clinical reviews

Breast Cancer Prevention: Time for Change

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abstract

Agency breast cancer prevention guidelines for other than hereditary cancers have not materially changed in 20 years; endocrine-targeted agents (then, tamoxifen; now, adding raloxifene and aromatase inhibitors) reduce good prognosis estrogen receptor (ER)–positive, progesterone receptor (PR)–positive cancers without reducing deaths from breast cancer. Across three tamoxifen placebo-controlled prevention trials (N = 23,360) begun almost 30 years ago, although there were 226 fewer breast cancer cases, there were nine more deaths from breast cancer in the tamoxifen groups. Following clinical advances, currently more than half of breast cancer cases are solved problems with extremely low risk of death. As endocrine-targeted agents commonly prevent these cancers, widespread implementation of current prevention strategies may not reduce deaths from breast cancer. Compared with other breast cancers, ER-positive, PR-negative cancers and triple-negative cancers have inferior survival (90.6% *v* 83.8% *v* 78.1%, respectively; $P < .001$). Against this background, in the Women's Health Initiative Dietary Modification randomized trial (N = 48,835), ER-positive, PR-negative cancers were statistically significantly reduced in the intervention group (hazard ratio, 0.77; 95% CI, 0.64 to 0.94) and deaths from breast cancer were reduced 21% ($P = .02$). In the Women's Health Initiative randomized, placebo-controlled trial evaluating conjugated equine estrogen (N = 10,739), ER-positive, PR-negative cancers were statistically significantly reduced in the intervention group (hazard ratio, 0.44; 95% CI, 0.27 to 0.74) and deaths from breast cancer were reduced 40% ($P = .04$). These findings suggest that reexamination of breast cancer risk reduction strategies and clinical practice is needed.

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INTRODUCTION

The first ASCO Technology Assessment on endocrine-targeted interventions for breast cancer risk reduction was published more than 20 years ago. At that time, the major conclusions were that the selective estrogen receptor modulator tamoxifen significantly reduced estrogen receptor (ER)–positive breast cancers but did not reduce deaths from breast cancer (breast cancer followed by death directly attributed to the cancer), arguably the most relevant clinical end point.[1]

Subsequently, there has been substantial progress in identifying the 5%-10% of breast cancers estimated to result from hereditary cancer related to pathogenic or likely pathogenic genetic variants and establishing effective interventions for early detection of those cancers including magnetic resonance imaging (MRI) screening and risk reduction bilateral mastectomy.[2] However, for most breast cancers, progress in prevention has been limited if the goal is to reduce deaths from breast cancer.

Now after 20 years, the fifth and most recent ASCO clinical practice guideline update for breast cancer prevention raised the threshold for pharmacologic intervention (from 1.67% to 3% 5-year risk with the Breast Cancer Risk Assessment Tool [BCRAT] or to 5% 10-year risk with the International Breast Intervention Study [IBIS] Tyrer-Cuzick Risk Calculator) with continued focus on endocrine-targeted prevention agents. Although more agents were identified, the efficacy findings were like those in the original report. The selective estrogen receptor modulators tamoxifen and raloxifene and the aromatase inhibitors exemestane and anastrozole all statistically significantly reduce the incidence of primarily ER-positive, progesterone receptor (PR)–positive breast cancers. However, for all four agents, the ASCO guideline authors report "there is no evidence for a survival advantage given for primary prevention," namely, there was no reduction in deaths from breast cancer.[3] In fairness, to date, none of the trials have been powered for breast cancer mortality; however, it is instructive to review the available evidence on this issue.

BREAST CANCER RISK REDUCTION TRIALS AND BREAST CANCER MORTALITY

In a meta-analysis of four randomized prevention trials, tamoxifen reduced the 10-year cumulative incidence

ASSOCIATED CONTENT

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of invasive breast cancers by 33% ($P < .0001$) and reduced the incidence of ER-positive cancers by 44% ($P < .0001$), whereas for ER-negative cancers, a nonsignificant 13% increase in incidence ($P = .4$) was seen.[4] There are three randomized trials evaluating tamoxifen with relatively long follow-up with information on deaths from breast cancer: the Royal Marsden Tamoxifen Prevention Trial,[5] the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1,[6] and the International Breast Cancer Intervention Study I (IBIS-I).[7] Across these three trials, when recruitment began in 1986 (Royal Marsden) or 1992, 23,360 women were randomly assigned to 5 years or 8 years (Royal Marsden) of tamoxifen, 20 mg/d or placebo. Although in the tamoxifen groups there were 226 fewer breast cancer cases (704 *v* 478) cases, respectively), there were nine more deaths from breast cancer in the tamoxifen compared with the placebo groups (55 *v* 46, respectively).[6,7] Such findings are consistent with tamoxifen mainly reducing breast cancers with favorable prognosis and those amenable to current curative therapies with limited impact on breast cancers that pose mortality risk.[8] Findings from these three trials and selected other trials with reported deaths from breast cancer are outlined in Table 1.[9,10]

