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Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women

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Abstract

Context—In the Women's Health Initiative estrogen plus progestin trial, after mean (SD) intervention of 5.6 (1.3) years (range 3.7 to 8.6 years) and mean follow-up of 7.9 (1.4) years, breast cancer incidence was increased by combined hormone therapy. However, breast cancer mortality results have not been previously reported.

Objective—To determine estrogen plus progestin effects on cumulative breast cancer incidence and mortality after a total mean follow-up of 11.0 (2.7) years thru August 14, 2009.

Design, Setting, and Participants—16,608 postmenopausal women, aged 50-79 years with no prior hysterectomy, were randomly assigned to combined conjugated equine estrogens (0.625 mg/d) plus medroxyprogesterone acetate (2.5 mg/d) or placebo. After the original trial completion date (March 31, 2005) re-consent was required for continued follow-up for breast cancer incidence and was obtained in 83%.

Main outcome measures—Invasive breast cancer incidence and breast cancer mortality.

Results—In intent-to-treat analyses including all randomized participants, censoring those on March 31, 2005 not-consenting for additional follow-up, estrogen plus progestin increased invasive breast cancers compared with placebo (385 [0.42%/yr] vs 293 [0.34%/yr] cases; hazard ratio [HR] 1.25, 95% confidence interval (CI) 1.07-1.46; P=.004). The breast cancers in the estrogen plus progestin group were similar in histology and grade but were more likely to be node

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positive (81 [23.7%] vs 43 [16.2%], respectively; P=0.03). Deaths directly attributed to breast cancer were greater in the estrogen plus progestin group (25 [0.03%/yr] vs 12 [0.01%/yr] deaths; HR, 1.96; 95% CI 1.00-4.04, P=.049) as were deaths from all causes occurring after a breast cancer diagnosis (51 [0.05%/yr] vs 31 [0.03%/yr] deaths; HR 1.57, 95% CI 1.01-2.48; P=.045).

Conclusions—Estrogen plus progestin increases breast cancer incidence with cancers more commonly node positive. Breast cancer mortality also appears to be increased with combined estrogen plus progestin use.

Introduction

Intervention in the Women's Health Initiative (WHI) randomized trial evaluating estrogen plus progestin in postmenopausal women was stopped after a mean (SD) of 5.6 (1.3) years when health risks exceeded benefits for combined hormone therapy. [1] Combined hormone therapy increased invasive breast cancers [1, 2] and delayed breast cancer diagnoses resulting in more advanced stage. [2, 3] Recently, when examined after 7.9 years (1.4) mean (SD) follow-up, the breast cancer risk associated with combined hormone therapy declined soon after discontinuation of hormones. [4] Nonetheless, questions of clinical relevance remain, including the cumulative, long term effect of estrogen plus progestin on breast cancer incidence and, whether breast cancer mortality is increased by combined hormone therapy use.

Most [5, 6,7] but not all, [8, 9] observational studies have suggested that breast cancers associated with combined menopausal hormone therapy have favorable characteristics, [5, 6, 7] less advanced stage [5,10] and less mortality risk. [7, 10, 11] As the issue of estrogen plus progestin influence on breast cancer mortality has not been addressed in a randomized trial setting, we provide updated information on breast cancer incidence and, for the first time, information on breast cancer mortality related to combined hormone therapy use in the WHI trial.

Methods

The WHI estrogen plus progestin trial has been previously described [1, 12, 13] and employed a study design approved by all Institutional Review Boards. [12, 14] Briefly, women were eligible if they were age 50-79 years, postmenopausal, and provided written informed consent. Excluded were women with prior hysterectomy, prior breast cancer or those with conditions precluding three year survival. Women using postmenopausal hormones required a 3-month wash-out period. Baseline mammograms and clinical breast exams not suggestive of cancer were required. Information on demographics, medical history, life-style, and breast cancer risk factors were collected with standardized self-report instruments. Medication use was assessed by interview-administered questionnaire. Time from menopause was defined as the interval from the onset of menopause to first hormone therapy or placebo use. [15] Adherence to study medication was assessed by dispensing history and serial pill counts by weighing returned pills.

Participants were randomized to conjugated equine estrogens (0.625 mg) and medroxyprogesterone acetate (2.5 mg) daily in a single tablet (Prempro;Wyeth Ayerst, Collegeville, PA) or an identical-appearing placebo. Randomization by permuted block

algorithm, stratified by clinical center and age group, [14] was determined at the WHI Clinical Coordinating Center and implemented at local clinical centers using a bar-code dispensing procedure for staff and participant blinding. Participants were contacted at 6-month intervals to collect clinical outcome information and there were annual clinic visits. Yearly mammography and clinical breast exams were required during the intervention phase and study drugs were withheld until completion and clearance of abnormal findings. After the active intervention ended, annual mammogram and breast exam were encouraged and information on their frequency was collected annually.

The total study population included 16,608 women with initial randomization on November 15, 1993. The study intervention phase ended on July 7, 2002 after net harm for combined hormone therapy use was identified [1] and participants were instructed to stop study medication. In the postintervention phase beginning on July 8, 2002, clinical visits and follow-up continued per protocol thru March 31, 2005 the original trial completion date. In the study extension phase, subsequent follow-up from April 1, 2005 thru August 14, 2009 for additional breast cancer incidence results required re-consent (obtained from 83% of 15,408 surviving participants, n=12,788).

Breast cancers were verified by centrally-trained, locally-based physician adjudicators after medical record and pathology report review. [16] Final adjudication and coding of histology, hormone receptor status (positive or negative) and HER-2 status (over-expressing or not), based on pathology report review, was performed at the WHI Clinical Coordinating Center using the Surveillance Epidemiology and End Results Coding System. [17] Attribution of cause of death was based on medical record review by the physician adjudicators, blinded to randomization allocation at the local clinical centers with final adjudication centrally. [16] The National Death Index (NDI) was run on all clinical trial participants at 2 to 3 year intervals.

Prior reports on invasive breast cancer initially included 349 cases identified during the intervention phase with mean (SD) follow-up 5.6 (1.3) years (median 5.6 years, range 4.6 to 8.6 years) [2] and 488 cases identified thru the original trial completion date with (mean (SD) follow-up of 7.9 (1.4) years. [4] The current report, based on a pre-planned analysis, includes 678 cases identified thru August 14, 2009 with a mean (SD) follow-up of 11.0 (2.7) years and includes breast cancer mortality information for the first time.

