Review Article

The Role of Menopausal Hormone Therapy in Women With or at Risk of Ovarian and Breast Cancers: Misconceptions and Current Directions

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For women who are candidates for menopausal hormone therapy (MHT), estrogen can provide relief from symptomatic menopause, decrease rates of chronic illnesses, and improve health-related quality of life. However, confusion surrounds the evidence regarding the impact of exogenous estrogen and progesterone on the breast and ovary. Available data regarding the risks of MHT (estrogen and/or progestin) related to the development of breast and ovarian cancer are often inconsistent or incomplete. Modern molecular and genetic techniques have improved our understanding of the heterogeneity of breast and ovarian cancer. This enhanced understanding of the disease has impacted our understanding of carcinogenesis. Treatment options have evolved to be more targeted toward hormonal therapy for certain subtypes of disease, whereas cytotoxic chemotherapy remains the standard for other histological and molecular subtypes. The role of MHT in the breast and ovarian cancer survivor, as well as women who are at high risk for the development of hereditary breast and ovarian cancer, remains controversial despite evidence that this treatment can improve quality of life and survival outcomes. Through this article, we examine the evidence for and against the use of MHT with a focus on women who have or are at high risk for breast and ovarian cancer. ***Cancer* 2019;125:499-514**. © *2018 American Cancer Society*.

KEYWORDS: hormone replacement therapy, ovarian cancer, breast cancer, cancer risk, hormone maintenance therapy, menopausal hormone therapy.

INTRODUCTION

Breast cancer is the most common cancer diagnosed in women in the United States, with approximately 268,670 cases per year.[1] Overall survival (OS) after a breast cancer diagnosis remains high (90%), and mortality has been declining over the last several decades.[1] Conversely, ovarian cancer remains the most lethal of the gynecologic malignancies and currently has an estimated 22,240 new cases and 14,070 deaths.[1] Advances in the treatment of ovarian cancer have led to improved median OS for women in the United States over the last several decades, thus an estimated 222,000 or more women with ovarian cancer are alive at any time.[2-4] Taken together, this means an increasing number of women are living longer with a history of ovarian or breast cancer. As treatments improve and women continue to live longer with breast and ovarian cancer, the role of interventions to improve quality of life and decrease mortality from other causes is an increasingly important issue.

Menopausal hormone therapy (MHT) has the potential to impact both quality of life and survival in women who become menopausal. Conflicting evidence, as well as misperception, exists regarding the role of MHT in carcinogenesis, cancer treatment, and quality of life for women who have or are at risk for ovarian or breast cancer. Our concern is that some of the refusal to suggest or consider MHT—particularly in younger patients who are at high risk for breast and ovarian cancer—originates from misunderstanding, misinterpretation, and misapplication of MHT studies in general. We herein provide some overview (and clarification) of these studies with an aim toward further understanding the evidence linking MHT with ovarian and breast cancer incidence, treatment, and quality of life.

HORMONAL INFLUENCES ON BREAST AND OVARIAN CANCER ETIOLOGY

Hormonal and reproductive influences on the tumorigenesis of breast cancer have been long recognized. Established risks for the development of breast cancer include low parity, early age at menarche, late age at menopause, and delayed childbearing.[5] Modern molecular subtyping by hormone receptor (HR) (estrogen receptor [ER] and/or progesterone receptor [PR]) status, cell of origin (luminal or basal), and human growth factor-neu receptor (HER2) status guides treatment and is predictive of

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DOI: 10.1002/cncr.31911, **Received:** May 17, 2018; **Revised:** November 1, 2018; **Accepted:** November 5, 2018, **Published online** December 20, 2018 in Wiley Online Library (wileyonlinelibrary.com)

prognosis. There are 2 predominantly HR-positive molecular subtypes (luminal A and luminal B) and 2 predominantly hormone-negative intrinsic subtypes (HER2 enriched and basal-like).[6,7] HR-positive tumors make up the majority (>70%) of invasive breast cancers. Reproductive and hormonal exposures are strongly linked to the development of HR-positive but not HR-negative breast cancers.[8,9]

Robust molecular and genetic data have emerged over the past decade to help clearly define the heterogeneity of ovarian cancer. A genetic predisposition is the strongest and most predictive risk factor for the development of ovarian cancer. In patients diagnosed with ovarian cancer, up to 24% will be identified as having a hereditary predisposition. Pathogenic mutations in *BRCA1* and *BRCA2* are found in 10% to 15% and account for up to 40% of heritable cases of ovarian cancer, but a number of other genes (including *BRIP1*, *RAD51C*, and *RAD51D*) have been identified as well.[10,11] A model of ovarian carcinogenesis that divides surface epithelial tumors into 5 main histologically defined subtypes (high-grade serous [70%], low-grade serous [<10%], endometrioid [<10%], clear cell [<10%], and mucinous ovarian carcinoma [3%]) has emerged. High-grade serous (HGS) carcinomas are defined by *TP53* mutations and are believed to originate in the fimbriated end of the fallopian tube. Germline genetic mutations are far more common among HGS ovarian cancers than other subtypes. Endometrioid and clear cell carcinomas often arise within endometriosis and are characterized by mutations in ARID1A, PIK3A, and PTEN mutations.[12-18] An increased risk of ovarian cancer among women with endometriosis when associated with infertility was first described in 2002 but has subsequently correlated epidemiologically to endometrioid and clear cell ovarian cancers.[19,20] That endometriosis is a hormonally mediated condition lends further credence to the hormonal influence of these subtypes of ovarian cancers.[15,18,21] The precursor lesion for low-grade serous (LGS) ovarian cancer is suspected to be tubal hyperplasia, and this subtype is associated with mutations of *BRAF*, *KRAS*, or *NRAS* and high levels of ER and PR expression.[15,22,23] Although mucinous tumors rarely arise from the ovaries, they can arise from teratomas and are characterized by overexpression of *KRAS* and amplification of *HER2*.[12,15,22,24,25]

PUTATIVE MECHANISMS BEHIND THE EFFECT OF HORMONES ON CARCINOGENESIS

Although epidemiologic and clinical studies provide strong evidence of a role of estrogens in breast and ovarian carcinogenesis, precise mechanistic actions on tumor formation are incompletely understood. Multiple ER pathways are associated with increased proliferation and inhibition of apoptosis within the breast, ovary, and fallopian tube. Estrogens exert genomic and nongenomic effects via interactions with 1 of 2 receptors, ERα or ERβ.[5] ERα activation leads to enhanced proliferation, whereas ERβ has an antiproliferative effect.[5,26] In the breast, fallopian tube, and ovary, the relative expression of receptors may contribute to tumorigenesis, and relative loss of ERβ is postulated to be a component of carcinogenesis.[27,28] Within the nucleus, estrogen binds to nuclear receptors directly associating with transcription factors to alter gene expression. Nuclear binding of ERα leads to transcriptional activation of multiple proto-oncogenes, including c-fos, c-myc, and HER2/neu; cell cycle regulating cyclins and growth factors. Additionally, estrogens provide a microenvironment primed for tumor development by enhancing local vascular supply and favoring an immunosuppressive environment.[29,30] Independent of ER activation, hormone metabolism generates free radicals that may act as mutagens.[5,27]

