

Changing Concepts: Menopausal Hormone Therapy and Breast Cancer

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Hormone therapy is still used by millions of women for menopausal symptoms. Concerns regarding hormone therapy and breast cancer were initially based on case reports and retrospective case-control studies. However, recent results from large prospective cohort studies and the Women's Health Initiative (WHI) randomized placebo-controlled hormone therapy trials have substantially changed concepts regarding how estrogen alone and estrogen plus progestin influence breast cancer. The preponderance of observational studies suggested that estrogen alone and estrogen plus progestin both increased the risk of breast cancer, with cancers commonly diagnosed at an early stage. However, substantially different results emerged from the WHI randomized hormone therapy trials. In the WHI trial evaluating estrogen plus progestin in postmenopausal women with an intact uterus, combined hormone therapy statistically significantly increased the risk of breast cancer and hindered breast cancer detection, leading to delayed diagnosis and a statistically significant increase in breast cancer mortality. By contrast, estrogen alone use by postmenopausal women with prior hysterectomy in the WHI trial did not substantially interfere with breast cancer detection and statistically significantly decreased the risk of breast cancer. Differential mammography usage patterns may explain differences between observational study and randomized trial results. In clinical practice, hormone therapy users have mammograms more frequently than nonusers, leading to more and earlier stage cancer detection. By contrast, in the WHI randomized trials, mammogram frequency was protocol mandated and balanced between comparison groups. Currently, the different effects of estrogen plus progestin vs estrogen alone on breast cancer are not completely understood.

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Concepts regarding menopausal hormone therapy and breast cancer have been evolving for decades. When exogenous estrogen was introduced into clinical practice for menopausal symptom management in the early 1940s, there were theoretical concerns regarding potential adverse effects on breast cancer, a cancer believed to be under the influence of reproductive hormones. Information linking use of exogenous estrogen to breast cancer risk initially came from case reports and retrospective case-control studies. Given the known limitations of such reports, perceptions about the nature of the relationship between hormone therapy and breast cancer developed slowly and controversy began. Subsequently, large-scale prospective observational studies that were designed to provide more reliable evidence were initiated in the 1980s and began reporting results in the 1990s (Table 1).

During this period, observational studies and biomarker studies of lipid profiles suggested that exogenous estrogen, alone or in combination with progestin, was beneficial for the prevention and treatment of osteoporosis (12), cardiovascular disease (13), and dementia (14) and had net favorable effects on diseases of aging (15), but this concept lacked clinical trial evidence. After more than 50 years of exogenous estrogen use in clinical practice, a strategy for the definitive assessment of this approach was proposed under the direct impetus of the late Dr Bernadine Healy, the first female Director of the US National Institutes of Health. Consequently, in

1993, the Women's Health Initiative (WHI) began two full-scale randomized placebo-controlled clinical trials that separately evaluated estrogen plus progestin (in women with an intact uterus) as well as estrogen alone (in women with a previous hysterectomy) (Figure 1, A) (16). Results that incorporate longer post-intervention follow-up from both trials are now available to inform the current understanding of the influence of hormone therapy on breast cancer and other chronic diseases in postmenopausal women.

To understand how concepts about hormone therapy and breast cancer have evolved over time, we compare and contrast findings from selected early case-control studies and case reports with results of randomized clinical trials and prospective cohort analyses. We address areas of agreement and controversies against a background of potential mediating mechanisms of action. Findings with estrogen alone are addressed separately from those with estrogen plus progestin.

Breast Cancer Hormonal Associations: Observational Study Findings

The concept that reproductive hormones influence breast cancer risk has a sound basis. Although it is beyond the scope of this review to provide a comprehensive assessment of all clinical findings from the past decades that informed the development of

concepts regarding exogenous estrogen use and breast cancer, we provide a timeline of selected studies to outline the overall pace of discovery (Table 1). In 1896, Beatson (1) reported that oophorectomy could result in the regression of breast cancer. Subsequent reports (3,7,19–21) described associations between reproductive events (such as a woman’s age at birth of first child, an earlier menarche, and a later menopause) and increased risks of breast cancer, suggesting a role for endogenous estrogen in breast cancer development. The finding that a previous oophorectomy was associated with lower breast cancer incidence solidified this relationship (2). An extensive body of evidence now supports the concept that, in postmenopausal women, higher endogenous estrogen levels are associated with an increased risk of breast cancer (22,23).

The higher incidence of breast cancer among women who used exogenous estrogen was initially reported in 1976 (5) (Table 1). In 1980, a case–control study with 138 breast cancers reported that the breast cancer risk ratio for cumulative estrogen doses greater than 1500 mg vs no hormone therapy was 2.5 (6). In 1989, in a prospective cohort of Swedish women, Bergkvist et al. (8) found a modestly increased risk of breast cancer associated with hormone therapy, particularly longer durations of use, compared with no hormone therapy use (after 9 years of use, relative risk = 1.7, 95% confidence interval [CI] = 1.1 to 2.7). However, an editorial in *The Lancet* (24) outlined the study limitations and, reflecting the then prevalent perspective, concluded “the Bergkvist data should not cause us to change our advice to patients.”

In the 1990s, new evidence emerged from two influential sources: a meta-analysis that consolidated data from previous case–control studies (10) and mature data from a large cohort study (9). The comprehensive collaborative reanalysis of 51 epidemiological studies of 52 705 women with breast cancer and 108 411 control subjects (80% of whom used estrogen alone) concluded that women who used hormone therapy had a statistically

significant increase in the risk of breast cancer and that the risk increased with increasing duration of use (10). Parallel analyses in the Nurses’ Health Study cohort found that estrogen alone and estrogen plus progestin were both associated with an increased risk of breast cancer (9). In 1998, tamoxifen, a selective estrogen receptor modulator that competes with estrogen for binding to the estrogen receptor, was shown to reduce the incidence of hormone receptor–positive breast cancer in a primary prevention trial (25).