Statistical Analysis

For this trial, a target sample size of 15,125 participants was calculated primarily on coronary heart disease considerations. As a result, power to detect a 15% increase in breast cancer was 55% after 9 years and 87% after 5 more years of follow-up. [12]

Comparisons of breast cancer characteristics were based on Fisher Exact and T tests. Age at menopause was defined as preciously described, [15] largely by age at last menstrual bleeding, bilateral oophorectomy date, or date menopausal hormone therapy was initiated.

Results for invasive breast cancer incidence and deaths from breast cancer were assessed with time-to-event methods based on the intention-to-treat principle. Analyses included all 16,608 randomized participants. Annualized percentages were calculated by dividing the

total number of events by total follow-up time (years). Hazard ratios were estimated from Cox regression models stratified by baseline age (5 year age groups) and randomization status in the WHI dietary modification trial. No distinction was made between the intervention phase and the post-intervention phase. In both phases, the breast cancer risk for estrogen plus progestin use was greater than one and approximately equal. The summary (Cox model) hazard ratios represent an average over the entire study period. In addition, the null hypothesis tests for breast cancer incidence and mortality do not assume proportionality. Event times were defined relative to the date of randomization with censoring defined by end of follow-up, loss-to-follow-up, or death from causes other than breast cancer. Kaplan-Meier curves describe cumulative breast cancer hazard rates over time. Competing risk curves were also computed and were nearly identical to the Kaplan-Meier estimates.

For breast cancer incidence analyses, women who didn't consent to active follow-up after March 31, 2005 were censored at that time. The original consent permitted continued follow-up for vital status. Analyses for deaths from breast cancer for women who didn't re-consent were censored at December 31,2005, early in the re-consent period, since mortality data in this group may be incomplete at more recent times. Additional mortality analyses censored women not re-consenting on March 31, 2005.

Secondary analyses were conducted to examine the potential impact of censoring due to lack of re-consent on study findings. Several analyses were carried out, including comparison of re-consent rates by baseline characteristics and randomization assignment, and adjusted HR analyses using both inverse probability weighting and multiple imputation. The inverse probability weighting analyses developed a logistic regression model for re-consenting using baseline factors and randomization assignment. For the multiple imputation method invasive breast cancer events or censoring times were imputed for the 2620 eligible participants who did not re-consent (1333 intervention and 1287 placebo) beginning on March 31, 2005. Cox regression models were then fit for each of 25 imputed datasets and the resulting regression parameter estimates were averaged. Adherence sensitivity analyses for breast cancer mortality were conducted by censoring follow-up six months after a participant became non-adherent (using less than 80% of study pills or starting non-protocol hormone therapy). Six subgroups of clinical interest were identified post-hoc and examined for breast cancer hazard ratio variation. Less than one would be expected to be positive by chance alone.

All analyses were conducted using SAS software, version 9.1 (SAS Institute incorporated, Carry NC). All statistical tests were two sided. This study is registered with ClinicalTrials.gov, number NCT00000611.

Results

The flow of participants throughout the study is outlined in a CONSORT diagram (Figure 1). Baseline characteristics for the initially randomized 16,608 participants have been previously published (eTable 1). [1, 2] Participant characteristics in the two randomization groups were closely comparable in both the initial and in the re-consented populations (eTables 2, 3). Those re-consenting were slightly younger and more likely to be white

compared to those not re-consenting. During the active intervention, study drugs were stopped at some time by 42% in the combined hormone and 38% in the placebo groups. [1]

Mammography frequency was comparable in the two randomization groups during the original trial period thru March 31, 2005 (annualized %, 80% vs 80% for hormone vs placebo, respectively). In the re-consented population in the extension phase, the percentage of women with one or more mammograms was also comparable in the randomization groups (86% vs 86% for hormone vs placebo, respectively).

The mean follow-up period (intervention plus post intervention) (SD) was 11.0 years (2.7) with a range of 0.1 to15.3 years) representing a total of 170,166 woman-years of follow-up. In intent-to-treat analysis, estrogen plus progestin increased invasive breast cancer incidence (385 [0.42% per year] vs 293 [0.34% per year] cases, respectively, HR 1.25; 95% CI 1.07-1.46, P=0.004) compared with placebo (Figure 2). Also depicted are quintiles of duration of study intervention indicated by the progressive shaded regions (representing 4.6, 5.2, 5.8, 6.7 and 8.6 years, respectively) based on the participant's time of entry on study and the end of study intervention.

A significantly larger fraction of breast cancers presented with positive lymph nodes in the combined hormone therapy compared to the placebo group 23.7% vs 16.2%,respectively, HR 1.78; 95% CI 1.23-2.58. There was no evidence of a differential effect of combined hormone therapy on receptor positive versus receptor negative tumors. Somewhat more tumors overexpressed HER 2 and were triple negative in the hormone therapy compared to placebo group (Table 1). However, as routine clinical determination of HER 2 status was introduced during the study course, missing values for this parameter were not uncommon.

In subgroup analyses, no significant interventions were seen among estrogen plus progestin use and breast cancer incidence with age, BMI, and Gail risk score (Figure 3). For women entering with no prior estrogen plus progestin use, HR was 1.16; 95% CI 0.98-1.37 compared to a HR of 1.85; 95% CI 1.25-2.80 for those with prior combined hormone therapy use (interaction P=0.03). The breast cancer incidence HR for women with < 1 year of prior estrogen plus progestin use was 2.16; 95% CI 1.15-4.24 (Figure 3). Women who first used hormone therapy closer to menopause (< 5 years) were at somewhat greater risk of developing breast cancer in the combined hormone therapy group but the interaction term was not significant (P=0.08).

More women died from breast cancer in the combined hormone therapy compared to placebo groups (25 [0.03% per year] vs 12 [0.01% per year] deaths, HR 1.96; 95% CI 1.00-4.04, P=0.049) (Figure 4A) representing 2.6 vs 1.3 deaths per 10,000 women per year, respectively. Restriction of the follow-up time to March 31, 2005 for women not re-consenting did not change the death from breast cancer finding (HR 1.96; 95% CI 1.01-4.05, P=0.048). Consideration of all-cause mortality after breast cancer diagnosis also provides similar results for the combined hormone therapy use (51 [0.05% per year] vs 31 [0.03% per year] deaths, respectively HR 1.57; 95% CI 1.01-2.48, P=0.045) (Figure 4B) representing 5.3 vs 3.4 deaths per 10,000 women per year, respectively.

Sensitivity analyses also suggest an adverse effect of combined hormone therapy on breast cancer mortality when follow-up times for each women are censored at non-adherence (14 vs 5 deaths, respectively, HR; 2.96; 95% CI 1.00-8.77, P=0.053). Inverse probability weighting and multiple imputation analyses to address potential imbalance associated with re-consent supports the primary analyses suggesting an elevation in deaths from breast cancer with estrogen plus progestin (inverse probability weighing summary HR 2.22; 95% CI 1.07-4.59; multiple imputation summary HR 2.12; 95% CI 1.02-4.40).