The mechanisms of progesterone's role in breast and ovarian carcinogenesis are even less clear than that of estrogen. PR is expressed as two isoforms, PRA and PRB, which are usually expressed at a 1:1 ratio in normal tissues, the relative expression of which is driven by activation of the ER.[31] Through its receptor, progesterone induces transcription and secretion of mitogenic factors.[32] Additionally, progesterone changes the microenvironment and activates pathways implicated in breast carcinogenesis when the ratio of PRA to PRB is altered. Increased PRB is the proliferative isoform and is required for mammary gland development and growth.[31] In the ovary, conversely, progesterone generally acts in an inhibitory fashion.[31,33,34] Progesterone effects promote apoptosis mediated by induction of TGF-β and cell cycle arrest at G0/G1.[33,34]

MENOPAUSAL HORMONE THERAPY CONTROVERSIES

Conjugated equine estrogen (CEE) was FDA approved in the early 1940s for treatment of menopausal symptoms. In the 1970s, an increase in the incidence of endometrial cancer in women who used menopausal estrogens led to a decline in the use of MHT. As a result, progestin was added to common MHT formulations, and the combination product was prescribed to women with a uterus. Multiple observational reports demonstrated reductions

in cardiovascular events in women using MHT, and in the 1990s, hormonal therapy was widely prescribed not only for management of symptomatic menopause but also for prevention of chronic diseases.[35,36]

On the basis of these reports, the largest trial of MHT in the general population, the Women's Health Initiative (WHI), was designed to randomly assign women to receive MHT or placebo to measure the effects of hormonal therapy on health outcomes. Postmenopausal women between the ages of 50 and 79 were accrued and enrolled at 40 centers in the United States from 1993 through 1998. A total of 27,347 women were enrolled; 16,608 women with a uterus were randomly assigned to oral CEE (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/d) or placebo, and 10,729 women with prior hysterectomy were randomly assigned to CEE (0.625 mg/d) alone or placebo. Because the primary efficacy outcome for the WHI trials was coronary artery heart disease and the primary safety outcome was invasive breast cancer, the average age at enrollment was 63 years.[37]

In 2002, increased risks of breast cancer, cardiac disease, stroke, and pulmonary embolism led to early closure of the estrogen plus progestin arm after only 5.2 years of follow-up.[37] Specific to breast cancer risk, for every 10,000 women taking estrogen-plus-progestin for 1 year, 9 additional cases of breast cancer were diagnosed, which met the trial's predetermined safety stopping rule. However, follow-up data from the WHI has demonstrated a complex pattern of risks and benefits of MHT.[38] Women taking hormones had fewer hip fractures and colorectal cancers and experienced improvements in vasomotor symptoms (Table 1).

Eighteen-year follow-up has demonstrated no association between all-cause, cardiovascular, or cancer mortality for women using MHT.[39] For women initiating MHT before menopause, a reduction in all-cause mortality was suggested but did not meet statistical significance.[36,39] The risks of adverse events related to MHT were much lower for younger women ages 50 to 59 and for those women with prior hysterectomy who received CEE alone (Fig. 1).[40,41] A post-WHI randomized trial, the Early versus Late Intervention Trial with Estradiol (ELITE) trial, randomly assigned 643 women to either placebo or estradiol valerate in early (<6 years) or late (>10 years) menopause. The results of this trial demonstrated a cardiovascular health benefit when MHT was initiated in women with early menopause.[42] A similar European trial, the Estrogen for the Prevention of Reinfarction Trial (ESPRIT), randomly assigned 1017 women to either placebo or estradiol valerate. After 10 years of treatment, women receiving MHT early after menopause had a significantly reduced risk of mortality, heart failure, or myocardial infarction, without any apparent increase in risk of cancer, venous thromboembolism, or stroke.[43] More recently, the Diet, Cancer, and Health Cohort reported a 20-year prospective cohort of 29,243 Danish women ages 50-64 and confirmed no association between MHT and overall mortality, regardless of composition and timing of therapy.[44]

TABLE 1. Health Effects of Menopausal Hormone Therapy With Combined Conjugated Equine Estrogen (0.625 mg/dL) and Medroxyprogesterone Acetate (2.5 mg/d) Reported in the Women's Health Initiative

Endpoint	CEE + MPA	CEE Alone
Invasive breast cancer	1.24 (1.01-1.53)	0.79 (0.61-1.02)
Coronary heart disease	1.18 (0.95-1.45)	0.94 (0.78-1.14)
Stroke	1.37 (1.07-1.76)	1.35 (1.07-1.70)
Pulmonary embolism	1.98 (1.36-2.87)	1.35 (0.89-2.05)
Colorectal cancer	0.62 (0.43-0.89)	1.15 (0.81-1.64)
Hip fracture	0.67 (0.47-0.95)	0.67 (0.46-0.96)
Deep vein thrombosis	1.87 (1.37-2.54)	1.48 (1.06-2.07)
Vertebral fracture	0.68 (0.48-0.96)	0.64 (0.44-0.93)
Gallbladder disease	1.57 (1.36-1.80)	1.55 (1.34-1.79)
Diabetes	0.81 (0.70-0.94)	0.86 (0.76-0.98)
Urinary incontinence	1.49 (1.36-1.63)	1.61 (1.46-1.79)
Vasomotor symptoms	0.36 (0.27-0.49)	0.72 (0.54-0.96)
Breast tenderness	3.93 (3.34-4.63)	2.48 (2.08-2.97)
Joint pain	0.72 (0.65-0.79)	0.91 (0.81-1.01)

Abbreviations: CEE, conjugated equine estrogen; MPA, medroxyprogesterone acetate.
All values are presented as hazard ratio (95% confidence interval) at the intervention phase.[139]

Physicians' prescribing patterns were dramatically impacted by the publication of the WHI, and MHT use dropped precipitously after 2002.[45] Subsequent analysis of the Surveillance, Epidemiology, and End Results (SEER) program indicated a significant decrease in breast cancer incidence in 2003, which coincided with the decrease in MHT use.[46] A subsequent analysis showed a similar correlation between the WHI and ovarian cancer incidence.[47] Current popular opinion maintains that MHT is a causative factor in the development of breast and ovarian cancers in women. Although short-term use of MHT for treatment of moderate to severe vasomotor symptoms in healthy women soon after menopause onset remains acceptable, physicians and patients remain fearful of prescribing and using MHT.[38,48] MHT is no longer routinely prescribed for primary or secondary prevention of cardiovascular disease or dementia in menopausal