Regarding potential mechanisms mediating hormone action on breast cancer, tumor expression of the estrogen receptor was found to correlate with clinical response to hormonal interventions such as tamoxifen (4,17,26). These findings suggested a relatively linear relationship among endogenous estrogen level, exogenous estrogen use, estrogen receptor activation, and breast cancer incidence.

When the WHI hormone therapy trials began in 1993, results of previous observational studies suggested that both estrogen alone and estrogen plus progestin increase the risk of breast cancer, with the increased risk with estrogen alone perhaps requiring longer exposures (Box 1). The preponderance of recent reviews and reports from large cohorts (27–29) has reached similar conclusions.

WHI: The Estrogen Plus Progestin Trial

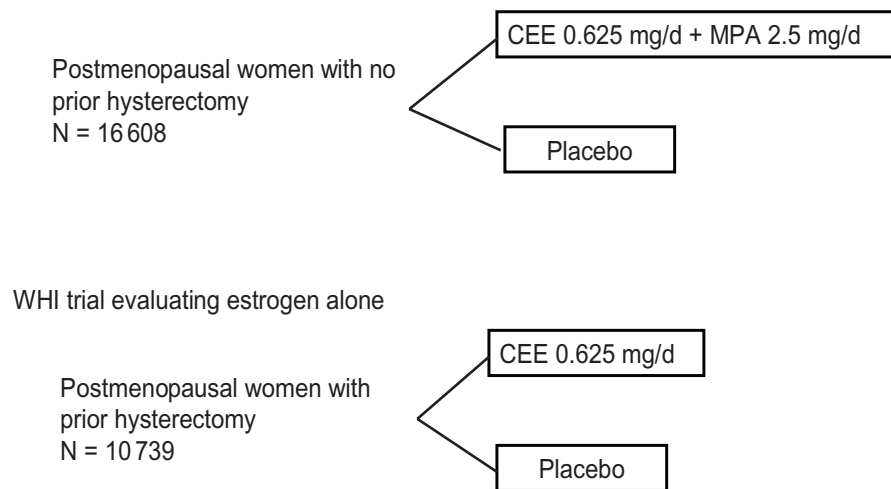
The WHI began two randomized placebo-controlled clinical trials to provide definitive assessment of the effects of estrogen alone (in women with prior hysterectomy) and of estrogen plus progestin (in women with an intact uterus). In the WHI clinical trial evaluating estrogen plus progestin in postmenopausal women with no previous hysterectomy, intervention was terminated early after mean follow-up of 5.6 years, when substantial evidence emerged of an adverse effect on breast cancer risk in the context

Table 1. Estrogen and breast cancer: findings from selected studies

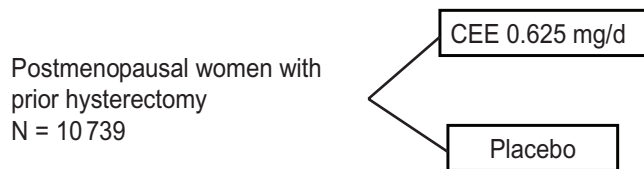
Year	First author (reference)	Study design	Finding
1896	Beatson (1)	Case report	Oophorectomy associated with breast cancer regressions
1968	Feinleib (2)	Cohort analysis	Oophorectomy associated with lower breast cancer risk
1970	MacMahon (3)	International collaborative study	Age at first birth related to breast cancer risk
1973	McGuire (4)	Summary, findings from clinical correlative studies	Estrogen receptor quantitative status correlated with clinical breast cancer response to hormone-directed therapy
1976	Hoover (5)	Incidence rate in cohort vs rate in general population	Exogenous estrogen alone associated with higher breast cancer risk
1980	Ross (6)	Case–control analysis	Exogenous estrogen associated with higher breast cancer risk
1983	Pike (7)	Analysis	Model of endogenous hormonal risk factors with breast cancer
1989	Bergkvist (8)	Cohort analysis	Exogenous estrogen alone and exogenous estrogen plus progestin both associated with higher breast cancer risk
1995	Colditz (9)	Cohort analysis	Exogenous estrogen alone and exogenous estrogen plus progestin both associated with higher breast cancer risk
1997	Collaborative Group on Hormonal Factors in Breast Cancer (10)	Collaborative reanalysis of 51 case–control studies	Hormone therapy (80% exogenous estrogen alone) associated with higher breast cancer risk
2003	Beral (11)	Cohort analysis with mammography at entry	Exogenous estrogen alone and exogenous estrogen plus progestin both associated with higher breast cancer risk. Trend for higher breast cancer mortality in estrogen plus progestin users

