Original Investigation

Overweight, Obesity, and Postmenopausal Invasive Breast Cancer Risk

A Secondary Analysis of the Women's Health Initiative Randomized Clinical Trials

Marian L. Neuhouser, PhD, RD; Aaron K. Aragaki, MS; Ross L. Prentice, PhD; JoAnn E. Manson, MD, MPH, DrPH; Rowan Chlebowski, MD, PhD; Cara L. Carty, PhD; Heather M. Ochs-Balcom, PhD; Cynthia A. Thomson, PhD, RD; Bette J. Caan, DrPH; Lesley F. Tinker, PhD, RD; Rachel Peragallo Urrutia, MD; Jennifer Knudtson, MD; Garnet L. Anderson, PhD

IMPORTANCE More than two-thirds of US women are overweight or obese, placing them at increased risk for postmenopausal breast cancer.

OBJECTIVE To investigate in this secondary analysis the associations of overweight and obesity with risk of postmenopausal invasive breast cancer after extended follow-up in the Women's Health Initiative (WHI) clinical trials.

DESIGN, SETTING, AND PARTICIPANTS The WHI clinical trial protocol incorporated measured height and weight, baseline and annual or biennial mammography, and adjudicated breast cancer end points in 67 142 postmenopausal women ages 50 to 79 years at 40 US clinical centers. The women were enrolled from 1993 to 1998 with a median of 13 years of follow-up through 2010; 3388 invasive breast cancers were observed.

MAIN OUTCOMES AND MEASURES Height and weight were measured at baseline, and weight was measured annually thereafter. Data were collected on demographic characteristics, personal and family medical history, and personal habits (smoking, physical activity). Women underwent annual or biennial mammograms. Breast cancers were verified by medical records reviewed by physician adjudicators.

RESULTS Women who were overweight and obese had an increased invasive breast cancer risk vs women of normal weight. Risk was greatest for obesity grade 2 plus 3 (body mass index [BMI], calculated as weight in kilograms divided by height in meters squared, >35.0) (hazard ratio [HR] for invasive breast cancer, 1.58; 95% CI, 1.40-1.79). A BMI of 35.0 or higher was strongly associated with risk for estrogen receptor–positive and progesterone receptor–positive breast cancers (HR, 1.86; 95% CI, 1.60-2.17) but was not associated with estrogen receptor–negative cancers. Obesity grade 2 plus 3 was also associated with advanced disease, including larger tumor size (HR, 2.12; 95% CI, 1.67-2.69; $P = .02$), positive lymph nodes (HR, 1.89; 95% CI, 1.46-2.45; $P = .06$), regional and/or distant stage (HR, 1.94; 95% CI, 1.52-2.47; $P = .05$), and deaths after breast cancer (HR, 2.11; 95% CI, 1.57-2.84; $P < .001$). Women with a baseline BMI of less than 25.0 who gained more than 5% of body weight over the follow-up period had an increased breast cancer risk (HR, 1.36; 95% CI, 1.1-1.65), but among women already overweight or obese we found no association of weight change (gain or loss) with breast cancer during follow-up. There was no effect modification of the BMI-breast cancer relationship by postmenopausal hormone therapy, and the direction of association across BMI categories was similar for never, past, and current hormone therapy use.

CONCLUSIONS AND RELEVANCE Obesity is associated with increased invasive breast cancer risk in postmenopausal women. These clinically meaningful findings should motivate programs for obesity prevention.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00000611

JAMA Oncol. doi:10.1001/jamaoncol.2015.1546
Published online June 11, 2015.

Invited Commentary

Author Audio Interview at jamaoncology.com

Supplemental content at jamaoncology.com

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Marian L. Neuhouser, PhD, RD, Cancer Prevention Program, Fred Hutchinson Cancer Research Center, 1100 Fairview Ave North, M4B402, Seattle, WA 98109-1024 (mneuhous@fredhutch.org).