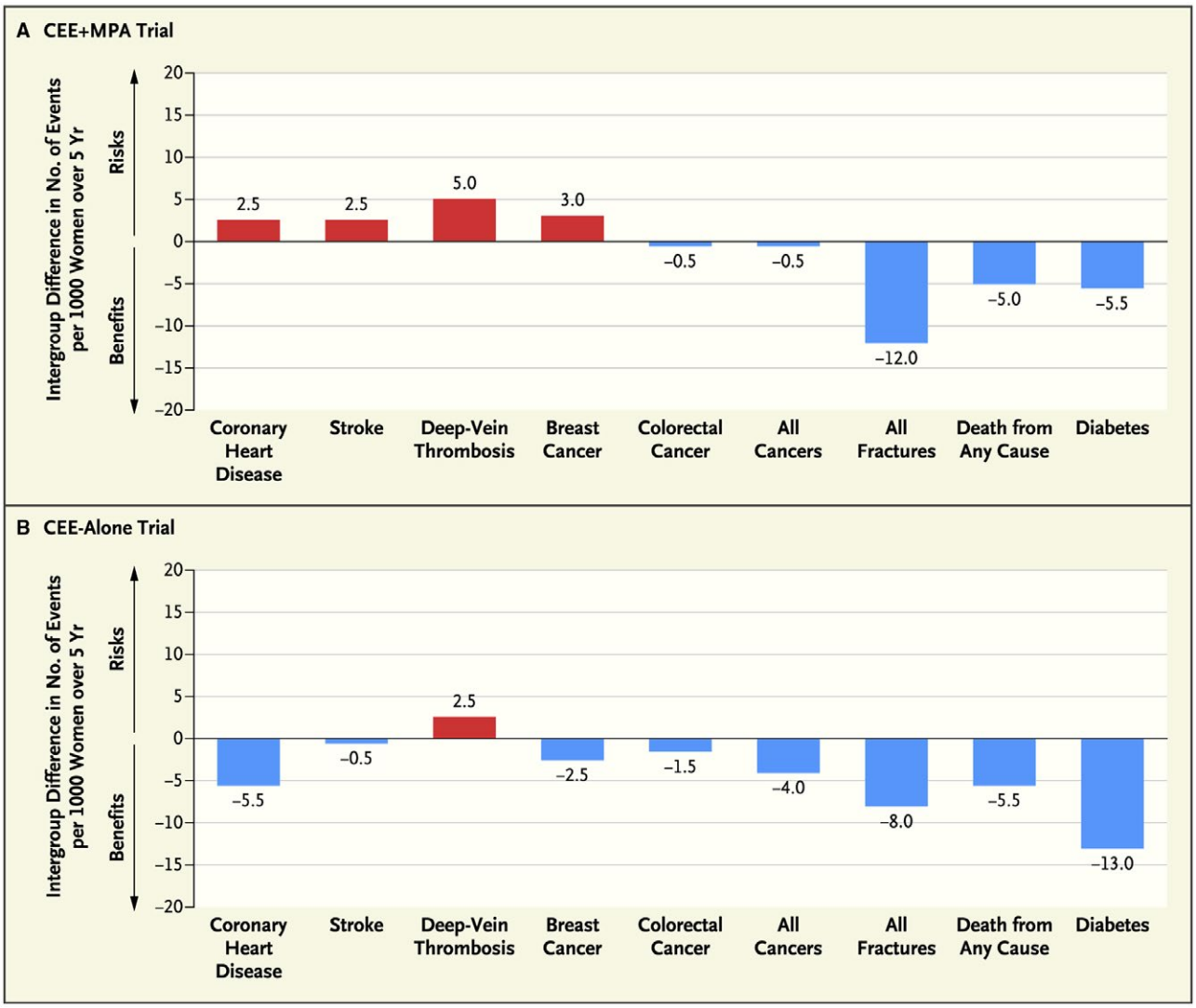

Figure 1. Estimated risks and benefits of menopausal hormonal therapy from the Women's Health Initiative for (A) conjugated equine estrogen (CEE) in combination with medroxyprogesterone acetate (MPA) and (B) CEE alone for women 50 to 59 years of age.[41]

women. Similarly, nonhormonal medications are used for first-line treatment of osteoporosis, with MHT reserved for cases when non-estrogen therapies are not sufficient. However, the lack of overall all-cause mortality (and cancer mortality) in the vast majority of studies and the net positive benefit seen among MHT subgroups have led some experts to propose a reconsideration of prescribing preventative MHT.[49-51]

MHT FOR WOMEN WITH IATROGENIC MENOPAUSE

Over 200,000 bilateral salpingo-oophorectomies are performed annually in the United States either at the time of hysterectomy, for treatment of ovarian pathology (benign or malignant), or as a risk-reducing procedure in women who are at genetic risk for the development of ovarian cancer.[52] For healthy women with iatrogenic menopause, symptoms tend to be more sudden in onset and more severe than for women undergoing natural menopause.[53] Elective oophorectomy at the time of hysterectomy in premenopausal women is associated with long-term health risks including increased all-cause mortality and cardiovascular disease.[54,55] Although the causative mechanism of the increased mortality risk is unknown, data suggest that hypo-estrogenism may play a role. In the Nurses' Health Study, a prospective

cohort study including over 29,000 women who had hysterectomy for benign disease, the greatest mortality risk was found in women <50 years of age who never used estrogen therapy compared with those with past or current estrogen therapy.[56] Women who undergo early surgical menopause also have a significantly increased risk for cardiovascular disease compared with premenopausal women.[57] MHT reduces cardiovascular disease risk and mortality among patients with early menopause as a result of oophorectomy.[56,58]

Early surgical menopause has also been associated with poor cognitive outcomes, including dementia and Parkinson disease.[54] This relationship has been found to be age dependent, with younger age at oophorectomy associated with increasing risk of cognitive impairment.[59] Other potential risks include development of depression, anxiety,[60] and sexual dysfunction.[61] A Mayo Clinic Cohort Study of Oophorectomy and Aging identified and followed premenopausal women over a 20-year period who underwent oophorectomy before the age of 50 years. An increased risk after bilateral oophorectomy for all-cause mortality (28%), coronary artery disease (33%), stroke (62%), cognitive impairment (60%), Parkinson disease (80%), osteoporosis and bone fractures (50%), and sexual dysfunction (40%-100%) was identified. The study revealed that the earlier the oophorectomy, the greater the risk. Interestingly, these effects were reduced by initiating estrogen only MHT at time of oophorectomy and continuing to age 51 or 52 to coincide with natural menopause. These observations argue for MHT as close to the onset of hormone deficiency as possible for cardiovascular, bone, and nervous system protection.[62]

DOES MENOPAUSAL HORMONE THERAPY CAUSE BREAST OR OVARIAN CANCER?