Figure 1. Women’s Health Initiative (WHI) Hormone Therapy Clinical Trials. **A)** Program design. The depicted study implementation details have been described previously (16–18). Entry criteria for both trials were similar, except that previous hysterectomy was required for estrogen-alone trial entry. Eligible were postmenopausal women aged 50–79 years with anticipated 3 years or greater survival. Exclusions included prior breast or endometrial cancer at any time or other cancer (except nonmelanoma skin cancer) within the previous 10 years. Hormone therapy users at screening were eligible after a 3-month washout. Despite similar eligibility, participant characteristics in the two trials differed, primarily with respect to factors that are associated with hysterectomy. Women in the estrogen-alone trial were heavier and more likely to have had bilateral oophorectomy and to have used hormone therapy in the past (18). Between 1993 and 1998, 10 739 women with prior hysterectomy were randomly assigned to estrogen alone (conjugated equine estrogen [CEE], 0.625 mg/d) or matching placebo and 16 808 women with an intact uterus were randomly assigned to estrogen plus progestin (conjugated equine estrogen, 0.625 mg/d plus medroxyprogesterone acetate [MPA], 2.5 mg/d) or a matching placebo. A mammogram and a clinical breast examination with no evidence of cancer were required for entry. Annual mammography and clinical breast examinations with negative findings were a prerequisite to dispensing ongoing study medication. Breast biopsies were clinically directed. Colorectal cancer screening was not protocol defined, but information on sigmoidoscopy and/or colonoscopy and fecal occult blood testing was collected semiannually. All cancer outcomes were verified by blinded medical record review. Depicted are the study designs of the WHI placebo-controlled clinical trials evaluating estrogen plus progestin and estrogen alone. **B)** Invasive breast cancer incidence by hormone therapy group. Hazard ratios (HRs) are from Cox proportional hazards regression models, stratified by age and randomization group in the WHI dietary modification trial and prior disease if applicable. CI = confidence interval; E + P = estrogen plus progestin; E alone = estrogen alone.

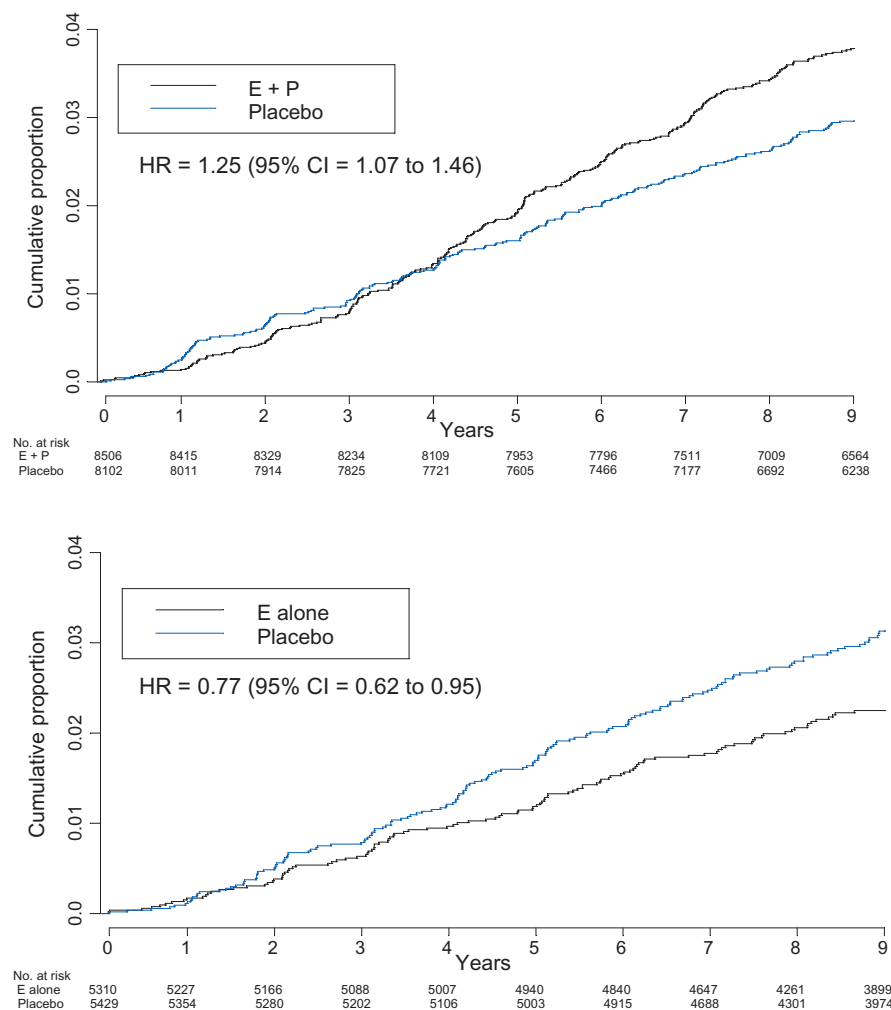
A WHI trial evaluating estrogen plus progestin



WHI trial evaluating estrogen alone



B



of an assessment that overall harms exceeded benefits for the combined hormone therapy group. By that time, approximately 40% of the participants had stopped taking study medication. Women who took estrogen plus progestin were at higher risk for

heart disease, blood clots, stroke, and breast cancer, but at lower risk for fracture and colon cancer. Since the initial report (30), detailed analyses by cancer site and with post-intervention follow-up have been published (31–35) (Table 2).

Box 1. Changing concepts regarding hormone therapy and breast cancer

Concepts in 2002

Combined estrogen plus progestin use

- Estrogen plus progestin increases breast cancer risk

Estrogen-alone use

- Estrogen alone increases breast cancer risk but may require longer duration exposure than combined estrogen plus progestin for an effect

Hormone therapy*

- Breast cancer associated with hormone therapy are mainly hormone receptor–positive cancers
- Breast cancers associated with hormone therapy are diagnosed at earlier stage
- Breast cancers associated with hormone therapy have a favorable prognosis

Current Concepts

Combined estrogen plus progestin use

- Estrogen plus progestin increases breast cancer risk and the effect on risk may be greater in women who initiate therapy closer to menopause†
- Estrogen plus progestin broadly increases breast cancer risk with the increase in risk not limited to hormone receptor–positive cancers†
- Estrogen plus progestin interferes with breast cancer mammographic detection resulting in cancers diagnosed at more advanced stage†
- Estrogen plus progestin increases breast cancer mortality†

Estrogen-alone use

- Estrogen alone reduces breast cancer risk
- Estrogen alone does not substantially interfere with breast cancer detection by mammography†

* Hormone therapy concepts refer to findings that are similar for estrogen-alone and estrogen plus progestin use or findings where estrogen alone and estrogen plus progestin were combined in analyses.