Discussion

In the WHI randomized placebo-controlled trial, conjugated equine estrogen plus medroxyprogesterone acetate increased invasive breast cancer incidence and the cancers were more commonly node positive. There were more deaths attributed to breast cancer (2.6 vs 1.3 per 10,000 women per year) and more deaths from all causes in women following a diagnosis of breast cancer (5.3 vs 3.4 per 10,000 women per year) in the combined hormone therapy group.

With some exceptions, [8, 9] the preponderance of observational studies have associated combined hormone therapy use with an increase in breast cancers which have favorable characteristics, [7] lower stage [5, 10] and longer survival compared to breast cancers diagnosed in non-users of hormone therapy [7, 10] However, in the WHI randomized trial, combined hormone therapy increased breast cancer risk and interfered with breast cancer detection leading to cancers diagnosed at more advanced stage. [2, 3] Now with longer follow-up, there remains a cumulative, statistically significant increase in breast cancers in the combined hormone therapy group and the cancers more commonly had lymph node involvement. The observed adverse influence on breast cancer mortality with combined hormone therapy can reasonably be explained by the influence on breast cancer incidence and stage.

The discrepancy between the current randomized clinical trial findings and observational studies with respect to breast cancer mortality likely are related to potential confounding in observational analyses. Observational studies which begin analyses at breast cancer diagnosis and adjust for stage [7, 18] potentially adjust away unfavorable consequences of estrogen plus progestin use. Menopausal hormone therapy users have mammography at more regular intervals than non-users, [19, 20] likely related to breast cancer concerns. Studies unable to control for mammography can be confounded by differences between screen detected and non-screen detected breast cancers. Screening more commonly identifies slow growing, favorable grade, hormone receptor positive breast cancers and diagnoses them at earlier stage. [21-23] Our findings are consistent with the observational Million Women Study where mammography was controlled and breast cancer mortality analyses began at cohort entry rather than diagnosis. There combined hormone therapy use was associated with higher breast cancer mortality (HR 1.22; 95% CI 1.00-1.48, P=0.05). [10]

Following the initial report [1]of this trial, a substantial decrease in breast cancer incidence occurred in the U.S. which was attributed [24, 25] to the marked decrease in menopausal hormone therapy use that occurred. [26] The adverse influence of estrogen plus progestin on

breast cancer mortality suggests that a future reduction in breast cancer mortality in the U.S. may be anticipated as well.

Accurate determination of cause of death after a breast cancer diagnosis is problematic given the potential interaction between common co-morbidities and cancer treatments. [27] Thus, the actual mortality risk related to breast cancer likely lies somewhere between the medical record attributed risk and consideration of all mortality following breast cancer diagnoses.

The relative influence of combined hormone therapy on both breast cancer mortality, in this report, and on lung cancer mortality, [28] was greater than its influence on cancer incidence. Reproductive hormones [29, 30] and especially progestin [31] are potent angiogenesis stimulators. Since increased angiogenesis increases both lung [33] and breast cancer metastases, [34] these findings suggest that angiogenesis stimulation by combined hormone therapy facilitates growth and metastatic spread of already established cancers. Unless the mortality risks of lung cancer and breast cancer can be mitigated, continued consideration of combined menopausal hormone therapy use for other than short term therapy in women with limiting climacteric symptoms not amendable to other therapies seems unwarranted.

The WHI trial results evaluating estrogen plus progestin have been generally accepted by health regulatory agencies. However, some continue to question the applicability of the results to current clinical practice [35, 36] emphasizing potential differences in coronary heart disease risk when hormone therapy is begun shortly after menopause. [15, 37] However, both prior analyses [38] and current analyses reflecting longer follow-up in this trial suggest a somewhat greater adverse hormonal effect on breast cancer incidence in women randomized closer to menopause with similar findings seen in the French E3N observational cohort. [39] Additionally, current analyses support our prior suggestion that durations of use only slightly longer than those in the trial are associated with increases in breast cancer risk. [40] Given these findings and the effect of combined hormone therapy to delay breast cancer diagnosis, [2, 3] a safe interval for combined hormone therapy use for breast cancer cannot be reliably defined.

Study strengths include the randomized, double-blind study design, a large and ethnically diverse study population, serial assessment of mammography and clinical breast exams, central adjudication of breast cancers, and the long follow-up. The lack of breast cancer therapy information and the modest number of deaths in women diagnosed with breast cancer are limitations as is the difficulty in attributing cause of death in breast cancer patients. For breast cancer mortality analyses, the wide confidence intervals with lower limits close to 1.0 imply some caution in interpretation. The relatively modest duration of study estrogen plus progestin use was limited by the net adverse effect of combined hormone therapy on clinical outcomes.

The decision to follow-up participants after the original study completion date for disease incidence required re-consent. The fact that 17% of women didn't re-consent may have influenced the estimation of combined hormone therapy's effect on breast cancer. However, in both the original randomized group and in the re-consented group, baseline characteristics were comparable in the hormone therapy and placebo groups. In addition, inverse

probability weighting and multiple imputation analyses to address this concern result in similar findings regarding estrogen plus progestin use and deaths from breast cancer.

In conclusion, estrogen plus progestin use increases the incidence of breast cancers and the cancers are more commonly node positive. Mortality data analyses suggest that breast cancer mortality may also be increased.