Breast Cancer

Before the publication of the WHI, an increase in the risk of breast cancer with MHT had been documented in the Nurses' Health Study. The relative risk (RR) of breast cancer was highest among the oldest women (65-69 years, 1.69; 60-64 years, 1.42; 55-59 years, 1.41; 50-54 years, 1.46; <50 years, 1.0).[63] The Collaborative Group for Hormonal Risk Factors in Breast Cancer subsequently conducted a comprehensive, international meta-analysis of individual data on 17,949 postmenopausal women with breast cancer and 35,916 controls, concluding that combined MHT is associated with breast cancer risk similar to that of later natural menopause (1.023 vs 1.028 RR per year of MHT use versus later menopause, respectively). The effect was reduced after discontinuation of MHT and had almost completely disappeared after about 5 years of cessation.[64] The majority of the data in this meta-analysis were derived from case control studies (>90%) relying on interviews or questionnaires to document MHT use, subjecting the results to recall bias. In the subset analysis of the prospective studies, the RR of breast cancer associated with MHT use was 1.09 and was not statistically significant.[64] However, evidence of increased breast cancer risk with combination MHT from the WHI superseded previous research.

The WHI reported an RR of 1.24 (95% confidence interval [CI] 1.01-1.53) with estrogen and progestin combined MHT. Breast cancers in women in the MHT arm also exhibited larger tumors compared with the placebo arm and more commonly demonstrated nodal involvement.[65] In addition, epidemiologic evidence of a decline in breast cancer incidence rates in the years immediately following the publication of the WHI was used as confirmation of the association between MHT and breast cancer.[46,66] Although the results of the WHI suggest that combined estrogen and progestin MHT was a causative factor in the development of breast cancer, consideration of several aspects of the trial put the results into context. Occult breast cancers may take years to develop into a mammographically detectable tumor. The decline in breast cancers in the early postintervention phase is, in retrospect, more suggestive that the increased breast cancer risk, and more advanced cancers seen in the combined MHT arm reflected the effect of the changes in the hormonal environment on previously existing cancers.[67,68] Also notable in the interpretation of the WHI data is that although the study began as a double-blinded study, due to data associating estrogen-only MHT with endometrial hyperplasia and cancer, the protocol was changed to randomly assign women with a uterus only to combined therapy. In addition, 40.5% of the estrogen plus progestin combined therapy arm participants were unblinded due to vaginal bleeding. The total participants who were unblinded in the treatment arm (44.4%) compared with the placebo arm (6.8%) could have introduced a detection bias during the trial, as well as that expected after trial termination.[69]

Longer-term evaluations of the breast cancers seen in the WHI participants have included some counterintuitive and unexpected results. In the estrogen plus progestin cohort of the WHI, breast cancers that developed included not only luminal malignancies, but also basal-like and HER2-enriched malignancies.[67,70]

Conversely, in the estrogen-only group of women with a prior hysterectomy, breast cancer incidence was reduced, as were deaths from breast cancer, an effect that persisted. The incidences of ductal in situ carcinoma, benign breast disease, and mammographic breast density with the WHI mirror the invasive carcinoma findings.[70] The elevated breast cancer risk seen in the estrogen and progestin arm of the WHI initially declined in the postintervention period, but then persisted with longer postintervention follow-up.[67,70]

A nested case-control study within the WHI examined sex hormone levels and breast cancer risk and found that women with lower pretreatment endogenous estrogen were at greater risk of breast cancer with combined estrogen plus progestin MHT.[71] With regard to exogenous hormone administration, in 2 post-WHI randomized trials of MHT in early menopause (<6 years following cessation of menses), with cardiovascular events as the primary outcome, no increase in breast cancer was observed.[42,43] These findings suggest a biologic difference in cancer risk on the basis of menopausal status, duration, and type of MHT. Because the impact and magnitude of MHT on breast cancer risk remains incompletely understood and there have been multiple trials with variable MHTs in differing populations and durations of use, caution is advised in applying population-based risks to an individual patient (Table 2). In general, it appears that some combination hormone use in menopause has an association with increased risk of breast cancer. However, the data concerning breast cancer risk support the overall safety of estrogen-only MHT after hysterectomy. Data regarding the overall risks and benefits may additionally support at least short-term use of combination MHT for women with an intact uterus that is initiated soon after menopause in younger women, despite the breast-specific risk.

Shortly after the first publication of the WHI on combined MHT, the results of the Million Women Study (MWS) were reported showing an increased risk of breast cancer with both estrogen and progestin as well as estrogen-only MHT.[72] The MWS was a cohort study of 1,084,110 women 50-64 years of age in the United Kingdom who were recruited between 1996-2001, who were followed up for cancer incidence and death. Half of the women reported MHT use. Women reporting current MHT use had an increased risk of breast cancer (RR, 1.66; 95% CI, 158-1.75) and breast cancer death (RR, 1.22; 95% CI, 1.00-1.48) compared with never users. However, women reporting past MHT use were not at increased risk. The MHT-associated breast cancer risk reported in the MWS was higher than that reported by the WHI, with the initial report showing an RR of 2.00 (95% CI, 1.88-2.12) for combined estrogen and progestin MHT and an RR of 1.30 (95% CI, 1.20-1.40) for estrogen only MHT. The breast cancer risk might have been overestimated for several reasons, including: 1) MHT use was more common in study participants than the general population, as was the incidence of breast cancer[73]; 2) the mean duration of follow-up was only 2.6 years; and 3) the average time to diagnosis of breast cancer was only 1.2 years, suggesting a possible detection bias as the majority of the cancers were diagnosed in the interval between screening mammograms occurred every 3 years.