Obesity is a major public health problem in the United States. Recent data demonstrate that the age-adjusted obesity (body mass index [BMI], calculated as weight in kilograms divided by height in meters squared, ≥30.0) prevalence is 34.9% among all adults 20 years or older while that for overweight plus obesity (BMI ≥ 25.0) is 68.5%.[1] Obesity has been associated with breast cancer risk in observational studies,[2,3] systematic reviews, and meta-analyses.[3-5] More recently, the 2012 Annual Report to the Nation on Cancer[6] concluded that overweight and obese women have a relative risk for postmenopausal breast cancer of 1.13 and 1.25, respectively, vs women of normal weight.

Despite relatively strong and consistent evidence that obesity may increase postmenopausal breast cancer risk, questions remain, including whether obesity is associated with breast cancer characteristics, such as tumor hormone receptor status and stage at diagnosis, or whether use of postmenopausal hormone therapy (HT) modifies the obesity-breast cancer association, because both obesity and HT alter a woman's hormone profile. Questions also remain regarding any interaction of race/ethnicity and obesity and breast cancer risk. Black women in the United States have higher rates of obesity[1] and lower breast cancer rates but higher mortality rates than non-Hispanic white women.[4] In this secondary analysis, we examine the associations of overweight and obesity with postmenopausal breast cancer risk in the Women's Health Initiative (WHI) clinical trials,[7,8] in which the protocol requirements specified baseline and annual or biennial mammograms and measured weights.

At a Glance

- Our research objective was to understand the relationship of obesity with breast cancer risk in the context of a clinical trial in which mammography and measured weights were part of the trial protocol, thus reducing the potential for ascertainment bias.
- We found that overweight and obese postmenopausal women have a significantly increased risk for invasive breast cancer, particularly for estrogen receptor–positive cancers. The risk is greatest for women with a body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) greater than 35.0, in whom the risk is 1.58 times the risk for women of normal weight.
- Obesity was also significantly associated with markers of poor prognosis; women with BMI greater than 35.0 were more likely to have tumors that were large, with evidence of nodal involvement and poorly differentiated tumors.
- We found no evidence for modification of the obesity-breast cancer association by use of postmenopausal hormone therapy.

Methods

Design details of the 3 overlapping WHI clinical trials have been published.[7] Briefly, women aged 50 to 79 years were recruited at 40 US clinical centers from 1993 to 1998. Women could be randomized to 1, 2, or all 3 clinical trials (1 of 2 hormone trials and trials of dietary modification (DM) and calcium and vitamin D supplementation). Eligibility criteria included being postmenopausal and anticipated 3 years' survival. Exclusions included prior breast cancer, other prior cancer (except nonmelanoma skin cancer) within 10 years, and conditions related to adherence and safety. Trial protocols were reviewed and approved by the institutional review boards at each clinical center and the Clinical Coordinating Center. All women signed informed consent. Reconsents were required to continue follow-up through the posttrial WHI Extension periods (2005-2010 and 2011-2016). Participants were not compensated.

For the HT trials, women with an intact uterus (n = 16 608) were randomized to oral conjugated equine estrogen (CEE) (0.625 mg/d) plus medroxyprogesterone acetate (MPA) (Prempro) (2.5 mg/d) or placebo. Women with a prior hysterectomy (n = 10 739) were randomized to oral CEE (Premarin) (0.625 mg/d) or placebo. Dietary modification trial participants were randomized to an intervention (n = 19 541) to reduce fat intake and increase fruit, vegetable, and grain consumption or a comparison group (n = 29 294). After 1 year, women could participate in the calcium plus vitamin D (CaD) trial, with randomization to a daily dose of vitamin D_3 (400 IU) and calcium (1000 mg) or placebo.

Height, weight, and waist and hip circumferences were measured at baseline and weight was measured at annual visits. Body mass index [2] was further defined as normal weight (BMI < 25.0); overweight (25.0 to < 30.0); obese, grade 1 (30.0 to < 35.0); and obese, grade 2 plus 3 (≥35.0).[1] Weight change (in percentage) was defined as [(annual visit weight − baseline weight)]/baseline weight × 100]. Baseline data were collected on demographic characteristics, smoking, alcohol, physical activity, medical history, and family history of breast cancer. Mammograms and clinical breast examinations were required at baseline and annually for women in the HT trials and baseline and biennially in the DM trial. Baseline serum sex hormone levels were available for 200 randomly selected HT trial participants.[9]

Details of outcomes data collection, adjudication, and primary trial results have been published.[10-15] Women were queried about new medical events every 6 months during the intervention and annually thereafter. Breast cancers and breast cancer characteristics (tumor hormone receptor status, histologic findings, stage, grade, tumor size, nodal involvement) were verified by medical records and pathology report review by physician adjudicators using the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) coding system. Vital status was collected through follow-up of participants and proxies and periodic searches of the National Death Index. Cause of death was determined by medical record and death certificate review.