With respect to aromatase inhibitors and deaths from breast cancer in the prevention setting, two trials are available: the NCIC Clinical Trials Group Mammary Prevention.3 trial (MAP.3) and the International Breast Cancer Intervention Study II (IBIS II). In MAP.3, 4,560 postmenopausal women were randomly assigned to exemestane 25 mg/d for 5 years or placebo. After 35 months follow-up, there was a 65% reduction in breast cancer incidence ($P = .002$) but the short follow-up, which has ended, precludes meaningful information on survival.[11] In IBIS II, 3,864 postmenopausal women were randomly assigned to 5 years of anastrozole (1 mg/d) or placebo and followed for 131 months. Anastrozole significantly reduced breast cancer incidence by 49% (85 *v* 165 cases, hazard ratio [HR], 0.51; 95% CI, 0.39 to 0.66; $P < .0001$) with a significant difference in ER-positive but not ER-negative cases. There were only five deaths from breast cancer seen (two in anastrozole and three in the placebo group; Table 1).[12] The limited number of deaths from breast cancer suggests that the strategy used to identify those at higher breast cancer risk mainly identified those at risk for breast cancers with favorable prognosis and those amenable to curative therapy. Thus, development and/or promotion of new prediction models that improve performance by more effectively defining risk of easily curable cancers will likely not decrease breast cancer mortality.

BREAST CANCER PREDICTION MODELS AND BREAST CANCER MORTALITY

The performance of commonly used models to predict breast cancer incidence repurposed to additionally predict breast cancer mortality risk (death from breast cancer) is largely unknown. As risk prediction models were developed to estimate overall breast cancer risk in mammography-screened populations, these models have greater accuracy in predicting risk of ER-positive, PR-positive cancers, which are more commonly diagnosed in such populations.[13,14] In one study, in the Breast Cancer Surveillance Consortium with 37,939 invasive breast cancers, findings from the BCRAT[15] were assessed for their predictive ability for breast cancer mortality. Of 6,021 deaths in the cohort, 2,993 (49.7%) were ascribed to breast cancer. Women originally predicted by BCRAT to be at higher 5-year risk of breast cancer incidence ($\geq 1.67\%$) had surprisingly lower risk of death from breast cancer compared with women with lower BCRAT 5-year incidence risk ($< 1.0\%$; HR, 0.72; 95% CI, 0.65 to 0.81).

Thus, higher BCRAT-predicted breast cancer incidence was not associated with greater risk of death from breast cancer. Similar findings were seen with two other predictive models (BCSC-1[16] and BCSC-5, the latter model incorporating mammogram breast density[17]). The authors concluded "current risk prediction models have limited utility in planning studies to evaluate breast cancer mortality reduction strategies."[18] Whether more recent strategies to refine breast cancer risk assessment by incorporating polygenic profiles will improve prediction for breast cancer mortality remains to be determined.

BREAST CANCER PROGNOSTIC CATEGORIES

On the basis of advances over the past few decades, several large categories of early-stage breast cancer now represent essentially solved problems, where, with appropriate therapy, risk of death from breast cancer is extremely low.[19,20] However, there are potential adverse consequences associated with a breast cancer diagnosis and associated therapy. The concept of solved problems is supported by concerted interest in de-escalation adjuvant strategies for such cases.[21] Tumor categories include node-negative, ER-positive, PR-positive, human epidermal growth factor receptor 2 (HER2)–negative cancers[20] (representing about 44% of recently diagnosed US breast cancers) and ≤ 2 cm, node-negative HER2-positive cancers[19] (representing about 10% of US breast cancers[22,23]). Thus, more than half of all breast cancers fit in this solved problem category and the percentage is even higher in women adherent to mammography screening guidelines. As ER-positive, PR-positive breast cancers are the cancers that endocrine-targeted agents prevent, widespread implementation of current strategies for risk assessment and intervention may not reduce deaths from breast cancer.