Ovarian Cancer

As for ovarian cancer risk, a significant association with combined MHT was not observed in the WHI.[74] However, because ovarian cancer is a relatively rare disease, studies large enough to answer this question have not been available. Over the last decade, meta-analyses and collaborative cohort groups have attempted to evaluate the risk of ovarian cancer with long-term MHT use (Table 2).[75-77] A large meta-analysis of estrogen therapy after hysterectomy published in 2009 demonstrated an increased ovarian cancer risk of 22% (95% CI, 18%-27%) for women using estrogen-only MHT. The most recent meta-analysis included over 20,000 women with ovarian cancer from 52 studies and showed that ovarian cancer risk was significantly greater in ever users than in never users of MHT when analyzed for both prospective studies (RR, 1.20; 95% CI, 1.15-1.26; $P < .0001$) and for all studies combined (RR, 1.14; 95% CI, 1.10-1.19; $P < .0001$). Risk was strongly related to temporal proximity of use, with current users incurring the most elevated risk; however, risk persisted as long as a decade after discontinuation of MHT.[77] A degree of caution should be used when interpreting the evidence, because these studies have some inherent biases and all the information regarding the specifics of MHT was not available for all studies. However, given the consistency of much of the data and the likely continued unavailability of homogenous, controlled, and prospective trials large enough to specifically answer this question, we must accept that this may represent an associated risk, particularly for estrogen. The risk seems to pale in the larger risk–benefit discussion of MHT for women. To put the risk into context, a prospective Danish registry study estimated the risk of MHT as approximately 1 additional ovarian cancer for 8300 women undergoing hormone therapy each year.[78]

TABLE 2. Invasive Breast and Ovarian Cancer Risk Associated With Menopausal Hormone Therapy

Trial	Trial Type	MHT	Mean Duration of MHT, y	Risk (95% CI)
Breast cancer				
Collaborative Group on Hormonal Factors in Breast Cancer[64]	Meta-analysis	Any	11	RR, 1.35 (1.21-1.49)
Women's Health Initiative[56,a]	Randomized controlled trial	Combined	5.6	HR, 1.24 (1.01-1.53)
Women's Health Initiative[40,a]	Randomized controlled trial	Estrogen alone	7.2	HR, 0.79 (0.61-1.02)
Danish Osteoporosis Prevention Study[43]	Randomized controlled trial	Estrogen	10.1	HR, 0.77 (0.62-0.95)
		Combined		HR, 0.90 (0.52-1.57)
Million Women Study[72,b]	Cohort study	Combined	3.7	RR, 1.08 (1.04-1.17)[c]
		Estrogen alone	7.2	RR, 1.68 (1.64-1.72)[d]
Nurses' Health Study[63]	Cohort study	Estrogen alone	14	RR, 1.32 (1.14-1.54)
		Combined		RR, 1.41 (1.15-1.74)
		Progesterone alone		RR, 2.24 (1.26-3.98)
Diet, Cancer, and Health Cohort[44]	Cohort study[e]	Any, current	NA	RR, 1.77 (1.61-1.95)[d]
		Any, previous		RR, 1.05 (0.91-1.20)[c]
		Estrogen alone		RR, 1.40 (1.21-1.63)
		Combined		RR, 1.98 (1.78–2.21)
Ovarian cancer				
Women's Health Initiative[74]	Randomized controlled study	Combined	5.6	RR, 1.58 (0.77-3.24)
Zhou et al[75]	Meta-analysis	Estrogen alone	NA	RR, 1.19 (1.01-1.4)
		Combined		RR, 1.01 (0.83-1.22)
Pearce et al[76]	Meta-analysis	Estrogen alone	NA	RR, 1.22 (1.18-1.2)
		Combined		RR, 1.10 (1.04-1.16)
Collaborative Group on Epidemiological Studies of Ovarian Cancer[77]	Meta-analysis	Estrogen alone	NA	RR, 1.32 (1.23-1.41)
		Combined		RR, 1.25 (1.16-1.34)
NIH-AARP Diet and Health Study[83]	Cohort study	Estrogen alone	≥10	RR, 2.15 (1.30-3.57)
		Combined	≥10	RR, 1.68 ((1.13-2.49)
Nurses' Health Study[80]	Cohort study	Estrogen alone	≥5	RR, 2.04 (1.41-2.97)
		Combined	≥5	RR, 0.93 (0.47-1.83)
Danish Sex Hormone Register Study[78]	Cohort study	Estrogen alone	7	RR, 1.31 (1.11-1.54)
		Combined		RR, 1.50 (1.34-1.68)
Finnish Cancer Registery[140]	Case-control study	Unspecified	<10	OR, NS
			>10	OR, 2.33 (1.04-5.19)
		Estrogen	>5	OR, 1.15 (0.99-1.32)
		Combined, sequential	>5	OR, 1.35 (1.12-1.63)
		Combined, continuous	>5	OR, 1.19 (0.77-1.85)

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not available; NS, not significant; OR, odds ratio; RR, relative risk.
[a]HR reported at the intervention phase.
[b]RR reported with follow-up at 3.6 years.
[c]RR of invasive breast cancer diagnosis in women with a history of past menopausal hormone therapy use.
[d]RR of invasive breast cancer diagnosis in women with current menopausal hormone therapy use.
[e]Adjusted for other factors.

The heterogeneity of ovarian cancer and the various histologic subtypes obfuscates the relationship between MHT exposure and malignancy risk. Not all the studies reporting on risk of ovarian cancer with MHT have had information about histologic subtypes, and until recently, important distinctions such as high-grade versus low-grade serous carcinomas were rarely included in tumor datasets.[77] In contrast to studies that associate estrogen use with the development of ovarian cancer, Trabert et al[79] showed via a nested case control study within the observational WHI study that baseline endogenous circulating estrogens vary substantially by histologic subtype and appeared associated with non-serous cancers and not with HGS tumors. Within the Nurses' Health Study, a significantly increased risk of serous ovarian cancer (RR, 1.66; 95% CI, 1.17-2.36) was seen only in current users of MHT who had greater than 5 years of use. The increased risk of endometrioid type malignancies was seen for women who were past users of MHT with an RR of 3.59 (95% CI, 1.41-9.14).[80] An analysis of another prospective study, the NIH-AARP Diet and Health study demonstrated MHT users were at increased risk for all histologic subtypes of ovarian cancers except for mucinous carcinomas. Compared with never users, women who used MHT

were at increased risk for serous carcinoma (RR, 1.33; 95% CI, 1.16, 1.53).[81] Two meta-analyses have additionally supported the increased risk with MHT for the serous and endometrioid subtypes of ovarian cancers only.[18,77] It should also be additionally that serum levels of exogenously administered estrogens in postmenopausal women may be several-fold higher than endogenous levels.[79]

Further complicating the understanding of the relationship between MHT and ovarian cancer risk is the established protective effect of oral contraceptive pills (OCPs). OCP use has been established to be associated with a reduced risk of ovarian carcinoma, and this risk reduction persists for up to 30 years after cessation of OCP use.[16,82] Widespread adoption of OCP use could explain some of the post-WHI decline in ovarian cancer incidence demonstrated with population level data.[47] In addition, limited data suggest that progestin use may decrease ovarian cancer risk.[76] Although several studies show the risk of ovarian cancer associated with estrogen-only therapy persists with combine MHT,[78,83] other studies demonstrate a mitigation of the risk associated with estrogen when progestin is added to MHT. The risk of ovarian cancer with estrogen use demonstrated in a large meta-analysis by Pearce et al[76] was statistically reduced when examined in comparison with combined estrogen plus progestin MHT. Within the Nurses' Health Study, continuous unopposed estrogen use was significantly associated with increased risk of ovarian cancer ($P < .001$; RR, 1.25 [95% CI, 1.12-1.38] for a 5-year increment of use), whereas continuous years of estrogen plus progestin use was not ($P = .77$; RR, 1.04 [95% CI, 0.82-1.32] for a 5-year increment of use).[80] A potential protective effect of progestins in ovarian cancer prevention has been supported by studies of progestin-only OCPs and limited observations that a higher dose of progestins in OCPs have a greater reduction of risk than lower-dose pills.[34,84,85] This observational evidence is supported by experiments in egg-laying hens in which progestin treatment led to significantly fewer cancers of the reproductive tract.[86] The role of hormonal therapy in the development of ovarian cancer remains unclear. Interactions between environmental, hormonal, and genetic factors are likely to impact ovarian cancer risk in an individual patient, but an understanding of the interplay and hierarchy of risk factors is rudimentary at this time.