† Findings that differ from concepts in 2002.

In the WHI randomized clinical trial, estrogen plus progestin was compared with placebo in postmenopausal women with an intact uterus, and compared with placebo, estrogen plus progestin increased the risk of invasive breast cancer by 24% ($P = .003$). In sensitivity analyses that excluded nonadherent participants, the risk of invasive breast cancer was increased by 49% ($P < .001$) (31). During the first 4 years of the trial (follow-up), fewer breast cancers were diagnosed in the estrogen plus progestin group than in the placebo group; thereafter, more breast cancers were diagnosed in the estrogen plus progestin group (Figure 1, B) (31). Estrogen plus progestin resulted in a higher cumulative frequency of abnormal mammograms vs placebo (35% vs 23%, $P < .001$) while reducing the mammographic sensitivity for breast cancer detection (32). Similarly, there were more clinically indicated breast biopsies in the estrogen plus progestin group vs placebo, but those biopsies less frequently diagnosed breast cancer (31,32). The statistically

significant increase in mammographic breast density associated with estrogen plus progestin (33) is one likely factor contributing to the poor diagnostic performance of mammograms and breast biopsies.

The relatively rapid influence of estrogen plus progestin use on breast cancer incidence is consistent with it having a predominant influence on preclinical already established cancers. In addition, the fact that longer duration of the combined hormone therapy had a greater effect on breast cancer risk (31,34) suggested an influence on breast cancer development as well.

After a mean cumulative follow-up of 11 years with 678 invasive breast cancers, a 25% increase in the risk of invasive breast cancer was seen with estrogen plus progestin compared with placebo ($P = .004$) (Table 3, Figure 1, B) (35). Proportionally more lymph node–positive cancers were observed in the combined hormone therapy group vs placebo ($P = .03$). There were numerically more estrogen receptor–positive, estrogen receptor–negative, HER2-overexpressing, and triple-negative (ie, hormone receptor–negative and HER2-nonoverexpressing) breast cancers in the estrogen plus progestin group vs the placebo group (Table 3) (35). Estrogen plus progestin had a greater influence on breast cancer if initiated closer to menopause (incidence of invasive breast cancer in the hormone therapy group compared with the placebo group: for therapy initiated <5 vs ≥ 5 years from menopause, hazard ratio [HR] = 1.41, 95% CI = 1.14 to 1.74 vs HR = 1.15, 95% CI = 0.96 to 1.37; $P_{\text{interaction}} = .08$).

The more advanced stage of breast cancers diagnosed in the estrogen plus progestin group was reflected in the mortality results. In the estrogen plus progestin group, the risk of death attributed to breast cancer was increased by a factor of 1.96 ($P = .049$), and the risk of deaths from all causes after a breast cancer diagnosis was increased by a factor of 1.57 ($P = .045$) (35).

The WHI findings for estrogen plus progestin and breast cancer are similar to those from observational studies with respect to incidence but differ from most reports with respect to breast cancer characteristics and clinical outcome (27,40). As in most observational studies (41), estrogen plus progestin use had a somewhat greater influence on cancers with some lobular histology in the WHI trial. Most, but not all (42), observational studies suggest that estrogen plus progestin use is mainly associated with estrogen receptor–positive early-stage breast cancers (43–45), and some report either no increase (46) or a decrease (47,48) in death rates following a breast cancer diagnosis while on hormone therapy. A review published in 2002 (49) cited five recent cohort studies that showed either no difference in mortality or decreased mortality after a breast cancer diagnosis in hormone therapy users compared with nonusers (relative risks of death ranged from 0.5 to 1.0). By contrast, in the WHI randomized trial, the increase in breast cancer incidence was not limited to favorable prognosis estrogen receptor–positive tumors: the cancers that were diagnosed had more lymph node involvement. In addition, breast cancer mortality, measured from initial randomization, was statistically significantly increased (35).

There has been interest in the potential modulating influence of body weight, as measured by body mass index [BMI], on the effects of menopausal hormone therapy on the risk of breast cancer. In several observational studies (10,41,50,51), the risk of

Table 2. Women’s Health Initiative hormone therapy trials: monitored clinical outcomes during active intervention and overall, by study, comparing hormone therapy with placebo*

Outcome	Estrogen plus progestin vs placebo		Estrogen alone vs placebo	
	Events during intervention phase	Events, overall	Events during intervention phase	Events, overall
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Invasive breast cancer	1.24 (1.01 to 1.54)	1.25 (1.07 to 1.46)	0.80 (0.62 to 1.04)	0.77 (0.62 to 0.95)
Coronary heart disease	1.29 (1.02 to 1.63)	1.11 (0.94 to 1.11)	0.91 (0.75 to 1.12)	0.95 (0.82 to 1.11)
Stroke	1.41 (1.07 to 1.85)	1.28 (1.05 to 1.56)	1.39 (0.62 to 1.04)	1.19 (0.98 to 1.43)
Pulmonary embolus	2.13 (1.39 to 3.25)	1.66 (1.22 to 2.25)	1.34 (0.87 to 2.06)	1.18 (0.87 to 1.60)
Endometrial cancer	0.83 (0.47 to 1.47)	0.78 (0.52 to 1.16)	Not applicable	Not applicable
Colorectal cancer	0.56 (0.38 to 0.81)	0.75 (0.57 to 1.00)	1.12 (0.77 to 1.63)	1.15 (0.81 to 1.64)
Hip fracture	0.66 (0.45 to 0.98)	0.78 (0.60 to 1.00)	0.61 (0.41 to 0.91)	0.92 (0.71 to 1.18)
Global index†	1.15 (1.03 to 1.28)	1.12 (1.03 to 1.21)	1.01 (0.91 to 1.12)	1.03 (0.95 to 1.11)
Dementia	2.05 (1.21 to 3.48)	Not reported	1.49 (0.83 to 2.66)	Not reported
Deaths (all causes)	0.97 (0.81 to 1.16)	1.04 (0.91 to 1.18)	1.04 (0.89 to 1.22)	1.02 (0.91 to 1.15)

