMS to review the 2017 Position Statement, evaluate new literature, assess the evidence, and reach consensus on recommendations, using the level of evidence to identify the strength of recommendations and the quality of the evidence. The Advisory Panel's recommendations were reviewed and approved by the NAMS Board of Trustees.

Hormone therapy remains the most effective treatment for vasomotor symptoms (VMS) and the genitourinary syndrome of menopause and has been shown to prevent bone loss and fracture. The risks of hormone therapy differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used. Treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation of the benefits and risks of continuing therapy.

For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefit-risk ratio is favorable for treatment of bothersome VMS and prevention of bone loss. For women who initiate hormone therapy more than 10 years from menopause onset or who are aged older than 60 years, the benefit-risk ratio appears less favorable because of the greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia. Longer durations of therapy should be for documented indications such as persistent VMS, with shared decision-making and periodic reevaluation. For bothersome genitourinary syndrome of menopause symptoms not relieved with over-the-counter therapies in women without indications for use of systemic hormone therapy, low-dose vaginal estrogen therapy or other therapies (eg, vaginal dehydroepiandrosterone or oral ospemifene) are recommended.

Key Words: Breast cancer – Cardiovascular disease – Cognition – Genitourinary syndrome of menopause – Hormone therapy – Menopause – Vasomotor symptoms.

This Position Statement uses gender-specific language as reflected in the referenced publications. However, The North American Menopause Society recognizes that some persons experiencing menopause may identify differently than with the gender and pronouns used in the statement.

This NAMS Position Statement has been endorsed by the American Association of Clinical Endocrinologists; the American Association of Nurse Practitioners; the American Medical Women's Association; the American Society for Reproductive Medicine; the Asociacion Argentina para el Estudio del Climacterio; the Asociacion Mexicana para el Estudio del Climaterio; the Australasian Menopause Society; the Canadian Menopause Society; the Chilean Climacteric Society; the Chinese Menopause Society; the Colombian Association of Menopause; the Czech Menopause and Andropause Society; the Dutch Menopause Society; the European Menopause and Andropause Society; the German Menopause Society; HealthyWomen; the Indian Menopause Society; the International Osteoporosis Foundation; the International Society for the Study of Women's Sexual Health; the Japan Society of Menopause and Women's Health; the Korean Society of Menopause; the Mexican College of Specialists in Gynecology and Obstetrics; the National Association of Nurse

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This position statement was developed by The North American Menopause Society (NAMS) 2022 Hormone Therapy Position Statement Advisory Panel consisting of representatives of the NAMS Board of Trustees and other experts in women's health: Stephanie S. Faubion, MD, MBA, FACP, NCMP, *Lead*; Carolyn J. Crandall, MD, MS, MACP, NCMP, FASBMR; Lori Davis, DNP, FNP-C, NCMP; Samar R. El Khoudary, PhD, MPH, FAHA; Howard N. Hodis, MD; Roger A. Lobo, MD; Pauline M. Maki, PhD; JoAnn E. Manson, MD, DrPH, MACP, NCMP; JoAnn V. Pinkerton, MD, FACOG, NCMP; Nanette F. Santoro, MD; Jan L. Shifren, MD, NCMP; Chrisandra L. Shufelt, MD, MS, FACP, NCMP; Rebecca C. Thurston, PhD, FABMR, FAPS; Wendy Wolfman, MD, FRCSC, FACOG. The NAMS Board of Trustees conducted an independent review and revision and approved the position statement.
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Practitioners in Women's Health; the Philippine Society of Climacteric Medicine; the Society of Obstetricians and Gynaecologists of Canada; the Spanish Menopause Society; the Taiwanese Menopause Society; and the Thai Menopause Society.

METHODS

An Advisory Panel of clinicians and research experts in the field of women's health and menopause were enlisted to review "The 2017 Hormone Therapy Position Statement of The North American Menopause Society," evaluate the literature published subsequently, and conduct an evidence-based analysis, with the goal of reaching consensus recommendations.

NAMS acknowledges that no single trial's findings can be extrapolated to all women. The Women's Health Initiative (WHI) is the largest, randomized, controlled trial (RCT) of hormone therapy in women aged 50 to 79 years, and its findings were therefore given prominent consideration. However, it is important to note that the WHI employed just one route of administration (oral), one formulation of estrogen (conjugated equine estrogens [CEE] 0.625 mg), and only one progestogen (medroxyprogesterone acetate [MPA] 2.5 mg), with limited enrollment of women with bothersome vasomotor symptoms (VMS; hot flashes, night sweats) who were aged younger than 60 years or who were fewer than 10 years from menopause onset—the group of women for whom hormone therapy is currently primarily indicated. In addition, the WHI trials did not include women with early or premature menopause. In achieving consensus, the panel took into consideration the level of evidence (RCTs>longitudinal studies>cross-sectional studies), sample sizes, risk of bias, data from meta-analyses and systematic reviews, and expert opinion from guidelines from other major medical societies, when appropriate.

"The 2022 Hormone Therapy Position Statement of The North American Menopause Society" was written after this extensive review of the pertinent literature and includes key points identified during the review process. The resulting manuscript was submitted to and reviewed and approved by the NAMS Board of Trustees.

When recommendations are provided, they are graded according to these categories:

- Level I: Based on good and consistent scientific evidence.
- Level II: Based on limited or inconsistent scientific evidence.
- Level III: Based primarily on consensus and expert opinion.

EXPLAINING HORMONE THERAPY RISK

Healthcare professionals caring for menopausal women should understand the basic concepts of relative risk and absolute risk to communicate the potential benefits and risks of hormone therapy and other therapies. Relative risk (risk ratio) is the ratio of event rates in two groups, whereas absolute risk (risk difference) is the absolute difference in the event rates between two groups.[1] Absolute risks are more useful to convey risks and benefits in the clinical setting.

Findings on hormone therapy from RCTs are generally considered to provide stronger evidence, and those from observational studies should be interpreted with greater caution, given the potential for confounding. Very small effect sizes may have more limited clinical or public health importance, especially if outcomes are rare (Table 1).[2]

Key points

- Findings from RCTs of hormone therapy can be interpreted with greater confidence than observational studies. (Level I)
- Smaller effect sizes may be less clinically relevant, particularly for rare outcomes. (Level I)

FORMULATION, DOSING, ROUTES OF ADMINISTRATION, AND SAFETY

Formulation

Estrogens

Available estrogen preparations include CEE, synthetic conjugated estrogens (CE), micronized 17β-estradiol, and ethinyl estradiol. Conjugated equine estrogens, used in the WHI trials, contain a mixture of CE purified from the urine of pregnant mares, including estrone sulfate. In postmenopausal women, estrone sulfate is a naturally occurring estrogen that serves as a precursor and intermediate for the formation of estrone (a weak estrogen) and estradiol (a more potent estrogen and the predominant estrogen in premenopausal and perimenopausal women). Synthetic CE is a blend of synthetic estrogen substances including estrone sulfate, equilin sulfate, and estradiol sulfate. Prescription formulations of micronized 17β-estradiol are identical to the structure of estradiol that is produced by the ovaries. Estradiol is reversibly converted to estrone. Ethinyl estradiol is a synthetic estrogen primarily used in combination with a progestin in hormone contraceptives.

Progestogens administered with estrogen

Progestogens (general category that includes synthetic progestins and progesterone) commonly coadministered with estrogen in women with a uterus include MPA, norethindrone acetate (NETA), and micronized progesterone (MP). Medroxyprogesterone acetate, levonorgestrel, and NETA are synthetic progestins, whereas MP is structurally identical to the progesterone produced by the corpus luteum.

Progestogen indication: need for endometrial protection

Chronic unopposed endometrial exposure to estrogen increases the risk for endometrial hyperplasia or cancer.[3,4] The menopause-related indication for progestogen use is to prevent endometrial overgrowth and the increased risk of endometrial cancer during estrogen therapy (ET) use. Women with an intact uterus using systemic ET should receive adequate progestogen, unless they are taking CEE combined with bazedoxifene (BZA).[5-7]

TABLE 1. *Frequency of adverse drug reactions*

Very common	≥1/10
Common (frequent)	≥1/100 and < 1/10
Uncommon (infrequent)	≥1/1,000 and < 1/100
Rare	≥1/10,000 and < 1/1,000 (≤10/10,000/y)
Very rare	<1/10,000

Council for International Organizations of Medical Sciences (CIOMS).[2]

Progestogen dose *and* duration of use are important to ensuring endometrial protection. When adequate progestogen is combined with systemic estrogen, the risk of endometrial neoplasia is not higher than in untreated women. In the WHI, use of continuous oral CEE plus MPA daily was associated with a risk of endometrial cancer similar to placebo (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.48-1.36),[8] with significant reduction of risk after a median 13 years' cumulative follow-up (HR, 0.67; 95% CI, 0.49-0.91).[9] A systematic review suggested an increased risk of endometrial hyperplasia with MP containing estrogen plus progestogen therapy (EPT).[4] A meta-analysis suggested increased risk of endometrial cancer (relative risk [RR], 1.2) with noncontinuous combined EPT (type of progestogen not specified) but not with continuous EPT.[10] Oral MP should be adequately dosed for prevention of endometrial hyperplasia (eg, 200 mg/d for 12-14 d/mo).[11,12] Off-label use of a levonorgestrel-containing intrauterine device to prevent endometrial hyperplasia may avoid adverse systemic effects of progestogens and can protect against unwanted pregnancy in women initiating hormone therapy for symptom management before their final menstrual period. There are limited clinical trial data to support this use.[13] In women using EPT, unscheduled bleeding occurring more than 6 months after initiation should be investigated.

Tissue-selective estrogen complex

Bazedoxifene, a selective estrogen-receptor modulator (SERM; estrogen agonist or antagonist), has been combined with CEE to form a tissue-selective estrogen complex (TSEC). Studies of up to 2 years in duration suggest that the combination of BZA plus CEE provides endometrial protection without the need for a progestogen.[7,14-16] In women using BZA plus CEE, unscheduled bleeding occurring more than 6 months after initiation should be investigated.

Dosing

Estrogen therapy

The therapeutic goal should be to use the most appropriate, often lowest, effective dose of systemic ET consistent with treatment goals. The appropriate dose of progestogen is added to provide endometrial protection if a woman has a uterus, unless CEE is combined with BZA.

Progestogen therapy

Progestogen dosing-regimen options that provide for endometrial safety are dependent on the potency of the progestogen and vary with the estrogen dose. Different types and doses of progestogens, routes of administration, and types of regimen (sequential or continuous-combined) may have different associations with health outcomes, and patient preference can and should be considered because many women will opt for regimens that avoid periodic menstrual bleeding.[17]

Routes of administration

For treating VMS, systemic estrogens can be prescribed as oral drugs; transdermal patches, sprays, and gels; or as vaginal rings. Meta-analysis of estrogen preparations found no evidence of a significant difference between transdermal EPT and oral EPT for alleviating VMS.[18] Transdermal estradiol and oral CEE are similarly effective in alleviating VMS[19]; however, clinical trials directly comparing risk of myocardial infarction (MI), stroke, breast cancer, and venous thromboembolism (VTE) associated with various estrogen routes and doses are lacking. Progestogens are available as oral drugs or combination patches with estrogen.

Nonoral routes of administration (eg, transdermal, vaginal) may offer potential advantages because nonoral routes bypass the first-pass hepatic effect; however, it is unknown whether nonoral routes of ET or EPT are associated with lower risk (vs oral routes) of VTE, breast cancer, and cardiovascular (CV) events because clinical trials have not been designed to examine those outcomes.

Safety

During the active treatment phase of the WHI, a higher incidence of breast cancer (risk is considered rare; Table 1) was seen in women assigned to CEE plus MPA compared with placebo but a reduced incidence in women assigned to CEE alone compared with placebo.[20] After a median of 20 years' follow-up (including intervention and postintervention follow-up), the lower incidence of breast cancer in women assigned to CEE alone versus placebo and the higher incidence of breast cancer in women assigned to CEE plus MPA persisted.[21] In contrast to findings of the WHI, observational data have shown that breast cancer risk was increased in women using either systemic ET or EPT and was duration-dependent.[22]

Meta-analysis of studies in which most participants (70%) were aged older than 60 years and had some degree of comorbidity shows that EPT is associated with small increases in the risk of a coronary event (after 1 y), VTE (after 1 y), stroke (after 3 y), breast cancer (after 5 y), and gallbladder disease (after 5 y); ET (included oral, transdermal, subcutaneous, and intranasal preparations without disaggregation of data by route of administration) increases the risk of VTE (after 1-2 y), stroke (after 7 y), and gallbladder disease (after 7 y). One trial examined outcomes in women aged 50 to 59 years who were relatively healthy and found that the only significantly increased risk was of VTE in women on EPT.[23] Although comparative RCT data are lacking, there may be less VTE risk associated with lower doses of oral ET than with higher doses.[24,25] Observational studies have not demonstrated an increased risk of VTE with transdermal ET, and limited observational data suggest less risk with transdermal versus oral ET, but comparative RCT data again are lacking.[26-28] The choice of progestogen may also affect risk for VTE, with MP potentially being less thrombogenic than other progestins.[26,28]

The WHI provided information on the rare risks of CEE combined with MPA. It is unknown whether oral MP-containing EPT similarly increases the risk of breast cancer, stroke, gallbladder disease, MI, or VTE because clinical trials have not yet been designed to examine these outcomes. Clinical trials are needed to establish the effect of different types of progestogens and different estrogen doses and administration routes on VTE risk.[29] Overall, ET and EPT are each associated with rare increased risk of gallbladder disease, stroke, VTE, and urinary incontinence; EPT also is associated with increased risk of breast cancer.[22,30] Studies

were not designed to determine whether the combination of BZA plus CEE further increases the risk of VTE beyond the increased risk conferred by CEE alone.

In women in the WHI aged 50 to 59 years, CEE plus MPA (average, 5.6 y of use) or CEE alone (average, 7.2 y of use in women with previous hysterectomy) did not increase cancer mortality or CV mortality after a median of 18 years' follow-up compared with placebo. In women aged 50 to 59 years at randomization, all-cause mortality was significantly reduced in the pooled trials versus placebo (HR, 0.69; 95% CI, 0.51-0.94). With age groups combined, breast cancer mortality was reduced in women using CEE alone (HR 0.55; 95% CI, 0.33-0.92), and Alzheimer disease or dementia mortality was reduced in women using CEE alone (HR, 0.74; 95% CI, 0.59-0.94) and in the pooled trials (HR, 0.85; 95% CI, 0.74-0.98) after a median of 18 years' follow-up.[31] After a median of 20 years' follow-up (including intervention and postintervention follow-up), the lower breast cancer mortality in women assigned to CEE alone versus placebo persisted, whereas breast cancer mortality was not significantly different in women assigned to CEE plus MPA versus placebo.[21]

Contraindications for oral and transdermal hormone therapy include unexplained vaginal bleeding; liver disease; prior estrogen-sensitive cancer (including breast cancer); prior coronary heart disease (CHD), stroke, MI, or VTE; or personal history or inherited high risk of thromboembolic disease.

Potential risks of hormone therapy for women aged younger than 60 years include the rare risk of breast cancer with EPT; endometrial hyperplasia and endometrial cancer with inadequately opposed estrogen; VTE; and gallbladder disease (Figure 1).[9]

More common adverse events (AEs) include nausea, bloating, weight gain, fluid retention, mood swings (progestogen related), breakthrough bleeding, headaches, and breast tenderness.

Key points

- The appropriate, often lowest, effective dose of systemic ET consistent with treatment goals that provides benefits and minimizes risks for the individual woman should be the therapeutic goal. (Level III)
- The various formulations, doses, and routes of prescription hormone therapy preparations have comparable high efficacy for relieving VMS. (Level I)
- Formulation, dose, and route of administration for hormone therapy should be determined individually and reassessed periodically. (Level III)
- Different hormone therapy doses, formulations, and routes of administration may have different effects on target organs, potentially allowing options to minimize risk. (Level II)
- The appropriate formulation, dose, and route of administration of progestogen is needed to counter the proliferative effects of systemic estrogen on the endometrium. (Level I)
- Overall, the increased absolute risks associated with EPT and ET are rare (<10/10,000/y) and include increased risk for VTE and gallbladder disease. In addition, EPT carries a rare increased risk for stroke and breast cancer, and if estrogen is inadequately opposed, an increased risk of endometrial hyperplasia and endometrial cancer. (Level I)
- The absolute risks are reduced for all-cause mortality, fracture, diabetes mellitus (EPT and ET), and breast cancer (ET) in women aged younger than 60 years (Figure 1).[9] (Level I)

FDA-APPROVED INDICATIONS

Vasomotor symptoms

Hormone therapy has been shown in double-blind RCTs to relieve VMS[32] and is FDA approved as first-line therapy for relief of moderate to severe VMS because of menopause.

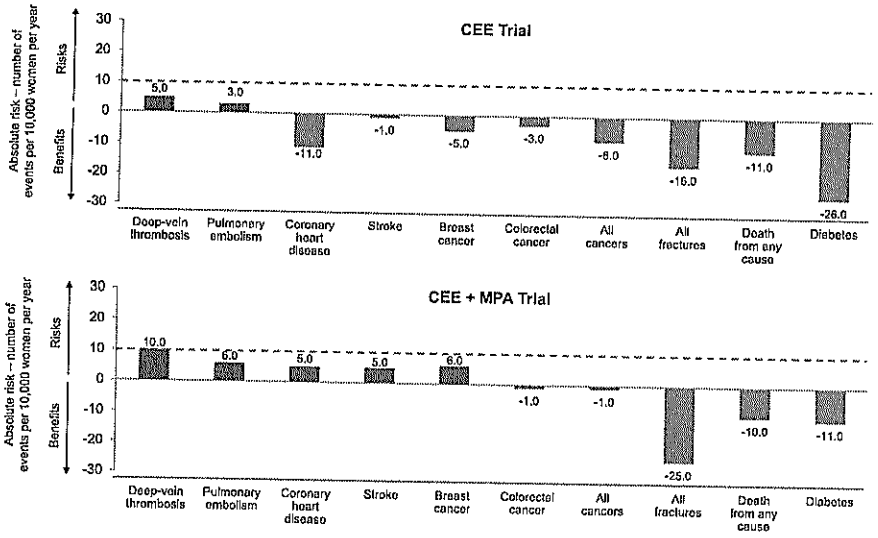

FIG. 1. Benefits and risks of the two hormone therapy formulations, conjugated equine estrogens (CEE) alone or in combination with medroxyprogesterone acetate (MPA), evaluated in the Women's Health Initiative for women aged 50 to 59 years. Risks and benefits are expressed as the difference in number of events (number in the hormone therapy group minus the number in the placebo group) per 10,000 women per year, with <10 per 10,000 per year representing a rare event (dashed red line). Adapted from Manson JE, et al.[9]

Prevention of bone loss

Hormone therapy has been shown in double-blind RCTs to prevent bone loss, and in the WHI, to reduce fractures in postmenopausal women without osteoporosis.[33,34] The FDA indication includes prevention, but not treatment, of postmenopausal osteoporosis. Nonestrogen medications are preferred for treatment of existing osteoporosis.

Premature hypoestrogenism

Hormone therapy is FDA approved for women with hypoestrogenism resulting from hypogonadism, bilateral oophorectomy (BO), or primary ovarian insufficiency (POI). Health benefits have been shown, with greater evidence for women with BO, for menopause symptoms and for prevention of bone loss and in observational studies, heart disease and cognitive decline or dementia.[35-44]

Genitourinary symptoms

Hormone therapy has been shown in RCTs to effectively treat symptoms of vulvovaginal atrophy (VVA).[45,46] Hormone therapy is FDA approved to treat moderate to severe symptoms of VVA and dyspareunia because of menopause but with the preference for low-dose vaginal therapy if solely prescribed for vulvar or vaginal symptoms.

Two vaginal therapies, vaginal ET and vaginal dehydroepiandrosterone (DHEA), have been FDA approved for treatment of moderate to severe dyspareunia, a symptom of VVA resulting from menopause. One oral therapy (a SERM) has FDA approval as well.

Key point

- Hormone therapy is FDA approved for four indications: moderate to severe VMS; prevention of osteoporosis in postmenopausal women; treatment of hypoestrogenism caused by hypogonadism, BO, or POI; and treatment of moderate to severe vulvovaginal symptoms. FDA guidance for treatment of genitourinary symptoms related to menopause in the absence of indications for systemic ET suggests the use of low-dose topical vaginal ET. (Level I)

COMPOUNDED BIOIDENTICAL HORMONES

The term *bioidentical hormone therapy* (similar to endogenous) can be misleading because there are both government-approved and compounded bioidentical hormone therapies. Government-approved (in the United States, FDA-approved) bioidentical hormones include estradiol, estrone, and MP, which are regulated and monitored for purity and efficacy. These are dispensed with package inserts containing extensive product information (based on RCTs) and may include black-box warnings for AEs. In contrast, compounded bioidentical hormone therapies are prepared by a compounding pharmacist using a provider's prescription. These therapies may combine multiple hormones (estradiol, estrone, estriol, DHEA, testosterone, progesterone) and use untested, unapproved combinations or formulations or are administered in nonstandard or untested routes such as subdermal implants, pellets, or troches.[47-50]

Compounded bioidentical hormone therapy has been prescribed or dosed on the basis of serum, salivary, or urine hormone testing; however, the use of such testing to guide hormone therapy dosing is considered unreliable because of differences in hormone pharmacokinetics and absorption, diurnal variation, and interindividual and intraindividual variability.[51-54]

There is a dearth of safety and efficacy data with little or no high-quality pharmacokinetic data to provide evidence of safety and efficacy of compounded bioidentical hormone therapy and insufficient evidence to support overall clinical use of compounded bioidentical hormone therapy for treatment of menopause symptoms. Compounded bioidentical hormone therapy presents safety concerns, such as minimal government regulation and monitoring, overdosing and underdosing, presence of impurities and lack of sterility, lack of scientific efficacy and safety data, and lack of a label outlining risks.[55]

Patient preference for compounded bioidentical hormone therapy should be discussed.[56] Prescribers should only consider compounded hormone therapy if women cannot tolerate a government-approved therapy for reasons such as allergies to ingredients in a government-approved hormone therapy formulation or for a dose or formulation not currently available in government-approved therapies. Patient preference alone should not be used to justify use of compounded bioidentical hormone therapy. Prescribers of compounded bioidentical hormone therapy should document the medical indication for a compounded bioidentical hormone over government-approved therapies.[55] In addition to including financial disclosures of prescribers, pharmacists, and pharmacies, compounding pharmacists should provide standardized content information, include warnings for potential AEs, note that the preparation is not government approved, and provide guidance on reporting AEs.

Key points

- Compounded bioidentical hormone therapy presents safety concerns, such as minimal government regulation and monitoring, overdosing and underdosing, presence of impurities and lack of sterility, lack of scientific efficacy and safety data, and lack of a label outlining risks. (Level I)
- Salivary and urine hormone testing to determine dosing are unreliable and not recommended. Serum hormone testing is rarely needed. (Level II/III)
- Shared decision-making is important, but patient preference alone should not be used to justify the use of compounded bioidentical hormone preparations, particularly when government-regulated bioidentical hormone preparations are available. (Level III)
- Situations in which compounded bioidentical hormones could be considered include allergies to ingredients in a government-approved formulation or dosages not available in government-approved products. (Level III)

MENOPAUSE SYMPTOMS

Vasomotor symptoms

Vasomotor symptoms are associated with diminished sleep quality, irritability, difficulty concentrating, reduced quality of

life,[57] and poorer health status.[58] Frequent VMS persisted on average 7.4 years in the Study of Women's Health Across the Nation[59] and appear to be linked to CV, bone, and cognitive risks.[60-65] Compared with placebo, ET alone or EPT was found to reduce weekly symptom frequency by 75% (95% CI, 64.3-82.3) and significantly reduce symptom severity (odds ratio [OR], 0.13; 95% CI, 0.07-0.23),[34] with no other pharmacologic or alternative therapy found to provide more relief. Considering the dose, there are no appreciable differences in the efficacy of oral versus nonoral formulations, but EPT appears slightly more effective than ET alone.

Lower doses of hormone therapy (oral CEE 0.3 mg; oral 17β-estradiol ≤0.5 mg; or estradiol patch 0.025 mg) may take 6 to 8 weeks to provide adequate symptom relief. Although the lowest dose-approved estradiol weekly patch (0.014 mg/d) appears effective in treating VMS,[66] it is FDA approved only for prevention of osteoporosis.

Progestogen-only formulations have been found to be effective in treating VMS,[67,68] including MPA 10 mg,[69] oral megestrol acetate 20 mg,[70] and MP 300 mg.[68] No long-term studies have addressed the safety of progestogen-only treatment of menopause symptoms.

Vasomotor symptoms return in approximately 50% of women when hormone therapy is discontinued.[71,72] There is no consensus about whether stopping abruptly or gradually tapering the dose is preferable.