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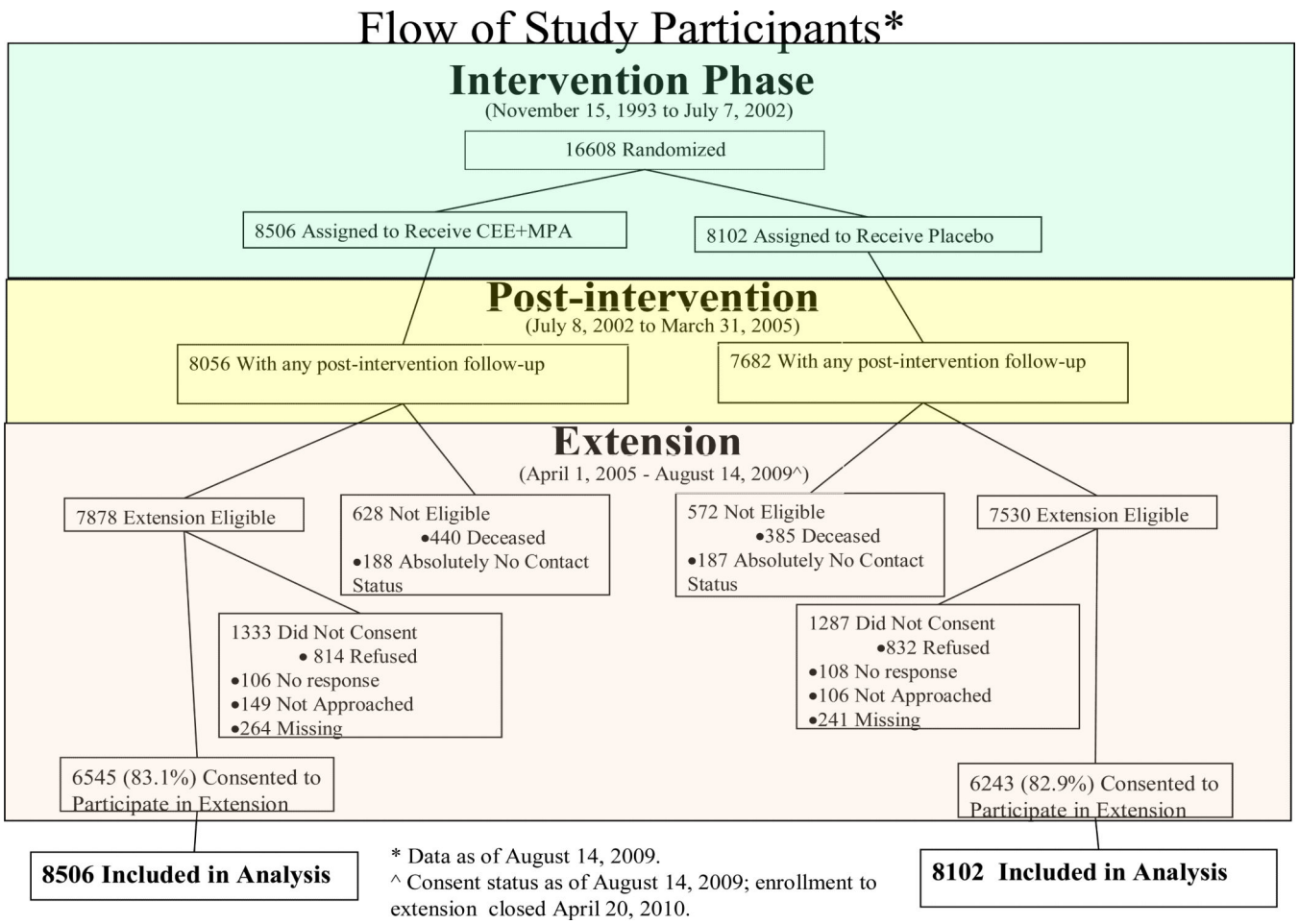

Figure 1.

Flow of study participants during the intervention, postintervention and extension phases. The post-intervention phase began on July 9, 2002 the day after participants were instructed to stop study medication use (conjugated equine estrogen plus medroxyprogesterone acetate or placebo) use. The post-intervention phase continues thru the original trial completion date (March 31, 2005). The extension phase began on April 1, 2005, and includes follow-up for participants who re-consented (83% of those eligible) thru August 14, 2009.

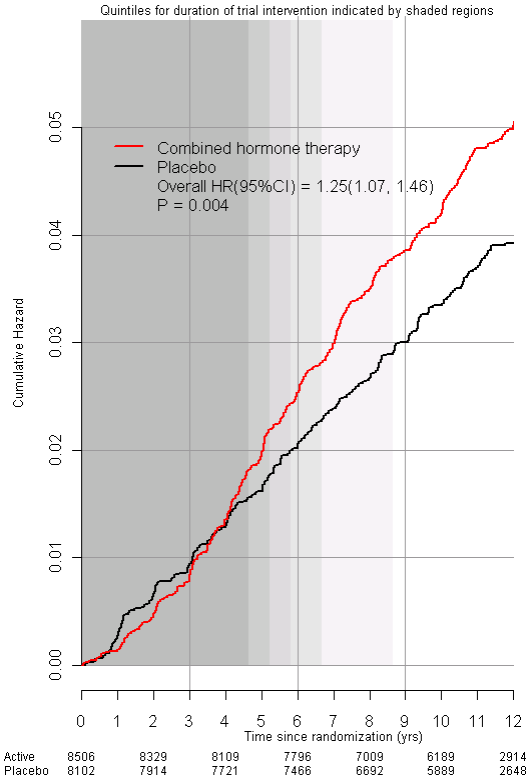

Figure 2.

Incidence of invasive breast cancer in the WHI clinical trial. Intent-to-treat Kaplan Meier cumulative hazard curves for incidence of invasive breast cancer by study group and time since randomization. Hazard ratios (HRs), 95% confidence intervals (CIs) and P values are from Cox regression models, stratified by age (5 year intervals) and randomization assignment in the WHI Dietary Modification trial. Quintiles of duration on study intervention (elapsed time from randomization until the intervention stopped on July 8, 2002) are indicated by the progressive shaded regions. For example, 80%, 60%, 40% and 20% of participants were in the intervention for at least 4.6 years, 5.2 years, 5.8 years and 6.7 years, respectively. All women stopped the intervention by 8.6 years (when shading ends).

	Active N (Ann%)	Placebo N (Ann%)	HR	95% CI	P-int
Age					**0.71**
50-59	111 (0.35%)	79 (0.26%)	1.31	(0.98, 1.76)	
60-69	178 (0.43%)	137 (0.35%)	1.23	(0.99, 1.54)	
70-79	96 (0.53%)	77 (0.44%)	1.21	(0.90, 1.64)	
BMI					**0.46**
Normal (< 25)	91 (0.33%)	69 (0.26%)	1.29	(0.94, 1.77)	
Overweight (25 - < 30)	137 (0.43%)	97 (0.32%)	1.34	(1.04, 1.75)	
Obese (>= 30)	156 (0.50%)	125 (0.44%)	1.14	(0.90, 1.44)	
Gail Risk					**0.85**
< 1.25	90 (0.29%)	75 (0.26%)	1.19	(0.88, 1.63)	
1.25 - < 1.75	134 (0.44%)	97 (0.33%)	1.29	(1.00, 1.69)	
>= 1.75	161 (0.53%)	121 (0.43%)	1.25	(0.99, 1.59)	
Prior E+P Use					**0.03**
No	312 (0.42%)	257 (0.36%)	1.16	(0.98, 1.37)	
Yes (Past/Current)	73 (0.44%)	36 (0.23%)	1.85	(1.25, 2.80)	
Prior E+P Duration					**0.21**
None	312 (0.42%)	257 (0.36%)	1.16	(0.98, 1.37)	
<= 1 yr	29 (0.50%)	14 (0.25%)	2.16	(1.15, 4.24)	
1 < - 5	27 (0.40%)	10 (0.16%)	2.19	(1.08, 4.80)	
> 5 yrs	17 (0.41%)	12 (0.34%)	1.10	(0.52, 2.40)	
Time from Menopause					**0.08**
< 5 yrs	130 (0.42%)	293 (0.34%)	1.41	(1.14, 1.74)	
>= 5 yrs	209 (0.41%)		1.15	(0.96, 1.37)	
Main Effect	**385 (0.42%)**	**293 (0.34%)**	**1.25**	**(1.07, 1.46)**	