Breast cancers not representing solved problems include triple-negative cancers (ER-negative, PR-negative, HER2-negative cancers), representing about 14% of US breast cancers and, not as well-recognized, ER-positive, PR-negative, HER2-negative cancers,[24] representing about

TABLE 1. Interventions and Breast Cancer Incidence and Deaths From Breast Cancer[9]

			Breast Cancer Incidence			Deaths From Breast Cancer		
Trial	**N**	**Follow-up[a]**	**Tamoxifen**	**Placebo**	**RR (95% CI)**	**Tamoxifen**	**Placebo**	
Royal Marsden[b]	2,494	13.2 years	82	104	0.78 (0.58 to 1.04)	12	9	Not reported
			Tamoxifen	**Placebo**	**HR (95% CI)**	**Tamoxifen**	**Placebo**	**OR (95% CI)**
NSABP P-1	13,388	74 months (mean)	145	250	0.57 (0.46 to 0.70)	12	11	Not reported
			Tamoxifen	**Placebo**	**HR (95% CI)**	**Tamoxifen**	**Placebo**	**OR (95% CI)**
IBIS-1	7,154	16.0 years (median)	251	350	0.71 (0.60 to 0.83)	31	26	1.19 (0.68 to 2.10)
			Anastrozole	**Placebo**	**HR (95% CI)**	**Anastrozole**	**Placebo**	
IBIS-II	3,864	131 months (median)	85	165	0.51 (0.39 to 0.66)	2	3	Not reported
			Exemestane	**Placebo**	**HR (95% CI)**	**Exemestane**	**Placebo**	**HR (95% CI)**
MAP.3	4,560	35 months (median)	11	32	0.35 (0.18 to 0.70)	1	0	Not reported
			Low-fat	**Control**	**HR (95% CI)**	**Low-fat**	**Control**	**HR (95% CI)**
WHI DM	48,835[a]	19.6 years (median)	1,299 (0.44%)	2,075 (0.46%)	0.95 (0.89 to 1.02)	132 (0.037%)	251 (0.047%)	0.79 (0.64 to 0.97)
			CEE	**Placebo**	**HR (95% CI)**	**CEE**	**Placebo**	**HR (95% CI)**
WHI CEE-alone	10,739	20.3 years (median)	238 (0.30%)	296 (0.37%)	0.78 (0.65 to 0.93)	30 (0.031%)	46 (0.046%)	0.60 (0.37 to 0.97)

NOTE. Reproduced and adapted from Powles et al[5], Fisher et al[6], Cuzick et al[7,12], Goss et al[11], Chlebowski et al.[29,37]

Abbreviations: CEE, conjugated equine estrogen; HR, hazard ratio; RR, relative risk; WHI, Women's Health Initiative.

[a]Follow-up for deaths from breast cancer end point.

[b]The Royal Marsden trial has updated information on breast cancer incidence after 18.4 years median follow-up: tamoxifen 108 cases versus placebo 134 cases (HR, 0.80; 95% CI, 0.54 to 0.97; $P = .076$). Mortality information was not included in that report.[10]

10% of US breast cancers.[22] This issue was examined in a recent report of findings among 826,599 women with HER2-negative breast cancers diagnosed from 2010 in the US National Cancer Data Base. Compared with women with ER-positive, PR-positive cancers, breast cancer overall survival was significantly lower in women with both ER-negative, PR-negative cancers and women with ER-positive, PR-negative cancers (90.6%, 78.1%, and 83.8%, respectively; both $P < .001$).[22] A biologic basis for the poor prognosis of ER-positive, PR-negative cancers comes from analyses in the SEER Oncotype Database. There, with 86,033 breast cancer cases, high-risk recurrence scores were statistically significantly associated with Black race and ethnicity, higher stage, and PR-negative tumors.[25]

Development of prediction models with breast cancer mortality as the primary end point should be a research focus. Findings from ongoing trials of breast cancer prediction models should report performance by prognostic subgroups including triple-negative cancers and ER-positive, PR-negative cancers. Particular attention should be placed on ER-positive, PR-negative cancers as this category has received only limited attention in the past.