Sleep disturbances

Sleep disturbances are common after menopause and begin in perimenopause. Sleep disruptions are strongly associated with VMS and a decreased quality of life. Poorer sleep quality has been associated with mood fluctuations, memory problems, metabolic syndrome, obesity, and other CV risk factors. Short (or very long) sleep duration, poor sleep quality, and insomnia have been associated with greater cardiovascular disease (CVD) risk.[73-76]

Hormone therapy in the form of low-dose estrogen or progestogen may improve chronic insomnia in menopausal women, with 14 of 23 studies reviewed showing positive results.[77] There is some evidence that transdermal ET may benefit sleep in perimenopausal women, independent of VMS.[78]

Oral MP has mildly sedating effects, reducing wakefulness without affecting daytime cognitive functions, possibly through a GABA-agonistic effect,[79] and should therefore be administered at night. A systematic review and meta-analysis concluded that MP improved sleep-onset latency but not sleep duration or sleep efficiency in RCTs in postmenopausal women.[80]

Genitourinary symptoms

The genitourinary syndrome of menopause (GSM) includes the signs and symptoms associated with menopause-related estrogen deficiency involving changes to the labia, vagina, urethra, and bladder and includes VVA.[81] Symptoms may include genital dryness, burning, and irritation; sexual symptoms of diminished lubrication and pain with sexual activity; and urinary symptoms of urgency, dysuria, and recurrent urinary tract infections (UTI). Estrogen therapy, specifically vaginal ET, is an effective treatment for GSM, with no evidence to suggest a difference in safety or efficacy between the various vaginal ET preparations.[45,82,83]

Low-dose vaginal ET preparations include creams, tablets, rings, and a softgel vaginal insert. The different preparations all contain estradiol, and one cream preparation contains CEE. One ring is available for long-term (3 mo) delivery of low-dose estradiol to the vagina, but another is aimed at providing systemic levels of estradiol. The low-dose vaginal estradiol products available result in minimal systemic absorption.[84-86] It is preferred to insert vaginal products (except for the vaginal ring) in the proximal, lower third of the vagina rather than in the upper third. This improves efficacy for genitourinary symptoms and attenuates estradiol absorption.[86]

Because of the potential risk of small increases in circulating estrogens,[87] the decision to use low-dose vaginal ET in women with breast cancer should be made in conjunction with their oncologists.[88,89] This is particularly important for women on aromatase inhibitors (AIs) with suppressed plasma levels of estradiol,[90] although no increased risk was seen in an observational trial of survivors of breast cancer on tamoxifen or aromatase therapy with low-dose vaginal ET during 3.5 years' mean follow-up.[91]

A progestogen is generally not indicated when ET is administered vaginally for GSM at the recommended low doses, although clinical trial data supporting endometrial safety beyond 1 year are lacking.[85] Vaginal bleeding in a postmenopausal woman requires thorough evaluation. Long-term follow up of women in the WHI observational study and in the Nurses' Health Study who used vaginal ET indicated no increased risk of adverse CV or cancer outcomes.[92,93]

Nonestrogen therapies that improve genitourinary symptoms and are approved for relief of dyspareunia in postmenopausal women include ospemifene[94] and intravaginal DHEA.[95]

Urinary tract symptoms (including pelvic floor disorders)

Vaginal ET increases the number of vessels around the periurethral and bladder neck region[96] and has been shown to reduce the frequency and amplitude of detrusor contractions to promote detrusor muscle relaxation.[97,98] Estrogen therapy, along with pelvic floor training, pessaries, or surgery, may improve synthesis of collagen and improve vaginal epithelium, but evidence for effectiveness for pelvic organ prolapse is lacking.[99]

Two large trials found that users of systemic hormone therapy (CEE 0.625 mg plus MPA 2.5 mg) had an increased incidence of stress incontinence.[100,101] Increased incontinence was found in women using oral ET alone (relative risk [RR], 1.32; 95% CI, 1.17-1.48) and in those using EPT (RR, 1.11; 95% CI, 1.04-1.18).[102] Vaginal estrogen use showed a decreased incidence of incontinence (RR, 0.74; 95% CI, 0.64-0.86) and overactive bladder, with one to two fewer voids in 24 hours and reduced frequency and urgency. A reduced risk of recurrent UTIs with vaginal but not oral estrogen has been shown in RCTs.[103,104]

Sexual function

Systemic hormone therapy and low-dose vaginal ET provide effective treatment of GSM, improving sexual problems by increasing lubrication, blood flow, and sensation in vaginal tissues.[105] Studies have not found a significant effect of ET on

sexual interest, arousal, and orgasmic response independent from its role in treating menopause symptoms.[106-108]

If systemic hormone therapy is indicated in women with low libido, transdermal ET formulations may be preferred to oral, given increased sex hormone-binding globulin and reduced bioavailability of testosterone with oral ET.[105,109,110]

Conjugated equine estrogens combined with BZA relieves dyspareunia and improves some aspects of sexual function in postmenopausal women.[111-114]

Key points

Vasomotor symptoms

- Vasomotor symptoms may begin during perimenopause, and frequent VMS may persist on average 7.4 years or longer. They affect quality of life and may be associated with CV, bone, and brain health. (Level I/II)
- Hormone therapy remains the gold standard for relief of VMS.
  - Estrogen-alone therapy can be used for symptomatic women without a uterus. (Level I)
  - For symptomatic women with a uterus, EPT or a TSEC protects against endometrial neoplasia. (Level I)
- Shared decision-making should be used when considering formulation, route of administration, and dose of hormone therapy for menopause symptom management, with adjustment tailored to symptom relief, AEs, and patient preferences. (Level III)
- Periodic assessment of the need for ongoing use of hormone therapy should be individualized on the basis of a woman's menopause symptoms, general health and underlying medical conditions, risks, treatment goals, and personal preferences. (Level III)
- Micronized progesterone 300 mg nightly significantly decreases VMS (hot flashes and night sweats) compared with placebo and improves sleep. Synthetic progestins have also shown benefit for VMS in some studies. No long-term study results are available, and use of progestogens without estrogen for either indication is off-label. (Level II)

Sleep disturbances

- During the menopause transition, women with VMS are more likely to report disrupted sleep. (Level I)
- Hormone therapy improves sleep in women with bothersome nighttime VMS by reducing nighttime awakenings. Estrogen may have some effect on sleep, independent of VMS. (Level II)

Genitourinary symptoms

- Low-dose vaginal ET preparations are effective and generally safe for the treatment of GSM, with minimal systemic absorption, and are preferred over systemic therapies when ET is used only for genitourinary symptoms. (Level I)
- For women with breast cancer, low-dose vaginal ET should be prescribed in consultation with their oncologists. (Level III)
- Progestogen therapy is not required with low-dose vaginal estrogen, but RCT data are lacking beyond 1 year. (Level II)
- Nonestrogen prescription FDA-approved therapies that improve VVA in postmenopausal women include ospemifene and intravaginal DHEA. (Level I)
- Vaginal bleeding in a postmenopausal woman requires thorough evaluation. (Level I)

Urinary tract symptoms (including pelvic floor disorders)

- Systemic hormone therapy does not improve urinary incontinence and may increase the incidence of stress urinary incontinence. (Level I)
- Low-dose vaginal ET may provide benefit for urinary symptoms, including prevention of recurrent UTIs, overactive bladder, and urge incontinence. (Level II)
- Hormone therapy does not have FDA approval for any urinary health indication. (Level I)

Sexual function

- Both systemic hormone therapy and low-dose vaginal ET increase lubrication, blood flow, and sensation of vaginal tissues. (Level I)
- Systemic hormone therapy generally does not improve sexual function, sexual interest, arousal, or orgasmic response independent of its effect on GSM. (Level I)
- If sexual function or libido are concerns in women with menopause symptoms, transdermal ET may be preferable over oral ET because of minimal effect on sex hormone-binding globulin and free testosterone levels. (Level II)
- Low-dose vaginal ET improves sexual function in postmenopausal women with GSM. (Level I)
- Nonestrogen alternatives FDA approved for dyspareunia include ospemifene and intravaginal DHEA. (Level I)

PRIMARY OVARIAN INSUFFICIENCY

Women with loss of ovarian function at a young age experience an extended period without ovarian hormones compared with women experiencing menopause at the typical age. Premature menopause is defined as menopause before age 40 years, and early menopause is defined as menopause that occurs between the ages of 40 and 45 years. Whereas menopause implies the permanent cessation of menses, POI describes the loss of ovarian function before age 40 years but with the potential for intermittent, transient return of hormone production and menstrual cycles. Women with early or premature loss of ovarian function at any age are at increased risk for AEs related to ovarian hormone deficiency. Causes of early or premature loss of ovarian function may be genetic, autoimmune, toxic, metabolic, and iatrogenic, including chemotherapy, radiation, and surgery.

Health risks of POI and premature menopause are well documented.[40,41] The strongest evidence from meta-analyses and systematic reviews links early loss of ovarian function to decreased quality of life and increased risk of fracture, CVD, heart failure, diabetes mellitus (DM), and overall mortality.[115-121] Other significant issues may include persistent VMS, loss of fertility, bone loss, genitourinary symptoms, sexual dysfunction, cognitive and mood changes, and increased risk of dementia, ophthalmic conditions, and depression.[40,41,122-124] Although these risks are generally because of estrogen deficiency, some of these risks may be reflective of premature aging, as evidenced in some studies by shortened telomere length.[125]

In addition to an increased risk of incident CVD, POI and premature menopause are associated with an increased risk of aortic stenosis, VTE, ischemic stroke, coronary artery disease, atrial fibrillation, and hypertension.[123,126] Early menopause is also associated with a decreased risk of breast cancer.[127]

The surgical removal of both ovaries leads to a much more abrupt loss of the ovarian steroids estrogen and progesterone than does natural menopause and includes a significant decrease in testosterone that does not occur with natural menopause.[128] Vasomotor symptoms as well as a variety of estrogen deficiency-related symptoms and diseases are more frequent and more severe after oophorectomy and can have a major effect on quality of life.[129,130] In meta-analyses, oophorectomy is associated with an increased risk of CVD,[131] cognitive dysfunction and dementia,[132] metabolic syndrome,[133] low bone mineral density (BMD),[134] and sleep disturbance,[135] with some evidence for elevated fracture risk.[136] Bilateral oophorectomy before age 40 is associated with elevated rates of incident CVD as well as mitral regurgitation, VTE, heart failure, coronary artery disease, and hypertension.[123] Other risks may include depression, anxiety, sexual dysfunction, bone loss, parkinsonism, DM, ophthalmologic conditions, and stroke, some of which have been shown in observational studies to be reduced by ET.[35]

Effective management of POI and premature or early menopause may include appropriate doses of hormone therapy, calcium with vitamin D, exercise, and screening to detect medical issues, as well as fertility counseling and mental health services.[40] Hormone therapy is recommended at least until the average age of menopause, approximately 52 years.[35,40,41] Oral contraceptives may be an alternative form of hormone therapy with contraceptive benefits, because spontaneous pregnancy may occur in about 5% of women with POI.[137] Higher doses of hormone therapy may provide better bone protection than oral contraceptives, but this is uncertain.[36,37,138]

Unless contraindications are present, ET is indicated for women who have had BO before the average age of menopause to treat VMS, improve BMD, and reduce the risk for osteoporosis.[139] Younger women may require higher doses to relieve symptoms and protect against bone loss.[41,140] Observational data reveal potential benefits of ET in reducing risk of cognitive impairment or dementia and CV mortality in women with early oophorectomy.[35,141] Estrogen therapy may improve aspects of sexual function and GSM, particularly in women with VMS who have had BO.[107] Vaginal estrogens are effective in treating symptoms of GSM.[45,46,142] Ovarian conservation is recommended, if possible, when hysterectomy for benign indications is performed in premenopausal women at average risk for ovarian cancer.[143]

Key points

- Women with POI and premature or early menopause may be at increased risk for fracture, CVD, heart failure, DM, overall mortality, persistent VMS, loss of fertility, bone loss, genitourinary symptoms, sexual dysfunction, cognitive and mood changes, increased risk of dementia, open-angle glaucoma, depression, and poor quality of life. (Level II)
- In the absence of contraindications, hormone therapy is recommended at least until the average age of menopause (approximately age 52 y), with an option for use of oral contraceptives in healthy younger women. (Level II)
- Results of the WHI trials in older women do not apply to women with POI or premature or early menopause. (Level II)
- In women with BO before the average age of menopause, early initiation of ET, with endometrial protection if the uterus is preserved, reduces VMS, genitourinary symptoms, risk for osteoporosis and related fractures, and likely CVD and overall mortality, with benefit seen in observational studies for CV mortality and cognitive impairment or dementia. (Level II)
- Fertility preservation and counseling should be explored for young women at risk for POI. (Level III)
- Ovarian conservation is recommended when hysterectomy is performed for benign indications in premenopausal women at average risk for ovarian cancer. (Level II)

SKIN, HAIR, AND SPECIAL SENSES

Estrogen therapy may benefit wound healing through modifying inflammation, stimulating granulation tissue formation, and accelerating re-epithelialization. Estrogen therapy increased epidermal and dermal thickness, increased collagen and elastin content, and improved skin moisture, with fewer wrinkles.[144] Although menopause is associated with a decrease in hair density and female pattern hair loss, research on the role of hormone therapy in mitigating these changes is lacking.[145]

In the WHI, ET reduced intraocular pressure in postmenopausal women and mitigated the risk for open-angle glaucoma in Black women.[146,147] Similar effects were not seen for EPT.[148] Further, hormone therapy decreased the risk of neovascular and soft drusen age-related macular degeneration but not early or late-stage macular degeneration.[149] Evidence on the effect of hormone therapy on cataract, dry eye disease, and optic nerve disorders is mixed, and good-quality RCTs are lacking.[150-152] Observational data linking hormone therapy to hearing loss is mixed.[153,154]

Little is known about olfactory changes and hormone therapy.[155] In small trials, hormone therapy appears to decrease dizziness or vertigo and improve postural balance.[156,157]

Key points

- Estrogen therapy appears to have beneficial effects on skin thickness and elasticity and collagen when given at menopause. (Level II)
- Changes in hair density and female pattern hair loss worsen after menopause, but research is lacking regarding a role for hormone therapy in mitigating these changes. (Level II)
- Hormone therapy appears to decrease the risk of neovascular and soft drusen age-related macular degeneration but not early or late-stage macular degeneration. (Level II)
- Estrogen therapy appears to reduce intraocular pressure and mitigate the risk for open-angle glaucoma in Black women. (Level II)
- Evidence of hormone therapy effects on cataracts, optic nerve disease, dry-eye disease, and hearing loss is mixed. (Level II)

- Little is known about hormone therapy effects on olfactory changes. (Level II)
- In small trials, hormone therapy appears to decrease dizziness or vertigo and improve postural balance. (Level II)

HORMONE THERAPY AND QUALITY OF LIFE

Quality of life is defined as an overall assessment of one's life in relation to one's goals and expectations. Quality of life can be applied to one's mental and physical health, which is termed health-related quality of life, or specifically to menopause, or menopause-specific quality of life, which emphasizes the bother and interference of menopause symptoms. Clinical trials indicate that in women with menopause symptoms, such as VMS, systemic hormone therapy (ET, EPT, TSECs) can improve menopause-specific quality of life.[158-160] These effects appear to be explained largely by the effect of hormone therapy on the frequency of these symptoms.

Key points

- Menopause symptoms are associated with poorer health-related and menopause-specific quality of life. (Level II)
- Systemic hormone therapy can improve menopause-specific quality of life in women experiencing menopause symptoms. (Level II)

OSTEOPOROSIS

Menopause is associated with increased bone resorption, and ET decreases bone resorption.[161] For osteoporosis treatment, hormone therapy has not been demonstrated in RCTs to reduce fractures in postmenopausal women with established osteoporosis; therefore, hormone therapy does not carry an FDA indication for treatment of osteoporosis.[162,163]

In women who have osteoporosis, hormone therapy has not been demonstrated in RCTs to decrease fracture risk. In the WHI, for women aged 50 to 79 years (N = 16,608), enrolled without regard to bone density or fracture risk, EPT (0.625 mg CEE plus 2.5 mg MPA) significantly increased lumbar spine and total hip BMD by 4.5% and 3.7%, respectively, relative to placebo and reduced fracture risk.[34] The BMD benefits of preventing bone loss persist as long as therapy is continued but abate rapidly when treatment is discontinued. Within a few months, markers of bone turnover returned to pretreatment values, whereas BMD fell to pretreatment levels within 1 to 2 years of stopping therapy.[164]

Women with POI experience long-term AEs on bone density, in addition to other health risks.[35,140] Higher-than-standard doses of hormone therapy may be needed to provide protection against bone-density loss in younger women, particularly those aged younger than 40 years and thus lower future osteoporotic fracture risk.[140,165]

In the setting of prevention, RCTs show that hormone therapy decreases fracture risk.[162,163] Various oral and transdermal estrogen preparations, alone or in combination with progestogens or BZA, have government approval for prevention of osteoporosis. A meta-analysis and a systematic review, based primarily on the WHI, demonstrated that 5 to 7 years of hormone therapy significantly reduced risk of spine, hip, and nonvertebral fractures.[166,167] During the WHI intervention phase in women of all ages, the CEE plus MPA group had six fewer hip fractures per 10,000 women and six fewer vertebral fractures per 10,000 women compared with the placebo group.[9] The CEE-alone group had six fewer hip fractures per 10,000 women and six fewer vertebral fractures per 10,000 women compared with the placebo group. However, in the subset of women aged 50 to 59 years at the time of treatment initiation, neither CEE plus MPA nor CEE alone was associated with decreased risk of hip fracture.

The reason that hormone therapy was not shown to reduce hip fracture in the subset of women aged 50 to 59 years in the WHI may be partly because of the lower baseline absolute risk of fracture in women aged between 50 and 59 years who did not have established osteoporosis.[9,168]

In the WHI hormone therapy trials, after hormone therapy discontinuation, there was a return of fracture risk to levels seen in women who had received placebo, with no excess fracture risk observed after discontinuation of hormone therapy.[169,170] There are no prospective fracture studies directly comparing the efficacy of hormone therapy in preventing fractures with other approved pharmacologic therapies.

Key points

- Hormone therapy prevents bone loss in healthy postmenopausal women, with dose-related effects on bone density. (Level I)
- Hormone therapy reduces fracture risk in healthy postmenopausal women. (Level I)
- Discontinuing hormone therapy results in rapid bone loss; however, no excess in fractures was seen in the WHI after discontinuation. (Level I)
- Hormone therapy is FDA approved for prevention of bone loss, but not for treatment of osteoporosis. (Level I)
- In the absence of contraindications, in women aged younger than 60 years or within 10 years of menopause onset, systemic hormone therapy is an appropriate therapy to protect against bone loss. (Level I)
- Unless contraindicated, women with premature menopause without prior fragility fracture or osteoporosis are best served with hormone therapy or oral contraceptives to prevent bone density loss and reduce fracture risk, rather than other bone-specific treatments, until the average age of menopause, when treatment may be reassessed. (Level II)
- Decisions regarding initiation and discontinuation of hormone therapy should be made primarily on the basis of extraskeletal benefits (ie, reduction of VMS) and risks. (Level III)

JOINT PAIN

Direct binding of estrogen to estrogen receptors acts on joint tissues, protecting their biomechanical structure and function and maintaining overall joint health, but the exact effect of estrogen on osteoarthritis remains controversial.[171-173] There is no clearly observed association between hormone therapy use and osteoarthritis.[171]

Meta-analyses of clinical trials of ET have reported inconsistent results. Thus, there is insufficient evidence to form strong conclusions regarding the effects of estrogen on osteoarthritis.[173]

In the WHI, women on CEE plus MPA had less joint pain or stiffness compared with those on placebo (47.1% vs 38.4%; OR, 1.43; 95% CI, 1.24-1.64) and more joint discomfort after stopping.[174] In the CEE-alone arm, women randomized to CEE had a statistically significant reduction in joint pain frequency after 1 year compared with the placebo group (76.3% vs 79.2%; $P = .001$).[175]

In the WHI, using arthroplasty as a clinical indicator of severely symptomatic osteoarthritis, the association of CEE alone with any arthroplasty was borderline significant (HR, 0.84; 95% CI, 0.70-1.00; $P = .05$), but CEE alone did not significantly reduce the risk of hip or knee arthroplasty. The EPT trial showed no relationship between hormone use and arthroplasty risk.[176]

Key points

- Women in the WHI and other studies have less joint pain or stiffness with hormone therapy compared with placebo. (Level I)
- There is a need for further understanding of estrogen's potential effect on joint health. (Level III)

SARCOPENIA

Frailty is associated with AEs such as falls, hospitalization, disability, and death.[177] Skeletal muscle has been shown to have estrogen receptors,[178] but there is a paucity of studies evaluating the interplay between estrogen and muscle. The regulation of energy intake and expenditure by estrogens in women has not been well studied, with limited basic and preclinical evidence supporting the concept that the loss of estrogen with menopause or oophorectomy disrupts energy balance through decreases in resting energy expenditure and physical activity.[179]

Reviews of preclinical studies and limited clinical studies of hormone therapy in postmenopausal women suggest a benefit on maintaining or increasing muscle mass and related connective tissue and improving strength and posttraumatic or postatrophy muscle recovery when combined with exercise.[180-182]

In the WHI hormone therapy trials, women assigned to ET or EPT (vs placebo) had early preservation of lean body mass after 3 years, but hormone therapy did not ameliorate long-term loss in lean body mass associated with aging.[183] Similarly, low-dose oral estradiol 0.25 mg per day plus cyclical MP did not significantly change skeletal muscle mass or lean body mass.[184]

Systematic reviews find that hormone therapy had neither a beneficial nor harmful association with muscle mass[185,186]; therefore, it is likely that interventions other than hormone therapy will have to be developed to aid in the retention of muscle in aging women.

Key points

- Development of frailty with aging is a health risk. (Level I)
- Sarcopenia and osteoporosis are related to aging, estrogen depletion, and the menopause transition. (Level II)
- Intervention to improve bioenergetics and prevent loss of muscle mass, strength, and performance is needed. (Level III)
- Preclinical studies suggest a possible benefit of ET when combined with exercise to prevent the loss of muscle mass, strength, and performance, but this has not been shown in clinical trials. (Level II)

GALLBLADDER AND LIVER

Estrogens increase biliary cholesterol secretion and saturation, promote precipitation of cholesterol in the bile, and reduce gallbladder motility, with increased bile crystallization.[187,188] Postmenopause use of estrogen is associated with an increased risk of cholelithiasis, cholecystitis, and cholecystectomy.[23] However, no associated risk of biliary cancer has been demonstrated.[189] The transdermal route of administration, which bypasses first-pass metabolism of the liver, has been associated with less risk of gallbladder disease in observational studies.[190] The attributable risk for gallbladder disease as self-reported in the WHI was an additional 47 cases per 10,000 women per year for CEE plus MPA and 58 cases per 10,000 women per year for CEE, both statistically significant ($P < .001$).[9]

Nonalcoholic fatty liver disease is more common after the menopause transition when the prevalence surpasses men.[191] Older women also have higher rates of severe hepatic fibrosis and greater mortality compared with men. Animal models have demonstrated a causal relationship between the loss of estrogen and increase in fatty liver and steatohepatitis, whereas observational studies show dietary factors also may exacerbate liver disease. Preclinical and observational studies suggest possible benefits of hormone therapy on liver fibrosis and fatty liver,[192] but more research is needed before definitive recommendations can be made.

Key points

- Risk of gallstones, cholecystitis, and cholecystectomy is increased with ET and EPT. (Level I)
- Observational studies report lower risk of gallstones with transdermal hormone therapy than with oral, and with oral estradiol compared with CEE, but neither observation is confirmed in RCTs. (Level II)
- In women with hepatitis C and with fatty liver, a slower fibrosis progression has been observed with use of hormone therapy, but RCTs are needed to establish the potential benefits and risks with liver disease. (Level II)

DIABETES MELLITUS, METABOLIC SYNDROME, AND BODY COMPOSITION

Metabolic syndrome and diabetes

In the WHI, women receiving continuous-combined CEE plus MPA had a statistically significant 19% reduction (HR, 0.81; 95% CI, 0.70-0.94; $P = .005$) in the incidence of type 2 DM, translating to 16 fewer cases per 10,000 person-years of therapy.[9] In the CEE-alone cohort, there was a reduction of 14% in new diagnoses of type 2 DM (HR, 0.86; 95% CI, 0.76-0.98), translating to 21 fewer cases per 10,000 person-years. A meta-analysis of published studies found that EPT reduced multiple components of the metabolic syndrome; incidence of type 2 DM was decreased by 30%.[193] A second, smaller meta-analysis confirmed these findings and reported that women with type 2 DM using ET or EPT had better glycemic control.[194] The benefit reverses when hormone therapy is discontinued. For these reasons, hormone therapy can be considered for symptomatic menopausal women with type 2 DM.

Weight and body composition

The menopause transition is associated with an increase in body fat and a decrease in lean body mass, which results in an increase in the fat-to-lean ratio and decreased basal metabolic rate. After controlling for body size and ethnicity, the average weight gain during midlife and the menopause transition is 1.5 lb per year.[195,196] Central fat distribution (gynoid-to-android pattern) also occurs after menopause after adjustment for aging, total body fat, and physical activity level.[196] By about 2 years after the final menstrual period, weight changes flatten.[197] Women who used hormone therapy did not have observable differences in the trajectory of weight or body fat gain compared with those who did not take hormones, although numbers are relatively small.

Estrogen-progestogen therapy either has no effect on weight or is associated with less weight gain in women who are using it than in women who are not.[198-202] In the WHI, women randomized to hormone therapy with CEE with or without MPA had no statistically significant difference in slowing of weight gain and a lesser increase in waist circumference over the first 3 years of use compared with those randomized to placebo. Increasing physical activity was independently associated with less weight gain over time.[195]

Key points

- Hormone therapy significantly reduces the diagnosis of new-onset type 2 DM, but it is not government approved for this indication. (Level I)
- Hormone therapy is not contraindicated in otherwise healthy women with preexisting type 2 DM and may be beneficial in terms of glycemic control when used for menopause symptom management. (Level II)
- Although hormone therapy may help attenuate abdominal adipose accumulation and weight gain associated with the menopause transition, the effect is small. (Level II)

COGNITION

Small clinical trials support the use of ET for cognitive benefits when initiated immediately after hysterectomy with bilateral oophorectomy.[203,204] Three large RCTs demonstrated neutral effects of hormone therapy on cognitive function when used early in the postmenopause period.[205-207]

Two hypotheses—the *critical window* or *timing* hypothesis and the *healthy-cell bias* hypothesis—provide a framework for understanding the scientific literature on hormone therapy and cognition, but neither has been definitively supported in RCTs of postmenopausal women. The critical window or timing hypothesis[208,209] holds that estrogen can confer cognitive benefits if given early in the menopause transition but that later use is neutral or detrimental. The healthy-cell bias hypothesis[210] holds that estrogen confers cognitive benefits when the neural substrate is "healthy" but not diseased, for example in a woman with DM.

Later initiation of hormone therapy

Several large clinical trials indicate that hormone therapy does not improve memory or other cognitive abilities and that CEE plus MPA may be harmful for memory when initiated in women aged older than 65 years.[211-213]

Alzheimer disease

Four observational studies provide support for the opinion that the timing of hormone therapy initiation is a significant determinant of Alzheimer disease risk, with early initiation lowering risk and later initiation associated with increased risk.[214-217] However, long-term effects may differ from short-term effects. Eighteen-year follow-up data from the WHI showed a reduction in Alzheimer disease mortality in women randomized to hormone therapy; this effect was significant for CEE alone but not for CEE plus MPA and was driven by women aged in their 70s at the time of enrollment.[31] Two nested case-control studies investigated the risk of dementia associated with hormone therapy use and showed no increased risk overall but did suggest an increased risk of Alzheimer disease, specifically, with the use of EPT for more than 5 years.[218]

All-cause dementia

In the WHI Memory Study, CEE plus MPA doubled the risk of all-cause dementia (23 cases/10,000 women) when initiated in women aged older than 65 years,[213] whereas CEE alone did not significantly increase the risk of dementia.[219] The effect of hormone therapy may be modified by baseline cognitive function, with more favorable effects in women with normal cognitive function before hormone therapy initiation.[220,221]

Key points

- In the absence of more definitive findings, hormone therapy is not recommended at any age to prevent or treat a decline in cognitive function or dementia. (Level I)
- Initiating hormone therapy in women aged older than 65 years increased the risk for dementia, with an additional 23 cases per 10,000 person-years seen in women randomized to CEE plus MPA in the WHI Memory Study. (Level I)
- The effect of hormone therapy may be modified by baseline cognitive function, with more favorable effects in women with normal cognitive function before hormone therapy initiation. (Level II)
- Estrogen therapy may have cognitive benefits when initiated immediately after hysterectomy with bilateral oophorectomy, but hormone therapy in the early natural postmenopause period has neutral effects on cognitive function. (Level II)

DEPRESSION

Depressive symptoms worsen as women transition through menopause, although evidence is mixed as to whether depressive disorders are more common during the menopause transition relative to premenopause. Most women who present with depressive disorders during the menopause transition are women with a history of depression before the menopause transition, and women with a history of depression are at high risk for recurrence during the menopause transition.[222]

For that reason, clinical guidelines recommend that clinicians screen for depression in women with a history of depression and use antidepressants or proven psychotherapies (eg, cognitive-behavior therapy, interpersonal therapy, mindfulness-based cognitive therapy) as the primary treatment for recurrent major depressive episodes.[223] Use of hormone therapy to treat menopause symptoms such as

VMS in midlife women with depression should be considered. Vasomotor symptoms increase the risk for elevated depressive symptoms, in part because of nocturnal VMS and sleep interruption,[224] and on a day-to-day basis, VMS co-occur with negative mood and predict negative mood the next day.[225] Vasomotor symptoms appear to be more strongly associated with the onset of depressive symptoms than depressive disorders.[226]

Estrogen therapy shows some efficacy in the management of depression in midlife women, but its effect varies by menopause stage. For perimenopausal women with depression, there is evidence that ET improves depressive symptoms to a degree similar to antidepressant medications.[227] This antidepressant effect of ET applies to perimenopausal women with and without VMS. In women with major depression treated with ET, depressive symptoms improve in relation to improvements in sleep but not VMS.[228] Estrogen therapy does not appear to be effective in treating depressive disorders in postmenopausal women, suggesting a window of opportunity in the perimenopause.[229] Little is known about the effects of EPT in treating depressive disorders at any menopause stage.