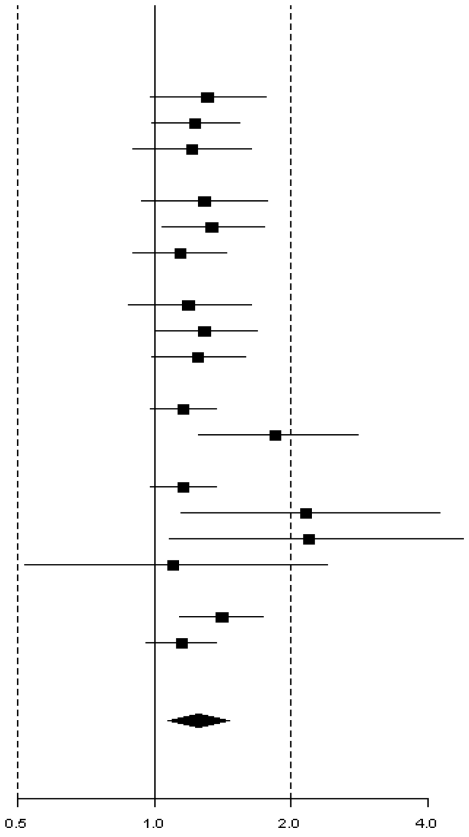

Figure 3.

Invasive breast cancer incidence by baseline characteristics and study group. Hazard ratios (combined hormone therapy vs. placebo) are from a Cox regression models stratified by age and randomization assignment in the dietary modification (DM) trial. For subgroup analyses, HR are allowed to vary by subgroup, and Cox regression models are stratified by age, randomization assignment in the WHI Dietary Modification trial, and subgroup. P-values are from Cox regression models for a 1-df test for trend. “Current use” refers to those reporting combined hormone therapy use at time of initial evaluation. A 3 month “wash out” was required before study entry. The time from menopause variable defined as the interval from the onset of menopause until first menopausal hormone therapy use or first study medication use (combined hormone therapy or placebo).

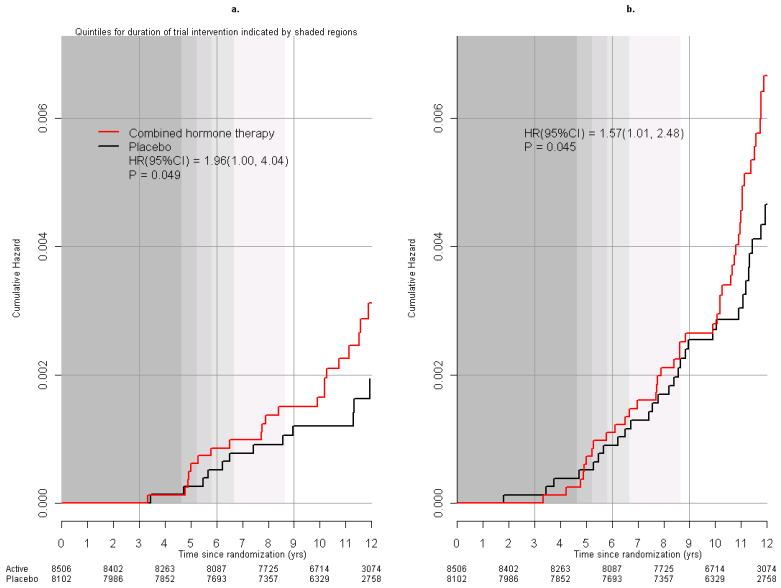

Figure 4.

Deaths after breast cancer in the WHI clinical trial. Kaplan Meier cumulative hazard curves for: A) deaths directly attributed to breast cancer by study group and time since randomization and B) deaths from all causes following a breast cancer diagnosis, by study group and time in the trial. Hazard ratios (HRs), 95% confidence intervals (CI) and P values are from Cox regression models, stratified by age (5 year intervals) and randomization assignment in the WHI Dietary Modification trial. Quintiles for duration of study intervention (elapsed time from randomization, until the intervention stopped on July 8, 2002) are indicated by the progressive shaded regions. For example, 80%, 60%, 40% and 20% of participants were in the intervention for at least 4.6 years, 5.2 years, 5.8 years and 6.7 years, respectively. All women stopped the intervention by 8.6 years.

Table 1

Invasive breast cancer characteristics by study groups

	Combined Hormone Therapy (n=385 invasive breast caners)		Placebo (n=293 invasive breast caners)		
	N	%	N	%	P-Value[1]
Tumor size, mean (SD), cm	1.7	(1.3)	1.5	(1.1)	0.11
Tumor size					0.34
No tumor found/no primary mass	1	0.3	2	0.7	
Microscopic focus or foci	9	2.5	15	5.5	
≤ 0.5 cm	38	10.5	27	9.9	
>0.5 - 1 cm	92	25.3	84	30.7	
>1 - 2 cm	146	40.2	98	35.8	
>2 cm	77	21.2	48	17.5	
Lymph nodes examined					0.80
No	39	10.3	28	9.6	
Yes[2]	341	89.7	263	90.4	
Number of positive lymph nodes					0.06
None	258	76.3	218	83.8	
1-3	60	17.8	34	13.1	
>3	20	5.9	8	3.1	
Positive lymph nodes					0.03
No	258	76.1	218	83.5	
Yes[3]	81	23.9	43	16.5	
SEER – stage					0.05
Localized	288	75.2	238	81.2	
Regional	86	22.5	46	15.7	
Distant	5	1.3	7	2.4	
Unknown	4	1.0	2	0.7	
SEER stage (regional/distant)					0.07
No	288	76.0	238	81.8	
Yes	91	24.0	53	18.2	
Histology					0.41
Ductal	238	62.1	195	66.6	
Lobular	36	9.4	20	6.8	
Ductal and Lobular	57	14.9	35	11.9	
Tubular	13	3.4	9	3.1	
Other	39	10.2	34	11.6	
Grade					0.51