WOMEN'S HEALTH INITIATIVE RANDOMIZED TRIALS AND BREAST CANCER MORTALITY

The Women's Health Initiative (WHI) investigators at 40 US clinical centers enrolled postmenopausal women between 1993 and 1998 in a series of randomized clinical trials to define the risks and benefits of strategies that potentially reduce the incidence of major chronic diseases, including breast cancer, in postmenopausal women.[26] The WHI clinical trials excluded women with prior breast cancer, and a baseline mammogram not suspicious for cancer was required. Serial mammograms were mandated (yearly in the hormone therapy trials and every 2 years in the dietary modification [DM] trial). All breast cancer outcomes were measured from random assignment. Mortality information was available on more than 98%.

WHI DM TRIAL

The WHI DM trial was testing a hypothesis posed more than 50 years ago that higher dietary fat intake was associated with higher breast cancer mortality.[27] In the WHI DM trial, 48,835 postmenopausal women were randomly assigned to a low-fat dietary pattern or a usual diet comparison group with breast cancer incidence as the primary study end point. During the

8.5-year dietary intervention, dietary fat intake was significantly but moderately reduced to 24.3% of energy; intakes of fruits, vegetables, and grains were all significantly increased; and body weight, while not an intervention target, was significantly reduced in the intervention group.[28]

Through 19.6 years median follow-up, although breast cancer incidence was lower in the intervention group, the finding was not statistically significant. However, the incidence of ER-positive, PR-negative breast cancers was significantly reduced in the intervention group through cumulative follow-up (HR, 0.77; 95% CI, 0.64 to 0.94). In addition, dietary intervention group participation was associated with a statistically significant lower risk of deaths from breast cancer (HR, 0.79; 95% CI, 0.64 to 0.97; $P = .02$; Table 1).[29] The breast cancer mortality findings were unchanged by analyses incorporating time-dependent weight change. To our knowledge, the WHI DM trial is the only randomized lifestyle intervention with breast cancer as a study end point to report such a positive result regarding the most important clinical outcome. The finding for deaths from breast cancer in the WHI DM trial is based on the distribution of 383 deaths from breast cancer, an event total nearly four times greater than the 97 deaths from breast cancer reported across five endocrine-targeted randomized prevention trials (Table 1).

The WHI low-fat dietary pattern, as implemented, represents dietary moderation, similar to the dietary intervention to stop hypertension (DASH), demonstrably achievable by many as reflected in 19,541 WHI dietary group participants.[29] Agency guidelines regarding lifestyle and breast cancer risk, almost exclusively on the basis of observational study results, should now consider incorporating findings regarding moderate fat intake reduction on the basis of randomized clinical trial evidence.

Regarding potential mediating mechanisms, host-related factors, including insulin resistance and metabolic syndrome, have long been associated with breast cancer.[30,31] In a WHI cohort analysis, lower insulin resistance levels, measured by the homeostasis model assessment of insulin resistance (HOMA-IR), were associated with lower breast cancer incidence (P trend = .02).[32] In subgroup analyses of WHI DM trial participants, intervention group participation was associated with significantly lower HOMA-IR levels[33] and lower metabolic syndrome frequency.[34] In the WHI DM trial, although participants with 3-4 metabolic syndrome components at entry were at higher risk of death from breast cancer, those randomly assigned to the dietary intervention had significantly greater reduction in this risk (HR, 0.31; 95% CI, 0.14 to 0.69; intervention $P = .01$). Thus, metabolic syndrome components are likely contributors to the reduction in deaths from breast cancer seen.[35]

WHI RANDOMIZED HORMONE THERAPY TRIALS

In the two WHI randomized hormone therapy trials, a common component was conjugated equine estrogen (CEE), approved by the US Food and Drug Administration for marketing in 1942, 80 years ago.[36] Nonetheless, hormone therapy's influence on breast cancer remains controversial with discordant findings from observational studies compared with randomized clinical trials.

WHI RANDOMIZED TRIAL OF ESTROGEN PLUS PROGESTIN

In the WHI trial evaluating estrogen plus progestin, among 27,347 postmenopausal women, the influence of CEE plus medroxyprogesterone acetate (MPA) on breast cancer and other health outcomes was examined in women with a uterus, whereas CEE alone was similarly examined in women with prior hysterectomy.[37] In both trials, the protocol-prespecified primary monitoring outcomes were coronary heart disease for benefit and breast cancer for harm.[37]