There is some evidence that ET enhances mood and improves well-being in nondepressed postmenopausal women.[205] Initial evidence suggests that hormone therapy (specifically transdermal estradiol with intermittent MP) may prevent the onset of depressive symptoms in euthymic perimenopausal women.[230]

Estrogen therapy may augment clinical response to antidepressants in midlife and older women, preferably when also indicated for other concurrent menopause-related symptoms such as VMS.[231]

Key points

- There is some evidence that ET has antidepressant effects of similar magnitude to that observed with antidepressant agents when administered to depressed perimenopausal women with or without concomitant VMS. (Level II)
- Estrogen therapy is ineffective as a treatment for depressive disorders in postmenopausal women. Such evidence suggests a possible window of opportunity for the effective use of ET for the management of depressive disorders during the perimenopause. (Level II)
- There is some evidence that ET enhances mood and improves well-being in nondepressed perimenopausal women. (Level II)
- Transdermal estradiol with intermittent MP may prevent the onset of depressive symptoms in euthymic perimenopausal women, but the evidence is not sufficient to recommend estrogen-based therapies for preventing depression in asymptomatic perimenopausal or postmenopausal women, and the risks and benefits must be weighed. (Level II)
- Estrogen-based therapies may augment clinical response to antidepressants in midlife and older women, preferably when also indicated for other menopause symptoms such as VMS. (Level III)
- Most studies on hormone therapy for the treatment of depression examined the effects of unopposed estrogen. Data on EPT or for different progestogens are sparse and inconclusive. (Level II)
- Estrogen is not government approved to treat mood disturbance. (Level I)

CARDIOVASCULAR DISEASE AND ALL-CAUSE MORTALITY

Observational data and reanalysis of older studies by age or time since menopause, including the WHI, suggest that for healthy women who are within 10 years of the menopause transition and who have bothersome menopause symptoms, the benefits of hormone therapy (ET or EPT) outweigh its risks, with fewer CVD events in younger versus older women.[9,31,219,232-242]

Initiation of hormone therapy fewer than 10 years after menopause onset

Surrogate markers of coronary heart disease

Surrogate markers of CHD are intermediate measures that have been associated with the development of CVD and events such as coronary artery calcification (CAC) and subclinical atherosclerosis. Some studies have suggested that initiating hormone therapy in symptomatic women within 10 years of menopause may have benefit in reduction of atherosclerosis progression as measured by CAC,[243-245] whereas RCTs in younger, recently postmenopausal women have not.[246,247] In the Early Versus Late Intervention Trial With Estradiol, hormone therapy (oral 17β-estradiol 1 mg/d plus progesterone vaginal gel 45 mg administered sequentially for women with a uterus) reduced subclinical atherosclerosis progression measured by carotid artery intima-media thickness after a median of 5 years when initiated within 6 years (median, 3.5 y) of menopause onset but not when initiated 10 or more years (median, 14.3 y) afterward.[246] The Kronos Early Estrogen Prevention Study in healthy postmenopausal women aged 42 to 58 years who received hormone therapy (oral CEE 0.45 mg/d; transdermal estradiol patch 50 μg/wk; each with sequential oral MP 200 mg for 12 d/mo) showed no effect on subclinical atherosclerosis progression.[247]

Meta-analyses of clinical outcomes

A 2015 *Cochrane* review of RCT data found that hormone therapy initiated fewer than 10 years after menopause onset lowered CHD in postmenopausal women (RR, 0.52; 95% CI, 0.29-0.96).[236] It also found a reduction in all-cause mortality (RR, 0.70; 95%, 0.52-0.95) and no increased risk of stroke but an increased risk of VTE (RR, 1.74; 95% CI, 1.11-2.73).

A 2020 systematic review and meta-analysis of RCTs published from 2000 to 2019 showed null effects of hormone therapy initiated fewer than 10 years after menopause or at an age younger than 60 years on all-cause mortality, stroke, and VTE.[248]

A 2019 systematic review and meta-regression analysis of RCTs that examined the timing hypothesis of hormone therapy compared with controls or nonusers of hormone therapy found that younger hormone therapy initiation (participants aged <60 y) was associated with lower odds of CHD (OR, 0.61; 95% CI, 0.37-1.00), all-cause mortality (OR, 0.72; 95% CI, 0.57-0.91), and cardiac mortality (OR, 0.61; 95% CI, 0.37-1.00) but with higher odds of a composite measure of incidence stroke, transient ischemic attack, and systemic embolism (OR, 1.40; 95% CI, 1.10-1.78).[249] However, the results for CHD, cardiac mortality, and all-cause mortality were all attenuated after excluding open-label trials in which the knowledge of active treatment may affect treatment options and outcomes. Direct comparisons

across these meta-analyses may not be applicable, given differences in inclusion/exclusion criteria and analytical methods that were applied in each analysis.

Cardiovascular outcomes in the Women's Health Initiative

Intervention phase

For CEE alone, CHD, MI, and coronary artery bypass grafting or *percutaneous coronary intervention* showed a lowered HR in women aged younger than 60 years and fewer than 10 years since menopause onset, including in intention-to-treat analyses.[9] In the 50- to 59-year-old age group, the HR for CHD was elevated but not statistically significant at 1.34 (95% CI, 0.82-2.19) for CEE plus MPA. When data from the two WHI trials were combined and analyzed, a reduction in all-cause mortality was shown in younger but not in older women; HRs in women aged 50 to 59 years, 60 to 69 years, and 70 to 79 years were 0.69 (95% CI, 0.51-0.94), 1.04 (95% CI, 0.87-1.25), and 1.13 (95% CI, 0.94-1.36), respectively ($P_{\text{for trend}} = .01$).[31]

Cumulative follow-up

For CEE alone, in the 13-year cumulative intervention and postintervention follow-up, significant age-treatment interaction was shown for MI such that only in the 50- to 59-year-old age group a reduction in MI risk was significant (HR, 0.60; 95% CI, 0.39-0.91).[9] Although a similar interaction was not significant for CHD and all-cause mortality, there was a significant reduction in CHD risk (HR, 0.65; 95% CI, 0.44-0.96) in this age group. In the 18-year intervention and postintervention cumulative follow-up, the reduction in all-cause mortality was shown to be statistically significant for the 50- to 59-year-old age group (HR, 0.79; 95% CI, 0.64-0.96),[31] although interaction between age and treatment was not significant. Additional analysis focusing on oophorectomy status in the CEE-alone trial revealed a significant age-treatment interaction for all-cause mortality; younger women with BO assigned to CEE alone showed a significant reduction in all-cause mortality compared with placebo (HR, 0.68; 95% CI, 0.48-0.96).[242]

Initiation of hormone therapy more than 10 years from menopause onset or in women aged older than 60 years

For women who initiated hormone therapy more than 10 years from menopause onset or aged older than 60 years, a 2015 *Cochrane* meta-analysis found no evidence that hormone therapy had an effect on CHD (RR, 1.07; 95% CI, 0.96-1.20) or all-cause mortality (RR, 1.06; 95% CI, 0.95-1.18), with an average follow-up of 3.8 years.[236] There was an increased risk of stroke (RR, 1.21; 95% CI, 1.06-1.38) and VTE (RR, 1.96; 95% CI, 1.37-2.80).

A 2020 systematic review and meta-analysis of RCTs showed similar results as the 2015 *Cochrane* analysis for older women who initiated hormone therapy.[248] Compared with placebo or nonusers of hormone therapy, initiating hormone therapy in women aged 60 years or older or after 10 years since menopause had a null effect on CHD (summary estimate, 1.00; 95% CI, 0.87-1.14) and all-cause mortality (summary estimate, 1.00; 95% CI 0.96-1.05) but was associated with higher risk of stroke (summary estimate, 1.17; 95% CI, 1.01-1.37) and VTE (summary estimate, 1.79; 95% CI, 1.39-2.29).

Similarly, in a 2019 systematic review and meta-regression analysis of RCTs testing the timing hypothesis, women who initiated hormone therapy relative to placebo or nonusers of hormone therapy aged 60 years or older showed a null effect on CHD and all-cause mortality but was associated with higher risk of a composite measure of incidence stroke, transient ischemic attack, and systemic embolism (OR, 1.52; 95% CI, 1.39-1.71).[249]

Attributable risk of stroke in women aged younger than 60 years or within 10 years of menopause onset

The 2015 *Cochrane* meta-analysis found no increased risk of stroke in women who initiated hormone therapy aged younger than 60 years or fewer than 10 years from menopause onset.[236] In subgroup analysis, the attributable risk of stroke in the WHI for women who initiated hormone therapy aged younger than 60 years or within 10 years of menopause onset was rare (<10/10,000 person-years) and statistically nonsignificant for CEE plus MPA, with an absolute risk of 5 per 10,000 person-years,[9,240] similar to other studies.[232]

Findings were inconsistent for CEE-alone in the WHI. For women aged 50 to 59 years at randomization, a decrease of 1 per 10,000 person-years was seen for stroke; whereas for women fewer than 10 years from menopause onset, an increase in 13 strokes per 10,000 person-years was seen.[9]

On the basis of only observational studies, lower doses of either oral[250] or transdermal[251] estrogen may confer less risk of stroke; no clear association with age has been found. No head-to-head data comparing oral to transdermal hormone therapy are available.

Venous thromboembolism

Women who began hormone therapy fewer than 10 years after menopause onset or who were aged younger than 60 years have higher risk of VTE compared with placebo (RR, 1.74; 95% CI, 1.11-2.73), according to the 2015 *Cochrane* meta-analysis.[236] In a 2020 systematic review and meta-analysis of RCTs published between 2000 and 2019, risk of VTE was elevated in women who initiated hormone therapy aged older than 60 years or after 10 years since menopause (summary estimate, 1.79; 95% CI, 1.39-2.29) and a null effect in women who initiated hormone therapy aged younger than 60 years or within 10 years of menopause (summary estimate, 0.69; 95% CI 0.25-1.93).[248] Lower doses of oral ET may confer less risk of VTE than higher doses,[24,25] but comparative RCT data are lacking. Micronized progesterone may be less thrombogenic than other progestins.[26] Transdermal hormone therapy has not been associated with VTE risk in observational studies, limited observational data and a systematic review suggest less risk with transdermal hormone therapy than oral[26,27,29]; however, comparative RCT data are lacking.

Areas of scientific uncertainty and need for randomized, controlled trial data

Although observational studies, meta-analyses of RCTs, and smaller RCTs with surrogate CVD risk markers suggest that hormone therapy may reduce CVD risk when initiated in women aged younger than 60 years and/or who are within 10 years of menopause onset, significant research gaps remain regarding dose, formulation, route of delivery, and duration of use. Furthermore,

because most RCTs are performed on North American and European women, future studies should also evaluate the role of ethnicity with respect to hormone therapy and CVD. Data are insufficient for risk related to long-term hormone therapy use in perimenopausal women and in postmenopausal women aged younger than 50 years.[23,252] Hormone therapy is not government approved for prevention of CVD.

Key points

- For healthy symptomatic women aged younger than 60 years or within 10 years of menopause onset, the favorable effects of hormone therapy on CHD and all-cause mortality should be considered against potential rare increases in risks of breast cancer, VTE, and stroke. (Level I)
- Hormone therapy is not government approved for primary or secondary cardioprotection. (Level I)
- Personal and familial risk of CVD, stroke, VTE, and breast cancer should be considered when initiating hormone therapy. (Level III)
- The effects of hormone therapy on CHD may vary depending on when hormone therapy is initiated in relation to a woman's age or time since menopause onset. (Level I)
- Initiation of hormone therapy in recently postmenopausal women reduced or had no effect on subclinical atherosclerosis progression and coronary artery calcification in randomized, controlled trials. (Level I)
- Observational data and meta-analyses show reduced risk of CHD in women who initiate hormone therapy when aged younger than 60 years or within 10 years of menopause onset. Meta-analyses show a null effect of hormone therapy on CHD after excluding open-label trials. (Level II)
- Women who initiate hormone therapy aged older than 60 years or more than 10 or 20 years from menopause onset are at higher absolute risks of CHD, VTE, and stroke than women initiating hormone therapy in early menopause. (Level I)

BREAST CANCER

Breast cancer affects approximately one in eight US women, so an understanding of the potential effect of hormone therapy on breast cancer risk is of considerable importance. Potential differences of the effects of ET, EPT, and CEE plus BZA on breast tissue may exist. Different types of estrogen or progestogen, as well as different formulations, timing of initiation, duration of therapy, and patient characteristics, may play a role in the effects of hormone therapy on the breast.

Estrogen-progestogen therapy

In the WHI, daily continuous-combined CEE plus MPA resulted in an increased risk of breast cancer, with nine additional breast cancer cases per 10,000 person-years of therapy.[9] The HR remained elevated at a median of 20 years' cumulative follow-up in the unblended, postintervention phase (HR, 1.28; 95% CI, 1.13-1.45).[21]

Estrogen-alone therapy

Compared with women who received placebo, women who received CEE alone in the WHI showed a nonsignificant reduction in breast cancer risk after an average of 7.2 years of randomization, with seven fewer cases of invasive breast cancer per 10,000 person-years of CEE (HR, 0.79; 95% CI, 0.61-1.02).[9] A significant reduction in breast cancer became evident in the postintervention phase, with a median 20 years' cumulative follow-up (HR, 0.78; 95% CI, 0.65-0.93).[21]

Longer duration of hormone therapy use

No large RCTs have assessed the effect of long duration of hormone therapy use. Both the ET and the EPT components of the WHI reported data for finite intervals because both were terminated early because of predefined safety considerations, with a median of 7.2 years for ET and 5.6 for EPT. Notably, although long-term follow-up at 13 and 20 years provided information about use for 5 to 7 years, no data were available regarding longer-term use. The recent pooled analysis of observational data in the Collaborative Group Study included information on duration of hormone therapy use in women starting hormone therapy when aged 45 to 54 years.[22] In each age category, the risk of breast cancer increased with duration of use. Specifically, for ET, the HRs increased from 1.23 (95% CI, 1.11-1.35) for 1 to 4 years of use, to 1.29 (95% CI, 1.21-1.37) for 5 to 9 years, to 1.44 (95% CI, 1.35-1.53) for 10 to 14 years, and to 1.61 (95% CI, 1.49-1.74) for 15 or more years. For EPT, increases for similar periods were 1.66 (95% CI, 1.55-1.78) for 1 to 4 years of use, 1.96 (95% CI, 1.87-2.05) for 5 to 9 years, 2.31 (95% CI, 2.18-2.44) for 10 to 14 years, and 2.68 (95% CI, 2.44-2.95) for 15 or more years.

Attributable risk of breast cancer

The attributable risk of breast cancer in women (mean age, 63 y) randomized to CEE plus MPA in the WHI is less than one additional case of breast cancer diagnosed per 1,000 users annually,[9] a risk slightly greater than that observed with one daily glass of wine, less than with two daily glasses, and similar to the risk reported with obesity and low physical activity.[253,254] Compared with placebo or nonusers of hormone therapy, there appears to be no additive effect of hormone therapy with age or elevated personal breast cancer risk factors on breast cancer incidence.[21,22,255-259] Although the relative risk of breast cancer associated with hormone therapy use is similar in women at average or high risk, the actual number of cases or attributable risk will be greater in women with an increased underlying risk.[86]

Use of hormone therapy in women with genetic risk factors for breast cancer

Observational evidence suggests that hormone therapy use does not further increase the relative risk of breast cancer in women with a family history of breast cancer, in women after oophorectomy for *BRCA 1* or *2* genetic variants, or in women having undergone a benign breast biopsy.[255-258,260-266] A prospective longitudinal cohort study of *BRCA 1* genetic variant carriers without prior history of breast cancer who underwent BO (mean age, 43.4 y) showed no increased risk of developing breast cancer associated with any use of hormone therapy after a mean follow-up of 7.6 years; however, there was a difference between ET and EPT, with a nonsignificant increase in breast

cancer risk associated with the latter.[266] Similarly, the Two Sister Study of 1,419 sister-matched cases of breast cancer in women aged younger than 50 years and 1,665 controls showed no increased risk of young-onset breast cancer with use of EPT (OR, 0.80; 95% CI, 0.41-1.59), and unopposed estrogen use was associated with a reduced diagnosis of young-onset breast cancer (OR, 0.58; 95% CI, 0.34-0.99).[267] The absolute risk of breast cancer is low in women with genetic variants who undergo risk-reducing BO at a young age, and use of hormone therapy is considered acceptable.

Role of type of hormone use, dose, and route of administration

Some but not all observational data suggest that MP and dydrogesterone may have a lesser association with breast cancer, whereas other synthetic progestogens such as MPA may have a more adverse effect.[268] Randomized trials are needed to confirm these findings. Preclinical data suggest that CEE may have lesser effects on occult breast cancer growth than estradiol,[269] but clinical data from observational studies, such as the Collaborative Group study, do not report a difference.[22] Regarding route, both oral and transdermal estrogens appear to have similar effects on number of breast cancers diagnosed, whereas vaginal estrogens have no effect. Insufficient clinical data on newer therapies such as TSECs, including CEE plus BZA, are available to assess their breast cancer risk,[270] although preclinical data suggest greater safety.[271]

Mammographic breast density and hormone therapy

Different hormone therapy regimens may be associated with increased breast density, which may obscure mammographic interpretation.[272] More mammograms and breast biopsies were performed in women receiving CEE plus MPA than placebo in the WHI.[273] In trials up to 2-years' duration, breast cancer, breast density, and breast tenderness showed no difference between oral CEE plus BZA and placebo.[274-276]

Hormone therapy after breast cancer

Two RCTs reported conflicting outcomes of breast cancer recurrence with hormone therapy. One study ("Hormonal Replacement Therapy After Breast Cancer—Is It Safe?") showed an elevated risk of breast cancer recurrence in hormone therapy users relative to nonusers after a median follow-up of 2.1 years (HR, 3.5; 95% CI, 1.5-8.1)[277] and 4 years, (HR, 2.4; 95% CI, 1.3-4.2),[278] whereas another trial (Stockholm Breast Cancer Study) showed no effect on breast cancer recurrence in hormone therapy users relative to nonusers after median follow-up of 4.1 years (HR, 0.82; 95% CI, 0.35-1.9)[279] and 10.8 years (HR, 1.3; 95% CI, 0.9-1.9) but did show an increased risk of breast cancer in the contralateral breast (HR, 3.6; 95% CI, 1.2-10.9).[280]

Although systemic use of hormone therapy in survivors of breast cancer is generally not advised, if symptoms of estrogen deficiency are severe and unresponsive to nonhormone options, women, in consultation with their oncologists, may choose hormone therapy after being fully informed about the risks and benefits. Several observational studies in women with a history of breast cancer have shown a decreased risk of recurrent breast cancer or neutral effects compared with nonusers.[281-286] In addition, mortality was reported to be reduced in breast cancer survivors who used hormone therapy relative to those who did not.[282,284] Four meta-analyses reported similar findings.[281,284-286] A confounding factor in all of these observational studies is that women at low risk of breast cancer recurrence are more likely to elect hormone therapy use than women at high risk.

Low-dose vaginal ET remains an effective treatment option for GSM in survivors of breast cancer, with minimal systemic absorption. Treatment with low-dose vaginal ET or DHEA may be considered if symptoms persist after an initial trial of nonhormone therapies and in consultation with an oncologist, with more concern for women on AIs.[88,90]

Breast cancer mortality and hormone therapy

Only one randomized trial, the WHI, examined breast cancer-specific mortality. After 20 years of median cumulative follow-up, CEE alone was associated with significantly lower breast cancer incidence (HR, 0.78; 95% CI, 0.65-0.93) and breast cancer mortality (HR, 0.60; 95% CI, 0.37-0.97) compared with placebo. In contrast, CEE plus MPA was associated with significantly higher breast cancer incidence (HR, 1.28; 95% CI, 1.13-1.45) but no significant difference in breast cancer mortality (HR, 1.35; 95% CI, 0.94-1.95) compared with placebo.[21]

The mortality risk of breast cancer in hormone therapy users has been reported to be reduced in many but not all observational studies.[287-295] The breast cancers in hormone therapy users (ET and EPT) appear in most (but not all) studies to have more benign histologic features (localized, smaller, better differentiated, lower mean tumor proliferation rate) than in hormone therapy nonusers. The most recent study, using a large data registry in Finland and comparing populations rates, reported a reduction in breast cancer mortality in users of both ET and EPT.[296] A confounding factor in all these studies is that hormone therapy users undergo more frequent mammograms and diagnostic examinations, especially with occurrence of signs or symptoms.[297-301] This is likely to result in earlier diagnosis and therefore more benign histologic features and lower mortality.

Key points

- The risk of breast cancer related to hormone therapy use is low, with estimates indicating a rare occurrence (less than one additional case per 1,000 women per year of hormone therapy use or three additional cases per 1,000 women when used for 5 years with CEE plus MPA). (Level I)
- Women should be counseled about the risk of breast cancer with hormone therapy, putting the data into perspective, with risk similar to that of modifiable risk factors such as two daily alcoholic beverages, obesity, and low physical activity. (Level III)
- The effect of hormone therapy on breast cancer risk may depend on the type of hormone therapy, duration of use, regimen, prior exposure, and individual characteristics. (Level II)
- Different hormone therapy regimens may be associated with increased breast density, which may obscure mammographic interpretation, leading to more mammograms or more breast biopsies and a potential delay in breast cancer diagnosis. (Level II)

- A preponderance of data does not show an additive effect of underlying breast cancer risk (age, family history of breast cancer, genetic risk of breast cancer, benign breast disease, personal breast cancer risk factors) and hormone therapy use on breast cancer incidence. (Level II)
- Insufficient data are available to assess the risk of breast cancer with newer therapies such as TSECs, including BZA plus CEE. (Level II)
- Observational evidence suggests that hormone therapy use does not further increase risk of breast cancer in women at high risk because of a family history of breast cancer or after bilateral salpingo-oophorectomy (BSO) for *BRCA 1* or *2* genetic variants. (Level II)
- Systemic hormone therapy is generally not advised for survivors of breast cancer, although hormone therapy use may be considered in women with severe VMS unresponsive to nonhormone options, with shared decision-making in conjunction with their oncologists. (Level III)
- For survivors of breast cancer with GSM, low-dose vaginal ET or DHEA may be considered in consultation with their oncologists if bothersome symptoms persist after a trial of nonhormone therapy. There is increased concern with low-dose vaginal ET for women on AIs. (Level III)
- Regular breast cancer surveillance is advised for all postmenopausal women per current breast cancer screening guidelines, including those who use hormone therapy. (Level I)

ENDOMETRIAL CANCER

Endometrial cancer is the most common gynecologic malignancy in the United States. Unopposed systemic ET in a postmenopausal woman with an intact uterus increases the risk of endometrial cancer, which is dose- and duration-related. Greater risk is seen with higher estrogen doses used for longer duration, and risk persists after discontinuation. Progestogen used continuously or cyclically for 10 to 14 days monthly significantly reduces this risk. With long-duration hormone therapy use, observational studies suggest a potentially increased risk of endometrial cancer with cyclic progestogen regimens compared with continuous progestogen use and with the use of MP compared with other progestogens.[3,4,302] In the WHI, women with a uterus receiving EPT had a lower risk of endometrial cancer than women randomized to placebo after 13 years of cumulative follow-up because of the baseline risk of endometrial cancer in postmenopausal women from endogenous estrogen production.[9] Adequate concomitant progestogen is recommended for a woman with an intact uterus when using systemic ET.

Low-dose vaginal ET does not appear to increase endometrial cancer risk,[92,93] although trials with endometrial biopsy end points are limited to 1 year in duration. Progestogen is not advised in women using low-dose vaginal ET for the treatment of GSM, although intermittent use may be considered in women at increased risk of endometrial cancer. Postmenopausal bleeding must be evaluated thoroughly in any woman, whether she is using hormone therapy or not, because this may be a sign of endometrial hyperplasia or cancer.

Hormone therapy after endometrial cancer

Although hormone therapy is generally contraindicated in women with estrogen-responsive cancers, hormone therapy may be used to treat bothersome menopause symptoms in women with low-grade, Stage I endometrial cancer after hysterectomy. Meta-analyses of retrospective studies, with one RCT, do not identify an AE on the risk of recurrence or survival in these cases.[303-306] A woman's oncologist should be included in shared decision-making. Systemic hormone therapy is not advised with high-grade, advanced-stage endometrial cancers or with endometrial stromal sarcomas or leiomyosarcomas, because there are insufficient studies assessing safety.[307,308]

Key points

- Unopposed systemic ET in a postmenopausal woman with an intact uterus increases the risk of endometrial cancer, so adequate progestogen is recommended. (Level I)
- Low-dose vaginal ET does not appear to increase endometrial cancer risk, although trials with endometrial biopsy end points are limited to 1 year in duration. (Level II)
- Use of hormone therapy is an option for the treatment of bothersome menopause symptoms in women with surgically treated, early stage, low-grade endometrial cancer in consultation with a woman's oncologist if nonhormone therapies are ineffective. (Level II)
- Systemic hormone therapy is not advised with high-grade, advanced-stage endometrial cancers or with endometrial stromal sarcomas or leiomyosarcomas. (Level II)

OVARIAN CANCER

Ovarian cancer causes more deaths than any other gynecologic malignancy. Use of oral contraceptives is associated with a significant reduction in ovarian cancer risk. Risk declines with longer duration of use, with risk reduction seen after 1 to 4 years of use, which persists for up to 30 years after oral contraceptive discontinuation.[309] Current and recent use of hormone therapy is associated with statistically significant but small increased risk of ovarian cancer in observational studies, principally for serous type, with an estimate of one additional ovarian cancer death in 1,700 to 3,300 hormone therapy users.[310,311] This risk is seen with combined EPT and ET alone and dissipates within 5 years of discontinuing hormone therapy. In the WHI, there was no significant increase in ovarian cancer risk with EPT.[9]

Hormone therapy after ovarian cancer

The use of hormone therapy after a diagnosis of epithelial ovarian cancer does not appear to affect recurrence risk or survival.[312,313] Although most studies are observational, this finding also is supported by two RCTs. Several studies identify improved survival in women with ovarian cancer who use hormone therapy, but this likely represents selection bias.[307] Use of hormone therapy is not advised in women with hormone-dependent ovarian cancers, including granulosa-cell tumors and serous carcinomas.[306,314] Tumors of low malignant potential (borderline) often affect younger women, with excellent survival rates. Limited data are available, but hormone therapy may be considered in women with completely resected disease, especially given the benefits of

hormone therapy in the setting of early menopause.[315] Short-term hormone therapy use appears safe in women with *BRCA1* and *BRCA2* genetic variants who undergo risk-reducing BSO before the average age of menopause.[308]

Key points

- Use of oral contraceptives is associated with a significant reduction in ovarian cancer risk. (Level I)
- Current and recent use of hormone therapy is associated with a small but statistically significant risk of ovarian cancer in observational studies, principally for serous type, although there was no increase in ovarian cancer risk in women randomized to EPT in the WHI. (Level II)
- In women with a history of ovarian cancer, benefits of hormone therapy use generally outweighs risks, especially with bothersome VMS or early menopause; use of hormone therapy is not advised in women with hormone-dependent ovarian cancers, including granulosa-cell tumors and low-grade serous carcinoma. (Level II)
- Short-term hormone therapy use appears safe in women with *BRCA1* and *BRCA2* genetic variants who undergo risk-reducing BSO before the average age of menopause. (Level II)

COLORECTAL CANCER

Colorectal cancer is the third most common cancer and the third leading cause of cancer death in US women.[309] Risk factors include physical inactivity, obesity, smoking, and decreased use of screening strategies, which may be more likely in hormone therapy nonusers. Observational studies generally support a reduced risk of colorectal cancer in current hormone therapy users compared with never users (HR, 0.6-0.8), with no benefit associated with past hormone therapy use.[310-312] In observational studies, both EPT and ET alone are associated with reduced colorectal cancer risk[313,314] and mortality.[315] Although confounding may contribute to the reduced risk of colorectal cancer seen in hormone therapy users, there is also biologic plausibility, because estrogen receptors are present in colonic epithelium,[316] and estrogen reduces colon cancer cell growth in vitro.[317]

In the WHI trials, use of CEE plus MPA, but not CEE alone, was associated with a reduced risk of colorectal cancer compared with placebo (HR, 0.62; 95% CI, 0.43-0.89).[9] Although EPT reduced the risk of colorectal cancer, the cancers that were detected in EPT users were more likely to be diagnosed at an advanced stage, with positive lymph nodes.[318] The reduced risk of colorectal cancer in EPT users was no longer seen during the postintervention phase of the WHI at 13 years, and there was no difference in colorectal cancer mortality with either EPT or ET alone.[31] The reason for disparate findings between observational studies and the WHI with regard to colorectal cancer risk and mortality is unclear.