* Results from (18,30,35–37). Active intervention phase: 5.6 years (mean) in estrogen plus progestin trial and 7.1 years (mean) in estrogen-alone trial. Results are reported for outcomes occurring during active intervention with study medications and overall including total follow-up for the estrogen plus progestin trial of 11.0 years (mean) for breast cancer and 7.9 years (mean) for other outcomes. For the estrogen-alone trial, total follow-up was 10.7 years (mean). HRs for hormone therapy vs placebo are from Cox proportional regression models stratified by age, randomization assignment in the dietary modification trial, and prior disease when applicable. CI = confidence interval; HR = hazard ratio.

† The global index measured time-to-first event for clinical conditions likely under hormone influence that were associated with increased risk for death (coronary heart disease, stroke, pulmonary embolus, hip fracture, invasive breast cancer, colorectal cancer, endometrial cancer [only in the combined hormone therapy trial], and death due to other causes) (4,16,38,39).

breast cancer associated with hormone therapy use was substantially higher in women of normal weight (ie, BMI < 25 kg/m²) compared with those who were overweight (BMI = 25–30 kg/m²) or obese (BMI ≥ 30 kg/m²). By contrast, in the WHI randomized trial, no interaction was observed between BMI and the influence of estrogen plus progestin on the risk of breast cancer (31). Even after additional follow-up and 678 invasive breast cancer cases, the increased risk of breast cancer associated with estrogen plus progestin use did not differ by BMI (BMI < 25 kg/m²: 29% increase; BMI = 25–30 kg/m²: 34% increase; BMI ≥ 30 kg/m²: 14%

Table 3. Distribution of invasive breast cancer characteristics in the WHI estrogen plus progestin clinical trial by randomization group*

Characteristic	Estrogen plus progestin	Placebo	HR of breast cancer (95% CI)
	No. (%)	No. (%)	
Invasive breast cancer (all)	385 (100)	293 (100)	1.25 (1.07 to 1.46)
Histology			
Ductal	238 (62.1)	195 (66.6)	1.16 (0.96 to 1.41)
Lobular	36 (9.4)	20 (6.8)	1.63 (0.94 to 2.81)
Ductal and lobular	57 (14.9)	35 (11.9)	1.55 (1.02 to 2.37)
Tubular	13 (3.4)	9 (3.1)	1.39 (0.59 to 3.25)
Other	39 (10.2)	34 (11.6)	1.10 (0.70 to 1.75)
Estrogen receptor†			
Positive	308 (86.5)	230 (87.5)	1.27 (1.07 to 1.51)
Negative	48 (13.5)	33 (12.5)	1.40 (0.90 to 2.18)
Progesterone receptor†			
Positive	262 (75.2)	194 (75.7)	1.29 (1.07 to 1.55)
Negative	86 (24.8)	62 (24.3)	1.31 (0.95 to 1.82)
ERBB2 (HER2) overexpression†			
Yes	54 (18.8)	26 (13.9)	2.00 (1.25 to 3.19)
No	233 (81.2)	161 (86.1)	1.37 (1.12 to 1.68)
Triple negative‡			
Yes	26 (9.1)	14 (7.4)	1.78 (0.93 to 3.41)
No	259 (90.9)	173 (92.6)	1.42 (1.17 to 1.72)

* Mean follow-up for analysis was 11.0 years, including 5.6 years of study medication intervention. HRs are from Cox proportional hazards regression models, stratified by age and randomization group in the Women’s Health Initiative dietary modification trial. CI = confidence interval; HR = hazard ratio.

† The percentage for each category reflects findings from tumors with available information. For example, of tumors with information on estrogen receptor status in the estrogen plus progestin group, 86.5% were positive and 13.5% were negative. Estrogen receptor status missing: 7.5% (estrogen plus progestin) vs 9.9% (placebo); Progesterone receptor status missing: 8.3% (estrogen plus progestin) vs 11.6% (placebo); HER2 status missing: 24.7% (estrogen plus progestin) vs 35.8% (placebo).

‡ Triple negative = estrogen receptor–negative, progesterone receptor–negative, and ERBB2 (HER2) not overexpressed.

increase) (35). No compelling hypothesis has been offered to explain this difference between observational study results and the WHI randomized clinical trial. It has been suggested (52) that the proportional increase in circulating estrogen level among postmenopausal women taking exogenous estrogens might be smaller in obese women compared with normal weight women. However, a 2009 study (53) reported that obese postmenopausal women had a greater increase in circulating free estradiol in response to oral estrogen compared with normal weight women.

Differences between the WHI randomized trial findings and those of observational studies may arise from methodological issues. The limited number of breast cancers in the randomized trial yield somewhat imprecise effect estimates, particularly in subgroups of interest such as HER2-overexpressing tumors and lobular carcinomas. In the WHI trial, mammogram frequency was protocol defined and comparable between groups. In other non-trial settings, hormone therapy users have mammograms more frequently compared with nonusers (34,54), likely because of concerns about breast tenderness and/or breast cancer. In one report from the Nurses' Health Study (54), 69% of hormone users reported having undergone screening mammography in the previous 2 years compared with only 44% of nonusers. In addition, the frequency of mammography is not reliably determined retrospectively by query (55). Consequently, confounding can occur in observational studies that are unable to accurately control for frequency of mammography because screened populations have more cancers detected than non-screened populations (54,56) and cancers in the screened population are diagnosed at earlier stage (57,58). Also, observational studies of breast cancer mortality that begin analyses at the time of cancer diagnosis (47,48) or control for stage (43,45) make analysis adjustments that mitigate adverse effects of combined hormone use on breast cancer incidence and characteristics. In this regard, the Million Women Study, which began analysis at cohort entry and controlled for previous mammography, also reported higher breast cancer mortality for women who were diagnosed with breast while using estrogen plus progestin compared with non-hormone therapy users (HR of death = 1.22; 95% CI = 1.00 to 1.48, $P = .05$) (11).