In the estrogen plus progestin trial in postmenopausal women with a uterus, 8,506 were randomly assigned to receive 0.625 mg/d CEE plus 2.5 mg/d MPA and 8,102 placebo. After 5.6 years median intervention and 20 years cumulative follow-up, CEE plus MPA was associated with statistically significantly higher breast cancer incidence (HR, 1.28; 95% CI, 1.13 to 1.45; $P < .001$) with a higher breast cancer mortality, which was not statistically significant (HR, 1.35; 95% CI, 0.94 to 1.95; $P = .11$). Publication of these findings, together with evidence of negative influence of CEE plus MPA on coronary heart disease, stroke, and pulmonary emboli in 2002,[38] resulted in a rapid, substantial, and sustained drop in hormone therapy use, especially for CEE plus MPA.[39] Beginning in mid-2002, a substantial decrease in age-adjusted breast cancer incidence emerged[40,41] with both the lower hormone therapy use and lower breast cancer incidence sustained through 2015.[42] Likely related to the sustained decrease in hormone therapy use, by one estimate, in comparison with 2002, there have been 126,000 fewer breast cancer cases through 2012 in the United States[43] following the WHI report of estrogen plus progestin findings.

WHI RANDOMIZED TRIAL OF ESTROGEN ALONE

In the estrogen-alone trial in postmenopausal women with prior hysterectomy, 5,310 women were randomly assigned to receive CEE alone and 5,429 placebo. After 7.2 years median intervention and 20.3 years cumulative follow-up, CEE alone was associated with significantly lower breast cancer incidence (HR, 0.78; 95% CI, 0.65 to 0.93; $P = .005$) with greatest influence on poor prognosis ER-positive, PR-negative cancers (HR, 0.44; 95% CI, 0.27 to 0.74). In addition, CEE alone significantly reduced deaths from breast cancer (HR 0.60; 95% CI, 0.37 to 0.97; $P = .04$).[37] To our knowledge, the WHI CEE-alone trial is the only randomized pharmacologic intervention with breast cancer as an end point to report such a finding. Although recognizing the finding as hypothesis-generating, it is reassuring that among participants in the 50- to 59-year-old

TABLE 2. Developments Influencing Breast Cancer Prevention Strategies

Breast cancer prevention guidelines for other than hereditary cancers have not materially changed in 20 years
SERMs and aromatase inhibitors largely reduce ER-positive, PR-positive cancers and reduction in deaths from breast cancer has not been established
In long-term follow-up of tamoxifen prevention trials, despite reduction in breast cancer incidence, numerically more deaths from breast cancer are seen in the tamoxifen group
The performance of models predicting breast cancer incidence to predict fatal breast cancers is largely unknown
Now, more than half of breast cancers are solved problems with extremely low risk of death. As these are cancers that endocrine-targeted agents commonly prevent, widespread implementation of current prevention strategies may not reduce deaths from breast cancer
Both triple-negative and ER-positive, PR-negative breast cancers have poor survival prognosis
In the WHI randomized Dietary Modification trial, a statistically significant reduction in ER-positive, PR-negative breast cancers and a statistically significant 20% reduction in deaths from breast cancer were seen in the dietary intervention group
In the WHI randomized trial evaluating CEE alone, a statistically significant reduction in ER-positive, PR-negative breast cancers and a statistically significant 40% reduction in deaths from breast cancer were seen in the intervention group
Taken together, these findings suggest that reexamination of current breast cancer risk reduction strategies is needed

Abbreviations: CEE, conjugated equine estrogen; ER, estrogen receptor; PR, progesterone receptor; SERM, selective estrogen receptor modulator; WHI, Women's Health Initiative.

subgroup, CEE alone was also associated with a decrease in all-cause mortality (HR, 0.79; 95% CI, 0.64 to 0.96).[44]

Discussion of the full range of health outcomes associated with CEE alone and CEE plus MPA is addressed elsewhere.[45] Given the safety profile of CEE-alone use and the favorable influence on breast cancer mortality, consideration could be given to further evaluation of CEE-alone use in selected younger postmenopausal women among the 25% of postmenopausal US women with prior hysterectomy. In the WHI trial, the CEE dose was 0.625 mg/d. Currently, CEE doses as low as 0.3 mg/d are US Food and Drug Administration–approved.[46] Breast cancer findings on such lower doses are unknown.