Statistical Analysis

Associations between obesity and breast cancer incidence and mortality are presented as hazard ratios (HRs) and 95% CIs from Cox models using event times measured as time from randomization. The proportional hazards assumption for the primary analysis was verified by Schoenfeld residuals ($P > .38$) and by visual inspection of linear time-varying coefficients. All analyses were stratified by baseline 5-year age groups, WHI

clinical trial randomization assignment(s), hysterectomy status, and study phase (intervention vs postintervention) and adjusted for age (continuous), race/ethnicity, education, parity, age at first birth, bilateral oophorectomy, family history of breast cancer, prior estrogen use and duration, prior estrogen plus progestin use and duration, smoking, diabetes mellitus, and alcohol consumption. Because mammography use was required by the WHI clinical trial protocol and compliance was good,[7,8] no additional adjustment for mammography use was applied. Breast cancer mortality data were collected as deaths attributed to breast cancer and as all deaths after breast cancer. Trend tests were computed using BMI categories as a continuous variable. When examining different breast cancer characteristics,[16] heterogeneity in BMI trends was tested using competing risk methods. Graphical representation of the shape of the relative risk relationship across BMI categories was created by fitting nonparametric splines to the multivariable adjusted HRs in R software, version 2.15.3 (R Foundation).

Associations of weight change with breast cancer risk were examined with similar Cox regression models stratified by baseline BMI category and using a time-dependent weight change variable updated with annual weight measurements and displayed in 5 categories: weight stable (±2% of baseline weight), 2% to 5% weight gain, more than 5% weight gain, 2% to 5% weight loss, or more than 5% weight loss. The trend test was based on these weight change categories, and the test for heterogeneity in trends between baseline BMI category was based on interaction tests.

The relationship between BMI and breast cancer incidence within HT-use subgroups was examined using similar approaches, and the *P* values were based on interaction tests. The HT-use subgroups were determined compositely by baseline self-report of HT use and randomization into the WHI clinical trial HT trials. Specifically, participants randomized to HT were categorized as "current," participants with no prior HT use were categorized as "never," and all others were categorized as "past." Finally, participants not randomized in the HT trial were categorized per their baseline HT use. In exploratory analyses, nonparametric fits (spline) of the multivariable association between invasive breast cancer risk and BMI were examined; smoothing parameter was chosen objectively via Akaike information criteria. Similar analyses also examined the nonparametric risk of weight and included height as a covariate. Unless otherwise noted, all analyses were conducted using SAS statistical software (version 9.3; SAS Institute Inc) and were not adjusted for multiple testing. Women with baseline weight (>135 kg or <35 kg) or BMI (>50.0 or <18.5) measurements were excluded; 67 142 of 68 132 participants and 3388 breast cancers were included in this study. See also the eMethods in the Supplement.

Results

Participant characteristics differed by baseline BMI category (**Table 1**). Obese women were likely to be younger, nonwhite, less educated, have had a hysterectomy or bilateral oophorectomy, have been treated for diabetes mellitus, were less likely to have used HT, and have reported less recreational physical activity compared with women of normal weight.

Women who were overweight; obese, grade 1; and obese, grade 2 plus 3 had an increased invasive breast cancer risk relative to women of normal weight (**Table 2**). The HRs increased as BMI increased and displayed a dose-response effect with the greatest risk for women with grade 2 plus 3 obesity (HR, 1.58; 95% CI, 1.40-1.79; $P < .001$ for trend). Tests of heterogeneity suggested that the association between BMI and breast cancer risk differed by hormone receptor status ($P < .001$). Body mass index was associated with an increased risk of estrogen- and progesterone-positive breast cancer, and the HRs increased at each BMI level, suggesting a dose-response relationship (HR, 1.86; 95% CI, 1.60-2.17 for BMI ≥ 35.0). In exploratory analyses, measures of central adiposity (waist circumference and waist-to-hip ratio) were added to the multivariable adjusted model of weight. Neither measure of central adiposity conferred any additional information ($P > .40$) beyond what was already explained by weight (data not shown).