USE OF ENDOCRINE THERAPY IN THE TREATMENT OF OVARIAN CANCER?

Although endocrine therapy with aromatase inhibitors (AIs) and selective ER modulators (SERMs) are part of the standard treatment of hormone-positive breast cancer, the role of estrogen modulation in ovarian cancer therapy is less clear. ER expression is observed in 60%-81% of ovarian cancers, and anti-estrogens can inhibit ER activity in ovarian cancer preclinical models. However, the clinical activity of endocrine therapy in ovarian cancer has been disappointing, with response rates reminiscent of many tested therapeutic agents that have been deemed inactive.[87-89] Small phase 2 studies have shown response rates of the AI letrozole in recurrent ovarian cancer to be 0%-15% (Table 3).[88,90] Despite low response rates to aromatase inhibition, clinical benefit rates (responses plus stable disease) of letrozole are estimated to be as high as 56% with duration of disease stability of 9.6 months.[91] Several clinical trials of the SERM tamoxifen (Table 3) have demonstrated an overall 10%-13% objective response rate and a 32%-35% disease stabilization rate.[88,92] Although a role for tamoxifen has been postulated for women with a history of ovarian cancer and an elevated CA-125 (biochemical recurrence), a clinical use has not been demonstrated.[93,94] A recent comprehensive review and meta-analysis estimated a clinical benefit rate of 41% (95% CI, 0.34%-0.48%) for any endocrine treatment, 43% (95% CI, 0.30-0.56%) for tamoxifen, 39% (95% CI, 0.29%-0.50%) for aromatase inhibitors, and 37% (95% CI, 0.26%-0.48%) for progestins in the treatment of ovarian cancer.[95] The small sample size of trials performed to date, study heterogeneity, and the lack of reporting on histologic subtyping or ER and PR status has led to poor-quality evidence regarding the usefulness of endocrine therapy in ovarian cancer.[95] In general, the effects seem marginal and the utility limited for most ovarian cancer types; however, increasing data support a benefit of endocrine therapy for the LGS subgroup of ovarian cancers. Although fewer than 10% of serous ovarian cancers are LGS, they tend to occur at a younger age than other ovarian histologic subtypes and are associated with prolonged OS and a relative insensitivity to chemotherapy.[96] These tumors have very high expression of ER and, to a lesser degree, PR.[97-99] ER and PR expression has been associated with subtype-specific prognosis, with the highest correlation for endometrioid and LGS cancers.[87]

A retrospective study identified 133 patients with LGS ovarian cancer treated with AIs or SERMs for recurrent disease. Despite an overall response rate of 9% (6 complete and 2 partial), the median time to progression reported was 7.4 months, and the median OS was

TABLE 3. Selected Studies Examining the Use of Estrogen Modulators in the Treatment of Ovarian Cancer

Study	N	Drug	CR, n (%)	PR, n (%)	SD, n (%)	PD, n (%)	Median Survival, mo	Median Time to Progression, mo	ER + Status
Selected studies of aromatase inhibitors in persistent or recurrent ovarian cancer									
Ramirez et al[141]	33	Letrozole	0	1 (3)	7 (21)	23 (70)	5.6 (NR) vs 10.9 (PR + SD)	2 (SD) vs 4 (PR)	33/33
Smyth et al[142]	42	Letrozole	0	7 (17)	11 (26)	24 (57)	11 (26% patients) PFS > 6 mo; 2 (5% patients) PFS > 2 y	NS	42/42
Gourley et al[143]	43	Letrozole	0	7 (16)	16 (37)	20 (47)	NS	NS	45/45
Papadimitriou et al[144]	27	Letrozole	1 (4)	3 (11)	5 (18)	18 (67)	26.5 (NR); not reached for R + SD	2.4 (NR) vs 17.6 (R + SD)	20/27
Bowman et al[145]	54	Letrozole	0	5 (9)	14 (26)	30 (56)	14	NS	16/54
Del Carmen et al[146]	53	Anastrozole	0	1 (2)	22 (42)	30 (57)	NS	2.8	Mixed ER–/ER+
Selected studies of tamoxifen in biochemical recurrences of ovarian cancer									
Kristeleit et al*[94]	20	20 mg bid	NA	NA	NA	NA	NS	5.6	NS
Hurteau et al*[93]	70	20 mg bid	NA	NA	NA	NA	33.2	4.5	NS
Selected studies of tamoxifen in persistent or recurrent ovarian cancer									
Karagol et al[147]	29	20 mg bid	1 (3)	2 (7)	6 (21)	20 (69)	3 (SD + PD) vs 15 (CR + PR)	NS	NS
Marth et al[148]	65	30-40 mg/d	2 (3)	2 (3)	50 (77)	11 (17)	5.5 (SD + PD) vs 6.2 (CR + PR)	NS	NS
Rolski et al[149]	47	40 mg/d	1 (2)	2 (4)	22(47)	22 (48)	NS	6.9	NS
Hatch et al[150]	105	20 mg bid	10 (10)	8 (8)	40 (38)	47 (45)	NS	3 (for PR and SD) vs 7.5 (CR)	62/105
Osborne et al[151]	51	100 mg/m^2 in 24 h (f/b with 20 mg bid)	1 (2)	0	0	50 (98)	NS	2	NS
Weiner et al[152]	31	40 mg/m^2 qd × 7 (f/b with 10 mg bid)	1 (3)	2 (6)	6 (19)	22 (71)	7 (NR) vs 16 (R)	14	4/11

Abbreviations: bid, twice a day; CR, complete response; ER, estrogen receptor; f/b, followed-by; NA, not applicable; NR, nonresponders; NS, not stated; PD, progressive disease; PR, partial response; qd, once a day; R, responders; SD, stable disease.