Key points

- Observational studies suggest a reduced incidence of colorectal cancer in current hormone therapy users, with reduced mortality. (Level II)
- In the WHI, EPT, but not ET alone, reduced colorectal cancer risk, although cancers diagnosed in EPT users were diagnosed at a more advanced stage. There was no difference in colorectal cancer mortality with either EPT or ET. (Level I)

LUNG CANCER

Lung cancer is the second most common cancer and the leading cause of cancer death in US women.[309] Smoking is the principal risk factor. An interaction between hormone therapy and lung cancer is biologically plausible because estrogen receptors (α and β) and aromatase are identified in both healthy lung tissue and lung cancers.[319,320] Non-small cell lung cancer, including adenocarcinoma and squamous cell carcinoma, is the most common type and the type affected by hormone therapy in observational studies and RCTs. Observational studies, including several large meta-analyses, are conflicting and in aggregate identify no consistent association between hormone therapy use and lung cancer risk.[321-327] Smoking may influence the association between hormone therapy use and lung cancer risk.[326] For women with lung cancer, the effect of hormone therapy use on survival is unclear, with studies showing improved, worsened, or no difference in risk of death.

In the WHI, in the intervention phase or after a median of 13 years' cumulative follow-up, the incidence of lung cancer did not differ significantly between placebo and treatment with CEE plus MPA or CEE alone.[9] In a post hoc analysis of the intervention phase of the WHI, women treated with CEE plus MPA had more deaths from lung cancer compared with placebo (HR, 1.71; 95% CI, 1.16-2.52).[328] Cancers were more likely to be poorly differentiated, with distant metastasis. This increase in lung cancer deaths was not seen with treatment with CEE alone[329] and dissipated over time after stopping hormone therapy.[330]

Key points

- There appears to be an overall neutral effect of hormone therapy on lung cancer incidence and survival. (Level II)
- Smoking cessation should be encouraged, with increased lung cancer surveillance for older smokers, including current or past users of hormone therapy. (Level I)

DURATION OF USE, INITIATION AFTER AGE 60 YEARS, AND DISCONTINUATION OF HORMONE THERAPY

Benefits of hormone therapy use generally outweigh risks for healthy women with bothersome menopause symptoms who are aged younger than 60 years or within 10 years of menopause onset. Because increasing risk is observed with advancing age and extended duration of use,[9,22] women are advised to use the appropriate dose for the time needed to manage their symptoms. Because many women will experience bothersome VMS for many years, long-duration hormone therapy use may be needed, and an arbitrary age-based stopping rule is not clinically appropriate. Frequent VMS persist on average 7.4 years and for many more than 10 years.[59,331] In a study of Swedish women aged older than 85 years, 16% reported hot flashes at least several times per week,[332] and up to 8% of women continue to have hot flashes for 20 years or longer after menopause.[333]

There are important questions related to long-duration hormone therapy use and discontinuation that are unanswered by

available data, because the WHI, the longest adequately powered blinded RCT, was limited to 5 to 7 years of therapy. In the WHI, initiating hormone therapy in women aged older than 60 years or more than 10 years beyond the onset of menopause was associated with greater risk, and initiating hormones in women aged older than 70 years was associated with the highest risk.[9] It is not known whether women who initiate hormone therapy at the time of menopause and continue use at older ages will incur the same risks as women initiating hormones later in life. The WHI studied only one formulation of oral hormones (CEE with or without MPA). Observational data suggest lower CVD risk, including VTE and stroke, with other hormone formulations and routes of administration, including transdermal estradiol, lower-dose estrogens, and different progestogens.[25,251,334-336] Mitigation of risk through the appropriate choice of dosing, formulation, and route of administration becomes increasingly important as women age and with longer duration of therapy. Factors that should be considered include severity of symptoms, effectiveness of alternative nonhormone and lifestyle interventions, and underlying risk for osteoporosis, CHD, cerebrovascular accident, VTE, and breast cancer. The decision regarding duration of treatment and when to stop hormone therapy must be considered in the context of the individualized risk-benefit profile, as well as the woman's personal preferences.[337,338]

Initiation after age 60 years

Initiation of hormone therapy in women aged older than 60 years or more than 10 years from menopause onset has complex risks and requires careful consideration, recognizing that there may be well-counseled women aged older than 60 years who choose to initiate or restart hormone therapy. For women requesting to initiate hormone therapy because of VMS appearing many years after menopause onset, further evaluation is needed. Although new-onset VMS in an older woman could be caused by estrogen-deficiency, hot flashes or night sweats may be related to an underlying medical problem (eg, obstructive sleep apnea, hyperthyroidism, carcinoid, lymphoma, Lyme disease, tuberculosis, HIV) or medication or substance use (eg, antidepressants, hypoglycemic agents, or withdrawal from alcohol or opioids).

Extended use after age 65 years

There is no general rule for stopping systemic hormone therapy in a woman aged 65 years. The Beers criteria from the American Geriatrics Society[339] has warnings against the use of hormone therapy in women aged older than 65 years. However, the recommendation to routinely discontinue systemic hormone therapy in women aged 65 years and older is neither cited or supported by evidence nor is it recommended by the American College of Obstetricians and Gynecologists or The North American Menopause Society.[340,341] Of note, the continued use of hormone therapy in healthy women aged older than 65 years at low risk for breast cancer and CVD is limited by insufficient evidence regarding safety, risks, and benefits.

For otherwise healthy women with persistent VMS, continuing hormone therapy beyond age 65 years is a reasonable option with appropriate counseling, regular assessment of risks and benefits, and shared decision-making. Hormone therapy also may be considered for prevention of fracture in healthy older women at elevated fracture risk when bothersome VMS persist or when hormone therapy remains the best choice because of lack of efficacy or intolerance of other fracture-prevention therapies.[23,340] Long-duration hormone therapy use and use in older women is not appropriate for reduction in the risk of CHD or dementia.[23,236,342] When providing hormone therapy to older women, clinicians must remain vigilant about risk stratification and potential mitigation strategies, such as switching from oral to transdermal hormone therapy, choice of progestogen, and lowering of dose.[337,338]

Discontinuation of hormone therapy

Controversy exists regarding how long hormone therapy may safely be used and when it should be discontinued. Based on findings from the WHI, breast cancer risk becomes detectable after 3 to 5 years in women using EPT. For women without a uterus using ET alone, breast cancer risk did not increase after 7 years, so a longer duration of hormone therapy use may be acceptable. There are few studies to guide the optimal way for women to stop hormone therapy, and VMS will recur in approximately 50% of women after discontinuation.[71] Data directly comparing the effects of abrupt discontinuation with those of slowly tapering are lacking,[343] although clinical experts generally advise gradually decreasing hormone therapy doses over time.[338,343] If hormone therapy is being used for prevention of osteoporosis, it is important to remember that protection against bone density loss and fracture prevention is lost rapidly with discontinuation.[164] Although VMS generally improve with time, GSM worsens with prolonged estrogen deficiency, so women should be provided with treatment options on discontinuation of systemic hormone therapy. Observational studies confirm the long-term safety of low-dose vaginal ET,[92,93] a highly effective treatment for GSM. In the absence of contraindications, a woman should determine her preferred hormone therapy formulation, dose, and duration of use, with ongoing assessment and shared decision-making with her healthcare professional.[337,338]

Key points

- The safety profile of hormone therapy is most favorable when initiated in healthy women aged younger than 60 years or within 10 years of menopause onset, so initiation of hormone therapy by menopausal women aged older than 60 years requires careful consideration of individual benefits and risks. (Level I)
- Long-term use of hormone therapy, including for women aged older than 60 years, may be considered in healthy women at low risk of CVD and breast cancer with persistent VMS or at elevated risk of fracture for whom other therapies are not appropriate. (Level III)
- Factors that should be considered include severity of symptoms, effectiveness of alternative nonhormone interventions, and underlying risk for osteoporosis, CHD, cerebrovascular accident, VTE, and breast cancer. (Level III)
- Hormone therapy does not need to be routinely discontinued in women aged older than 60 or 65 years. (Level III)

- Mitigation of risk through use of the lowest effective dose and potentially with a nonoral route of administration becomes increasingly important as women age and with longer duration of therapy. (Level III)
- Longer durations or extended use beyond age 65 should include periodic reevaluation of comorbidities with consideration of periodic trials of lowering or discontinuing hormone therapy. (Level III)
- For women with GSM, low-dose vaginal ET may be considered for use at any age and for extended duration, if needed. (Level III)
- In the absence of contraindications, a woman should determine her preferred hormone therapy formulation, dose, and duration of use, with ongoing assessment and shared decision-making with her healthcare professional. (Level III)

SUMMARY

Hormone therapy formulation, dose, regimen, route of administration, and the timing of initiation of therapy likely produce different effects, although these have yet to be evaluated in head-to-head RCTs. There is a significant difference in the benefits and risks of ET alone compared with EPT. Decision-making surrounding the use of hormone therapy should be individualized, with recommendations for the use of the appropriate dose, duration, regimen, and route of administration required to manage a woman's symptoms and to meet treatment goals. Given the more favorable safety profile of ET alone, longer durations may be more appropriate. Risk stratification by age and time since menopause is recommended. Transdermal routes of administration and lower doses of hormone therapy may decrease risk of VTE and stroke; however, comparative RCT data are lacking.

Personalization with shared decision-making remains key, with periodic reevaluation to determine an individual woman's benefit-risk profile. Benefits may include relief of bothersome VMS, prevention of bone loss and reduction of fracture, treatment of GSM, and improved sleep, well-being, and quality of life. Absolute attributable risks for women in the 50- to 59-year-old age group or within 10 years of menopause onset are low, whereas the risks of initiation of hormone therapy for women aged 60 years and older or who are further than 10 years from menopause onset appear greater, particularly for those aged 70 years and older or more than 20 years from menopause onset, with more research needed on potential risks of longer durations of use.

Women with POI and premature or early menopause have higher risks of bone loss, heart disease, and cognitive or affective disorders associated with estrogen deficiency. In observational studies, these risks appear to be mitigated if ET is given until the average age of menopause, at which time treatment decisions should be reevaluated. In limited observational studies, women who are *BRCA*-positive and have undergone risk-reducing BO appear to receive similar benefits from receiving hormone therapy, with minimal to no increased risk of breast cancer. There is a paucity of RCT data about the risks of extended duration of hormone therapy in women aged older than 60 or 65 years, although observational studies suggest a potential rare risk of breast cancer with increased duration of hormone therapy. It remains an individual decision in select, well-counseled women aged older than 60 or 65 years to continue therapy. There are no data to support routine discontinuation in women aged 65 years.

For select survivors of breast and endometrial cancer, observational data show that use of low-dose vaginal ET for those who fail nonhormone therapy for treatment of GSM appears safe and greatly improves quality of life for many. The use of systemic hormone therapy needs careful consideration for survivors of estrogen-sensitive cancers and should only be used for compelling reasons in collaboration with a woman's oncologist after failure of nonhormone therapies.

Additional research is needed on the thrombotic risk (VTE, pulmonary embolism, and stroke) of oral versus transdermal therapies (including different formulations, doses, and durations of therapy). More clinical trial data are needed to confirm or refute the potential beneficial effects of hormone therapy on CHD and all-cause mortality when initiated in perimenopause or early postmenopause. Additional areas for research include the breast effects of different estrogen preparations, including the role for SERM and TSEC therapies; optimal progestogen or SERM regimens to prevent endometrial hyperplasia; the relationship between VMS and the risk for heart disease and cognitive changes; and the risks of POI. Studies are needed on the effects of longer use of low-dose vaginal ET after breast or endometrial cancer; extended use of hormone therapy in women who are early initiators; improved tools to personalize or individualize benefits and risks of hormone therapy; the role of aging and genetics; and the long-term benefits and risks on women's health of lifestyle modification or complementary or nonhormone therapies if chosen in addition to or over hormone therapy for VMS, bone health, and CVD risk reduction.

CONCLUSIONS

- Hormone therapy is the most effective treatment for VMS and GSM and has been shown to prevent bone loss and fracture.
- Risks of hormone therapy differ for women, depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is needed. Treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation.
- For women aged younger than 60 years or within 10 years of menopause onset and without contraindications, the benefit-risk ratio appears favorable for treatment of bothersome VMS and for the prevention of bone loss and reduction of fracture. Based on the WHI RCTs, longer duration may be more favorable for ET than for EPT.
- For women who initiate hormone therapy more than 10 or 20 years from menopause onset or when aged 60 years or older, the benefit-risk ratio appears less favorable than for younger women because of greater absolute risks of CHD, stroke, VTE, and dementia.
- For GSM symptoms not relieved with nonhormone therapies, low-dose vaginal ET or other government-approved therapies (eg, vaginal DHEA or oral ospemifene) are recommended.

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"The 2022 Hormone Therapy Position Statement of The North American Menopause Society" has been designated a CME activity for all NAMS members. NAMS members should log in to the NAMS website, www.menopause.org, and then select Online CME in the Member Center. CME credit will be available from July 1, 2022, to July 1, 2023.

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NAMS Position Statement

The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society

Abstract

Objective: To update and expand the 2013 position statement of The North American Menopause Society (NAMS) on the management of the genitourinary syndrome of menopause (GSM), of which symptomatic vulvovaginal atrophy (VVA) is a component.

Methods: A Panel of acknowledged experts in the field of genitourinary health reviewed the literature to evaluate new evidence on vaginal hormone therapies as well as on other management options available or in development for GSM. A search of PubMed was conducted identifying medical literature on VVA and GSM published since the 2013 position statement on the role of pharmacologic and nonpharmacologic treatments for VVA in postmenopausal women. The Panel revised and added recommendations on the basis of current evidence. The Panel's conclusions and recommendations were reviewed and approved by the NAMS Board of Trustees.

Results: Genitourinary syndrome of menopause affects approximately 27% to 84% of postmenopausal women and can significantly impair health, sexual function, and quality of life. Genitourinary syndrome of menopause is likely underdiagnosed and undertreated. In most cases, symptoms can be effectively managed. A number of over-the-counter and government-approved prescription therapies available in the United States and Canada demonstrate effectiveness, depending on the severity of symptoms. These include vaginal lubricants and moisturizers, vaginal estrogens and dehydroepiandrosterone (DHEA), systemic hormone therapy, and the estrogen agonist/antagonist ospemifene. Long-term studies on the endometrial safety of vaginal estrogen, vaginal DHEA, and ospemifene are lacking. There are insufficient placebo-controlled trials of energy-based therapies, including laser, to draw conclusions on efficacy and safety or to make treatment recommendations.

Conclusions: Clinicians can resolve many distressing genitourinary symptoms and improve sexual health and the quality of life of postmenopausal women by educating women about, diagnosing, and appropriately managing GSM. Choice of therapy depends on the severity of symptoms, the effectiveness and safety of treatments for the individual patient, and patient preference. Nonhormone therapies available without a prescription provide sufficient relief for most women with mild symptoms. Low-dose vaginal estrogens, vaginal DHEA, systemic estrogen therapy, and ospemifene are effective treatments for moderate to severe GSM. When low-dose vaginal estrogen or DHEA or ospemifene is administered, a progestogen is not indicated; however, endometrial safety has not been studied in clinical trials beyond 1 year. There are insufficient data at present to confirm the safety of vaginal estrogen or DHEA or ospemifene in women with breast cancer; management of GSM should consider the woman's needs and the recommendations of her oncologist.

Key Words: Dyspareunia – Genitourinary syndrome of menopause – Ospemifene – Vaginal dehydroepiandrosterone – Vaginal dryness – Vaginal estrogen – Vulvovaginal atrophy.

Genitourinary syndrome of menopause (GSM) describes the symptoms and signs resulting from the effect of estrogen deficiency on the female genitourinary tract. Symptoms associated with GSM are highly prevalent, affecting approximately 27% to 84% of postmenopausal women.[1-4] In one report of more than

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900 women undergoing routine examinations, GSM was identified in 84% of women 6 years after menopause.[4] Principal symptoms included vaginal dryness, painful sex, burning, and dysuria. In contrast to vasomotor symptoms (VMS) that usually improve over time, GSM is generally progressive without effective therapy. Despite the high prevalence of GSM and lack of improvement without treatment, only a minority of affected women seek help or are offered treatment by their healthcare providers.[5,6]

In a survey of 1,858 US postmenopausal women with genitourinary symptoms, 50% had never used any therapy for this problem.[6] The reluctance of women as well as healthcare providers to initiate discussion of genitourinary symptoms and safety concerns about hormone therapies contribute to limited assessment and treatment of GSM.[7,8]

The genitourinary syndrome of menopause often has significant adverse effects on a woman's sexual health and quality of life (QOL).[9] Women who are not sexually active also experience bothersome symptoms of GSM, affecting activities of daily living.[10] In the *Vaginal Health: Insights, Views & Attitudes* (VIVA) online survey of 3,520 postmenopausal women in six countries, 45% reported experiencing vaginal symptoms, and 75% felt that their symptoms negatively affected their lives.[11] In 500 US women in the VIVA survey, of the 48% with vaginal discomfort, the most common symptoms were vaginal dryness and pain during intercourse.[5] Women in VIVA in the United States reported these adverse events (AEs) of vaginal discomfort:

- Negative effect on their lives (80%)
- Adverse effects on sexual intimacy (75%)
- Feeling less sexual (68%)
- Feeling old (36%)
- Negative consequences on marriage/relationship (33%)
- Negative effect on self-esteem (26%)
- Lower QOL (25%)

In a survey of 3,046 US women, *Real Women's Views of Treatment Options for Menopausal Vaginal Changes* (REVIVE),[7] women reported that their vulvovaginal atrophy (VVA) symptoms:

- Led to some loss of intimacy (85%)
- Detracted from enjoyment of sex (59%)
- Interfered with their relationship (47%)
- Negatively affected sleep (29%)
- Adversely affected general enjoyment of life (27%)

This updated position statement reviews the science of genitourinary aging and assesses the safety and effectiveness of available treatment options for postmenopausal women with GSM.

METHODS

A nine-member Panel composed of expert clinicians and researchers in the field of genitourinary health reviewed the literature to evaluate new evidence on management strategies, including vaginal estrogens, vaginal dehydroepiandrosterone (DHEA), ospemifene, and other management options available or in development for symptomatic GSM. A literature search was conducted using the terms "genitourinary syndrome of menopause/GSM," "vulvovaginal atrophy/VVA," "atrophic vaginitis," "dyspareunia," "vaginal dryness," and "vaginal lubrication." If evidence was contradictory or inadequate to form a conclusion, a consensus-based opinion was established.

The Panel's completed draft of the updated Position Statement was submitted to the NAMS Board of Trustees for additional review, comments, and edits. The Board is composed of both clinicians and researchers from multiple specialties and disciplines. The Board approved the Position Statement with edits after final Panel review.

TERMINOLOGY

Genitourinary syndrome of menopause describes the symptoms and signs resulting from the effect of estrogen deficiency on the female genitourinary tract, including the vagina, labia, urethra, and bladder.[12] This syndrome includes genital symptoms of dryness, burning, and irritation; urinary symptoms and conditions of dysuria, urgency, and recurrent urinary tract infections (UTIs); and sexual symptoms of pain and dryness. Physical changes and signs are varied. Women may experience some or all of the symptoms and signs, which must be bothersome for a diagnosis of the syndrome. Other causes of similar signs and symptoms must be ruled out, including vulvovaginal dermatoses, infection, or cancer.

Vulvovaginal atrophy is a component of GSM.[13] Although VVA was the commonly used term in the past to describe the genitourinary changes of menopause, it has limitations. Vulvovaginal atrophy describes the appearance of the genital tissues but not the associated symptoms. It does not include urinary tract changes related to estrogen deficiency, and the term *atrophy* has negative associations for women. The term genitourinary syndrome of menopause was developed during a consensus conference of experts[12] and subsequently was accepted as the preferred term by many medical societies, including The North American Menopause Society and the American College of Obstetricians and Gynecologists.

ANATOMY AND PHYSIOLOGY

The genital and lower urinary tract share a common embryologic origin in women, with the urethra, bladder trigone, vulvar vestibule, and the upper vagina all derived from the same estrogen receptor (ER)-rich primitive urogenital sinus tissue.[14] The vulva is also derived from the urogenital sinus, but the epithelium of the labia majora is of ectodermal origin. The vagina is composed of an inner stratified squamous epithelium, a middle muscular layer, and an outer fibrous layer. In the presence of endogenous estrogen after puberty and before menopause, the lining of the vagina is characterized by a thickened, rugated surface that is well vascularized and lubricated in most women.

Estrogen is a dominant regulator of vaginal and lower urinary tract physiology. Estrogen receptor-α is present in

the vaginal tissues of both premenopausal and postmenopausal women, whereas ER-β appears to have no or low expression in postmenopause vaginal tissue. Estrogen therapy (ET) does not appear to affect the presence of ER-β.[15,16] Estrogen receptor density is highest in the vagina, with decreasing density across the external genitalia to the skin. The density of the androgen receptor is the reverse. There are low levels in the vagina and higher levels in the external genitalia. Progesterone receptors are found in the vagina and the transitional epithelium of the vulvovaginal junction.[17]

Estrogen receptors have also been found on autonomic and sensory neurons in the vagina and vulva. Estrogen therapy has been reported to decrease the density of sensory nociceptor neurons in the vagina. This function may serve to decrease the discomfort associated with GSM.[18] With respect to the lower urinary tract, estrogen and progesterone receptors have been identified in the urethra, bladder, and pelvic floor muscles.[14]

The changing physiology of the vaginal epithelium after menopause is not completely understood. On the basis of a cell-culture model that used vaginal-cervical epithelial cells, diminished estrogen levels and aging were found to be independent factors in decreasing vaginal-cervical paracellular permeability, a change potentially related to vaginal dryness.[19] With atrophy, wet-mount microscopy shows more than one white blood cell per epithelial cell and immature vaginal epithelial cells with relatively large nuclei (parabasal cells). Cytology shows an increase in parabasal and intermediate cells, and superficial cells decrease or are absent.[20] Immune cell populations seem to be similar or slightly decreased in number, with similar cytolytic capacity as before menopause.[21-23] However, some studies show differences in inflammatory markers in the vaginal fluid of postmenopausal women compared with premenopausal women.[24]

Hormone changes throughout the life cycle influence the vaginal microbiome from birth through postmenopause.[25,26] During the reproductive years, the presence of a microbial community dominated by *Lactobacillus* species is associated with a lower pH and lower risk for bacterial vaginosis (BV), sexually transmitted infections, UTIs, and HIV infection.[27-35]

After menopause, women are less likely to have a *Lactobacillus*-dominant vaginal bacterial community and less likely to have a low vaginal pH.[26,36,37] Although cultivation-based studies show a significantly lower quantity of vaginal *Lactobacillus* in postmenopausal women,[37] several newer sequencing studies observe that close to half have a high proportion of lactobacilli.[38,39] In one study, a higher proportion of *Lactobacillus* correlated inversely with examiner-reported dryness in postmenopausal women,[38] but in another study, there was no association between *Lactobacillus* dominance and the severity of patient-reported symptoms.[40]

The vaginal bacteria community of postmenopausal women has many similarities with that of reproductive-aged women with BV: high pH,[36] higher diversity,[41] and an abnormal Nugent score.[42] In many women with GSM, however, these abnormalities reflect a decline in lactobacilli rather than an increase in the prevalence of pathogens.[42,43] Treatment with systemic or topical estrogen is associated with an increase in detection of vaginal lactobacilli.[44,45] This suggests that for many postmenopausal women, the best approach to promoting a healthy vaginal microbial community is not antibiotic therapy (as though treating BV) but rather vaginal estrogen therapy.

PRESENTATION

The diagnosis of GSM requires the presence of both characteristic examination findings and bothersome symptoms. The most commonly reported symptoms include irritation of the vulva, inadequate vaginal lubrication, burning, dysuria, dyspareunia, and vaginal discharge. Symptoms adversely affecting sexual function are often the most distressing.[12,46,47]

Signs of GSM include labial atrophy, vaginal dryness, introital stenosis, clitoral atrophy, and phimosis of the prepuce. Severe GSM can result in a vaginal surface that is friable and hypopigmented, with petechiae, ulcerations, and tears, as well as urethral findings such as caruncles, prolapse, or polyps. Bleeding may occur from minimal trauma, such as speculum insertion. Genitourinary atrophic changes increase the likelihood of trauma, pain, recurrent UTIs, bleeding with or after sex, and absence of sexual activity.[20,47]

The genitourinary syndrome of menopause most commonly develops in the setting of hypoestrogenism associated with natural menopause. Hypoestrogenic states also may occur in the setting of primary ovarian insufficiency (POI), surgical menopause (bilateral oophorectomy with or without hysterectomy), hypothalamic amenorrhea, the postpartum state and breastfeeding, use of gonadotropin-releasing hormone agonists or aromatase inhibitors (AIs), and cancer treatments such as surgery, pelvic radiation therapy, or chemotherapy that render ovaries inactive, either temporarily or permanently.

Several studies suggest that early estrogen deficiency caused by premature menopause or POI is associated with more severe sexual dysfunction compared with age-matched controls.[48,49] Younger women with vaginal atrophy and dyspareunia may be especially distressed by changes in sexual function.

Women with surgical menopause often present with a more severe GSM symptom profile than do women with natural menopause, likely because of the concomitant, abrupt, and persistent 50% decline in circulating androgen levels that occurs in addition to the loss of estradiol.[50,51] Genitourinary syndrome of menopause that develops in the setting of chemotherapy-induced menopause has been associated in some studies with greater sexual dysfunction and distress[52-54] and with poorer QOL outcomes.[55-58] Younger women with GSM related to induced menopause from cancer treatment may be especially distressed by changes in sexual function.[52,55] The stress, fatigue, and mood changes that accompany a cancer diagnosis and its treatment also contribute to sexual problems.

Aromatase inhibitors reduce breast cancer recurrence by blocking conversion of androgens to estrogens and

inducing a profound estrogen-deficiency state. The magnitude and duration of estrogen deficiency induced by AIs result in the development of severe GSM in most survivors, particularly given that extended duration therapy is now typical.[59-61] Compared with tamoxifen, AIs result in a greater incidence of vaginal dryness and dyspareunia, causing a large percentage of AI users to express dissatisfaction with their sex lives.[60,62-64]

EVALUATION AND DIAGNOSIS

The evaluation of GSM includes a history and pelvic examination. A medical history may identify contributing factors, alternative etiologies, and effective therapeutic interventions. The pelvic examination should identify signs consistent with GSM and eliminate other pathologic conditions that may cause similar symptoms.