	Combined Hormone Therapy (n=385 invasive breast caners)		Placebo (n=293 invasive breast caners)		
	N	%	N	%	P-Value[1]
Well differentiated	100	26.1	67	22.9	
Moderately differentiated	140	36.6	116	39.6	
Poorly differentiated/anaplastic	92	24.0	77	26.3	
Unknown	51	13.3	33	11.3	
Estrogen receptor					0.81
Positive	308	80.0	230	78.5	
Negative	48	12.5	33	11.3	
Borderline	0	0.0	1	0.3	
Unknown/Not Done/Missing	29	7.5	29	9.9	
Progesterone receptor					0.92
Positive	262	68.1	194	66.2	
Negative	86	22.3	62	21.2	
Borderline	5	1.3	3	1.0	
Unknown/Not Done/Missing	32	8.3	34	11.6	
HER2 overexpression					0.17
Yes	54	14.0	26	8.9	
No	233	60.5	161	54.9	
Borderline	3	0.8	1	0.3	
Unknown/Not Done/Missing	95	24.7	105	35.8	
Triple negative tumor					0.61
Triple negative(ER-/PR-/HER2-)	26	6.8	14	4.8	
Other (includes borderline)	259	67.3	173	59.0	
Unknown/Missing ER/PR/HER2 all/some	100	26.0	106	36.2	

[1] P-value based on Fisher's exact test of association. Bracket indicates the subset of categories for a tumor characteristic that were tested for association with randomization assignment. If there is no bracket, then all categories for a tumor characteristic were tested for association with tumor characteristic.

[2] Ten instances (5 active and 5 placebo) where lymph nodes were examined but number examined was not specified.

[3] Two instances (1 active and 1 placebo) where positive nodes determined but number of positive nodes not specified.

eTable 1

Baseline characteristics of all trial participants by randomization group (n=16608)

	Combined hormone therapy (n=8506)		Placebo (n=8102)		
	N	%	N	%	P-Value
Age group at screening					0.79
50-59	2837	33.4	2683	33.1	
60-69	3854	45.3	3655	45.1	
70-79	1815	21.3	1764	21.8	
Race/ethnicity					0.31
White	7141	84.0	6805	84.0	
Black	548	6.4	574	7.1	
Hispanic	471	5.5	415	5.1	
American Indian	25	0.3	30	0.4	
Asian/Pacific Islander	194	2.3	169	2.1	
Unknown	127	1.5	109	1.3	
Education					0.19
0-8 years	202	2.4	177	2.2	
Some high school	373	4.4	362	4.5	
High school diploma/GED	1615	19.1	1609	20.0	
School after high school	3357	39.7	3060	38.0	
College degree or higher	2915	34.4	2839	35.3	
Gail 5year risk					0.76
< 1.25	2806	33.0	2717	33.5	
1.25 - < 1.75	2859	33.6	2703	33.4	
≥ 1.75	2841	33.4	2682	33.1	
Age at menarche					0.83
≤11	1725	20.3	1670	20.7	
12-13	4578	54.0	4334	53.7	
≥ 14	2182	25.7	2061	25.6	
Years since menopause					0.49
< 5 yrs	1313	17.1	1225	16.3	
5 - <10 yrs	1467	19.1	1486	19.8	
10 - <15 yrs	1613	21.0	1567	20.9	
≥ 15 yrs	3286	42.8	3230	43.0	
Number of term pregnancies					0.38
Never pregnant/Never had term pregnancy	860	10.2	833	10.3	
1	690	8.1	661	8.2	
2	1908	22.5	1708	21.2	
3	2020	23.9	1952	24.2	

	Combined hormone therapy (n=8506)		Placebo (n=8102)		
	N	%	N	%	P-Value
4	1416	16.7	1412	17.5	
5+	1575	18.6	1500	18.6	
Age at first birth, y (categories)					0.18
Never pregnant/No term pregnant	860	11.2	833	11.5	
< 20	1124	14.6	1117	15.4	
20 - 29	4996	64.8	4698	64.6	
30+	727	9.4	624	8.6	
Number of months breastfed					0.82
Never brstfd	3813	45.3	3669	45.8	
brstfd ≤ 1 year	3150	37.5	2971	37.1	
brstfd > 1 year	1446	17.2	1366	17.1	
Oral contraceptive use ever	3695	43.4	3447	42.5	0.24
Oral contraceptive duration					0.25
< 5 yrs	1982	53.7	1781	51.7	
5 - < 10 yrs	825	22.3	808	23.5	
≥ 10 yrs	886	24.0	855	24.8	
HRT use status					0.45
Never used	6277	73.8	6022	74.4	
Past user	1671	19.7	1587	19.6	
Current user	554	6.5	490	6.1	
Unopposed estrogen use ever	903	10.6	865	10.7	0.90
Unopposed estrogen use					0.81
Non-user	7603	89.4	7237	89.3	
< 5 yrs	677	8.0	659	8.1	
≥ 5 yrs	226	2.7	205	2.5	
Estrogen + progesterone use ever	1516	17.8	1396	17.2	0.32
Estrogen + Progest Duration					0.27
Non-user	6990	82.2	6706	82.8	
< 5 yrs	1050	12.3	997	12.3	
≥ 5 yrs	466	5.5	399	4.9	
Time since quitting HT					0.58
Current	554	6.5	490	6.1	
Past, < 5 yrs	726	8.5	673	8.3	
Past, ≥ 5 yrs	945	11.1	914	11.3	
Never	6277	73.8	6022	74.4	
Number of first deg female relatives with breast cancer					0.23

	Combined hormone therapy (n=8506)		Placebo (n=8102)		
	N	%	N	%	P-Value
None	6954	87.3	6676	88.2	
1	927	11.6	816	10.8	
2 or more	82	1.0	79	1.0	
Benign breast disease					0.86
No	6340	83.6	6278	83.3	
Yes, 1 biopsy	956	12.6	972	12.9	
Yes, 2+ biopsies	290	3.8	288	3.8	
Body-mass index (kg/m2), baseline					0.89
< 25	2579	30.4	2479	30.8	
25 - < 30	2992	35.3	2835	35.2	
≥ 30	2899	34.2	2737	34.0	
Dietary energy(kcal)					0.40
≤ 1322 kcal	2687	32.7	2610	33.3	
1322 < - 1841 kcal	2779	33.8	2678	34.2	
> 1841 kcal	2752	33.5	2545	32.5	
Percent energy from fat					0.46
≤ 29.6 percent	2709	33.0	2588	33.0	
29.6 < - 37.2 percent	2764	33.6	2694	34.4	
> 37.2 percent	2745	33.4	2551	32.6	
Physical act (METS/wk)					0.73
≤ 3.5 METS/wk	2658	34.6	2603	34.3	
3.5 < - 12.8 METS/wk	2508	32.7	2467	32.5	
> 12.8 METS/wk	2505	32.7	2526	33.3	
Alcohol use					0.25
Non Drinker	3601	42.5	3471	43.0	
≤ 1 drink/day	3821	45.1	3546	44.0	
> 1 drink/day	1047	12.4	1048	13.0	
Smoking status					0.85
Never	4178	49.6	3999	50.0	
Past	3362	39.9	3157	39.5	
Current	880	10.5	838	10.5	
NSAIDs	2853	33.5	2767	34.2	0.41

Due to information missing for some variables, category denominators do not alw ays equal group total shown in column heading.