In terms of observational studies, a meta-analysis of observational studies with 108,647 postmenopausal breast cancer cases with matched controls found both CEE and estradiol use associated with statistically significant excess breast cancer risk.[47] However, smaller randomized trials of estrogen alone provide a similar signal regarding breast cancer as seen in the WHI trial. In a meta-analysis of five randomized trials with 2,426 participants and 45 breast cancers, there were fewer breast cancers in the estrogen-alone group, which was not statistically significant (relative risk, 0.61; 95% CI, 0.34 to 1.09; $P = .15$). However, when findings were combined with WHI estrogen-alone randomized trial results, estrogen-alone use was associated with a lower breast cancer incidence (relative risk, 0.77; 95% CI, 0.64 to 0.93; $P = .01$; Table S17, Supplementary appendix).[47]

A leading hypothesis for the CEE-alone breast cancer findings, with both preclinical[48,49] and clinical[50] support, is that a period of estrogen deprivation results in changes whereby tumor sensitivity to estrogen-induced apoptosis occurs. Early in the CEE-alone trial, breast cancer reduction was greater in women with a gap time (time from menopause to initiation of CEE alone) of 5 or more years.[51] However, with cumulative follow-up, this effect was attenuated, suggesting other mechanisms besides a period of estrogen deprivation[52] are involved.

SUMMARY AND CONCLUSIONS

Developments influencing breast cancer prevention strategies presented in this report are summarized in Table 2. Taken together, these findings support recommendations for clinical practice and breast cancer prevention research, which are given below.

For clinical practice

Although available evidence suggests endocrine-targeted agents may not reduce breast cancer mortality, the adverse medical, physical, and psychosocial consequences of a breast cancer diagnosis and related therapies are well-documented.[53,54] As there is clinical benefit from reducing breast cancer incidence, current guidelines for breast cancer risk reduction[3,55] can be endorsed.

On the basis of randomized clinical trial findings, a low-fat dietary intervention can be recommended to decrease breast cancer mortality.

Use of CEE alone, in postmenopausal women with prior hysterectomy to reduce breast cancer mortality, should await agency guideline recommendation.

The long-term risk of breast cancer associated with estrogen plus progestin use should be recognized.

For breast cancer prevention research

For breast cancer prediction models,

1. evaluation should not be based solely on total breast cancer prediction,
2. results of prediction models regarding higher-mortality breast cancers (triple-negative and ER-positive, PR-negative) should be routinely reported, and
3. an optimal breast cancer risk prediction model end point should be death from breast cancer.

For breast cancer prevention guidelines, findings from the WHI randomized trials should be reviewed and considered for guideline inclusion including the following:

1. The low-fat dietary pattern from the WHI DM trial

2. CEE alone in postmenopausal women with prior hysterectomy from the WHI HT trial

The finding that CEE alone in a full-scale randomized clinical trial setting reduced deaths from breast cancer by 40%, a finding that has not been demonstrated for any other pharmacologic intervention, warrants further clinical attention (optimal dose, target population, sequence with endocrine-targeted therapies, etc) to determine how this intervention could fit in breast cancer prevention strategies.

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REFERENCES

1. Chlebowski RT, Collyar DE, Somerfield MR, et al: American Society of Clinical Oncology technology assessment on breast cancer risk reduction strategies: Tamoxifen and raloxifene. J Clin Oncol 17, 1999 (suppl; abstr 1939)
2. Pal T, Agnese D, Daly M, et al: Points to consider: Is there evidence to support BRCA1/2 and other inherited breast cancer genetic testing for all breast cancer patients? A statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med 22:681-685, 2020
3. Visvanathan K, Fabian CJ, Bantug E, et al: Use of endocrine therapy for breast cancer risk reduction: ASCO clinical practice guideline update. J Clin Oncol 37: 3152-3165, 2019
4. Davies C, Godwin J, Gray R, et al: Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: Patient-level meta-analysis of randomised trials. Lancet 378:771-784, 2011
5. Powles TJ, Ashley S, Tidy A, et al: Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. J Natl Cancer Inst 99:283-290, 2007
6. Fisher B, Costantino JP, Wickerham DL, et al: Tamoxifen for the prevention of breast cancer: Current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst 97:1652-1662, 2005
7. Cuzick J, Sestak I, Cawthorn S, et al: Tamoxifen for prevention of breast cancer: Extended long-term follow-up of the IBIS-I breast cancer prevention trial. Lancet Oncol 16:67-75, 2015
8. Chlebowski RT: IBIS-I tamoxifen update: Maturity brings questions. Lancet Oncol 16:7-9, 2015
9. Chlebowski RT, Aragaki AK, Prentice RL: Dietary moderation and deaths from breast cancer. J Clin Oncol 38:3071-3072, 2020
10. Detre SI, Ashley S, Mohammed K, et al: Immunohistochemical phenotype of breast cancer during 25-year follow-up of the Royal Marsden Tamoxifen Prevention Trial. Cancer Prev Res (Phila) 10:171-176, 2017
11. Goss PE, Ingle JN, Ales-Martinez JE, et al: Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med 364:2381-2391, 2011
12. Cuzick J, Sestak I, Forbes JF, et al: Use of anastrozole for breast cancer prevention (IBIS-II): Long-term results of a randomised controlled trial. Lancet 395: 117-122, 2020
13. Burke JP, Power C, Gorey TF, et al: A comparative study of risk factors and prognostic features between symptomatic and screen detected breast cancer. Eur J Surg Oncol 34:149-153, 2008