History

Because women may not spontaneously report symptoms of GSM and related sexual concerns, providers should inquire about symptoms in all perimenopausal and postmenopausal women as part of a routine review of systems. The EMPOWER survey queried 1,858 menopausal US women with symptoms suggestive of GSM and found that in women who had never used any treatment, almost three-quarters had never discussed their symptoms with a healthcare provider.[6] The main reason for this reticence was the assumption that GSM was simply a natural part of aging with which women needed to live. Results of the *Women's Voices in the Menopause* survey revealed that in more than 1,000 US respondents, one-third of those with vaginal discomfort had not spoken with anyone regarding their condition and one-third preferred that discussion regarding vaginal discomfort be initiated by their healthcare providers.[65]

These survey results underscore the importance of clinicians being proactive in asking menopausal women whether symptoms suggestive of GSM are present. The goal of the history is to determine whether symptoms of GSM are present, whether they are bothersome, and how they affect the woman's sexual health and QOL. In the absence of symptoms, atrophic changes noted on examination do not necessarily require treatment, although women should be informed that these changes may worsen over time without proactive management.

Symptoms similar to GSM result from many other conditions. The differential diagnosis includes allergic or inflammatory conditions (eg, lichen sclerosus, erosive lichen planus, desquamative inflammatory vaginitis, contact dermatitis, and cicatricial pemphigoid), vulvovaginal candidiasis and other infections, trauma, foreign bodies, malignancy, vulvodynia, vestibulodynia, chronic pelvic pain, provoked pelvic floor hypertonia (previously known as vaginismus), and other medical conditions (eg, diabetes, lupus erythematosus) or psychological disorders. An alternate etiology is more likely in women with chronic or recurrent vulvovaginal symptoms that were present before menopause.

Documentation of GSM should include a description of symptoms, including time of onset, duration, level of associated distress, and effect on QOL. A sexual history that includes partner relationship(s), current level and types of sexual activity, and the effect of GSM symptoms on sex life and partner relationships is useful in determining management strategies. Previous interventions should be discussed, including their efficacy and adverse effects.

For a woman with a history of cancer, additional information is relevant, including cancer site, age at diagnosis, hormone receptor status, treatments (past, current), and type of menopause (spontaneous or induced). Cancer treatments, especially surgery and radiation therapy, can damage the vaginal epithelium, the vascular supply, and the anatomy of the vaginal canal. Some treated women experience a narrowed or foreshortened vagina. Genitourinary changes associated with cancer treatments can produce pain with pelvic examinations, dyspareunia, recurrent UTIs, and an increased risk of vaginal infections.[52,66]

Physical examination

The pelvic examination helps to exclude other vulvovaginal conditions that can cause similar symptoms. As GSM progresses, examination of the external genitalia often reveals reduced mons pubis and labia majora bulk, reduced labia minora tissue and pigmentation, and prominence (telescoping) and erythema of the urethral meatus. Urethral caruncle, a benign outgrowth of inflammatory tissue arising from the posterior urethral meatus, is common in postmenopausal women and likely related to hypoestrogenism. The clitoris may recede and in some cases become completely flush with the surrounding tissue. The vestibular tissue may become pale.

If the introitus is noted to be narrow, use of a narrow pediatric vaginal speculum with lubricant is appropriate. The vaginal mucosa may appear smooth (loss of rugation), shiny, and dry. Minimal blunt trauma from the speculum may result in petechiae (reflecting mucosal thinning) or bleeding (friability). With progression of GSM, attenuation of the vaginal fornices may be apparent, and the cervix may appear flush with the vaginal apex.

With atrophic vaginitis, brown or yellow (sometimes malodorous) discharge may be present. With severe GSM, there may be such shortening of the vaginal vault and narrowing of the introitus that speculum insertion and visual inspection of the vaginal vault as well as cervix may not be possible.

Although the vaginal maturation index (VMI) and vaginal pH are routinely assessed in clinical trials, they are not essential to make a diagnosis of GSM in clinical practice. With GSM, vaginal pH is typically greater than 5.0. Wet-mount microscopy shows more than one white blood cell per epithelial cell, immature vaginal epithelial cells with relatively large nuclei (parabasal cells), and reduced or absent lactobacilli. Repopulation with diverse flora can occur,

including enteric organisms commonly associated with UTIs.[67] The appearance of the wet mount in severe GSM may be difficult to distinguish from that of desquamative inflammatory vaginitis or vaginal erosive lichen planus.[68] A culture or vulvovaginal biopsy should be considered if there are atypical findings or if the vulvovaginal symptoms fail to resolve after a trial of vaginal estrogens or DHEA.

A woman's symptoms do not always correlate with physical findings. For example, a woman who is not sexually active may have few symptoms, despite signs of advanced genitourinary atrophy on examination. In contrast, a woman with an active sex life may complain of dryness and discomfort with sex, whereas the pelvic examination suggests only mild atrophy. Of note, women who are not sexually active also may be bothered by symptoms related to GSM, including discomfort with exercise or dysuria and benefit from treatment. Thus, both history and examination are essential to making a correct diagnosis.

TREATMENT

The primary goal of treating GSM is to alleviate symptoms. For the woman with GSM, after excluding other causes of her symptoms, treatment can be approached in a stepwise fashion based on symptom severity. First-line therapies for less-severe symptoms include nonhormone vulvar and vaginal lubricants with sexual activity and long-acting vaginal moisturizers used regularly (several times/wk). Although not supported by clinical trials, regular, gentle vaginal stretching exercises (eg, pain-free insertion of a finger or dilator) or sexual activity may reduce GSM symptoms. Prescription therapies include low-dose vaginal estrogens, vaginal DHEA inserts, and oral ospemifene. For women with moderate to severe dyspareunia associated with GSM with concurrent VMS, transdermal and oral HT are effective options. Symptom reduction may take 1 to 3 months, and continued therapy is generally required because symptoms are likely to recur on cessation of treatment. Outcomes data on the symptom recurrence rate are lacking.

Some women may already have vaginal narrowing or provoked pelvic floor hypertonia limiting vaginal penetration. Gentle stretching of the vagina with the use of lubricated vaginal dilators of graduated sizes (or an expandable dilator) can play an important role in restoring and maintaining vaginal function for penetration. Reinitiating regular sexual activity once vaginal penetration is again comfortable, if desired, may help to maintain vaginal pliability. Many women with this condition benefit from referral for pelvic floor physical therapy (PFPT).[69,70] Starting pharmacologic treatment to restore tissue integrity before initiating vaginal dilatation and/or PFPT may facilitate progress.

Nonprescription therapies

Lubricants and moisturizers

First-line therapies to alleviate symptoms of GSM include over-the-counter (OTC) nonhormone vaginal lubricants and moisturizers, a number of which are available (Table 1), but few clinical studies have been conducted on the efficacy of these products.

TABLE 1. *Examples of nonhormone therapeutic options for dyspareunia secondary to GSM*

Lubricants	Moisturizers
Water based	Replens
Astroglide Liquid	Me Again
Astroglide Gel Liquid	Femincase
Astroglide	K-Y SILK-E
Good Clean Love	Luvena
Just Like Me	Revaree
K-Y Jelly	Silken Secret
Pre-Seed	Hyalo-gyn
Slippery Stuff	
Liquid Silk	
YES WB	
SYLK	
Sliquid	
Silicone based	
Astroglide X	
ID Millennium	
K-Y Intrigue	
Pink	
Pjur Eros	
Uberlube	
Sliquid	
Oil based	
Elégance Women's Lubricants	
Olive oil	
YES OB	

A vaginal moisturizer is a bioadhesive product used regularly, most often two to three times a week, irrespective of the timing of sexual activity. The goal of use is to reduce daily symptoms of GSM as well as to facilitate comfortable sexual activity. Data suggesting improvement in genitourinary symptoms with nonhormone treatments are sparse, and to date, there are no adequately powered, randomized, double-blind, placebo controlled studies directly comparing low-dose vaginal estrogen therapies or vaginal DHEA with commonly used nonhormone treatments. One randomized, controlled, but short-term study demonstrated effectiveness of a pH-balanced gel compared with placebo in women treated for breast cancer. Mild irritation with administration was noted.[71] In a randomized, controlled trial (RCT; N = 302), a significant improvement in most bothersome symptom severity was seen in all three arms: the vaginal estradiol tablet (plus placebo gel), vaginal moisturizer (plus placebo tablet), and dual placebo arms.[72] In that trial, the placebo gel likely had lubricating properties.

Vaginal lubricants are used by both (or all) partners to decrease discomfort caused by friction during sex. Regular use has also been associated with increase in pleasure and ease of orgasm.[73] In a review and meta-analysis, the effect of lubricant use on symptom severity could not be compared in studies because of heterogeneity. However, the meta-analysis of sexual function outcomes showed a small advantage to hormone-based therapies over lubricants in restoring sexual function.[74] One small crossover study in survivors of breast cancer demonstrated greater benefit with silicone-based lubricants compared with water based.[75]

In studies examining the safety of personal moisturizers and lubricants, investigators found that a number of water-based products are hyperosmolar.[76,77] This characteristic is associated with epithelial cellular toxicity and damage in cultures of epithelial cells and ectocervical explants. Near iso-osmolar and silicone-based lubricants did not have this effect. The World Health Organization recommends an osmolarity of less than 1,200 mOsm/kg.[78] One jelly and one moisturizer also were found to be toxic to lactobacilli. There are very few data on the health and safety effects of lubricants that contain flavors (sugar), warming properties, or solvents and preservatives such as propylene glycol and parabens. One study on the use of vaginal products in women aged 18 to 65 years reported a 2.2-fold risk of BV in women using petroleum jelly compared with controls and increased colonization with candida species with users of oils compared with nonusers.[79]

Because there are no published reports on the irritation potential of OTC vaginal lubricants and moisturizers, women can test these on a small patch of skin for 24 hours before using them intravaginally. If the product they test successfully on the skin still causes irritation in the vagina, a woman can switch to an iso-osmolar, propylene glycol-free, or silicone-based product (Table 1). It is noteworthy that oil-based lubricants can erode condoms; however, most brands of water-based and silicone-based lubricants are latex safe and condom compatible.

Hyaluronic acid

Hyaluronic acid is a polymer found in cartilage and other soft tissues in the body that is added to many commercial skincare and wound-healing products because of its purported effect of drawing moisture to any area to which it is applied. In four small RCTs comparing hyaluronic acid to placebo or vaginal ET, the former was associated with a similar decrease in severity of dryness and dyspareunia.[80-83] To date, there is no evidence that products with hyaluronic acid have a greater benefit than nonhyaluronic acid lubricants or moisturizers.

Herbal products

Herbal products appear ineffective for GSM. The Herbal Alternatives for Menopause study, a double-blind RCT in 351 women, identified no change in vaginal dryness, vaginal cytology, follicle-stimulating hormone or estradiol levels following treatment for 1 year with black cohosh, a multibotanical supplement, or soy.[84]

Prescription therapies

For women with persistent GSM symptoms after nonhormone interventions, prescription therapies may provide greater benefit.

Vaginal estrogen

Estrogen delivered vaginally provides sufficient estrogen to relieve genitourinary symptoms with minimal absorption and is preferred over systemic therapy when only genitourinary symptoms are present.[85,86] When systemic HT is needed to treat other menopause symptoms, a woman also will generally derive satisfactory resolution of her genitourinary symptoms, although additional low-dose vaginal estrogen may be added if needed.

Efficacy studies of low-dose vaginal ET use both subjective and objective outcome measures. Subjective effects are often assessed using patient-reported outcome measures that include improvements in symptoms such as dyspareunia, vaginal dryness, and lower urinary tract symptoms and clinician-reported outcomes such as the appearance of the vulvovaginal tissues. Objective outcomes include decreases in vaginal pH, increases in the number of vaginal lactobacilli, and favorable shifts in the vaginal and/or urethral cytology (greater numbers and percentages of superficial cells and fewer numbers and percentages of parabasal cells).[87,88]

Efficacy

Low-dose vaginal ET is available in several forms, including cream (estradiol, estrone, and conjugated estrogens), a slow-release estradiol intravaginal ring, and an estradiol vaginal tablet and insert. Products vary in dosage and formulation (Table 2).[89-97] All approved products have proven efficacy in placebo-controlled RCTs.[86,98-111] In the United States, FDA requires efficacy data for treatment of a specific, most bothersome symptom, which includes dyspareunia, vaginal dryness, vaginal/vulvar irritation, vaginal soreness, dysuria, or bleeding associated with sexual activity. Dyspareunia and vaginal dryness are the most common indications for low-dose vaginal ET.

The comparative efficacy of the various forms of vaginal ET was evaluated in a 2016 Cochrane review comparing 19 trials.[112] This review concluded that all tested products alleviated symptoms of vaginal dryness and dyspareunia with similar efficacy. Comparative analyses of these trials are limited by variations in methods and outcome measures, small sample sizes, lack of blinding, and substantial heterogeneity of results. Some trials of the same estrogen preparation used different doses or dosing schedules. Some trials included preparations not approved for use in the United States or in Canada.

Vaginal estrogen and urinary symptoms

In a 2014 systematic review that included 44 RCTs, assessment of urinary symptoms was variable, leading to a lower quality of evidence for the effectiveness of vaginal estrogen for urinary symptoms compared with vulvovaginal symptoms.[113] This review reported moderate-quality evidence supporting vaginal ET in the treatment of urge incontinence and recurrent UTIs and low or very-low quality evidence supporting the use of vaginal ET for improvement of dysuria, urinary frequency and urgency, nocturia, and stress incontinence.

A Cochrane review of vaginal ET for urinary incontinence determined that vaginal ET improves incontinence (relative risk [RR], 0.74; 95% confidence interval [CI], 0.64-0.86) but

TABLE 2. *Government-approved therapies for genitourinary syndrome of menopause in the United States and Canada*

Type	Composition	Product name	Commonly used starting dose	Commonly used maintenance dose	Typical serum estradiol level (pg/mL)
Vaginal creams	17B-estradiol 0.01% (0.1 mg active ingredient/g)	Estrace vaginal cream[a]	0.5-1 g/d for 2 wk	0.5-1 g 1-3 times/wk	Variable
	Conjugated estrogens (0.625 mg active ingredient/g)	Premarin vaginal cream	0.5-1 g/d for 2 wk	0.5-1 g 1-3 times/wk	Variable
	Estrone 0.1% (1 mg active ingredient/g)	Estragyn vaginal cream[b]		0.5-4 g/d, intended for short-term use; progestogen recommended	Variable
Vaginal inserts	17B estradiol inserts	Imvexxy[a]	4 or 10 μg/d for 2 wk	1 insert twice/wk	3.6 (4 μg) 4.6 (10 μg)
	Estradiol hemihydrate tablets	Vagifem Yuvafem	10 μg/d for 2 wk	1 tablet twice/wk	5.5
	Prasterone (DHEA) inserts	Intrarosa	6.5 mg/d	1 insert/d	5
Vaginal ring	17β estradiol	Estring	2 mg ring releases approx 7.5 μg/d	Replace ring every 90 days	8
Oral tablet	Ospemifene	Osphena[a]	60 mg/d	1 tablet by mouth/d	N/A

DHEA, dehydroepiandrosterone.
Products not marked are available in both the United States and Canada.
[a]Available in the United States but not Canada.
[b]Available in Canada but not the United States.
Estrace[89]; Premarin[90]; Estragyn[91]; Imvexxy[92]; Vagifem[93]; Yuvafem[94]; Intrarosa[95]; Estring[96]; Osphena.[97]

that systemic estrogen alone and in combination with a progestogen worsens incontinence (RR, 1.32; 95% CI, 1.17-1.48 and RR, 1.11; 95% CI, 1.04-1.18, respectively).[114] Most of these studies were conducted for reasons other than urinary symptoms, failed to use validated tools to assess symptom severity and QOL, and showed statistically significant but not clinically relevant changes. For example, in the Heart and Estrogen/Progestin Replacement Study, women randomized to systemic oral estrogen plus progestogen therapy experienced 0.7 more leak episodes per week compared with 0.1 fewer episodes in the placebo group, but both changes met the a priori definition of "no change in incontinence severity."[115]

Few trials have been conducted comparing vaginal ET to other treatments for postmenopausal urinary tract symptoms. Two small trials comparing vaginal ET (conjugated equine estrogens) to pelvic floor muscle therapy (PFMT) for urinary incontinence favored PFMT over vaginal estrogen,[114] but a trial that compared estriol alone to estriol combined with pelvic floor rehabilitation favored combined therapy.[69] A comparison of the estradiol ring to oral oxybutynin showed similar efficacy for treatment of overactive bladder but with different AEs; oxybutynin resulted in more dry mouth, constipation, and blurry vision, whereas the estradiol ring resulted in more vaginal discharge.[116] When women present with both vulvovaginal and urinary symptoms, an initial trial of vaginal ET is prudent. If urinary symptoms are not sufficiently improved or resolved after 3 months of vaginal ET, the use of other evidence-based therapies for urinary tract symptoms is warranted.[117]

Recurrent UTI, defined as the occurrence of two culture-proven UTIs in 6 months or three culture-proven UTIs in 1 year, commonly affects postmenopausal women and is a component of GSM.[118] Treatment of GSM with vaginal ET (conjugated equine estrogen cream or low-dose estradiol vaginal ring) in a small RCT reduced the frequency of recurrent UTIs in postmenopausal women.[119] An RCT of vaginal estriol cream (0.5 mg) in postmenopausal women with recurrent UTIs led to a significant decrease in number of UTI episodes per year (0.5 compared with 5.9).[120] In another randomized trial, the low-dose estradiol ring was found to prolong the time to next recurrence in postmenopausal women with recurrent UTIs and to decrease the number of recurrences per year (RR, 0.64).[121]

Women who use a vaginal pessary for treatment of uterovaginal prolapse are often advised to use vaginal ET to facilitate pessary use and to limit potential complications such as vaginal discharge and vaginal wall erosions. Prospective data are lacking, but observational studies show lower discontinuation rates and less vaginal discharge when pessary users are treated with vaginal ET.[122]

Safety

Low-dose vaginal ET has a more favorable risk profile than systemic ET because estrogen doses are significantly lower (Table 2).[89-97] Estrogens are systemically absorbed from the vagina in a dose-dependent manner, and in general, serum estrogen levels reported with use of low-dose vaginal ET remain within the postmenopause range.[123] A review of systemic estradiol measurements reported baseline levels in normal, untreated postmenopausal women of 3.1 pg/mL to 4.9 pg/mL using highly sensitive assays such as liquid or gas chromatography/mass spectroscopy and levels that were undetectable to 10.5 pg/mL using the less-sensitive radioimmunoassay.[85] Serum estradiol levels with use of the low-dose vaginal ring (releasing approximately 7.5 μg/d) ranged from 5 pg/mL to 10 pg/mL.[107,124,125] Serum estradiol levels with use of the 10-μg vaginal tablet ranged from 3 pg/mL

to 11 pg/mL.[126-128] Serum estradiol levels after daily use of the 4-μg and 10-μg vaginal insert for 14 days were 3.6 pg/mL and 4.6 pg/mL, respectively, which was not statistically different from placebo (4.3 pg/mL). After twice weekly use for 84 days, there was no difference in serum estradiol levels compared with baseline or placebo.

Serum estradiol levels associated with use of vaginal estradiol cream are derived from older data using higher doses and less-sensitive assays that lack accuracy for lower estrogen levels.[129] Use of estradiol cream 0.5 mg (500 μg) daily for 3 weeks resulted in no change in serum estradiol levels.[130] In contrast, another study showed that daily use of estradiol cream 0.2 mg (200 μg) daily resulted in serum estradiol levels that rose from a baseline of 16.6 pg/mL to 37.2 pg/mL after 3 weeks of use.[131] Use of 0.3 mg conjugated estrogens (CE) cream 3 times weekly for 6 months produced no change in serum estradiol or estrone levels.[132] Of note, CE contains a significant number of compounds, some estrogenic and some antiestrogenic, so serum estradiol and estrone levels after use of CE may not reflect actual estrogenic activity. Vaginal bleeding, breast pain, and nausea have been reported in some trials of vaginal estrogen cream. These symptoms are dose related and suggest that the dose was large enough to result in significant systemic absorption.

Adverse events associated with use of vaginal ET include vaginal discharge, vulvovaginal candidiasis, vaginal bleeding, and breast pain. Differing AE profiles may reflect variations in product formulation and dose.[133,134]

The risks typically associated with systemic ET, including breast and endometrial cancer and cardiovascular disease (CVD), have been evaluated in several trials of vaginal ET. Clinical trial data beyond 1 year are lacking, however, because the longest duration of any RCT was 52 weeks.[135] Endometrial safety was assessed in two systematic reviews that included RCTs and large observational studies.[136,137] In 20 RCTs, 2,983 women were exposed to vaginal ET for up to 1 year. There was one case of endometrial cancer (0.03%) and 12 cases of endometrial hyperplasia (0.4%). The cases were sporadic and their incidence similar to the baseline rate in the general population. A 2016 Cochrane review of RCTs reported no significant differences among vaginal estrogen formulations in terms of endometrial thickness or hyperplasia or the proportion of women with AEs.[112] Large observational studies evaluating longer exposures to vaginal ET identified no increase in endometrial cancer. In the Women's Health Initiative-Observational Study, the rate of endometrial cancer was not statistically different in users of vaginal ET compared with nonusers (1.3 vs 1 case per 1,000 woman-years, respectively). Thus, occurrence of endometrial cancer and hyperplasia with low-dose vaginal ET use is rare and consistent with rates in the general population.

The risk of venous thromboembolism (VTE) was not increased with vaginal ET use in a 2016 Cochrane review, a 2020 systematic review of RCTs, and three large observational studies.[112,135,137-139] Of note, systematic, prospective data for women at high risk of VTE are lacking.

A prospective cohort study of approximately 45,000 women in the Women's Health Initiative Observational Study examined risks associated with vaginal ET use. Outcomes assessed included coronary heart disease (CHD), invasive breast cancer, stroke, pulmonary embolism, hip fracture, colorectal cancer, endometrial cancer, and death. The findings were very reassuring, with no increased risk of CVD or cancer in postmenopausal women using vaginal estrogens.[135] Another prospective cohort study of approximately 54,000 postmenopausal women in the Nurses' Health Study also was very reassuring regarding the safety of vaginal ET. There was no increase in health outcomes assessed with vaginal ET use, including CVD (total myocardial infarction, stroke, pulmonary embolism/VTE), hip fracture, and cancer (total invasive, breast, endometrial, ovarian, and colorectal).[138] In a 2019 meta-analysis, investigators used individual participant data from 58 observational studies reported between 1992 and 2018 to assess associations between hormone therapy and breast cancer.[140] Use of vaginal estrogen was not found to be associated with risk of breast cancer.

Potential contraindications to vaginal estrogen therapy

Although most women with GSM are candidates for low-dose vaginal ET, use is contraindicated in women with undiagnosed vaginal/uterine bleeding and should be used with caution in women with estrogen-dependent neoplasia. Management of GSM in women with nonhormone-dependent cancers is similar to that for women without a cancer history. Low-dose vaginal ET has not been studied in women at increased risk of thrombosis, but may be used with caution given minimal systemic absorption, the absence of a hepatic first-pass effect, and minimal, if any, effect on prothrombotic factors. Of note, in large observational studies, neither vaginal estrogen nor systemic transdermal formulations of ET have been associated with an increased risk of VTE.[139]

Although circulating estrogen concentrations generally remain within the menopause range with low-dose vaginal ET, the package insert for these products includes the same boxed warning regarding risk of endometrial cancer, breast cancer, cardiovascular disorders, and probable dementia that accompanies systemic HT products. Women must be educated about the differences between low-dose vaginal and systemic ET and be prepared for the boxed warning, or else they may not initiate prescribed treatment.

Vaginal estrogen products

Several low-dose vaginal estrogen products have been government approved for use in the United States and Canada, including cream (estradiol, estrone, and conjugated estrogens), a slow-release estradiol intravaginal ring, and an estradiol vaginal tablet and insert (Table 2).[89-97] Vaginal estrogen creams are generally used two to three times weekly, estradiol tablets and inserts used twice weekly, and the estradiol ring changed every 3 months. Estrogen creams, tablets and inserts are used daily for 2 weeks at the initiation of treatment for more rapid improvement in symptoms (Table 2).[89-97] One vaginal ET

product (Femring) delivers a *systemic* dose of estradiol and is approved for the treatment of VMS in addition to GSM.[141] Femring should not be confused with Estring, which delivers a low dose of estradiol and is indicated only for GSM. There are no data to suggest an advantage for initial use of combined systemic and vaginal estrogen in cases of severe GSM.

Therapy with low-dose vaginal estrogen can be individualized to identify the lowest dose and frequency of use that provides the desired effect. Although efficacy is similar among the available products, estrogen creams dispensed with an applicator may offer more immediate soothing relief of symptoms, possibly because of the emollient nature of the carrier. Another potential advantage of the creams is that they can be digitally applied directly to the vulvar and vestibular tissues. However, some women consider the creams messy, and some report sensitivity to the vehicle used in the creams. With estrogen cream delivery, the user has the responsibility of preparing the dose because the amount of cream inserted is not in a prepackaged dosing unit—potentially leading to use of higher-than-recommended doses. The clinical implications of potential male partner estrogen absorption remain unknown.

Low-dose estradiol tablets and inserts are convenient, fixed-dose vaginal estrogen formulations. Although two doses of the vaginal tablet (25 μg and 10 μg) were shown to be effective, only the lower dose (10 μg) is available in the United States and Canada.[101,102,107-109,111,142] There are two approved doses of the vaginal insert (4 μg and 10 μg), with the 4-μg dose providing the lowest available formulation of vaginal ET.[143-145]

The sustained-release, low-dose estradiol vaginal ring provides 90 days of continuous estradiol. Effective relief of genitourinary symptoms, including dyspareunia, dysuria, and urge incontinence, has been consistently documented in RCTs with this estrogen delivery system.[99,100,103-107] The estradiol ring may change position or dislodge with bowel movements, Valsalva maneuvers, douching, or vaginal sexual penetration, particularly in women with uterovaginal prolapse or hysterectomy. Vaginal ring users are encouraged to remove and replace their own vaginal rings unless discomfort or limited dexterity makes such self-care difficult. The ring can remain in the vagina during sexual activity. There are no data to suggest an allergic reaction to the silicone product. If there is significant stenosis of the vagina, regular use of graduated vaginal dilators after initiation of estrogen cream, tablet, or insert may be necessary before an estrogen ring can be inserted.

Given similar efficacy among vaginal estrogen formulations, women should be provided with information on all options, with personal preference guiding choice. Although some women prefer estrogen creams to allow for vulvar and vestibular as well as vaginal application, others find creams messy and dislike cleaning the applicator after use. Because creams do not provide a specific, fixed dose of estrogen, other options may be preferred if careful dosing and predictable results of serum estrogen levels are desired. Vaginal estradiol tablets and inserts are convenient, requiring only twice weekly application after 2 weeks of daily use. The tablet is placed in the vagina with a plastic applicator, whereas the insert is placed with a finger. Preference for insertion method may determine product choice. For women who are comfortable using a vaginal ring, this formulation is convenient, requiring placing a new ring only four times yearly. Vaginal estrogen formulations are often costly, and variation in price, depending on a woman's particular insurance coverage, also may be a factor in product choice.