Gail risk score incorporates age, history of benign disease (atypia staus unknown in the Women's Health Initiative), age at menarche, age at first live birth, race/ethnicity, and numbers of mothers and sisters with breast cancer

NSAIDs = use of aspirin, ibuprofen, prescription NSAIDs, or the related analgesic, acetaminophen

Time from menopause was defined as previously described[15], as the interval from the onset of menopause to first menopausal hormone therapy use or first use of study medication (hormone or placebo).

eTable 2

Baseline characteristics of trial participants that re-consented by randomization group (n=12788)

	Combined hormone therapy (n=6545)		Placebo (n=6243)		
	N	%	N	%	P-Value
Age group at screening					0.75
50-59	2266	34.6	2128	34.1	
60-69	3019	46.1	2887	46.2	
70-79	1260	19.3	1228	19.7	
Race/ethnicity					0.97
White	5616	85.8	5357	85.8	
Black	406	6.2	401	6.4	
Hispanic	291	4.4	261	4.2	
American Indian	16	0.2	14	0.2	
Asian/Pacific Islander	132	2.0	128	2.1	
Unknown	84	1.3	82	1.3	
Education					0.27
0-8 years	94	1.4	90	1.5	
Some high school	230	3.5	238	3.8	
High school diploma/GED	1254	19.3	1225	19.8	
School after high school	2569	39.5	2329	37.6	
College degree or higher	2363	36.3	2317	37.4	
Gail 5year risk					0.91
< 1.25	2117	32.3	2041	32.7	
1.25 - < 1.75	2237	34.2	2125	34.0	
≥ 1.75	2191	33.5	2077	33.3	
Age at menarche					0.79
≤11	1372	21.0	1279	20.6	
12-13	3539	54.2	3377	54.3	
≥ 14	1617	24.8	1563	25.1	
Years since menopause					0.52
< 5 yrs	1071	18.0	988	17.0	
5 - <10 yrs	1199	20.2	1206	20.8	
10 - <15 yrs	1267	21.3	1242	21.4	
≥ 15 yrs	2410	40.5	2370	40.8	
Number of term pregnancies					0.37
Never pregnant/Never had term pregnancy	661	10.1	627	10.1	
1	529	8.1	488	7.9	
2	1480	22.7	1319	21.2	
3	1573	24.1	1538	24.7	

	Combined hormone therapy (n=6545)		Placebo (n=6243)		
	N	%	N	%	P-Value
4	1104	16.9	1103	17.7	
5+	1171	18.0	1140	18.3	
Age at first birth, y (categories)					0.30
Never pregnant/No term pregnant	661	11.1	627	11.1	
< 20	825	13.8	820	14.6	
20 - 29	3913	65.6	3702	65.7	
30+	564	9.5	482	8.6	
Number of months breastfed					0.96
Never brstfd	2912	44.9	2782	45.1	
brstfd ≤ 1 year	2416	37.3	2285	37.0	
brstfd > 1 year	1152	17.8	1103	17.9	
Oral contraceptive use ever	2960	45.2	2789	44.7	0.53
Oral contraceptive duration					0.47
< 5 yrs	1564	52.9	1438	51.6	
5 - < 10 yrs	669	22.6	667	23.9	
≥ 10 yrs	726	24.5	681	24.4	
HRT use status					0.64
Never used	4798	73.3	4619	74.0	
Past user	1282	19.6	1200	19.2	
Current user	462	7.1	421	6.7	
Unopposed estrogen use ever	682	10.4	645	10.3	0.87
Unopposed estrogen use					0.88
Non-user	5863	89.6	5598	89.7	
< 5 yrs	518	7.9	496	7.9	
≥ 5 yrs	164	2.5	148	2.4	
Estrogen + progesterone use ever	1215	18.6	1131	18.1	0.51
Estrogen + Progest Duration					0.61
Non-user	5330	81.4	5112	81.9	
< 5 yrs	840	12.8	798	12.8	
≥ 5 yrs	375	5.7	333	5.3	
Time since quitting HT					0.80
Current	462	7.1	421	6.7	
Past, < 5 yrs	576	8.8	531	8.5	
Past, ≥ 5 yrs	706	10.8	669	10.7	
Never	4798	73.3	4619	74.0	
Number of first deg female relatives with breast cancer					0.30

	Combined hormone therapy (n=6545)		Placebo (n=6243)		
	N	%	N	%	P-Value
None	5371	87.4	5149	88.1	
1	715	11.6	633	10.8	
2 or more	58	0.9	63	1.1	
Benign breast disease					0.79
No	4904	83.6	4843	83.2	
Yes, 1 biopsy	740	12.6	759	13.0	
Yes, 2+ biopsies	222	3.8	218	3.7	
Body-mass index (kg/m2), baseline					0.19
< 25	1998	30.7	1949	31.4	
25 - < 30	2278	35.0	2215	35.7	
≥ 30	2240	34.4	2038	32.9	
Dietary energy(kcal)					0.43
≤ 1322 kcal	1996	31.5	1966	32.4	
1322< - 1841 kcal	2215	34.9	2117	34.9	
> 1841 kcal	2130	33.6	1980	32.7	
Percent energy from fat					0.44
≤ 29.6 percent	2157	34.0	2065	34.1	
29.6 < - 37.2 percent	2114	33.3	2077	34.3	
> 37.2 percent	2070	32.6	1921	31.7	
Physical act (METS/wk)					0.46
≤ 3.5 METS/wk	1996	33.7	1913	32.7	
3.5 < - 12.8 METS/wk	1940	32.8	1936	33.0	
> 12.8 METS/wk	1987	33.5	2010	34.3	
Alcohol use					0.76
Non Drinker	2671	41.0	2559	41.1	
≤ 1 drink/day	3003	46.1	2832	45.5	
> 1 drink/day	844	12.9	828	13.3	
Smoking status					0.94
Never	3288	50.7	3139	50.9	
Past	2597	40.0	2452	39.8	
Current	600	9.3	577	9.4	
NSAIDs	2194	33.5	2133	34.2	0.44

Due to information missing for some variables, category denominators do not always equal group total shown in column heading.