Obesity was associated with more advanced disease, including larger tumor size ($P = .02$), positive lymph nodes ($P = .06$), and regional or distant stage at diagnosis ($P = .05$) (Table 2 and eFigure 1 in the Supplement). Body mass index was strongly associated with breast cancer mortality only for obesity grade 2 plus 3 (HR, 2.25; 95% CI, 1.51-3.36; $P < .001$) and mortality after invasive breast cancer for all obesity grades (grade 1, HR, 1.37; 95%, CI 1.04-1.79; and grade 2 plus 3, HR, 2.11; 95% CI, 1.57-2.84; $P < .001$).

Women who gained more than 5% of their baseline weight during follow-up had a modest increased risk (HR, 1.12; 95% CI, 1.00-1.25; $P = .08$ for trend) compared with women with stable weight, but there was no change in risk for women who lost weight (**Table 3**). Subgroup analyses suggested that associations between weight change and breast cancer risk was modified by baseline BMI ($P = .05$ for interaction). Women with normal BMI who gained more than 5% of their body weight during follow-up increased their breast cancer risk relative to women with stable weight (HR, 1.36; 85% CI, 1.11-1.65), but neither weight gain nor loss further changed risk for overweight and obese women.

A priori subgroup analyses investigated whether associations of BMI with invasive breast cancer risk varied by age, race/ethnicity, and HT use (**Table 4** and eFigure 2 in the Supplement). Baseline age modified the association of BMI with cancer risk such that the associations seemed slightly weaker among the youngest women ($P = .05$ for interaction), but the overall obesity-breast cancer risk relationship remained strong. There was no evidence of effect modification of the BMI-invasive breast cancer relationship by race/ethnicity ($P = .34$ for interaction). Among women with an intact uterus, use of estrogen and progestin did not modify the association of BMI with cancer risk because the data support a similar trend between BMI and breast cancer risk across the estrogen and progestin use categories ($P = .78$ for interaction). Among women with a prior hysterectomy, data were suggestive, but not conclusive, of an interaction between estrogen use alone and BMI in relation to breast cancer risk ($P = .11$ for interaction). In

Table 1. Baseline Characteristics of 67 142 Women's Health Initiative Clinical Trial Participants by Baseline BMI