Vaginal dehydroepiandrosterone

Dehydroepiandrosterone (also known as prasterone) is a steroid hormone that is an intermediate in the biosynthesis of androgens and estrogens. A low-dose DHEA vaginal insert used daily with an applicator is approved in the United States and Canada for the treatment of moderate to severe dyspareunia in menopausal women (Table 2).[89-97] Dehydroepiandrosterone is transformed by vaginal mucosal cells to estrogens, including estradiol, and to androgens, including testosterone.[146] Twelve-week RCTs have demonstrated the efficacy of DHEA 6.5 mg daily in improving the VMI, vaginal pH, dyspareunia, and vaginal dryness in menopausal women with GSM. Vaginal discharge was the most common AE, reported by 6% of study participants. In 422 women receiving DHEA for 52 weeks, endometrial sampling demonstrated inactive or atrophic endometrium in all participants.[147]

Ospemifene

Ospemifene is an estrogen agonist/antagonist and the only orally available product approved for treatment of vaginal dryness and moderate to severe dyspareunia. It is available in the United States, but not in Canada.[97,148] Twelve-week RCTs have demonstrated the efficacy of ospemifene 60 mg daily in improving VMI, vaginal pH, dyspareunia, vaginal dryness, and genital exam findings.[149-151] A 52-week efficacy and safety extension study in 180 women showed sustained improvements on visual examination of the vagina, with no cases of VTE, endometrial hyperplasia, or cancer.[152] Vasomotor symptoms were the most common AE, with rates of 2% in the placebo group and 7.2% in the group taking 60 mg of ospemifene. Ospemifene was shown to reduce recurrent UTIs in a 6-month retrospective observational study.[153]

The prescribing information for ospemifene contains precautions similar to those for estrogens and other estrogen agonist/antagonists, including an increased risk of endometrial cancer and CVD.[97] With regard to breast cancer, labeling states that ospemifene should not be used in women with known or suspected breast cancer because the drug has not been adequately studied in this group. Ospemifene has, however, demonstrated antiestrogenic activity in preclinical models of breast cancer.[154] In ex vivo human breast tissue, ospemifene inhibited proliferation and opposed stimulation caused by estradiol similar to but not as potently as the estrogen agonist/antagonists tamoxifen and raloxifene.[155] Ospemifene 60 mg has been associated with decreased risk

for breast cancer and breast cancer recurrence in preliminary studies.[156]

Duration of therapy and monitoring

Improvement in GSM symptoms typically occurs within a few weeks of starting therapy[157]; however, treatment for 12 weeks may be needed for maximum benefit. In the absence of contraindications, therapy should be continued as long as needed for symptom management as symptoms will recur upon discontinuation. Clinical trial safety data are limited to 1 year, but observational studies demonstrate safety with long-term use.

Based on available limited safety data, use of a progestogen[112,126] and routine endometrial surveillance[112,158,159] are not recommended in low-risk women using low-dose vaginal ET. Women at increased risk of endometrial cancer because of obesity or diabetes may warrant endometrial surveillance. Because uterine bleeding is generally a sign of endometrial proliferation, any spotting or bleeding requires a thorough evaluation that may include transvaginal ultrasound (TVU) and/or endometrial biopsy.

Testosterone

Topical testosterone cream has been used for the treatment of vulvovaginal conditions, including lichen sclerosus and vestibulodynia, despite limited efficacy data.[160,161] Although not government approved for this indication, there are limited data supporting the use of vaginal testosterone cream for the treatment for GSM. A 4-week pilot trial of 20 postmenopausal women with breast cancer found that vaginal testosterone (150 μg and 300 μg) improved dyspareunia, vaginal dryness, and VMI without increasing estradiol; median testosterone level increased from 15.5 ng/dL to 21.5 ng/dL ($P = .02$).[162] A 12-week RCT in 76 menopausal women taking AIs after treatment for early stage breast cancer who reported vaginal dryness, dyspareunia, or reduced libido compared the low-dose estradiol vaginal ring with compounded vaginal testosterone cream. Symptoms of GSM and sexual desire improved in both treatment arms. The observation that levels of serum estradiol were increased in trial participants at baseline complicates interpretation of these findings.[163] Existing clinical trial data are insufficient to recommend the use of vaginal testosterone for GSM.[164] Longer and larger studies are needed to assess safety and efficacy.

Energy-based therapies

Vulvovaginal energy-based devices including lasers (fractional CO_2, Erbium:YAG) and radio-frequency devices are under investigation as treatments for GSM, but none have FDA approval for this indication. In a 2018 Safety Communication, FDA issued a public warning about the use of these devices for vaginal cosmetic purposes, stating that the effectiveness and safety of the devices have not yet been established.[165]

Vulvovaginal energy-based devices are thought to improve vaginal health by causing microtrauma, which induces collagen formation, angiogenesis, and epithelial thickening. The fractional CO_2 laser has demonstrated safety and efficacy in tissues of the skin, face, and neck.[166-169] Using a probe adapted to the vagina, fractional CO_2 vaginal laser therapy induces similar morphologic changes in the vagina, and data from small studies support improvement in GSM symptoms of vaginal dryness and dyspareunia.[170-178] Several RCTs have compared laser therapy to vaginal ET. Overall, no treatment was superior to another, and the studies were not designed to assess noninferiority.[179-182] Radiofrequency devices are nonablative and emit focused electromagnetic waves that heat the superficial layers of the tissue. Several RCTs evaluating the efficacy of energy-based devices in the treatment of GSM are in progress.

Safety

Adverse events associated with energy-based therapies include discomfort during treatments, vaginal scarring, vaginal lacerations on resumption of intercourse, and persistent and/or worsening dyspareunia.[183] These treatments are costly and generally not covered by insurers.

Consensus statements regarding the use of energy-based therapies for GSM treatment have been published by several professional societies summarizing the small but growing body of evidence as well as concerns about safety.[184-187] Additional randomized, prospective, sham-controlled trials of adequate size and scope are necessary before these therapies can be routinely recommended for treatment of GSM.

Treatment considerations in women with breast cancer

Treatment of GSM in women with breast cancer can be complicated by 1) adjuvant treatment (AIs or tamoxifen), which lower estrogen concentrations or antagonize estrogen effects; 2) product labeling; 3) limited clinical trial data in patients with breast cancer or survivors; and 4) absence of agreement between the oncology community and other practitioners involved in genitourinary and sexual healthcare. Many women with breast cancer and GSM will benefit from the regular use of vaginal moisturizers, lubricants for sexual activity, and PFPT. For persistent symptoms, other therapies may be beneficial, including topical lidocaine, low-dose vaginal ET, vaginal DHEA, ospemifene, and vaginal energy-based therapies.[188-191]

For women with breast cancer, low-dose vaginal ET is contraindicated according to FDA class labeling. However, off-label use of several products may be acceptable because of their very low systemic absorption.[192] Low-dose vaginal ET formulations, including the estradiol tablet, insert, and ring, result in serum estradiol within the postmenopausal range and similar to placebo.[145,146] Several organizations, including the American College of Obstetricians and Gynecologists, have endorsed the use of low-dose vaginal estrogens in women with breast cancer, including ER-positive disease. A systematic review and meta-analysis also suggests safety, based on the use of low-dose vaginal ET in survivors of breast cancer using concomitant AIs.[193] Many oncologists allow the use of low-dose vaginal ET or vaginal DHEA in their patients with

breast cancer when GSM symptoms persist after trials of nonhormone interventions and QOL is adversely affected.

Use of vaginal DHEA for GSM in women with breast cancer is not contraindicated, but US labeling advises caution because estrogen is a metabolite of DHEA.[95] Although vaginal DHEA has not been studied in women with a history of breast cancer, levels of estradiol and testosterone remain within the postmenopause range.[194]

Ospemifene is not recommended for treatment of GSM in women with known or suspected breast cancer because the drug has not been adequately studied in this group. Preliminary data on ospemifene suggest both a decreased risk of incident breast cancer and a reduced risk of breast cancer recurrence with this therapy.[156]

Clinical trials of laser therapy for GSM in survivors of breast cancer provide limited evidence for safety and efficacy in this patient population.[195-197] These studies generally do not have either a positive or sham control, a shortcoming of many of the studies on these devices.

Education

Healthcare providers should educate women about GSM and the urogenital changes that often occur with menopause. Many women are unaware that vaginal dryness, recurrent UTIs, discomfort with sexual activity, and other GSM symptoms are a consequence of estrogen deficiency. Unlike VMS that typically improve with time, GSM symptoms often worsen in the absence of treatment. Women also may not know that effective and safe OTC and prescription therapies are available. Women who are sexually active are more likely to notice GSM symptoms and seek care, but sexually inactive women also will benefit from education about GSM. Women who are concerned about future urogenital function may consider *preventive* use of lubricants, moisturizers, vaginal dilators, or prescription therapies, but there is no evidence to support this approach. It is unknown whether treatment to preserve sexual function or prevent the future occurrence of GSM is indicated in the absence of urogenital symptoms.

CONCLUSIONS AND RECOMMENDATIONS

- Education about and screening for GSM is recommended for perimenopausal and postmenopausal women. [Level C]
- First-line therapies for women with GSM include nonhormone lubricants with sexual activity and regular use of long-acting vaginal moisturizers. [Level A]
- For women with moderate to severe GSM and those who do not respond to lubricants and moisturizers, several safe and effective options are available:
  - Low-dose vaginal ET [Level A]
  - Vaginal DHEA [Level A]
  - Ospemifene [Level A]
  - Systemic ET (when VMS are also present) [Level A]
- For women with a history of breast or endometrial cancer, management depends on a woman's preferences, symptom severity, and understanding of potential risks after consultation with her oncologist. [Level C]
- Although product labeling for low-dose vaginal ET notes risks associated with systemic HT (including CHD, stroke, VTE, breast and endometrial cancer), these risks are highly unlikely given minimal systemic absorption and reassuring findings from clinical trials and observational studies. [Level B]
- Use of a progestogen is not recommended with low-dose vaginal ET, although women at increased risk of endometrial cancer may warrant endometrial surveillance. Endometrial safety clinical trial data are not available for use longer than 1 year, although observational studies are reassuring regarding longer-term use. [Level B]
- Routine endometrial surveillance is not recommended for asymptomatic women using low dose vaginal ET. Transvaginal ultrasound or intermittent progestogen therapy may be considered for women at increased risk of endometrial cancer. [Level C]
- Spotting or bleeding in a postmenopausal woman requires a thorough evaluation that may include TVU and/or endometrial biopsy. [Level A]
- Energy-based therapies, including vaginal laser and radiofrequency devices, require long-term, sham-controlled safety and efficacy studies before their routine use can be recommended. [Level C]
- Therapy for GSM should be continued, with appropriate clinical follow up, for as long as bothersome symptoms are present. [Level C]

Strength of Recommendation

- Level A Supported by sufficient, consistent scientific evidence
- Level B Supported by limited or inconsistent evidence
- Level C Based primarily on expert opinion

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Implant-Based Breast Reconstruction after Risk-Reducing Mastectomy in BRCA Mutation Carriers: A Single-Center Retrospective Study

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Abstract: Women with BRCA gene mutations have a higher lifetime risk of developing breast cancer. Furthermore, cancer is usually diagnosed at a younger age compared to the wild-type counterpart. Strategies for risk management include intensive surveillance or risk-reducing mastectomy. The latter provides a significant reduction of the risk of developing breast cancer, simultaneously ensuring a natural breast appearance due to the preservation of the skin envelope and the nipple-areola complex. Implant-based breast reconstruction is the most common technique after risk-reducing surgery and can be achieved with either a submuscular or a prepectoral approach, in one or multiple stages. This study analyzes the outcomes of the different reconstructive techniques through a retrospective review on 46 breasts of a consecutive, single-center case series. Data analysis was carried out with EpiInfo version 7.2. Results of this study show no significant differences in postoperative complications between two-stage tissue expander/implant reconstruction and direct-to-implant (DTI) reconstruction, with DTI having superior aesthetic outcomes, especially in the prepectoral subgroup. In our experience, the DTI prepectoral approach has proven to be a safe and less time-consuming alternative to the submuscular two-stage technique, providing a pleasant reconstructed breast and overcoming the drawbacks of subpectoral implant placement.

Keywords: breast cancer; BRCA mutation; risk-reducing mastectomy; breast reconstruction; direct-to-implant breast reconstruction; prepectoral breast reconstruction; acellular dermal matrix

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1. Introduction

Patients with mutations in BRCA 1 and BRCA 2 genes have an increased chance of developing breast cancer, with a reported lifetime risk ranging from 56% to 84%. The diagnosis is often made at a younger age if compared to the healthy non-carrier population [1–7]. BRCA-mutated patients can undergo a close clinical and instrumental follow-up, aiming at early diagnosis, or can opt for risk-reducing mastectomy (RRM), with the latter becoming progressively popular after 2013 due to the so-called "Angelina Jolie effect" [8]. The comparison between the two options has shown that risk-reducing surgery, eliminating the potential source of the disease, provides a better protection against breast cancer than intensive screening alone [9–11], decreasing the risk by 90–95% [12–14]. In the setting of risk-reducing surgery, nipple-sparing mastectomy (NSM) is considered the technique of choice, especially for patients with mild-to-moderate breast size, thanks to its superior cosmetic results and improved patient-reported satisfaction [15,16]. Skin-reducing mastectomy (SRM) is a feasible option in case of large breasts that require correction of ptosis [17]. Almost every patient who undergo risk-reducing mastectomy ask for breast reconstruction, with the majority of them opting for implant-based approaches instead of flap-based or combined ones [18–21]. Implants can be placed either over or under the pectoralis major

muscle, in two stages or in a single-stage procedure, also referred as direct-to-implant (DTI) reconstruction [22]. However, the ideal timing of breast reconstruction and the optimal location of prosthetic implants are still debated and change over time following the advancements in reconstructive surgery [23]. Techniques have gradually shifted from two-stage fully submuscular tissue expander (TE)-assisted reconstruction to single-stage partially submuscular (dual-plane) and prepectoral reconstruction. Therefore, in recent years, the direct-to-implant approach has become widespread, representing a true paradigm shift in breast reconstruction [24]. This is mainly due to several factors: the improvement in mastectomy techniques and surgical skills, the growing trend in skin- and nipple-sparing mastectomies [25], the introduction of hybrid breast reconstruction with the use of additional ancillary procedures like fat grafting [26] and the development of new tissue perfusion assessment tools such as indocyanine green (ICG) fluorescence angiography [27]. Moreover, the advent of bioengineered acellular dermal matrices (ADM) has represented another critical aspect that contributed to this shift [28–30]. ADMs are ready-to-use, non-immunogenic biocompatible materials that integrate with the host's tissues and promote tissue vascularization and cellular proliferation. The introduction of ADMs in the surgeon's armamentarium have allowed a dramatic increase in the reconstructive potentialities in the field of breast reconstruction, thanks to their ability to provide additional coverage to the implants, especially if they are placed directly under the subcutaneous tissue, to actively shape the lower pole and to reduce the rates of capsular contracture [31].

To date, the choice of the appropriate procedure among the broad reconstructive scenario (one-stage vs. two-stage, prepectoral vs. partially or totally subpectoral) is made upon surgeon's preferences, but must be based on patient's requirements, careful patient selection and meticulous evaluation of potential risk factors [32].

The aim of this study is to analyze, through a retrospective analysis of a consecutive single-center case series, the comparative outcomes of the different implant-based reconstructive techniques, and orient clinical decisions in the setting of breast reconstruction after risk-reducing mastectomy.

2. Materials and Methods

2.1. Study Design and Patient Selection

This study was designed as a single-center case series and was performed through a retrospective review of 32 consecutive BRCA-mutated women (46 breasts) who underwent bilateral or unilateral risk-reducing mastectomy and subsequent implant-based breast reconstruction at the authors' institution (Plastic and Reconstructive Surgery Unit, University Hospital "Paolo Giaccone", Palermo) from January 2018 to March 2022. The study received the approval of the Ethical Committee of the University Hospital "Paolo Giaccone" of Palermo.

2.2. Data Collection

Demographic, clinical, intraoperative and postoperative characteristics of patients were collected through a retrospective screening of medical records (see Tables 1–3). Major complications were defined as complications that resulted in implant loss and/or could not be managed conservatively, requiring additional surgical procedures under general anesthesia. Pain intensity was recorded daily from the first postoperative day through a self-reported pain assessment scale, the Numerical Rating Scale (NRS), whose validity is supported in the literature [33,34]. Average postoperative pain was defined as the mean of patient-reported pain scores in the first three postoperative days. Patient-reported satisfaction was evaluated 6 months postoperatively, when patients were asked to answer to the question "How much are you satisfied with the overall result of your breast reconstruction?", giving a score ranging from 1 (minimally satisfied) to 10 (fully satisfied). Similarly, surgeon-reported satisfaction was assessed through a survey administered to ten experienced plastic surgeons who did not participate to the operation, where they were asked to evaluate the cosmetic result of the reconstruction in a rating scale ranging from 0 (worst result) to 10 (best result). In this study, the surgeon-reported outcome is defined for each patient as the mean of surgeon-reported satisfaction scores.

Table 1. Demographic and clinical characteristics of the study population.

Variable	*n* = 32
Age (mean ± SD, range) (years)	49.7 ± 6.1 (35–61)
BRCA mutation type (No, %)	
Type 1	28 (87.50%)
Type 2	4 (12.50%)
BMI (mean ± SD, range) (kg/m^2)	25.0 ± 4.4 (19.3–32.7)
Obesity (BMI ≥ 30) (No, %)	
Yes	6 (18.75%)
No	26 (81.25%)
Smoking status (No, %)	
Smoker	4 (12.5%)
Non-smoker	28 (87.5%)
Alcohol consumption (No, %)	
Yes	4 (12.5%)
No	28 (87.5%)
Coffee consumption (No, %)	
Yes	20 (62.5%)
No	12 (37.5%)
Diabetes mellitus (No, %)	
Yes	0 (0.00%)
No	32 (100.00%)
Previous adjuvant/neoadjuvant chemotherapy (No, %)	
Yes	10 (31.25%)
No	22 (68.75%)
Previous radiotherapy (No, %)	
Yes	14 (43.75%)
No	18 (56.25%)
Previous hormonal therapy (No, %)	
Yes	6 (18.75%)
No	26 (81.25%)
Previous breast cancer (No, %)	
Unilateral	14 (43.75%)
Bilateral	4 (12.50%)
None	14 (43.75%)
Previous breast surgery (lumpectomy/quadrantectomy) (No, %)	
Unilateral	14 (43.75%)
Bilateral	4 (12.50%)
None	14 (43.75%)
Previous SLNB [1] (No, %)	
Unilateral	8 (25.00%)
Bilateral	2 (6.25%)
None	22 (68.75%)
Previous ALND [2] (No, %)	
Unilateral	2 (6.25%)
Bilateral	0 (0.00%)
None	30 (93.75%)
Previous ovarian cancer (No, %)	
Yes	2 (6.25%)
No	30 (93.75%)
Previous prophylactic BSO [3] (No, %)	
Yes	10 (31.25%)
No	22 (68.75%)
Current diagnosis of breast cancer in contralateral breast (No, %)	
Yes	18 (56.25%)
No	14 (43.75%)

[1] Sentinel lymph node biopsy [2] Axillary lymph node dissection [3] Bilateral salpingo-oophorectomy.

Table 2. Intraoperative and postoperative characteristics of the twenty-three operated breasts.

Variable	*n* = 46
Type of risk-reducing mastectomy (No, %)	
Nipple-sparing mastectomy with inframammary fold incision	26 (56.52%)
Nipple-sparing mastectomy with periareolar incision	4 (8.70%)
Skin-reducing mastectomy with wise pattern incision	14 (30.43%)
Skin-sparing mastectomy	2 (4.35%)
Occult cancer in risk-reducing mastectomy specimen	
Yes	4 (8.7%)
No	42 (91.3%)
Type of breast reconstruction (No,%)	
Single-stage Prepectoral with ADM [1]	16 (34.78%)
Single-stage Prepectoral without ADM [1]	2 (4.35%)
Single-stage Dual-plane with ADM [1]	6 (13.05%)
Single-stage Dual-plane with Bostwick's Autoderm technique	4 (8.69%)
Two-stage Subpectoral (TE [2] followed by implant)	12 (26.08%)
Two-stage Dual-plane with ADM (TE [2] followed by implant)	2 (4.34%)
Other	4 (8.69%)
TE [2] used (No, %)	18 (39.13%)
TE [2] size (mean ± SD, range) (cc)	438.89 ± 108.33 (300–600)
Implant used (No, %)	44 (95.65%)
Implant volume (mean ± SD, range) (cc)	436.59 ± 81.42 (240–525)
Implant shape (No, %)	
Round	20 (43.48%)
Anatomical	24 (52.17%)
Unreported	2 (4.35%)
Additional lipofilling (No, %)	6 (13.04%)
Lipofilling volume (mean ± SD, range) (cc)	130 ± 44.34 (70–200)
ADM [1] used (No, %)	26 (56.52%)
Braxon®	16 (34.78%)
SurgiMend®	8 (17.39%)
Native®	2 (4.35%)
Drain duration (mean ± SD, range) (days)	8.83 ± 4.88 (4–20)
Total drain amount [3] (mean ± SD, range) (mL)	336.26 ± 287.25 (16–1139)
Complications (No, %)	10 (21.74%)
Major	8 (17.39%)
Minor	2 (4.35%)

[1] Acellular dermal matrix [2] Tissue expander [3] Defined as the sum of daily collections from the first postoperative day until removal.

Table 3. Postoperative characteristics of the study population.

Variable	*n* = 16
Average postoperative pain [1] (mean ± SD, range) (NRS)	3.32 ± 2.13 (0–6)
Length of hospital stay (mean ± SD, range) (days)	9.38 ± 5.39 (4–24)
Patient-reported satisfaction (mean ± SD, range) (0 to 10 scale)	7.25 ± 1.28 (5–9)
Surgeon-reported outcome [2] (mean ± SD, range) (0 to 10 scale)	6.51 ± 1.82 (3.4–8.6)

[1] Defined as the mean of patient-reported pain scores (NRS) in the first three postoperative days [2] Defined as the mean of surgeon-reported scores for each patient.

2.3. Statistical Analysis

Statistical analysis was carried out with EpiInfo software version 7.2.4.0 (Epi Info™, CDC, Division of Health Informatics & Surveillance, Center for Surveillance, Epidemiology & Laboratory Services, 2020). In descriptive statistics, mean, standard deviation and range were reported for continuous variables, whereas frequency and percentage were listed

for categorical variables. The Welch–Satterthwaite T-test was used to analyze means of continuous variables and a two-tailed Fisher's exact test was used to compare frequencies of categorical variables. Contingency tables and odds ratios (OR) were used to measure the association between risk factors and the outcome of interest. Concordance between quantitative variables was calculated with Pearson's correlation coefficient (R). Statistical significance was set at $p < 0.05$.

2.4. Surgical Indications

- In mild-to-moderate size breasts with no ptosis, risk-reducing mastectomy was preferentially carried out through a conventional NSM with an inframammary fold (IMF) approach.
- In cases of medium-sized breasts with additional ptosis, an inferior hemi-periareolar incision was chosen. A superiorly based nipple-areola complex (NAC) adipodermal flap was raised and a circumferential region around the NAC was dehepitelialized with the purpose of performing a concomitant periareolar pexis.
- In large and ptotic breasts, risk-reducing mastectomy was performed through an SRM, in order to provide a simultaneous mastopexy in addition to the preservation of the NAC. A bipedicled superiorly and-inferiorly based NAC adipodermal flap was raised to provide additional coverage to the underlying implant.
- We never performed primary free NAC grafting in our series, because we always relied, even in larger breasts, on the improved vascular supply provided by the bipedicled NAC-bearing flap.

Risk-reducing mastectomy was performed following the anatomical plane of the superficial fascia dividing the subcutaneous tissue from the underlying breast parenchyma, in order to remove as much gland as possible [35,36]. Sharp dissection with cold scissors or blade was preferred over monopolar electrocautery in order to avoid potential heat-induced injury to mastectomy flaps. Intraoperatively, perfusion of NAC and mastectomy flaps was evaluated clinically through direct assessment of skin quality (color, amount of preserved subcutaneous fat, lack of dermal layer exposure), temperature, bleeding of incision edges and capillary refill [37,38]. If perfusion was uncertain, skin viability was confirmed with an infracyanine green-photodynamic eye (IFCG-PDE) imaging system (PDE, Hamamatsu Photonics K.K., Hamamatsu, Japan) [39,40]. IFCG is a solution that contains the same fluorophore found in indocyanine green (ICG) but differs because is iodine-free and iso-osmolar with blood. We preferred IFCG because it has the same properties as ICG and can also be safely employed in patients allergic to iodine, showing a more favorable toxicity profile [41]. Mastectomy flap thickness was evaluated as well. In case of inadequate thickness of the residual mastectomy flaps (<10 mm), poor skin perfusion regardless of the thickness, significant tension in wound closure or other conditions that could potentially jeopardize tissue vascularization, DTI reconstruction was abandoned in favor of a two-stage procedure.

Then, the reconstruction proceeded as follows:

- In cases of two-stage submuscular reconstruction, a tissue expander (TE) was placed in a pocket dissected under the pectoralis major muscle. Expansion was carried out every week during the postoperative course. When the desired volume of the submuscular pocket was reached, the TE was removed and replaced with a permanent implant during a secondary surgery.
- In one-stage dual-plane reconstruction, a partially submuscular pocket was created. The implant was placed under the pectoralis major muscle and covered in its superior two thirds by the muscle and in its inferior third by a bovine/porcine ADM sling (SurgiMend® PRS, Integra LifeSciences, Plainsboro, New Jersey or Native®, Decomed S.r.l., Venezia, Italy) sutured superiorly to the inferior margin of the muscle and inferiorly to the rectus sheath. This provided coverage of the lower pole of the implant. Alternatively, Bostwick's autoderm technique was employed for the

same purpose [42]. The choice between the two options was made upon surgeon's preferences and availability of viable dermal flaps.

- If one-stage ADM-assisted prepectoral reconstruction was performed, a pre-shaped porcine ADM sheet (Braxon®, Decomed S.r.l., Venezia, Italy) was rehydrated in sterile saline for about 5 to 10 min. Then, it was put on a sterile desk and wrapped around the implant. The edges of the matrix were sutured, and the excess parts were trimmed. The enveloped implant was placed above the pectoralis major muscle and anchored to the chest wall through 3 to 5 cardinal sutures. Additional quilting sutures were put between the ADM and the subcutaneous layer. Fixation of the ADM avoided any migration or rotation of the implant and ensured adequate contact between the collagen membrane and the surrounding vascularized tissues.
- In cases of ADM-free prepectoral reconstruction, the prosthesis was laid down on the pectoralis major muscle without further coverage.

The choice between round and anatomical implants mainly depended on breast characteristics before mastectomy and patient's desires, preferably opting for anatomical implants if a superior lower pole projection and a more "natural" appearance was advocated.

2.5. Perioperative Care

Patients were asked to wear a post-surgical compression bra from the first postoperative day and for at least one month after surgery. Drains were removed when their content was lower than 30 mL per day for two consecutive days. If no complications occurred, patients were usually discharged in 5 to 7 days. Patients were followed-up at 1, 2 and 4 weeks and at 3 and 6 months postoperatively in order to detect even tardive complications and evaluate long-term clinical outcomes.

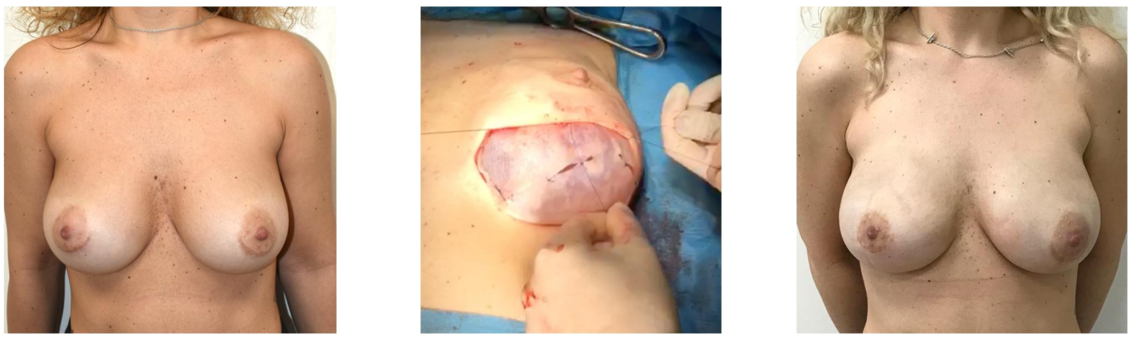
2.6. Secondary Procedures

In case of unsatisfactory cosmetic results, when requested by the patient, one or more fat grafting sessions were performed in order to correct aesthetic imperfections and camouflage implant edges visible through thin mastectomy flaps. The donor areas (abdomen, flanks or thighs) were infiltrated with tumescent (Klein's) solution and the fat was then suctioned by hand through the use of 1 to 3 mm liposuction cannulas. Then, the collected fat was processed by centrifugation for 3 min at 3000 RPM as described by Coleman [43]. Finally, oil and blood were discarded, and the purified fat was injected into the breast in a subcutaneous plane with a blunt infiltration cannula.