78.2 months. Patients with ER-positive/PR-positive disease produced a longer median time to progression of (8.9 vs 6.2 months), but this difference did not reach statistical significance.[100] A more recent, second retrospective study of 203 patients with stage II-IV LGS ovarian cancer examined the role of endocrine therapy after primary cytoreductive surgery and platinum-based chemotherapy. Out of these 203 patients, 133 patients underwent observation and 70 received either letrozole (54.3%), tamoxifen (28.6%), leuprolide acetate (7.1%), anastrazole (2.9%), depot medroxyprogesterone (1.4%), or a combination of therapies (5.8%). The mean duration of therapy was 33.3 months (1-223.2 months), and the median follow-up was 80.8 months.[101] The median progression-free survival (PFS) was longer for the endocrine therapy group (64.9 vs 26.4 months; $P < .001$); however, the median OS was not significantly different. Women without measurable disease had a longer OS when treated with postoperative endocrine therapy compared with observation. Although ER and PR expression data were available for approximately one third of patients, there did not appear to be an association with receptor status and PFS/OS benefit. This finding and others like it are difficult to interpret in terms of the putative receptor pathway of activity, suggesting possible alternative mechanisms of action or potentially an overcall of treatment activity.

Initial experience in replacing chemotherapy altogether with endocrine therapy has been reported recently. A retrospective report of 27 stage II-IV LGSC patients who all received either AIs or SERMs after surgery found that only 6 patients (22.2%) had tumor recurrence and only 2 patients (7%) died of disease. Though the median PFS and OS had not been reached, the 3-year PFS and OS were 79% and 92.6%, respectively.[99] Despite the limitations of these studies, endocrine therapy appears to be a reasonable treatment strategy for recurrent LGSC and can be considered as maintenance therapy. A phase 3 randomized trial that is currently in development will examine the role of AI therapy prospectively compared with patients who undergo observation.[99]

MHT IN THE BREAST CANCER SURVIVOR

Because standard adjuvant therapy to reduce the risk of recurrence for hormone receptor–positive tumors

TABLE 4. Invasive Breast Cancer Events Associated With Menopausal Hormone Therapy in the Breast Cancer Survivor in the Stockholm and HABITS Randomized Trials

Trial	MHT	Mean Duration of MHT, y	Mean Follow-up, y	New Breast Cancer Event, HR (95% CI)
HABITS[a]	Continuous combined; sequential combined; continuous estrogen	1.9	4	2.4 (1.3-4.2)
Stockholm[b]	Cyclic combined; spacing out combined; continuous estrogen	2.6	10.8	1.3 (0.9-1.9)
Combined data				1.8 (1.03-3.10)

Abbreviations: CI, confidence interval; HR, hazard ratio; MHT, menopausal hormone therapy.
[a]Choice of MHT was directed by local practice. If MHT was not specified, women were prescribed cyclic combined, sequential combined, and continuous estrogen based on years from menopause and presence of an intact uterus.
[b]Women in the MHT arm who were <55 years of age were randomly assigned to cyclic combined treatment of estradiol 2 mg/d for 21 days with the addition of medroxyprogesterone acetate (MPA) 10 mg/d for the last 10 days. In women >55 years of age, the spacing out regimen was used (estradiol 2 mg for 84 days with MPA 20 mg added for the last 14 days). Women without a uterus were treated with 2 mg/d of estradiol valerate.

involves anti-estrogen therapy with AIs or SERMs, the use of MHT to treat menopausal symptoms in survivors of breast cancer is controversial. Postmenopausal symptoms associated with estrogen deprivation often lead to decreased quality of life,[102] and the actual effect of MHT on breast cancer recurrence or mortality is unknown.

Several observational studies have suggested that MHT in a breast cancer patient does not adversely impact recurrence and mortality, although the studies were heterogeneous and patient selection was not controlled due to the nature of the investigations.[103-105] To date, there have been 3 prospective trials investigating the effect of MHT on breast cancer survivors yielding mixed results. In 1996, a randomized trial in patients with a history of breast cancer or ductal in situ carcinoma completed the recruitment of 100 of 261 (38%) of women who were approached for enrollment. The primary endpoint of the trial was acceptability of MHT in breast cancer survivors, and these results were consistent with previous survey studies showing that up to 50% of breast cancer patients would use MHT for menopausal symptoms if given under medical supervision. Notably, significant reductions in vasomotor symptoms were observed in the intervention group. Although there was no difference in recurrence rates between to the 2 groups, this study was not designed to detect a difference in oncologic outcomes.[106] Two additional randomized trials concurrently investigated MHT use and oncologic outcomes(Table 4). The Hormonal Replacement After Breast Cancer—Is it Safe? (HABITS) trial was closed at interim analysis because of a lack of benefit and increased risk of breast cancer. The HABITS trial randomly assigned 447 women (powered for 1300 participants) with menopausal symptoms who had completed treatment for stage 0-II breast cancer to MHT versus observation for 2 years. Concomitant use of tamoxifen, but not an aromatase inhibitor, was allowed. Most patients received combined MHT (80% in MHT arm and 70% in non-MHT arm) and more women in the MHT arm had hormone-positive cancers (62.3% vs 54.5%). The trial was stopped in 2003 when interval analysis demonstrated increased recurrence rates in the MHT arm (hazard ratio [HR], 1.8; 95% CI, 1.03-3.1). With a median follow-up of 4 years, the increased rate of new breast cancer events in the MHT arm persisted (HR, 2.4; 95% CI, 1.3-4.2), but no difference in breast cancer–specific OS was identified.[107] The Stockholm trial randomly assigned 378 breast cancer survivors to MHT or observation for 5 years. The trial was closed prematurely with reporting of interim analysis of the HABITS trial. In contrast with the HABITS trial, with 10.8 years of follow-up, there was no difference in new breast cancer events (HR, 1.3; 95% CI, 0.9-1.9) and no difference in breast cancer mortality between groups. Within the subset analysis of new breast cancer events, the rate of contralateral cancer was significantly higher in the MHT group (HR, 3.6; 95% CI, 1.2-10.9).[108] The conflicting results of the HABITS and Stockholm trials could be attributed to differences in the MHT interventions and trial participants. The Stockholm trial encouraged minimizing continuous combined MHT with 1-week breaks in treatment or spacing out of regimens. There were more node-positive patients in the HABITS trial (26% vs 16%), and more patients in the Stockholm trial were undergoing tamoxifen therapy (52% vs 21%).[109]

For women currently undergoing treatment for breast cancer or those with a personal history of breast cancer, the use of vaginal estrogen to relieve hypoestrogenic urogenital symptoms has not been associated with an increased risk of cancer recurrence and is considered safe.[110] Systemic MHT has been implicated in an increased risk of breast cancer in all histologic

subtypes of this disease, but not in ER-negative cancers.[111] Although systemic MHT use after a breast cancer diagnosis is not recommended, for select patients the quality of life benefits may outweigh the risks. These patients should be carefully counseled regarding the risks and benefits before initiating therapy. Additional research is needed to further define the oncologic risk with MHT use in breast cancer patients, specifically with regard to the influences of concurrent adjuvant endocrine therapy, the molecular subtype of the primary tumor, and MHT formulations.