14. Crispo A, Barba M, D'Aiuto G, et al: Molecular profiles of screen detected vs. symptomatic breast cancer and their impact on survival: Results from a clinical series. BMC Cancer 13:15, 2013
15. Costantino JP, Gail MH, Pee D, et al: Validation studies for models projecting the risk of invasive and total breast cancer incidence. J Natl Cancer Inst 91: 1541-1548, 1999
16. Anothaisintawee T, Teerawattananon Y, Wiratkapun C, et al: Risk prediction models of breast cancer: A systematic review of model performances. Breast Cancer Res Treat 133:1-10, 2012
17. Tice JA, Cummings SR, Smith-Bindman R, et al: Using clinical factors and mammographic breast density to estimate breast cancer risk: Development and validation of a new predictive model. Ann Intern Med 148:337-347, 2008
18. Sherman ME, Ichikawa L, Pfeiffer RM, et al: Relationship of predicted risk of developing invasive breast cancer, as assessed with three models, and breast cancer mortality among breast cancer patients. PLoS One 11:e0160966, 2016
19. Tolaney SM, Barry WT, Dang CT, et al: Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med 372:134-141, 2015
20. Andre F, Ismaila N, Henry NL, et al: Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: ASCO clinical practice guideline update-integration of results from TAILORx. J Clin Oncol 37:1956-1964, 2019
21. Piccart MJ, Hilbers FS, Bliss JM, et al: Road map to safe and well-designed de-escalation trials of systemic adjuvant therapy for solid tumors. J Clin Oncol 38: 4120-4129, 2020
22. Dauphine C, Moazzez A, Neal JC, et al: Single hormone receptor-positive breast cancers have distinct characteristics and survival. Ann Surg Oncol 27: 4687-4694, 2020
23. Alanko J, Tanner M, Vanninen R, et al: Triple-negative and HER2-positive breast cancers found by mammography screening show excellent prognosis. Breast Cancer Res Treat 187:267-274, 2021
24. Cancello G, Maisonneuve P, Rotmensz N, et al: Progesterone receptor loss identifies luminal B breast cancer subgroups at higher risk of relapse. Ann Oncol 24: 661-668, 2013
25. Hoskins KF, Danciu OC, Ko NY, et al: Association of race/ethnicity and the 21-gene recurrence score with breast cancer–specific mortality among US women. JAMA Oncol 7:370-378, 2021
26. Anderson GL, Manson J, Wallace R, et al: Implementation of the Women's Health Initiative study design. Ann Epidemiol 13:S5-S17, 2003
27. Carroll KK, Gammal EB, Plunkett ER: Dietary fat and mammary cancer. Can Med Assoc J 98:590-594, 1968
28. Prentice RL, Caan B, Chlebowski RT, et al: Low-fat dietary pattern and risk of invasive breast cancer: The Women's Health Initiative randomized controlled dietary modification trial. JAMA 295:629-642, 2006
29. Chlebowski RT, Aragaki AK, Anderson GL, et al: Dietary modification and breast cancer mortality: Long-term follow-up of the Women's Health Initiative randomized trial. J Clin Oncol 38:1419-1428, 2021
30. Goodwin PJ: Host-related factors in breast cancer: An underappreciated piece of the puzzle? J Clin Oncol 26:3299-3300, 2008
31. Lohmann AE, Goodwin PJ, Chlebowski RT, et al: Association of obesity-related metabolic disruptions with cancer risk and outcome. J Clin Oncol 34:4249-4255, 2016
32. Pan K, Nelson RA, Wactawski-Wende J, et al: Insulin resistance and cancer-specific and all-cause mortality in postmenopausal women: The Women's Health Initiative. J Natl Cancer Inst 112:170-178, 2020
33. Shikany JM, Margolis KL, Pettinger M, et al: Effects of a low-fat dietary intervention on glucose, insulin, and insulin resistance in the Women's Health Initiative (WHI) Dietary Modification trial. Am J Clin Nutr 94:75-85, 2011
34. Neuhouser ML, Howard B, Lu J, et al: A low-fat dietary pattern and risk of metabolic syndrome in postmenopausal women: The Women's Health Initiative. Metabolism 61:1572-1581, 2012