Public Health Consequences of the WHI Hormone Therapy Trial

After the WHI reported the net adverse effects of estrogen plus progestin (30,59), hormone therapy use among postmenopausal women in the United States rapidly decreased over 1 year from approximately 40%–20% (60). A corresponding and substantial population-based decrease in breast cancer incidence was observed, particularly for estrogen receptor-positive breast cancers in women aged 50–69 years, which was attributed to the decreased use of hormone therapy (61,62). Although a relationship between a decrease in combined hormone therapy use and a decrease in breast cancer incidence has been generally supported in other populations in the United States (63), Germany (64), Australia (65), France (66), and Canada (67), the potential influence of changes in mammography use on the rapid decrease in breast cancer raised concerns. These concerns have been largely addressed by analyses of the WHI hormone trial, in which almost

all participants discontinued study medication as instructed (68). In that randomized trial setting, the risk of breast cancer rapidly decreased after intervention ended while annual mammography utilization was comparable in the two randomization groups (34) (Figure 2).

The rapid decrease in largely estrogen receptor-positive breast cancers seen in the United States and other countries is biologically reasonable given that a sudden change in hormonal environment likely represents a therapeutic intervention for subclinical breast cancers. In the WHI randomized trial, the influence of combined hormone therapy on breast cancer incidence does not appear to be limited to hormone receptor-positive cancers. However, in the clinic, extensive clinical trial and practical experience indicates that, for patients with established breast cancer, only hormone receptor-positive breast cancers respond to hormone-targeted therapies (38,69).

Such a treatment effect would largely be a one-time phenomenon because such a large-scale decrease in hormone therapy use in a population would not be duplicated year to year. Although a lower incidence of hormone receptor-positive breast cancer has been maintained in the US population through at least 2005 (63), studies of subsequent trends in annual breast cancer incidence have provided mixed results with reports of continued decline (66), stabilization (63), and subsequent increase (70). The complex interplay among withdrawal of estrogen plus progestin, subsequent breast cancer incidence, and associated societal and medical factors, such as increasing obesity and use of medications that have a potential influence on breast cancer such as bisphosphonates (39) and metformin (71), will influence subsequent breast cancer incidence trends.

WHI: The Estrogen-Alone Trial

In the WHI randomized placebo-controlled clinical trial evaluating estrogen alone in postmenopausal women with a previous hysterectomy, intervention ended at a mean follow-up of 7.1 years because of an increased risk of stroke and the absence of overall clinical benefit, despite a decrease in the risk of fracture (18). By that time, 54% of participants had stopped taking study medications. Other monitored outcomes, including coronary heart disease, pulmonary emboli, colorectal cancer, and hip fracture, were not influenced by the use of estrogen alone; however, there were fewer breast cancers in the estrogen-alone group compared with the placebo group (Table 2), but the difference was not statistically significant. In addition, subgroup analyses suggested that estrogen alone may be associated with more favorable outcomes in younger women compared with older women (18,36).

Breast Cancer: Randomized Trial Findings, Estrogen Alone

In the estrogen-alone trial, as in the WHI estrogen plus progestin trial, the designated primary outcome for benefit was a reduction in coronary heart disease and the designated primary adverse outcome was an increase in incidence of invasive breast cancer (72). There was a lower breast cancer incidence seen with estrogen-alone use compared with placebo during the 5.9 years