Gail risk score incorporates age, history of benign disease (atypia staus unknown in the Women's Health Initiative), age at menarche, age at first live birth, race/ethnicity, and numbers of mothers and sisters with breast cancer

NSAIDs = use of aspirin, ibuprofen, prescription NSAIDs, or the related analgesic, acetaminophen

Time from menopause was defined as previously described[15], as the interval from the onset of menopause to first menopausal hormone therapy use or first use of study medication (hormone or placebo).

eTable 3

The number and percentage of all eligible participants from the original population that consented by baseline characteristics and randomization group

	Combined hormone therapy (n=7878 eligible)		Placebo (n=7530 eligible)		
	N	%	N	%	P-Value
Overall	**6545**	**83.1**	**6243**	**82.9**	**0.78**
Age group at screening					0.86
50-59	2266	84.0	2128	83.8	
60-69	3019	84.1	2887	84.3	
70-79	1260	79.2	1228	78.5	
Race/ethnicity					0.11
White	5616	85.0	5357	84.5	
Black	406	80.2	401	77.1	
Hispanic	291	65.1	261	66.9	
American Indian	16	66.7	14	56.0	
Asian/Pacific Islander	132	74.2	128	82.6	
Unknown	84	72.4	82	82.0	
Education					0.46
0-8 years	94	51.4	90	57.3	
Some high school	230	71.4	238	72.6	
High school diploma/GED	1254	83.7	1225	81.6	
School after high school	2569	82.5	2329	82.7	
College degree or higher	2363	86.8	2317	86.7	
Gail 5 year risk					0.54
< 1.25	2117	80.2	2041	80.1	
1.25 - < 1.75	2237	84.4	2125	85.0	
≥ 1.75	2191	84.7	2077	83.7	
Age at menarche					0.04
≤11	1372	85.5	1279	82.5	
12-13	3539	83.4	3377	83.8	
≥ 14	1617	80.4	1563	81.6	
Years since menopause					0.54
< 5 yrs	1617	85.3	1563	84.6	
5 - <10 yrs	1071	86.3	988	85.4	
10 - <15 yrs	1199	83.2	1206	84.7	
≥ 15 yrs	1267	81.2	1242	80.5	
Number of term pregnancies					0.51
Never pregnant/Never had term pregnancy	661	83.0	627	82.8	

	Combined hormone therapy (n=7878 eligible)		Placebo (n=7530 eligible)		
	N	%	N	%	P-Value
Mean ± SD	529	83.0	488	80.1	
Age at first birth, y (categories)					>0.99
Never pregnant/No term pregnant	661	83.0	627	82.8	
< 20	825	80.6	820	80.0	
20 - 29	3913	84.4	3702	84.1	
30+	564	84.3	482	83.7	
Number of months breastfed					0.70
Never brstfd	2912	82.7	2782	81.8	
brstfd ≤ 1 year	2416	82.7	2285	83.0	
brstfd > 1 year	1152	85.6	1103	85.5	
Oral contraceptive use ever	2960	85.4	2789	85.7	0.50
Oral contraceptive duration					0.36
< 5 yrs	1564	84.4	1438	85.7	
5 - < 10 yrs	669	86.0	667	86.1	
≥ 10 yrs	726	86.9	681	85.2	
Unopposed estrogen use ever	682	82.5	645	81.5	0.68
Unopposed estrogen use					0.59
Non-user	5863	83.3	5598	81.3	
< 5 yrs	518	83.2	496	83.1	
≥ 5 yrs	164	80.0	148	82.2	
Estrogen + progesterone use ever	1215	85.0	1131	85.9	0.40
Estrogen + Progest Duration					0.67
Non-user	5330	82.6	5112	82.3	
< 5 yrs	840	84.4	798	85.3	
≥ 5 yrs	375	86.4	333	87.6	
Number of first deg female relatives with breast cancer					0.74
None	5371	84.9	5149	84.7	
1	715	83.1	633	82.8	
2 or more	58	80.6	63	85.1	
Benign breast disease					0.89
No	4904	83.1	4843	83.0	
Yes, 1 biopsy	740	84.6	759	83.6	
Yes, 2+ biopsies	222	82.2	218	81.3	
Body-mass index (kg/m2), baseline					0.03
< 25	1998	84.4	1949	84.1	

	Combined hormone therapy (n=7878 eligible)		Placebo (n=7530 eligible)		
	N	%	N	%	P-Value
25 - < 30	2278	81.9	2215	83.6	
≥ 30	2240	83.1	2038	80.9	
Dietary energy (kcal)					0.96
≤ 1322 kcal	1996	80.8	1966	80.7	
1322 < - 1841 kcal	2215	85.0	2117	85.2	
> 1841 kcal	2130	83.6	1980	83.6	
Percent energy from fat					0.78
≤ 29.6 percent	2157	85.5	2065	84.8	
29.6 < - 37.2 percent	2114	82.8	2077	83.0	
> 37.2 percent	2070	81.3	1921	81.6	
Physical act (METS/wk)					0.85
≤ 3.5 METS/wk	1996	81.4	1913	80.5	
3.5 < - 12.8 METS/wk	1940	83.7	1936	83.6	
> 12.8 METS/wk	1987	84.7	2010	84.7	
Alcohol use					0.54
Non Drinker	2671	80.5	2559	80.3	
≤ 1 drink/day	3003	84.4	2832	84.7	
> 1 drink/day	844	87.3	828	85.7	
Smoking status					0.63
Never	3288	83.1	3139	83.3	
Past	2597	84.1	2452	83.9	
Current	600	79.4	577	77.3	
NSAIDs	2194	83.5	2133	83.4	0.96

Due to information missing for some variables, category denominators do not always equal group total shown in column heading.

Gail risk score incorporates age, history of benign disease (atypia staus unknown in the Women's Health Initiative), age at menarche, age at first live birth, race/ethnicity, and numbers of mothers and sisters with breast cancer

NSAIDs = use of aspirin, ibuprofen, prescription NSAIDs, or the related analgesic, acetaminophen

Time from menopause was defined as previously described[15], as the interval from the onset of menopause to first menopausal hormone therapy use or first use of study medication (hormone or placebo).

As seen, consent rates were comparable for demographic and risk factor distribution for the two randomization groups.