35. Pan K, Aragaki AK, Neuhouser ML, et al: Low-fat dietary pattern and breast cancer mortality by metabolic syndrome components: A secondary analysis of the Women's Health Initiative (WHI) randomised trial. Br J Cancer 125:372-379, 2021
36. Stefanick ML: Estrogens and progestins: Background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration. Am J Med 118:64-73, 2005 (suppl 12B)
37. Chlebowski RT, Anderson GL, Aragaki AK, et al: Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the Women's Health Initiative randomized clinical trials. JAMA 324:369-380, 2020
38. Rossouw JE, Anderson GL, Prentice RL, et al: Risks and benefits of estrogen plus progestin in healthy postmenopausal women: Principal results from the Women's Health Initiative randomized controlled trial. JAMA 288:321-333, 2002
39. Tsai SA, Stefanick ML, Stafford RS: Trends in menopausal hormone therapy use of US office-based physicians, 2000-2009. Menopause 18:385-392, 2011
40. Ravdin PM, Cronin KA, Howlader N, et al: The decrease in breast-cancer incidence in 2003 in the United States. N Engl J Med 356:1670-1674, 2007
41. Chlebowski RT, Kuller LH, Prentice RL, et al: Breast cancer after use of estrogen plus progestin in postmenopausal women. N Engl J Med 360:573-587, 2009
42. Chlebowski RT, Aragaki AK, Anderson GL, et al: Forty-year trends in menopausal hormone therapy use and breast cancer incidence among postmenopausal black and white women. Cancer 126:2956-2964, 2020
43. Roth JA, Etzioni R, Waters TM, et al: Economic return from the Women's Health Initiative estrogen plus progestin clinical trial: A modeling study. Ann Intern Med 160:594-602, 2014
44. Manson JE, Aragaki AK, Rossouw JE, et al: Menopausal hormone therapy and long-term all-cause and cause-Specific mortality: The Women's Health Initiative randomized trials. JAMA 318:927-938, 2017
45. Manson JE, Chlebowski RT, Stefanick ML, et al: Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. JAMA 310:1353-1368, 2013
46. Tang WY, Grothe D, Keshishian A, et al: Pharmacoeconomic and associated cost savings among women who were prescribed systemic conjugated estrogens therapy compared with those without menopausal therapy. Menopause 25:493-499, 2018
47. Collaborative Group on Hormonal Factors in Breast Cancer: Type and timing of menopausal hormone therapy and breast cancer risk: Individual participant meta-analysis of the worldwide epidemiological evidence. Lancet 394:1159-1168, 2019
48. Jordan VC: The 38th David A. Karnofsky lecture: The paradoxical actions of estrogen in breast cancer—survival or death? J Clin Oncol 26:3073-3082, 2008
49. Jordan VC: Molecular mechanism for breast cancer incidence in the Women's Health Initiative. Cancer Prev Res (Phila) 13:807-816, 2020
50. Ellis MJ, Gao F, Dehdashti F, et al: Lower-dose vs high-dose oral estradiol therapy of hormone receptor-positive, aromatase inhibitor-resistant advanced breast cancer: A phase 2 randomized study. JAMA 302:774-780, 2009
51. Anderson GL, Chlebowski RT, Aragaki AK, et al: Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: Extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. Lancet Oncol 13:476-486, 2012

52. Santen RJ, Yue W: Cause or prevention of breast cancer with estrogens: Analysis from tumor biologic data, growth kinetic model and Women's Health Initiative study. Climacteric 22:3-12, 2019
53. Moore HCF: Breast cancer survivorship. Semin Oncol 47:222-228, 2020
54. Runowicz CD, Leach CR, Henry NL, et al: American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. J Clin Oncol 34:611-635, 2016
55. Owens DK, Davidson KW, Krist AH, et al: Medication use to reduce risk of breast cancer: US Preventive Services Task Force recommendation statement. JAMA 322:857-867, 2019

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