3. Results

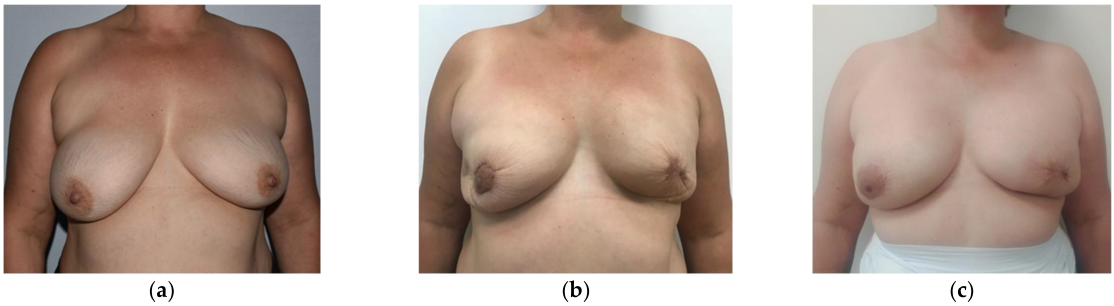
The mean age was 49.7 ± 6.1 years (range 35–61 years). About nineteen percent of patients were obese (BMI > 30 kg/m^2). Eighteen patients had a past history of breast cancer, fourteen received radiation therapy and ten underwent prophylactic bilateral salpingo-oophorectomy. Demographic and clinical characteristics of patients are summarized in Table 1. Regarding intraoperative characteristics, fourteen patients underwent bilateral risk-reducing mastectomy, whereas eighteen underwent unilateral risk-reducing mastectomy with contralateral therapeutic mastectomy for breast cancer, with a total amount of forty-six breasts operated on with risk-reducing intent. In the majority of cases (65.2%) the type of risk-reducing mastectomy was an NSM. Eighteen patients underwent immediate reconstruction, and fourteen patients underwent staged reconstruction with tissue expanders. The mean volume of tissue expanders was 438.9 cc (range 300–600). As concerns breast implants, the mean volume was 436.6 cc (range 240–525). Twenty implants were round and 24 were anatomical. Acellular dermal matrices were used in twenty-six reconstructions. The most used ADM was Braxon® (16/26). The drainage was removed after an average period of 8.8 days (range 4–20). The length of hospitalization ranged between 4 and 24 days (median = 8 days). The majority of patients had an uneventful recovery. Six breasts received additional lipofilling, with a mean amount of injected fat of 130 cc (Tables 2 and 3). Detailed surgical information about the forty-six operated breasts are provided in Table 4.

Comparison between single-stage and two-stage reconstruction showed that patients with prior diagnosis of breast cancer who underwent breast and lymph node surgery or with a history of previous radiation therapy were preferentially treated with TE-assisted reconstruction at our institution (Table 5). Postoperative complications occurred in 10 breasts (5 major and 2 minor, overall complication rate = 21.7%) and were more common in the two-stage subgroup (33.3% vs. 14.3%), but this difference was not statistically significant; complications included two capsular contractures leading to implant explantation, six major skin necroses that required a return to the theatre and two minor nipple-areola-complex necroses that were managed conservatively. No seroma, hematoma or infection occurred (Table 6). In univariate analysis, none of the examined characteristic was predictive for postoperative complications at a significance level of $p < 0.05$. Nevertheless, although not significant, staged reconstruction (OR = 2.85), active smoking (OR = 9.66), previous hormonal therapy (OR = 4.84), radiotherapy (OR = 2.27), axillary surgery (sentinel lymph node biopsy and axillary lymph node dissection) (ORs = 4.81 and 3.91) or bilateral salpingo-oophorectomy (OR = 2.85) and the presence of occult cancer in risk-reducing mastectomy specimens (OR = 3.91) were associated with the highest chance of developing complications during the postoperative course (Table 7). Pearson's Correlation coefficient (R) showed a strong positive correlation between patient-reported satisfaction (mean = 7.3) and surgeon-reported outcome (mean = 6.5) assessed at the 6-month follow-up (R = 0.9166, $p = 0.001361$). Some clinical cases are shown in Figures 1 and 2.



(**a**) (**b**) (**c**)

Figure 1. Thirty-five year-old woman with mutation in BRCA 1 gene who underwent bilateral risk-reducing nipple-sparing mastectomy with inframammary fold approach and subsequent prepectoral direct-to-implant reconstruction with ADM-wrapped implants. (**a**) Preoperative view; (**b**) intraoperative view of the left breast showing the acellular dermal matrix wrapped around the implant and anchored to the pectoralis major fascia; (**c**) postoperative view at 6 months.



(**a**) (**b**) (**c**)

Figure 2. Forty-nine year-old patient with mutation in BRCA 2 gene and current diagnosis of left invasive breast cancer who underwent therapeutic skin-sparing mastectomy, contralateral risk-reducing nipple-sparing mastectomy with periareolar incision and staged submuscular tissue expanders/implants reconstruction. (**a**) Preoperative view; (**b**) postoperative view 3 months after bilateral tissue expander placement; (**c**) final result 6 months after exchange of tissue expanders with definitive implants.

Table 4. Detailed surgical information about the forty-six operated breasts.

n	Side	Mastectomy (Incision)	Reconstruction	TE Size (cc)	BI Size (cc)	BI Shape	BI Manufacturer	Lipofilling Volume (cc)	ADM	Complications
1	R	NSM (IMF)	Two-stage submuscular	450	500	Round	Motiva	/	/	
2	R	NSM (IMF)	One-stage prepectoral	/	475	Round	Motiva	/	Braxon®	
3	L	NSM (IMF)	One-stage prepectoral	/	475	Round	Motiva	/	Braxon®	
4	R	NSM (IMF)	One-stage prepectoral	/	360	Anatomical	Polytech	/	/	
5	R	SRM	One-stage prepectoral	/	440	Anatomical	Mentor	/	Braxon®	
6	L	SRM	One-stage prepectoral	/	525	Round	Motiva	/	Braxon®	
7	R	NSM (IMF)	One-stage prepectoral	/	440	Anatomical	Mentor	/	Braxon®	
8	L	NSM (IMF)	One-stage prepectoral	/	440	Anatomical	Mentor	/	Braxon®	
9	R	SRM	One-stage prepectoral	/	475	Round	Motiva	/	Braxon®	Skin necrosis
10	L	SRM	One-stage prepectoral	/	475	Round	Motiva	/	Braxon®	Skin necrosis
11	R	NSM (P)	Two-stage submuscular	350	500	Round	Mentor	/	/	
12	R	NSM (IMF)	Two-stage submuscular	300				/	/	Baker grade III caspular contracture w/TE removal
13	R	NSM (P)	One-stage dual-plane	/	280	Anatomical	Allergan	/	Native®	
14	R	NSM (IMF)	Two-stage submuscular	500	520	Anatomical	Allergan	/	/	
15	R	NSM (T)	One-stage dual-plane	/	400	Anatomical	Allergan	/	SurgiMend®	
16	L	NSM (T)	One-stage dual-plane	/	400	Anatomical	Allergan	/	SurgiMend®	
17	R	SRM	Two-stage submuscular	400	520	Anatomical	Allergan	70	/	
18	L	SSM	Two-stage submuscular	400	520	Anatomical	Allergan	120	/	Partial NAC necrosis (minor complication)
19	R	NSM (IMF)	One-stage dual-plane	/	360	Anatomical	Allergan	/	/	
20	L	NSM (IMF)	One-stage dual-plane	/	360	Anatomical	Allergan	/	/	
21	R	NSM (IMF)	Two-stage dual-plane	350	310	Round	Allergan	/	SurgiMend®	
22	R	SRM	Other	600	475	Round	Motiva	200	SurgiMend®	Skin necrosis
23	L	SRM	Other	600	475	Round	Motiva	/	/	
24	R	NSM (IMF)	Two-stage submuscular	450	500	Round	Motiva	/	/	
25	R	NSM (IMF)	One-stage prepectoral	/	475	Round	Motiva	/	Braxon®	
26	L	NSM (IMF)	One-stage dual-plane	/	360	Anatomical	Allergan	/	/	
27	R	NSM (IMF)	Two-stage dual-plane	350	310	Round	Allergan	/	SurgiMend®	

Table 4. *Cont.*

n	Side	Mastectomy (Incision)	Reconstruction	TE Size (cc)	BI Size (cc)	BI Shape	BI Manufacturer	Lipofilling Volume (cc)	ADM	Complications
28	R	NSM (IMF)	Two-stage submuscular	300				/	/	Baker grade IV caspular contracture w/TE removal
29	L	SRM	Other	600	475	Round	Motiva	/	/	
30	R	SRM	One-stage prepectoral	/	440	Anatomical	Mentor	/	Braxon®	
31	L	SRM	One-stage prepectoral	/	525	Round	Motiva	/	Braxon®	
32	R	NSM (IMF)	Two-stage submuscular	500	520	Anatomical	Allergan	/	/	
33	R	NSM (T)	One-stage dual-plane	/	400	Anatomical	Allergan	/	SurgiMend®	
34	L	NSM (T)	One-stage dual-plane	/	400	Anatomical	Allergan	/	SurgiMend®	
35	L	SRM	One-stage prepectoral	/	475	Round	Motiva	/	Braxon®	Skin necrosis
36	R	NSM (P)	Two-stage submuscular	350	500	Round	Mentor	/	/	Partial NAC necrosis (minor complication)
37	R	SRM	Other	600	475	Round	Motiva	170	SurgiMend®	Skin necrosis
38	R	NSM (P)	One-stage dual-plane	/	280	Anatomical	Allergan	/	Native®	
39	R	SRM	Two-stage submuscular	400	520	Anatomical	Allergan	90	/	
40	L	SSM	Two-stage submuscular	400	520	Anatomical	Allergan	130	/	
41	R	NSM (IMF)	One-stage dual-plane	/	360	Anatomical	Allergan	/	/	
42	R	NSM (IMF)	One-stage prepectoral	/	440	Anatomical	Mentor	/	Braxon®	
43	L	NSM (IMF)	One-stage prepectoral	/	440	Anatomical	Mentor	/	Braxon®	
44	R	SRM	One-stage prepectoral	/	475	Round	Motiva	/	Braxon®	Skin necrosis
45	L	NSM (IMF)	One-stage prepectoral	/	475	Round	Motiva	/	Braxon®	
46	R	NSM (IMF)	One-stage prepectoral	/	360	Anatomical	Polytech	/	/	

BI: breast implant; IMF: inframammary fold; P: periareolar; T: inverted T; TE: tissue expander; ADM: acellular dermal matrix; NAC: nipple-areola complex.

Table 5. Comparison between single-stage and two-stage reconstruction.

Variable	Single-Stage (Prepectoral/ Dual Plane Cohort)	Two-Stage (TE-Assisted Submuscular Cohort)	Mean Difference (95% CI)	*p*-Value
Age	47.9	52.0	−4.1 (−10.3–2.1)	0.1783
BMI	24.6	25.4	−0.8 (−5.9–4.4)	0.7455
Obesity	11.1%	28.6%	−17.5% (−64.9–30.0%)	0.4348

Table 5. *Cont.*

Variable	Single-Stage (Prepectoral/ Dual Plane Cohort)	Two-Stage (TE-Assisted Submuscular Cohort)	Mean Difference (95% CI)	*p*-Value
Smoking status	11.1%	14.3%	−3.2% (−4.2–3.6%)	0.8635
Alcohol consumption	0.0%	28.6%	−28.6% (−7.6–18.8%)	0.1820
Coffee consumption	66.7%	57.1%	9.5% (−47.3–66.4%)	0.7223
Diabetes mellitus	0.0%	0.0%	–	–
Previous chemotherapy	22.2%	42.9%	−20.6% (−75.4–34.1%)	0.4258
Previous radiotherapy	11.1%	85.7%	−74.6% (−113.7–−35.5%)	**0.0012**
Previous hormonal therapy	0.0%	42.9%	−42.9% (−90.6–4.9%)	0.0716
Previous breast cancer	33.3%	85.7%	−52.4% (−99.8–−5.0%)	**0.0329**
Previous breast surgery	33.3%	85.7%	−52.4% (−99.8–−5.0%)	**0.0329**
Previous SLNB	0.0%	71.4%	−71.4% (−118.8–−24.0%)	**0.0117**
Previous ALND	0.0%	14.3%	−14.3% (−48.1–19.5%)	0.3506
Previous ovarian cancer	11.1%	0.0%	11.1% (−14.5–36.7%)	0.3466
Previous prophylactic BSO	44.4%	14.3%	30.2% (−18.7–79.1%)	0.2057
Current breast cancer in contralateral breast	44.4%	71.4%	−27.0% (−81.8–27.8%)	0.3080
Contralateral therapeutic mastectomy	44.4%	71.4%	−27.0% (−81.8–27.8%)	0.3080
Additional lipofilling	0.0%	33.3%	−33.3% (−72.7–6.08%)	0.0856
ADM use	78.6%	22.2%	56.4% (17.0–95.7%)	**0.0078**
Drain duration	8.4	9.4	−1.0 (−5.1–3.1)	0.6141
Total drain amount	271.9	436.3	−164.4 (−470.6–141.8)	0.2602
Complications	14.3%	33.3%	−19.1% (−60.5–22.4%)	0.3406
Postoperative pain	3.06	3.67	−0.6 (−2.1–0.90)	0.3944
Hospital stay	8.6	10.4	−1.9 (−7.6–3.9)	0.4923
Occult cancer in RRM	0.0%	22.2%	−22.2% (−55.5–11.0%)	0.1649
Implant volume in RRM	413.2	477.5	−64.3 (−133.6–5.1)	0.0671
Current SLNB in contralateral breast	22.2	71.4	−49.2% (−100.3–1.9%)	0.0578
Current ALND in contralateral breast	0.0%	14.3%	−14.3% (−48.1–19.5%)	0.3506
Patient-reported satisfaction	7.5	7.0	0.5 (−2.0–3.0)	0.6252
Surgeon-reported outcome	7.2	5.8	1.4 (−1.8–4.7)	0.3095

SLNB: sentinel lymph node biopsy; ALDN: axillary lymph node dissection; RRM: risk reducing mastectomy; TE: tissue expander; ADM: acellular dermal matrix; BSO: bilat salpingo-oophorectomy. Bold numbers correspond to statistically significant values ($p < 0.05$).

Table 6. Summary and univariate analysis of postoperative complications.

	Total	Single-Stage (Prepectoral/ Dual Plane Cohort)	Two-Stage (TE-Assisted Submuscular Cohort)	*p*-Value
No. of breasts	46	28	18	–
Overall complications (No,%)	10 (21.7)	4 (14.3)	6 (33.3)	0.3406
Seroma (No,%)	0 (0.0)	0 (0.0)	0 (0.0)	–
Hematoma (No,%)	0 (0.0)	0 (0.0)	0 (0.0)	–
Infection (No,%)	0 (0.0)	0 (0.0)	0 (0.0)	–
Wound dehiscence (No,%)	0 (0.0)	0 (0.0)	0 (0.0)	–
Capsular contracture (No,%)	2 (4.4) *	0 (0.0)	2 (11.1) *	0.3466
Major skin/NAC necrosis (No,%)	6 (13.0)	4 (14.3)	2 (11.1)	0.8320
Minor skin/NAC necrosis (No,%)	2 (4.4)	0 (0.0)	2 (11.1)	0.3466
Implant loss (No,%)	2 (4.4) *	0 (0.0)	2 (11.1) *	0.3466
Red breast syndrome (No,%)	0 (0.0)	0 (0.0)	0 (0.0)	–
Rippling/Wrinkling (No,%)	0 (0.0)	0 (0.0)	0 (0.0)	–
Implant malposition (displacement/rotation)	0 (0.0)	0 (0.0)	0 (0.0)	–

NAC: nipple-areola complex; TE: tissue expander * Capsular contracture leading to implant removal (both complications occurred in the same patient).

Table 7. Univariate analysis of risk factors for postoperative complications (OR, mean difference and *p*-values).

	OR (95% CI)	Mean Difference (95% CI)	*p*-Value
Staged reconstruction	2.85 (0.34–29.63)		0.3428
Age		0.51 (−4.20–5.22)	0.8194
BMI		1.22 (−3.19–5.64)	0.5403
Obesity	0.00 (0.00–6.54)		1.0000
Active smoking	9.66 (0.59–350.34)		0.1073
Alcohol consumption	0.00 (0.00–13.13)		1.0000
Coffee consumption	1.19 (0.14–12.11)		1.0000
Diabetes mellitus	–		–
Previous chemotherapy	1.31 (0.13–11.29)		1.0000
Previous radiotherapy	2.27 (0.27–23.27)		0.6175
Previous hormonal therapy	4.84 (0.38–63.52)		0.1937
Previous breast cancer	1.19 (0.14 –12.11)		1.0000
Previous breast surgery	1.19 (0.14 –12.11)		1.0000

Table 7. *Cont.*

	OR (95% CI)	Mean Difference (95% CI)	*p*-Value
Previous SLNB	4.81 (0.54–53.00)		0.1421
Previous ALND	3.91 (0.09–174.42)		0.3953
Previous ovarian cancer	0.00 (0.00–68.40)		1.0000
Previous prophylactic BSO	2.85 (0.34–29.63)		0.3428
Current breast cancer in contralateral breast	0.33 (0.01–3.23)		0.6106
Contralateral therapeutic mastectomy	0.33 (0.01–3.23)		0.6106
ADM use	1.19 (0.14–12.11)		1.0000
Drain duration		6.10 (−2.41–14.61)	0.1203
Total drain amount		148.14 (−247.50–543.79)	0.3810
Postoperative pain		0.42 (−0.84–1.68)	0.4728
Hospital stay		7.32 (−3.36–18.00)	0.1348
Occult cancer in RRM	3.91 (0.09 –174.42)		0.3953
Implant volume		60.70 (12.02–109.37)	**0.0174**
TE size		−8.33 (−407.24–390.57)	0.9388
Current SLNB in contralateral breast	0.51 (0.02–5.25)		1.0000
Current ALND in contralateral breast	0.00 (0.00–68.40)		1.000

SLNB: sentinel lymph node biopsy; ALDN: axillary lymph node dissection; RRM: risk reducing mastectomy; TE: tissue expander; ADM: acellular dermal matrix; BSO: bilat
salpingo-oophorectomy. Bold numbers correspond to statistically significant values ($p < 0.05$).

4. Discussion

Our study shows that, although non suitable for all cases, DTI prepectoral breast reconstruction can be considered a safe and convenient alternative to staged breast reconstruction if performed in carefully selected patients, with a meticulous surgical technique and an accurate intraoperative evaluation of skin flaps perfusion. It is minimally invasive, provides a natural-appearing breast with higher patient-reported satisfaction and no significant increase in terms of postoperative complications, simultaneously avoiding the additional costs and visits related to tissue expander placement.

In the field of risk-reducing surgeries, there is no "standard" operation and a huge variety of techniques have been developed, differing for NAC and/or skin preservation and type of incision. The most common techniques are NSM and SRM [44]. In this series, NSM was the most common type of risk-reducing mastectomy, accounting for about two-thirds of patients, and we preferentially adopted an inframammary fold approach. In large and ptotic breasts (30.4%), we preferred a SRM through a wise pattern incision and a bipedicled adipodermal NAC flap. In fact, in these patients, NSM is usually contraindicated due to the significant risk of NAC necrosis [45]. Conversely, our technique proved to be safe in terms of NAC survival: we reported no cases of NAC necrosis after SRM. We experienced four cases of major skin necrosis (8.7%) in patients who underwent SRM and subsequent ADM-assisted PBR, but none of them ended in reconstructive failure thanks to the protection ensured by the bipedicled adipodermal flap, which provided complete vascularized coverage of the implant, preventing its direct exposure. Caputo et al. and Maruccia et al. described similarly low rates of skin necrosis (6.1% and 8.7%, respectively) after SRM and no cases of implant loss, thanks to the combination of an ADM with an inferior dermal flap in PBR [46,47].

In our series, when feasible, an immediate breast reconstruction (IBR) was preferred over a staged one. The literature suggests that IBR provides many advantages: a reduced operating time, a shorter length of hospitalization [48–50] and the avoidance of the multiple visits needed for tissue expansion [51–55]. Additionally, an immediate reconstruction increases women's quality of life after risk-reducing surgery, favorably impacts on patient-reported satisfaction and psychological well-being [56–59] and is superior in terms of cosmetic results [60]. Finally, in case of PBR, the result is a more "natural" breast (the implant is placed in the same anatomical compartment formerly occupied by the surgically excised parenchyma) [25,37,51,61–64], with better lower pole projection [65–67], enhanced definition of IMF [68–71] and a more accurate predictability in size and symmetry [72].

In this study, patients who underwent IBR had a shorter hospital stay (mean 8.6 vs. 10.4 days), a shorter drain duration (mean 8.4 vs. 9.4 days), a lower drain amount and less postoperative pain (3.06 vs. 3.67) in comparison to those who were treated with a two-stage breast reconstruction. Both surgeon-reported outcome (7.2 vs. 5.8) and patient-reported satisfaction (7.5 vs. 7.0) were superior in the single-stage group. Our findings confirm those reported in the literature: in two different studies, Casella et al. and Cattelani et al. showed higher Q scores in patients who had a prepectoral IBR in comparison with patients treated with dual-plane IBR or staged TE-assisted reconstruction [73,74]. Bernini et al. reported that the surgeon's judgment on aesthetic outcome was excellent in 91% of prepectoral reconstructions and 65% of subpectoral ones and this finding was coherent with patient subjective perception [25].

However, in our cohort, a strict adherence to rigorous inclusion criteria was paramount before proceeding to an IBR, especially if a prepectoral approach was chosen, in order to prevent complications. In fact, due to the partially or totally subcutaneous positioning of the implant, any skin-related problem could lead to implant exposure and therefore compromise the reconstructive outcome [75]. In our experience, the ideal candidates were patients with small-to-moderate and non-ptotic breasts [74,76–79], no associated comorbidities and an adequate thickness of mastectomy flaps. Regarding obesity, a high BMI is generally considered a relative contraindication to IBR. It lowers the chance of flap viability and increases the overall complication rate [19,24,37,77,80–82], particularly the

probability of seroma occurrence [19,83,84]. In our retrospective study the mean BMI in patients who underwent IBR was 24.6 kg/m^2. Differently from the literature, we also chose to include for IBR overweight or slightly obese patients (11.1%); in this group, the major complication rate was higher (30% vs. 7.7%) but overall acceptable; of note, complications never led to implant removal or complete reconstructive failure. Similarly to us, Downs et al. widened the reconstructive indication for IBR to patients with a BMI ranging from 25 to 35 kg/m^2, even considering mild obesity an advantage for PM, since fat patients tend to have a thicker subcutaneous layer and could benefit from better perfused skin flaps [19].

In our study, the choice of an IBR was also conditioned by intraoperative clinical assessment of residual skin flap thickness. In the literature, there is no unanimous consensus on the best cutoff thickness: according to Nahabedian et al., a thickness greater than 10 mm is essential to proceed to immediate PBR [77,85]. In a MRI study performed by Frey et al. on 379 NSMs, an absolute mastectomy flap thickness lower than 8 mm or a low postoperative-to-preoperative thickness ratio was strongly predictive of ischemic complications, regardless of the type of reconstruction [86]. In two other studies, it was demonstrated that a mastectomy flap thickness less than 5 and 8 mm, respectively, represents a significant risk factor for ischemic complications [87,88].

In our series, we preferred to be more conservative and conventionally adopted a cutoff of 1 cm to establish whether patients were eligible for prepectoral IBR.

Concerning tissue perfusion, in patients with uncertain flap viability, we performed instrumental assessment of skin vascularization through IFCG fluorescence and a near-infrared camera (PDE), which is considered the best tool to predict mastectomy flap survival [85], and oriented the clinical decision towards a single or two-stage reconstruction. However, despite the use of IFGG angiography, we were unable to foresee four out of the six cases of major skin necrosis. These four cases occurred bilaterally in two patients who, although they were active smokers, expressed a strong intention to be treated in a single stage with a prepectoral implant and accepted the increased risk for complications. This occurrence further highlighted the relevance of appropriate patient selection to prevent potentially harmful complications.

In our series, two-stage TE-assisted reconstruction was restricted to patients who did not meet the inclusion criteria or in whom the mastectomy flaps were too thin or poorly perfused after ICG-PDE instrumental evaluation. In particular, active smokers, immunosuppressed patients and women with poorly controlled diabetes mellitus (HbA1c > 7.5%) were preferentially excluded from IBR and better served with a staged submuscular reconstruction [23,64,77,89]. In fact, providing as it does an additional layer between the skin and the prosthetic device, a two-stage subpectoral reconstruction was a safer and most appropriated alternative in patients at high risk of postoperative complications and implant exposure [90–92]. However, this reconstruction has many drawbacks related to the detachment and the manipulation of the pectoralis major, such as animation deformity [19,66,93–96], upper implant displacement [37], persistent postoperative pain [97] and loss of muscle function with shoulder impairment [51,64,79,94,98,99]. Moreover, it allows for a suboptimal aesthetic outcome, with a final result that consists of a flat and "contrived" breast mound with low projection and no natural ptosis, due to the constriction exerted by the muscle on the underlying implant [62,100]. A potential advantage of TE-assisted reconstruction is that lipofilling can be performed at the same time as inserting the definitive implant. However, in our opinion this type of reconstruction should be strictly limited to the cases mentioned above.

An important aspect to take into account is the use of ADMs in IBR.

An ADM is a biological graft derived from human, porcine or bovine tissues that acts like a scaffold that is gradually vascularized and populated by the host's cells. Thanks to the absence of cellular and antigenic components, an ADM is a non-immunogenic material that helps to avoid the drawbacks related to the host's immunological response. Moreover, it overcomes the disadvantages related to autologous tissue grafts and synthetic

materials, represented by a secondary donor-site morbidity and a high risk of infection, respectively [31,101].

The use of ADM has become widespread in several fields of reconstructive surgery, including burns, breast and abdominal wall reconstructive surgery and gynecologic and genitourinary surgery. Additionally, their usefulness has been demonstrated in the treatment of hidradenitis suppurativa [102]. ADMs can be used alone or, alternatively, co-grafted with split thickness skin grafts (STSGs) [103]. In their study, Lee et al. showed that the combined use has a synergistic effect and results in a better scar quality than STSG alone [104].

In breast reconstructive surgery, these matrices provide an additional envelope around the implant, creating a biological interface between the prosthesis and the surrounding tissues and preventing its direct exposure in case of wound dehiscence [94].

In our study, complete or partial ADM coverage was used in 22/28 immediate reconstructions. Braxon® is manufactured as a pre-shaped ADM and was employed in 16 breasts for complete implant coverage in cases of immediate prepectoral breast reconstruction, while Surgimend® and Native® ADMs are provided as sheets and were used in 6 breasts for the coverage of the lower pole of the prosthesis in case of immediate dual-plane breast reconstruction.