MHT IN THE OVARIAN CANCER SURVIVOR

Although ovarian cancer primarily impacts postmenopausal women, amelioration of climacteric symptoms following an ovarian cancer diagnosis is an even more important concern for younger women.[112] A meta-analysis combining 6 studies with 451 women who received postdiagnosis MHT and 1070 control patients has demonstrated no statistically significant difference in survival outcomes when women with ovarian cancer are treated with MHT.[113] Several observational studies have demonstrated no increased risk of recurrence with MHT in this patient population and have suggested a possible benefit.[114-116] Two prospective studies have randomly assigned patients with ovarian cancer to receive MHT or not.[117,118] In the first of these trials, 59 patients received estrogen-only MHT and 66 control patients did not. All stages of disease were included, and the mean follow-up time in the study was 42 months. MHT compared with no treatment yielded disease-free intervals of 34 and 27 months and OS of 44 and 34 months, respectively, but were not statistically significant.[117] A European randomized, multicenter phase 3 trial enrolled 150 patients with stage III disease from 1990 to 1995 but was unfortunately closed early due to slow accrual. Surprisingly, results of long-term follow-up (19 years) of this intention to treat analysis demonstrated improved PFS and OS in the 75 estrogen users compared with a control group of 75 nonusers, both of which were statistically significant.[118]

The evidence to date examining the use of MHT in the ovarian cancer survivor is limited by the heterogeneity of tumor types included in the patient populations. Many studies have included low malignant potential tumors. Given the evolving role of HT and HMT in the treatment of LGS ovarian cancers, MHT would appear contraindicated in this group of women (though without direct evidence to conclude so). This finding is unfortunate given the relatively younger age of the patients and the improved long-term survival time compared with high-grade serous carcinoma. However, for younger women and women with other ovarian cancer subtypes, the benefits of reduction in vasomotor and other postmenopausal symptoms and the current data favoring improved survival support the recommendation of MHT.

THE ROLE OF MHT IN WOMEN AT RISK OF DEVELOPING BREAST AND OVARIAN CANCER (PREVIVORS)

Identification of genes such as *BRCA 1/2* that predispose women to breast and ovarian cancer has led to a new class of cancer patients referred to as "previvors." These patients are known to have a pathogenic genetic mutation and a subsequently higher lifetime risk of developing cancer, but they do not have a cancer diagnosis. For women with a diagnosis of *BRCA1/2* or other mutations predisposing them to breast and ovarian cancer, risk-reducing salpingo-oophorectomy (RRSO) with or without hysterectomy and/or mastectomy between the ages of 35-40 or when childbearing is complete is recommended, because this procedure has been demonstrated to be useful in cancer prevention.[119-122] A decrease in breast cancer risk and breast cancer–specific mortality as high as 50% likely contributes to the all-cause mortality reduction from RRSO in *BRCA1/2* mutation carriers.[123-126] Despite the known cancer prevention benefit of RRSO, the long-term effects on overall health and quality of life remain critical questions for premenopausal previvors considering the procedure. Symptoms of surgical menopause resulting from RRSO can include hot flashes, vaginal dryness, sexual dysfunction, sleep disturbances, and changes in cognition. These symptoms of estrogen withdrawal are prevalent adverse effects for women after RRSO and may impact health-related quality of life.[127-130] When mastectomy is combined with RRSO, menopausal and quality of life symptoms appear to be amplified, perhaps due to the effect of altered body image.[131] Fear of these symptoms can also influence previvors' willingness to undergo risk-reducing surgery as well as their postprocedure satisfaction with their decision.[128]

Although MHT can mitigate the adverse effects of surgical menopause, previvors and physicians are often wary of its use due to perceived risks of cancer promotion.[130,132,133] Small studies have shown no increased risk of breast cancer from MHT in *BRCA1* mutation carriers who have undergone menopause and who have

no personal history of cancer.[133-137] A recent prospective trial of 872 carriers of BRCA1 mutation carriers provides further evidence of the safety of MHT in this population. For previvors using combined estrogen and progestin MHT in this cohort, the risk of breast cancer was similar to nonusers (10.3% vs 10.7%). The use of estrogen-only MHT appeared protective in women with a previous hysterectomy; with a notable, but not statistically significant, 8% reduction in breast cancer per year of use.[138] These findings are consistent with the overall reduction in breast cancer seen in the estrogen-only arm of the WHI; in addition, they may sway patients and providers toward consideration of hysterectomy at the time of RRSO to allow for estrogen-only MHT postoperatively.

CONCLUSIONS

Despite a modern emphasis of precision medicine in cancer care, the role of hormonal modulation in the development, treatment, and management of climacteric symptoms after diagnosis requires further study to better define this group of patients as well as the situations in which this approach would inflict harm versus provide benefits. Although some preclinical and epidemiologic evidence seemingly contradicts individual experience in observational or small randomized studies, there are data available to help counsel women about general and specific risks and benefits. What seems clear is that the generalized approach of hormonal avoidance in all patients is both misguided and potentially harmful. The risks of MHT in the general population—particularly for women in early menopause—are small, and benefits to quality of life may outweigh risks for many, particularly in light of the overall data showing either a beneficial or neutral effect on all-cause mortality. In women without a personal history of breast cancer who may be at risk for familial breast and ovarian cancer and who undergo premature menopause, the data may be more limited but seem to also indicate that the benefits outweigh the risks for most women. For the individual breast or ovarian cancer survivor, decisions about hormonal therapy and/or MHT are hampered by the limitations of the existing medical literature on this topic, which includes many small trials that failed to reach accrual. At least for ovarian cancer, the available evidence suggests either a neutral effect or a possible benefit to MHT in terms of survival. In light of the limitations of the existing evidence, particularly for breast and some histologies of ovarian cancer, decisions will depend on the age of the patient, the presence of symptoms of menopause, and the molecular and hormonal characteristics of the tumor. We are concerned that the generalized fear and misinformation regarding MHT may be preventing women who have had or are at high risk for breast and ovarian cancer from receiving information and access to MHT when appropriate. Our hope is that continued education will allow providers who are involved in the care of these patients to remain unbiased and open to discussion of use based on a balance of current evidence—and that where controversy remains, there will be continued commitment to studies that further clarify the group of individuals in whom the benefits outweigh the risks.

FUNDING SUPPORT

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES

Robert M. Wenham reports being a research fund recipient, consultant, advisor, steering committee or DSMB member, or speaker for Tesaro, Clovis Oncology, Genentech, Merck, Ovation Diagnostics, Janseen, Mersana, Amgen, and Tapimmune.

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