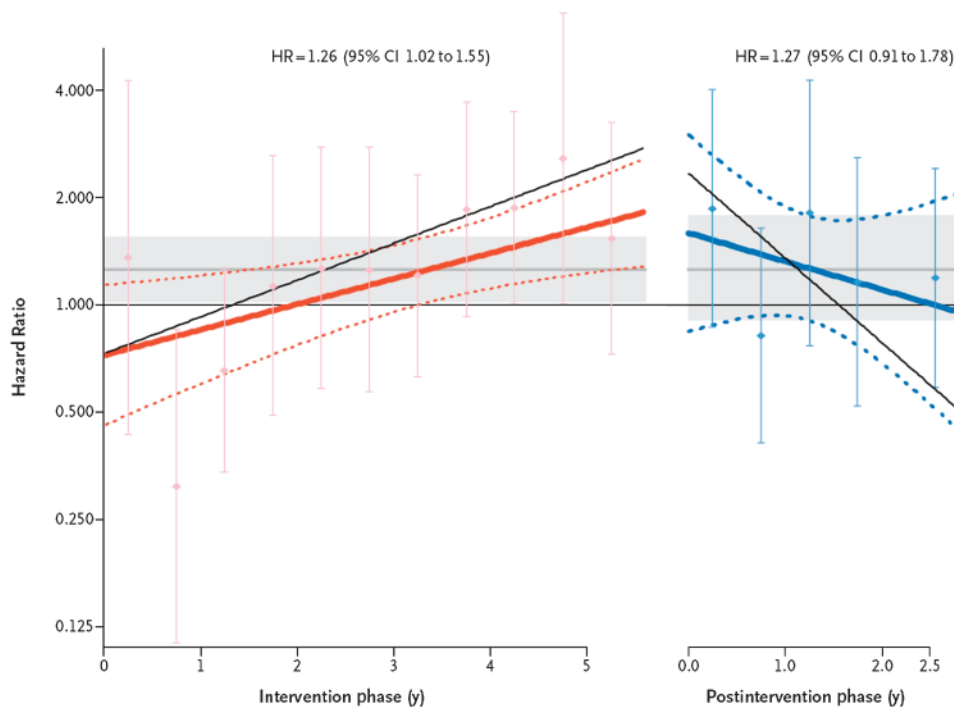


Figure 2. Breast cancer risk during intervention and after intervention in the Women’s Health Initiative Estrogen Plus Progestin Trial. Depicted are time-varying linear hazard ratios (solid red and blue lines) and 95% confidence intervals (95% CIs) (dashed lines) for the effect of estrogen plus progestin vs placebo on breast cancer incidence during the intervention (left) and post-intervention (right) phases of the Women’s Health Initiative randomized clinical trial. Circles and error bars represent hazard ratios of breast cancer and 95% CIs, respectively, for

analyses based on events during each 6-month period. Results for a sensitivity analyses, with events censored 6 months after participants became nonadherent (defined as using <80% of study pills or starting non-protocol hormone therapy) are depicted by the slanting thin black solid lines in the intervention and post-intervention phases. The shaded areas indicate the overall mean and 95% CIs for the hazard ratios in the intervention and post-intervention phases. Modified from and reproduced with permissions from New England Journal of Medicine (34).

(median) of intervention, but the difference was not statistically significant (73). In adherence-adjusted analyses at that time based on events during the intervention, use of estrogen alone was associated with a statistically significant 33% lower incidence of breast cancer ($P = .03$). After longer follow-up (10.7 years [mean]), use of estrogen alone was associated with a statistically significant 23% lower incidence of invasive breast cancer ($P = .02$) (Figure 1, B and Table 2) (36). Similar to the WHI findings with combined hormone therapy, estrogen alone increased the frequency of breast biopsies compared with placebo (74). In contrast to estrogen plus progestin, use of estrogen alone did not substantially interfere with breast cancer detection by mammography (74) and increased mammographic density only by a modest 1% compared with placebo (75).

In the WHI trial, women who started using estrogen alone less than 5 years after menopause (ie, women who had a short gap time) did not demonstrate a reduction in breast cancer incidence compared with the reduction seen in women who started using estrogen alone 5 or more years after menopause (76,77). However, this interaction with gap time was not statistically significant. The concept that breast cancer risk associated with hormone therapy use could vary based on gap time was reported initially in the WHI (108) and later in the French E3N cohort (78). In the Million Women Study, an increased risk of breast cancer with estrogen alone was seen only in participants who initiated hormone use within 5 years of menopause (28). Because women in these cohorts more commonly began using estrogen within 5 years of meno-

pause, gap time considerations can perhaps explain why cohort analyses associated estrogen use with higher breast cancer incidence but not why a statistically significant lower breast cancer incidence with estrogen alone use was seen in the WHI randomized trial (36,77).

As outlined above, an imbalance in the use of mammography with greater screening for hormone users could explain some of the increase in breast cancer incidence with estrogen alone seen in cohort studies because screened populations have more cancers detected than unscreened populations (56). In this regard, in a large US cohort with reliable information on serial mammography use, a somewhat lower breast cancer incidence was reported for estrogen-alone use (relative risk = 0.92, 95% CI = 0.84 to 1.00) (42), and a recent update of the Nurses’ Health Study cohort found estrogen exposures for more than 20 years were required before an increase in breast cancer incidence was seen (79).

The long-term effect of estrogen use on the risk of breast cancer should be considered still an open question. Nonetheless, some of the substantial differences between findings from the preponderance of observational studies and those from the WHI randomized trial regarding the use of 5 years of estrogen alone and the risk of breast cancer remain unexplained. Future observational studies should include only populations for which reliable information on serial mammography use is available. In summary, in the WHI randomized trial, estrogen-alone use was associated with a statistically significant decrease in breast cancer incidence.

Current Concepts: Potential Mediating Mechanisms of Action of Hormone Therapy on Breast Cancer

Recently, investigators from the randomized placebo-controlled primary prevention MAP.3 trial reported that the aromatase inhibitor exemestane, which substantially reduces estrogen levels in postmenopausal women, reduced breast cancer incidence by 65% ($P = .002$) (80). Consequently, a biological understanding of the relationship between estrogen and breast cancer must account for clinical trial results showing that both estrogen addition, by conjugated equine estrogen use, as well as estrogen reduction, by aromatase inhibitor use, lower breast cancer incidence. These apparently paradoxical findings are nonetheless consistent with preclinical studies over the past decade indicating there are complex time- and condition-dependent changes in the influence of estrogen on breast cancers based on evidence from mammary tumor preclinical models (81,82).

Typically, estrogen stimulates breast cell proliferation and inhibits apoptosis (82). However, preclinical studies have found changes in breast tumor gene expression profile after a period of estrogen deprivation (82–84), and in this environment, estrogen administration induces apoptosis (85,86). Two pathways have been identified as regulating estrogen-induced apoptosis: the extrinsic hormone receptor-mediated death regulatory pathway, which involves an increase in Fas ligand (87), and the receptor-independent intrinsic mitochondrial pathway, which involved the release of cytochrome C (88).

These preclinical findings are reflected in breast cancer outcomes in the clinic. For example, high-dose estrogen as diethylstilbestrol is a recognized breast cancer therapy, albeit one with high level of toxicity (89,90). Moreover, Ellis et al. (91) found that some tumors in patients with metastatic breast cancer that progressed after a period of aromatase inhibitor use (ie, estrogen deprivation) subsequently regressed in response to relatively low-dose estradiol use (91).