Characteristic	BMI Subgroup, No. (%)[a]			
	Normal, <25.0	Overweight, 25.0 to <30.0	Obese, Grade 1, 30.0 to <35.0	Obese, Grade 2 + 3, ≥35.0
Age at screening, y				
50-59	6485 (35.5)	7954 (32.8)	5265 (34.7)	3742 (39.4)
60-69	7949 (43.6)	11 323 (46.8)	7153 (47.2)	4538 (47.7)
70-79	3814 (20.9)	4941 (20.4)	2749 (18.1)	1229 (12.9)
Race/ethnicity				
White	15 813 (86.7)	20 040 (82.7)	11 930 (78.7)	7011 (73.7)
Black	863 (4.7)	2162 (8.9)	1999 (13.2)	1794 (18.9)
Hispanic	565 (3.1)	1081 (4.5)	750 (4.9)	437 (4.6)
American Indian	55 (0.3)	92 (0.4)	79 (0.5)	62 (0.7)
Asian/Pacific Islander	726 (4.0)	517 (2.1)	171 (1.1)	68 (0.7)
Unknown	226 (1.2)	326 (1.3)	238 (1.6)	137 (1.4)
Education				
High school/GED or less	3557 (19.6)	5668 (23.6)	4143 (27.5)	2704 (28.6)
School after high school	6731 (37.1)	9626 (40.0)	6224 (41.3	3985 (42.2)
College degree or higher	7847 (43.3)	8754 (36.4)	4703 (31.2)	2756 (29.2)
Hysterectomy at randomization	6487 (35.6)	10 245 (42.3)	6885 (45.4)	4541 (47.8)
Term pregnancies, No.				
Never been pregnant/no term pregnancy	2133 (11.8)	2474 (10.3)	1490 (9.9)	992 (10.5)
1	1612 (8.9)	2001 (8.3)	1211 (8.0)	790 (8.3)
2	4750 (26.2)	5610 (23.3)	3281 (21.7)	1983 (21.0)
3	4597 (25.3)	5884 (24.4)	3567 (23.6)	2177 (23.0)
≥4	5057 (27.9)	8142 (33.8)	5540 (36.7)	3521 (37.2)
Age at first birth, y				
Never pregnant/no term pregnancy	2133 (12.7)	2474 (11.3)	1490 (10.9)	992 (11.6)
<20	1993 (11.9)	3359 (15.3)	2610 (19.0)	1977 (23.2)
20-29	11 239 (66.8)	14 442 (65.8)	8613 (62.8)	5003 (58.6)
≥30	1452 (8.6)	1669 (7.6)	1002 (7.3)	563 (6.6)
Family history of female relative with breast cancer	3106 (18.0)	3966 (17.3)	2498 (17.4)	1567 (17.5)
Bilateral oophorectomy	2986 (16.7)	4487 (19.0)	3038 (20.6)	1974 (21.5)
Treated diabetes mellitus, pills or injections	278 (1.5)	836 (3.5)	1022 (6.7)	1059 (11.1)
Smoking status				
Never	9156 (50.7)	12 236 (51.1)	7788 (52.0)	4786 (50.9)
Past	7057 (39.1)	9777 (40.8)	6211 (41.4)	4130 (44.0)
Current	1834 (10.2)	1935 (8.1)	991 (6.6)	481 (5.1)
Duration of unopposed estrogen use				
None	12 160 (66.7)	15 779 (65.2)	10 144 (66.9)	6520 (68.6)
Past user	2406 (13.2)	3403 (14.1)	2147 (14.2)	1363 (14.3)
Current user	3664 (20.1)	5027 (20.8)	2864 (18.9)	1619 (17.0)
<5 y[b]	2384 (13.1)	3322 (13.7)	2179 (14.4)	1440 (15.1)
5 to <10 y	1168 (6.4)	1666 (6.9)	986 (6.5)	577 (6.1)
>10 y	2559 (14.0)	3463 (14.3)	1864 (12.3)	975 (10.3)
Duration of estrogen + progesterone use				
None	12 883 (70.6)	18 478 (76.3)	12 238 (80.7)	8021 (84.4)
Past user	1756 (9.6)	2147 (8.9)	1164 (7.7)	629 (6.6)
Current user	3604 (19.8)	3588 (14.8)	1761 (11.6)	856 (9.0)
<5 y[b]	2807 (15.4)	3034 (12.5)	1696 (11.2)	887 (9.3)
5 to <10 y	1475 (8.1)	1507 (6.2)	732 (4.8)	382 (4.0)
>10 y	1083 (5.9)	1199 (5.0)	499 (3.3)	218 (2.3)
HT randomization group				
CEE active	1090 (6.0)	1798 (7.4)	1351 (8.9)	987 (10.4)

(continued)

Table 1. Baseline Characteristics of 67 142 Women's Health Initiative Clinical Trial Participants by Baseline BMI (continued)

Characteristic	BMI Subgroup, No. (%)[a]			
	Normal, <25.0	Overweight, 25.0 to <30.0	Obese, Grade 1, 30.0 to <35.0	Obese, Grade 2 + 3, ≥35.0
CEE placebo	1076 (5.9)	1915 (7.9)	1367 (9.0)	975 (10.3)
CEE + MPA active	2521 (13.8)	2992 (12.4)	1816 (12.0)	1047 (11.0)
CEE + MPA placebo	2419 (13.3)	2835 (11.7)	1651 (10.9)	1052 (11.1)
Not randomized	11 142 (61.1)	14 678 (60.6)	8982 (59.2)	5448 (57.3)
DM randomization group				
Intervention	5005 (27.4)	6944 (28.7)	4451 (29.3)	2863 (30.1)
Comparison group	7500 (41.1)	10 452 (43.2)	6748 (44.5)	4226 (44.4)
Not randomized	5743 (31.5)	6822 (28.2)	3968 (26.2)	2420 (25.4)
Total energy expenditure/wk from physical activity, mean (SD), MET-hr	13.9 (14.1)	11.1 (12.4)	8.5 (11.0)	6.4 (9.5)
Height, mean (SD), cm	162.5 (6.4)	161.9 (6.3)	161.6 (6.2)	161.3 (6.4)
Weight, mean (SD), kg	60.2 (6.2)	71.9 (6.6)	84.3 (7.4)	101.1 (11.1)
Waist circumference, mean (SD), cm	75.4 (6.7)	86.1 (7.6)	96.5 (8.3)	108.3 (10.0)
Hip circumference, mean (SD), cm	97.1 (5.8)	105.5 (6.1)	114.3 (7.1)	127.0 (9.7)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CEE, conjugated equine estrogen; DM, diet modification; GED, General Educational Development examination; HT, hormone therapy; MET, metabolic equivalent; MPA, medroxyprogesterone acetate.