In four breasts, a dual-plane reconstruction was achieved with the use of Bostwick's autoderm technique [42]. Only two patients underwent PBR using polyurethane-coated implants without ADM support, having an uneventful postoperative course and no reported complications. This ADM-free technique simultaneously eliminated the disadvantages connected to the submuscular implant placement and the added costs related to a staged procedure and to the employment of a biological matrix [22]. Thus, although less common and more dangerous in case of skin breakdown, this procedure seems promising, and our intent is to extend its application in our future studies.

Recently, several studies highlighted the problem of increased rates of capsular contracture (CC) (as high as 20%) [72] in IBR without soft-tissue support [105–108]. However, it has been demonstrated that the adjunctive use of acellular dermal matrices has a protective role against CC [109–118], dramatically reducing its occurrence thanks to the decreased inflammatory response to the implant and the absence of direct mechanical stress over the prosthesis [119–123]. In a systematic review of complications following PBR, Wagner et al. reported an overall incidence of CC of 8.8%, that was further stratified into ADM-assisted (2.3%) and non-ADM assisted (12.4%) cohorts, highlighting a huge difference between the two groups [124]. In our IBR cohort, we experienced no cases of capsular contracture in the DTI group at a 6-month follow-up, both in the ADM-assisted and in the non-ADM-assisted subgroups, but this result could be related to the short follow-up.

The overall complication rate was 21.7%. We experienced no cases of seroma, hematoma or infection. Approximately 13% of patients had a major skin or NAC necrosis. Our finding are not dissimilar to that reported by Chun et al., who described major flap necrosis in 11.8% of patients [125]. Interestingly, all patients who developed mastectomy skin necroses underwent ADM-assisted reconstruction. This is a well-known issue and is coherent with the increased rate of flap necrosis reported in the literature in ADM cohorts [126]. We had no cases of early implant explantation and only two cases (4.4%) of late implant explantation that occurred in two patients who developed capsular contracture after a two-stage submuscular reconstruction; however, this rate is significantly lower than that reported in the literature (17%) [83,127]. The reason of this low incidence in our study is that most complications were managed conservatively and did not require the implant's removal, thanks to the additional protection provided by the ADM and/or the bipedicled adipodermal flap in immediate prepectoral reconstructions, and by the pectoralis muscle together with the ADM or the Bostwick's autoderm in the immediate dual-plane reconstructions.

Six patients required further fat grafting as a correcting procedure. In these patients the aesthetic result was unpleasant due to poor flap quality after mastectomy and supervened postoperative skin necrosis that was managed through additional surgical operations or

secondary wound healing. The defects were corrected with lipofilling, which allowed us to increase the breast volume and to camouflage the cosmetic imperfections [25,28,99,128,129].

Complications were more common in patients who underwent two-stage reconstruction (33.3% vs. 14.3%), but this difference was not statistically significant. Several other comparative studies have shown that the chance of postoperative complication in IBR does not differ significantly to the other implant-based reconstructive procedures [110,130–140]. In our PBR cohort, the major complication rate was comparable to that found in the remaining patients (18.1% vs. 16.7%). Notably, in the literature, PBR is generally recommended for women requiring implants <400 cc [76], while our experience deals primarily with reconstructions achieved through the use of larger devices (mean = 468.1 cc). The complication rate was slightly higher than we expected in these patients, which can be justified by the higher tension in mastectomy flaps and their reduced perfusion, produced by a mismatch between implant volume and pocket size [126,141]. Published research is conflicting regarding the occurrence of complications in this particular subset of women. Salibian et al. and Chatterjee et al. performed two systematic reviews on PBR and found similar pooled complication rates [134,142]. Conversely, other authors found an increased risk of postoperative complications such as infection, flap necrosis and implant loss [19,51,79], and a higher rate of secondary revisions, up to 87% [28,29,53,82,118,143,144].

Given the small sample size, no association was found between the examined risk factors and the occurrence of postoperative complications. However, although these results did not reach statistical significance, active smoking (OR = 9.66), previous hormonal therapy (OR = 4.84), prior axillary surgery and the presence of incidental breast carcinoma in the mastectomy specimen (OR = 3.91) showed the highest odds ratios and may be associated with an increased likelihood of developing complications in larger cohorts. BMI was slightly higher in patients who had complications (25.66 vs. 24.43, $p = 0.5403$), but, in a difference from the literature [139], obesity was not found to increase the probability of developing any kind of sequelae in the postoperative course ($p = 1.000$).

Limitations of this study comprehend its retrospective nature and the relatively small number of examined patients. Further prospective studies with a larger sample size and a longer follow-up are advisable in order to overcome biases and obtain statistical results with stronger evidence.

5. Conclusions

Risk-reducing mastectomy is often performed in genetically predisposed, highly demanding patients who ask for a seamless and non-mutilating reconstruction, no pectoralis major disruption with preservation of muscular strength and no need for postoperative physiotherapy with a fast return to daily activities. For these reasons, it is important to perform a minimally invasive procedure with a low complication rate and good functional and cosmetic results. Direct-to-implant PBR seems to adequately fit these requirements, representing the latest frontier in breast reconstruction and emerging as a viable alternative to TE-assisted procedures.

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ORIGINAL ARTICLE – BREAST ONCOLOGY

Impact of Bilateral Prophylactic Mastectomy and Immediate Reconstruction on Health-Related Quality of Life in Women at High Risk for Breast Carcinoma: Results of the Mastectomy Reconstruction Outcomes Consortium Study

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ABSTRACT

Background. Although bilateral prophylactic mastectomy (BPM) can reduce the risk of breast cancer, the decision to proceed surgically can have significant consequences and requires careful deliberation. To facilitate decision making for women at high risk for breast carcinoma, the risks and benefits of BPM should be well-elucidated. We sought to determine the effects of BPM and immediate reconstruction on health-related quality-of-life outcomes among a multisite cohort of women at high risk for breast carcinoma.

Methods. Patient-reported outcome data were prospectively collected as part of the Mastectomy Reconstruction Outcomes Consortium Study, and data on a subgroup of 204 high-risk women who elected to have BPM and immediate reconstruction were evaluated. Baseline scores were compared with scores at 1 or 2 years after reconstruction.

Results. Satisfaction with breasts and psychosocial well-being were significantly higher at both 1 and 2 years ($p < 0.01$); however, anxiety was significantly lower at 1 or 2 years ($p < 0.01$) and physical well-being of the chest and upper body was significantly worse at 1 year ($p < 0.01$).

Conclusion. Our results highlight the impact of BPM and immediate reconstruction on health-related quality-of-life outcomes in this setting. BPM and reconstruction can result in significant, positive, lasting changes in a woman's satisfaction with her breasts, as well as her psychosocial well-being. Furthermore, presurgery anxiety was significantly reduced by 1 year post-reconstruction and remained reduced at 2 years. With this knowledge, women at high risk for breast carcinoma, and their providers, will be better equipped to make the best individualized treatment decisions.

Women with no known risk factors for breast carcinoma have an estimated lifetime risk of developing breast cancer of approximately 12%. This means that one of every eight women in the general population will develop breast cancer during her lifetime.

In contrast, BRCA mutation carriers and women with a strong family history of breast carcinoma have an estimated lifetime risk of 45–67%.[1–3] These high-risk women are advised to consider strategies aimed at reducing their risk of breast cancer, such as extensive and regular surveillance, chemoprevention, or surgical removal of both healthy breasts—known as bilateral prophylactic mastectomy (BPM).

Selecting the most appropriate risk-reducing option is not a straightforward task.[4] The decision-making process must take into account not only the effect that each risk-

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reducing strategy has on cancer risk and survival but also the impact of each approach on overall quality of life.

BPM has proven to be the most effective option in reducing cancer risk. A recent meta-analysis suggests that BPM may decrease the risk of developing breast cancer by >90%.[5,6] However, the irreversible approach of removing both healthy breasts is invasive and carries with it the potential for surgical complications. The long-term consequences for women who choose BPM, with or without reconstruction, may also include significant changes in body image as well as psychosocial, sexual, and physical well-being.

A recent systematic review attempted to collate the existing body of literature on patients' perceptions of outcomes following BPM.[7] This review suggests that, in general, patients report both high psychosocial well-being and favorable body image after BPM. Furthermore, the favorable outcomes do not change significantly over time. However, the studies in this review were limited by methodological issues: all 22 studies were observational, with the majority relying on ad hoc questionnaires without demonstrated reliability or validity. Additionally, a majority of these studies used generic questionnaires, such as the 36-Item Short-Form Survey, which are not sufficiently sensitive to measure physical and mental changes in women undergoing BPM with or without reconstruction. Finally, the majority of studies evaluated outcomes at one or more times following surgery but failed to control for preoperative baseline measures of breast satisfaction and health-related quality of life. Without any baseline frame of reference for women with healthy breasts in this setting, it is difficult to put any postoperative data into context.

The purpose of this investigation was to evaluate the effects of BPM and immediate reconstruction on health-related quality of life in a multisite population of women at high risk for breast cancer. It is theorized that, with this knowledge, patients at high risk for breast carcinoma, and their providers, will be better equipped to make informed, individualized treatment decisions and set appropriate expectations for risk-reducing surgery.

METHODS

Patient Recruitment

Patient-reported outcome (PRO) data were prospectively collected as part of the Mastectomy Reconstruction Outcomes Consortium (MROC) Study, a 5-year, prospective, multicenter cohort study funded by the National Cancer Institute (NCI; 1RO1CA152192). Fifty-seven plastic surgeons from 11 centers across the US (Michigan, New York, Illinois, Ohio, Massachusetts, Washington, DC, Georgia, and Texas) and Canada (British Columbia and Manitoba) contributed patients undergoing breast reconstruction after mastectomy to the study. Institutional Review Board approval was obtained from all participating sites, and patients were consented in person by a research study assistant.

Eligibility Criteria

Women were eligible to participate in the MROC study if they were aged 18 years or older and undergoing first-time, immediate or delayed, bilateral or unilateral post-mastectomy breast reconstruction for cancer treatment or prophylaxis. The choice of reconstructive procedure was based on patient and surgeon preference. The current investigation included a subgroup of MROC patients at high risk for breast cancer who underwent BPM and immediate reconstruction. For the analyses of 1- and 2-year outcomes, women who underwent immediate placement of a tissue expander (TE), but did not undergo an exchange to implant within 11 months of TE placement, were excluded as their 1-year assessments will likely reflect the outcomes associated with the recent exchange. In addition, women who experienced reconstructive failure were excluded as no PRO data were collected from them once they experienced failure. Reconstructive failure was defined as the premature loss of a TE or permanent implant resulting in the absence of a breast mound.

Data Collection

Patients completed the PRO measures (PROMs) preoperatively and at 1 and 2 years after surgery. The following PROMs were used: BREAST-Q,[8] Numerical Pain Rating Scale (NPRS), Short-Form McGill Pain Questionnaire (SF-MPQ),[9] General Anxiety Disorder 7-Item (GAD-7) scale,[10] Patient Health Questionnaire-9 (PHQ-9),[11] and the Patient-Reported Outcome Measurement Information System-29 (PROMIS-29).[12] Patients were encouraged to complete the electronic questionnaires remotely; if they were unable to do so, a paper version was provided in the clinic or by mail.

Patient-Reported Outcome Instruments

The BREAST-Q is a validated PROM that consists of independent scales measuring various aspects of outcomes following specific breast surgeries.[8] The instrument was developed and validated with adherence to guidelines set by the Scientific Advisory Committee of the Medical Outcomes Trust (2002) and the US FDA. Four subscales of the BREAST-Q Reconstructive module, i.e. 'satisfaction with breasts', 'psychosocial well-being', 'physical well-being', and 'sexual well-being', were included in the

analysis. Using the Q-score, scores on the subscales were transformed to a number from 0 to 100, with higher numbers signifying better outcomes.

Pain was evaluated using the NPRS and the SF-MPQ. The NPRS asks patients to rate the 'intensity' of their pain on a 0–10 numerical rating scale, and the SF-MPQ provides an additional qualitative assessment of pain, distinct from the 'intensity alone' rating of the NPRS. More specifically, the sensory subscale of the SF-MPQ quantifies the sensory dimensions of pain experience, including its mechanical, spatial, and temporal characteristics, while the affective subscale provides a measure of the subjective unpleasantness or suffering associated with pain.

Anxiety was measured using the GAD-7, a seven-item scale shown to have good reliability and validity. Higher scores on the scale are strongly associated with functional impairment. Depressive symptoms were evaluated using the PHQ-9, a nine-item depression scale of the Patient Health Questionnaire used for screening, diagnosing, and monitoring symptoms over time. The nine items of the PHQ-9 are based directly on the nine diagnostic criteria for major depressive disorder in the diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV).

Finally, the seven domains (anxiety, depression, physical function, fatigue, sleep disturbance, satisfaction with social role, and pain interference) of the PROMIS-29, a National Institutes of Health-funded, validated PRO instrument, were administered.

Statistical Methods

Clinical and demographic characteristics of patients were summarized and are presented as counts (percentages) for categorical variables and medians (ranges) for continuous variables. Mean within-person changes of PRO scores were calculated, with adjustment for clinical sites (hospitals). The within-person change was defined as an individual's PRO score at 1 or 2 years minus that at baseline. To reduce potential bias from missing PROs at 1 or 2 years, mean within-person changes at each follow-up assessment time were weighted by the inverse of the probability of nonmissing response. The probability of response was estimated using a separate logistic regression model fit for each outcome measure, with nonmissing response status as the dependent variable, and baseline patient characteristics and baseline values for the outcome variables from all eligible study participants as predictors. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA), and statistical significance was set at 0.05.

RESULTS

In total, 217 women who underwent BPM and immediate reconstruction past their 1-year follow-up assessment time were identified (Supplementary Fig. 1). From this cohort, outcomes analyses excluded four women who received a TE procedure but did not undergo an exchange to implant within 11 months of TE placement, and nine women who experienced reconstructive failure. Thus, the remaining 204 women were considered eligible for the 1-year outcomes analysis, and, similarly, 149 women were considered eligible for 2-year outcomes analyses as they had reached 2 years of follow-up and did not experience reconstruction failure (Table 1).

Of the 204 women in the initial cohort, 133 (64.3%) had TE/implant reconstruction, 18 (9.9%) had single-stage implant reconstruction, and 55 (25.8%) had autologous reconstruction (Table 1). Clinical and demographic characteristics of the cohort of women eligible for 1-year outcomes analyses are summarized in Table 2. In this cohort of patients, 60% had simple mastectomies, and 40% had nipple-sparing mastectomies. The majority of patients were White (94.6%) with no comorbidities (84.3%). The median age was 41.0 years, and the median body mass index (BMI) was 24.9 kg/m^2.

Mean within-person changes in PRO scores, after adjusting for missingness, between baseline and 1 year, and between baseline and 2 years, are summarized in Table 3. At both 1 and 2 years, patients experienced significantly higher satisfaction with their breasts (year-1 mean difference, 9.13 [$p = 0.001$]; year-2 mean difference, 10.71 [$p = 0.001$]) [Fig. 1] and higher psychosocial well-being (year-1 mean difference, 5.96 [$p = 0.003$]; year-2 mean difference, 7.9 [$p = 0.003$]), compared with baseline. Patients' anxiety levels, which were measured using both

TABLE 1 Patient sample size by procedure type, postoperative time, and failure status

Procedure type	1-year postoperatively			2 years postoperatively		
	Not failed	Failed	Total	Not failed	Failed	Total
Single-stage implant	18	3	21	12	3	15
Tissue expander/implant	133	4	137	99	2	101
Autologous	53	2	55	38	2	40
Total	204	9	213	149	7	156

TABLE 2 Baseline clinical and demographic characteristics of the cohort of women eligible for 1-year outcomes analyses ($N = 204$)

Characteristic	Patients
Age, years [median (range)]	41.0 (43.0)
BMI, kg/m^2 [median (range)]	24.9 (41.0)
Race	
White	192 (94.6)
Black	4 (2.0)
Other	7 (3.5)
Ethnicity	
Hispanic or Latino	8 (4.0)
Non-Hispanic or Latino	192 (96.0)
Education	
High school or less	10 (4.9)
Some college	26 (12.8)
College degree with or without some graduate work	105 (51.7)
Master or doctoral degree	62 (30.5)
Household annual income, US$	
<50,000	20 (10.1)
50,000–99,000	72 (36.2)
100,000 or more	107 (53.8)
Marital status	
Married or partnered	167 (82.7)
Not married or partnered	35 (17.3)
Employment status	
Full-time employed, including student	130 (64.4)
Part-time employed	24 (11.9)
Unemployed	48 (23.8)
Type of mastectomy	
Nipple-sparing	80 (39.2)
Simple or modified radical mastectomy	124 (60.8)
Type of reconstruction	
Tissue expander/implant	133 (65.2)
Silicone	127 (62.3)
Saline	6 (2.9)
Single-stage implant	18 (8.8)
Silicone	16 (7.8)
Saline	2 (1.0)
Autologous tissue	53 (26.0)
TRAM	11 (5.4)
DIEP	30 (14.7)
SIEA	4 (2.0)
Mixed	8 (3.9)
Charlson Comorbidity Index	
0	172 (84.3)
1	29 (14.2)
≥2	3 (1.5)
Smoking status	
Never	146 (73.0)
Previous	51 (25.5)
Current	3 (1.5)
Complications	
None	166 (81.4)
Minor only	19 (9.3)
Major, with or without minor	19 (9.3)

Data are expressed as *n* (%), unless otherwise specified

BMI body mass index, *DIEP* deep inferior epigastric perforator, *SIEA* superficial inferior epigastric artery, *TRAM* transverse rectus abdominis muscle

the GAD-7 and the PROMIS-29, were significantly lower at 1 and 2 years than at baseline. Sexual well-being was restored to baseline levels at 1 year, and remained stable.

In contrast, patients' physical well-being of the chest and upper body, as measured using the Breast-Q, was significantly worse at 1 and 2 years, compared with baseline (year-1 mean difference, −8.64 [$p = 0.001$]; year-2 mean difference, −5.09 [$p = 0.079$]). In addition, pain levels, which were measured using the SF-MPQ sensory scale, were higher at 1 year (mean difference, 1.17 [$p = 0.04$]). There were no significant differences in the SF-MPQ affective scales after surgery, compared with baseline.

DISCUSSION

The performance of BPM in women at high risk for breast carcinoma has increased 12% per year during the last decade.[13] It has been hypothesized that heightened awareness of genetic breast cancer, increased use of genetic testing, and improvements in postmastectomy reconstruction techniques have contributed to the higher rates of BPM.

When considering BPM, patients should be informed not only of the impact that prophylactic surgery has on cancer incidence and survival but also of the expected health-related quality-of-life outcomes. Ultimately, the decision to proceed with risk-reducing surgery should be driven by how the risk-to-benefit profile of the approach matches the patient's values and health preferences.

A recent qualitative evaluation found that the majority of women undergoing prophylactic mastectomy were dissatisfied with their decision-making process, stating that their need for information was not adequately met.[14] This underscores the need for high-quality data regarding how the performance of BPM and reconstruction in women at high risk for breast cancer affects their quality of life.

The results of this investigation suggest that high-risk women experience significant improvements in body image (satisfaction with breasts) and psychosocial well-

TABLE 3 Within-person change of patient-reported outcomes between baseline and postoperative years 1 and 2

Patient-reported outcome (range)[a]	Baseline [mean (SD)]	Baseline versus year 1 [$N = 204$]		Baseline versus year 2 [$N = 149$]	
		Mean difference[b] (95% CI)	p Value	Mean difference[b] (95% CI)	p-Value
BREAST-Q					
Satisfaction with breasts (0–100)	59.3 (20.5)	9.1 (5.4, 12.9)	0.001	10.7 (5.6, 15.8)	0.001
Psychological well-being (0–100)	70.6 (17.2)	6.0 (2.6, 9.3)	0.003	7.9 (3.5, 12.4)	0.003
Physical well-being (0–100)	87.1 (12.0)	−8.6 (−12.3, −5.0)	0.001	−5.1 (−10.9, 0.8)	0.079
Sexual well-being (0–100)	58.0 (20.9)	−1.1 (−4.7, 2.5)	0.504	−1.2 (−6.5, 4.0)	0.601
PHQ-9 total score (0–27)	3.2 (3.4)	−0.4 (−1.2, 0.3)	0.197	−0.5 (−2.5, 1.6)	0.626
GAD-7 total score (0–21)	4.5 (4.5)	−2.2 (−2.9, −1.5)	<0.001	−2.3 (−3.5, −1.2)	0.002
PROMIS-29					
Anxiety (40.3–81.6)	56.4 (9.1)	−10.0 (−12.2, −7.8)	<0.001	−8.1 (−10.9, −5.3)	<0.001
Depression (41.0–79.4)	46.7 (7.0)	−1.5 (−2.9, −0.2)	0.033	−1.1 (−3.1, 0.8)	0.219
Fatigue (33.7–75.8)	46.9 (9.5)	−0.8 (−2.6, 1.0)	0.353	−0.1 (−4.0, 3.7)	0.941
Pain interference (41.6–75.6)	43.6 (5.1)	1.2 (−0.5, 3.0)	0.135	1.3 (−0.4, 3.0)	0.121
Physical function (22.9–56.9)	54.9 (5.2)	−1.6 (−3.6, 0.3)	0.083	−0.5 (−1.7, 0.8)	0.416
Satisfaction with participation in social roles (29.0–64.1)	55.5 (8.6)	0.0 (−1.7, 1.6)	0.946	−0.9 (−3.4, 1.6)	0.420
Sleep disturbance (32.0–73.3)	51.7 (3.9)	0.6 (−0.6, 1.7)	0.289	0.2 (−1.2, 1.5)	0.780
SF-MPQ					
Sensory (0–33)	1.2 (2.4)	1.2 (0.1, 2.3)	0.040	1.0 (−0.5, 2.4)	0.164
Affective (0–12)	0.8 (1.4)	−0.2 (−0.6, 0.1)	0.145	−0.4 (−1.3, 0.4)	0.245
NPRS (0–10)	0.4 (1.2)	0.4 (−0.1, 0.8)	0.084	0.3 (−0.2, 0.7)	0.215

CI confidence interval, *GAD-7* General anxiety disorder 7-item scale, *NPRS* numerical pain rating scale, *PHQ-9* Patient Health Questionnaire-9, *PRO* patient-reported outcome, *PROMIS-29* patient-reported outcome measurement information system-29, *SD* standard deviation, *SF-MPQ* Short-Form McGill Pain Questionnaire

[a] For the BREAST-Q, a higher score indicates better outcome; for the PHQ-9, GAD-7, SF-MPQ, and NPRS, a higher score indicates worse outcome; and for the PROMIS-29, a higher score indicates better outcome if the concept is positively worded (e.g., physical function) and worse outcome if the concept is negatively worded (e.g., anxiety)

[b] Difference is defined as the value of PRO at postoperative 1 or 2 years minus that of baseline

being at 1 and 2 years after BPM and successful completion of postmastectomy reconstruction. Our findings also indicate that, for women who successfully undergo these procedures, general anxiety is significantly reduced following surgery. However, these benefits are not without costs; chest and upper body morbidity appears to worsen in these women postoperatively and remains affected at 2 years.

These results are generally similar to those found by Frost et al., who performed a cross-sectional study evaluating outcomes in 572 women at a mean of 14.5 years after BPM.[15] Of their cohort, 93% completed postmastectomy reconstruction using implants, 5% underwent BPM alone, and 2% had unknown reconstruction status. The study used an ad hoc questionnaire consisting of single-item, ordinal scales to measure the effects of BPM on a range of psychosocial and social domains. Overall, 70% of women were 'satisfied or very satisfied' with the procedure. Additionally, 74% reported a diminished level of emotional concern about developing breast cancer. However, in contrast to our current findings, only 16% of women in their series reported favorable effects on satisfaction with their body appearance, whereas 48% reported no change and 36% reported diminished or greatly diminished satisfaction with appearance. It may be that these findings by Frost et al., which represent longer-term outcomes, differ from the intermediate outcomes in the current investigation due to the length of follow-up.

However, it is also noteworthy that the ad hoc questionnaire used in their study was created using a compilation of nonvalidated, single-item scales, and that they asked women to reflect on their experiences at 14.5 years from surgery. This methodologic approach may limit the confidence that can be placed in their findings. Additionally, Frost et al. recruited patients who had undergone BPM and reconstruction as early as 1960. Since then, decades of improvements to both the surgical techniques and the materials used in postmastectomy reconstruction have generally improved cosmetic outcomes. It may thus be hypothesized that, in general,

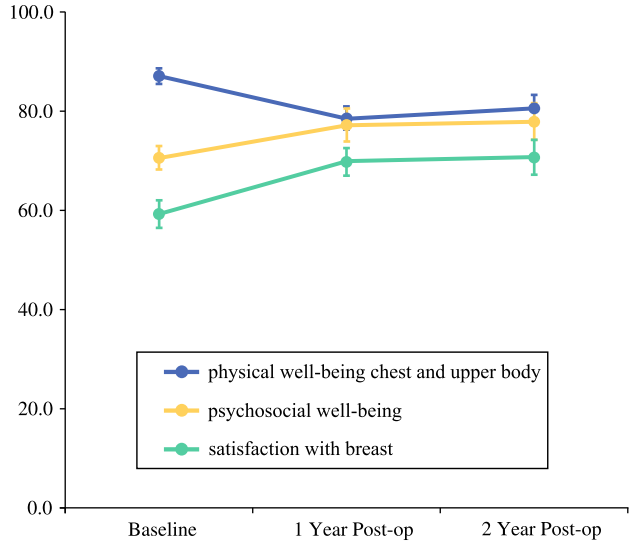

FIG. 1 Overall mean of BREAST-Q scores. *Post-op* postoperatively

patients' perception of their overall appearance following postmastectomy reconstruction has improved as significant strides have been made in the field of reconstructive surgery.

Similarly, a Cochrane systematic review reported that women who have BPM generally report satisfaction with their decision.[16] Interestingly, cosmetic satisfaction after BPM was consistently less favorable. Data were derived from eight different sources, ranging from patient written responses to personal interviews to ad hoc questionnaires. Physical morbidity was generally defined as a return to the operating room for a perioperative or implant complication and did not address sensory morbidity or pain symptomatology after surgery.

Key strengths of this current investigation include the use of preoperative assessments, which provide a baseline with which to compare patients' postoperative outcomes; the use of multiple, well-validated, reliable PROMs, including a breast reconstruction-specific survey instrument (the BREAST-Q); and the ability to reliably quantify the magnitude of effect that the surgical intervention may have on outcomes from a patient perspective. The study's multisite design, which may have minimized the potential effects of an individual provider and/or institution, is a further strength.

The limitations of this study include the potential for volunteer bias. Our study sample contains only patients who elected to undergo risk-reducing surgery, thus constituting a self-selected population. Additionally, this study does not evaluate outcomes in women who chose BPM *without* reconstruction; thus, the role that reconstruction plays in the determination of postoperative satisfaction cannot be directly elucidated. Furthermore, although the MROC study has a multisite design, the majority of sites were based within larger academic centers, which may limit the generalizability of results to those in community practices and less urban locations. Similarly, these results represent only outcomes up to 2 years following surgery in relatively educated, higher income, mostly White women who had BPM and successful reconstruction. It is not clear that these results can be generalized beyond this population and/or time frame. Finally, it has been suggested that satisfaction associated with BPM and reconstruction may be compromised by a postoperative complication. Future evaluation of the impact of these and other clinical and demographic variables on patients' perception of outcomes following BPM and reconstruction is thus warranted.

CONCLUSIONS

The results of this study highlight the possible health-related quality of life benefits of BPM and immediate reconstruction for women at high risk for breast carcinoma. More specifically, this approach may provide positive, lasting changes in a woman's satisfaction with her breasts, as well as her psychosocial well-being. Furthermore, surgery can result in a significant reduction in anxiety during the postoperative period. Ultimately, this knowledge provides clinicians and patients alike with high-quality data to inform and improve their clinical decision-making process.

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