A period of estrogen deprivation also can result in enhanced estrogen receptor expression whereby even low levels of endogenous estrogen can stimulate breast tumor growth. This action may be mediated not only by increased expression of estrogen receptor alpha but also increased expression of MAP kinase and mTOR pathways (92). As a result, the substantial 90%–95% reduction in estradiol levels associated with aromatase inhibitor use can result in tumor regression (93).

The findings in the clinic, taken together with preclinical evidence, suggest that many breast cancers that present in postmenopausal women can survive only a limited range of estrogen exposures. As a result, a substantial change in the estrogen environment—either by increasing estrogen with exogenous estrogen use or decreasing estrogen with an aromatase inhibitor—can inhibit breast tumor growth.

The influence of estrogen on the full range of estrogen receptor-mediated signaling pathways has not yet been integrated into a comprehensive model regarding estrogen and breast cancer risk. In addition to estrogen-dependent action on nuclear DNA via binding to estrogen receptors, there are estrogen-dependent actions mediated without involvement of estrogen receptors

through other transcription factors. Activation of estrogen receptors can also be mediated through other pathways not involving estrogen (86). Interactions between estrogen and mitochondrial DNA (94) as well as membrane estrogen receptor-mediated activation of second messenger and protein kinase signaling have also been described (21). In the future, a better understanding of interactions among these pathways and how they influence breast cell proliferation and apoptosis will likely lead to more accurate breast cancer risk assessments and new therapeutic strategies.

Whereas estrogen alone and combined estrogen plus progestin have different influences on breast cancer risk, the mechanisms that mediate these differential effects on the breast of adding progestin to estrogen are not established (95,96). A mechanistic explanation of the breast cancer findings from the WHI must also address the completely opposite effects of estrogen plus progestin and estrogen alone on the risk of endometrial cancer in women with a uterus, that is, estrogen alone increases risk and progestin addition mitigates the estrogen-associated risk (97). Preclinical studies suggest that progestin stimulation of breast cell proliferation (98,99) and angiogenesis (100), which leads to growth and metastatic spread of established cancers, as well as progestin stimulation of stem cells by a paracrine receptor-associated mechanism involving nuclear factor- κ B ligand (RANKL), represent two potential mediators of the adverse influence of adding progestin to estrogen on breast cancer risk (98,101). Given the complex, condition-dependent, and conflicting findings from experimental studies, further clinical studies are needed to clarify the influence of progestin on human breast cancer.

Preparation, Dose, and Schedule Considerations

The WHI hormone therapy trials evaluated conjugated equine estrogen with or without medroxyprogesterone acetate, hormone preparations that represent the vast majority of menopausal hormone therapy still being used in US clinical practice (102). However, large observational studies that have incorporated other estrogen plus progestin regimens, including those with estradiol and progesterone-like progestins that are more frequently used in Europe, have generally reported similar breast cancer findings, namely an increase in breast cancer risk associated with estrogen plus progestin use (11,29,78,103). In contrast to most progestins, micronized progesterone has less influence on breast cancer cell proliferation in preclinical studies (104) and on breast epithelial proliferation in a small randomized trial in primates (105). Although estrogen regimens that include micronized progesterone (which is used mainly in France) are less strongly associated with an increased risk of breast cancer compared with other progestins (29,106,107), they also provide limited protection against endometrial cancer (HR of endometrial cancer for current users vs never users = 2.42; 95% CI = 1.53 to 3.83) (97). These results, which require confirmation, suggest that micronized progesterone may provide a trade-off between an increased risk of endometrial cancer and a decreased risk of breast cancer. On balance, however, the current results provide no compelling evidence of the relative overall safety of micronized progesterone combinations with regard to cancer.

Summary

In Box 1, we present current concepts regarding breast cancer and hormone therapy, giving substantial weight to findings from the WHI randomized clinical trials, and concepts that were prevalent in 2002, before the initial reports of the WHI hormone therapy trials, the maturation of large prospective cohorts, and expanding preclinical evidence regarding mediating mechanisms of action. In the WHI trials, fewer breast cancers were seen in postmenopausal women with a previous hysterectomy who were receiving estrogen alone (36). In contrast, estrogen plus progestin statistically significantly increased breast cancer incidence (31,35) and breast cancer mortality (35).

Although the absolute risk of death due to breast cancer associated with estrogen plus progestin use is relatively modest, from a public health perspective, a near doubling of breast cancer deaths with estrogen plus progestin (35) represents a considerable concern. Finally, unlike coronary heart disease, where risk was increased only in the first few years of use (108,109) and was lower in women who initiated hormone use closer to menopause (108), the risk of developing breast cancer continues to increase with longer duration of use (35,37) and appears to be somewhat greater in women who start hormone therapy near menopause (77,110). In addition, because estrogen plus progestin interferes with breast cancer detection and delays diagnosis (31,32), it is not possible to define a safe interval for estrogen plus progestin use with respect to breast cancer risk.

There are caveats regarding concepts that have emerged from the WHI hormone therapy trials. The findings are limited to the duration of intervention and adherence achieved in the trials; cancer effects of longer duration hormone therapy cannot be inferred from these data. Furthermore, nonadherence likely attenuated the effect estimates.

In summary, concepts regarding menopausal hormone therapy and breast cancer have undergone considerable change in the last decade (Table 1). Randomized clinical trial data suggest that estrogen plus progestin is associated with increases in breast cancer incidence and death from breast cancer, whereas approximately 5 years of estrogen alone use in postmenopausal women with a previous hysterectomy is associated with reduced breast cancer incidence. Although the underlying complex biology provides a framework for understanding the mechanisms mediating these hormone effects, currently they are not completely understood.

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