[a] *P* value is adjusted for age, race/ethnicity, education, and hysterectomy. *P* < .001 for all comparisons except family history of female relative with breast cancer (*P* = .30), DM randomization group (*P* = .84), and HT randomization groups (*P* = .97).

[b] Duration; corresponds to past or current use.

particular, a low incidence rate for the referent normal weight group (annualized percentage, 0.23%) among women who never used estrogen alone was associated with linear, dose-response risk estimates for overweight (HR, 1.66; 95% CI, 1.06-2.60); obesity, grade 1 (HR, 2.16; 95% CI, 1.38-3.39); and obesity, grade 2 plus 3 (HR, 2.63; 95% CI, 1.32-2.00). For the subgroup defined as "current use" of estrogen alone, the BMI-associated risk was increased only for current users of estrogen alone who were obese, grade 1 (HR, 1.35 [95% CI, 1.07-1.71]), or obese, grade 2 plus 3 (HR, 1.47 [95% CI, 1.12-1.92]). A post hoc analysis that contrasted subgroups defined by never used estrogen alone and ever used estrogen alone (past or current use) was more suggestive of effect modification; HRs were 1.01 (95% CI, 0.83-1.22), 1.28 (95% CI, 1.04-1.58), and 1.44 (95% CI, 1.14-1.83) among women who ever used estrogen alone for overweight; obese, grade I; and obese, grade 2 plus 3, respectively (*P* = .04 for interaction). In a sensitivity analysis differentiating between prior estrogen and progestin use or estrogen use alone use among the posthysterectomy group, a similar association was observed between BMI and breast cancer among women who never used estrogen alone or estrogen and progestin. Specifically, HRs were 1.65 (95% CI, 1.02-2.68), 2.30 (95% CI, 1.42-3.73), and 2.80 (95% CI, 1.70-4.60) for overweight; obese, grade 1; and obese, grade 2 plus 3, respectively.

We next examined whether the interpretation of results varied by the type of obesity measure used: BMI or weight, including height as a covariate. The multivariable-adjusted risk for the BMI–invasive breast cancer association was mostly linear for most (middle 90%) of the distribution (eFigure 3A in the Supplement) and plateaued near 40.0; the 5th and 95th BMI percentiles were 21.3 and 39.3, respectively. However, the multivariable-adjusted risk associated with weight (kilograms) was nonlinear (eFigure 3B in the Supplement) even among the middle 90% of participants; the 5th and 95th percentiles were 54.5 kg and 104.5 kg, respectively.

To better understand the shapes of the curves for the BMI and weight models in which the breast cancer rates increase with both measures but are attenuated at the highest BMI levels (eFigure 3 in the Supplement), we explored the relationship between the sex hormones and BMI. Smoothed estimates of baseline mean levels of estradiol, estrone, and the protein SHBG in the available subset of 200 participants were plotted against BMI (**Figure**). Estradiol had a linear relationship with BMI, but the association between estrone and BMI dampens for grade 2 plus 3 obesity. Finally, the sharp decrease observed between mean serum SHBG concentrations and increasing BMI levels off for grade 2 plus 3 obesity.

Discussion

The WHI clinical trial examined the association of overweight and obesity with invasive breast cancer risk in postmenopausal women. Unlike many observational studies, weight, height, and body circumferences were measured at baseline and annually using a standardized protocol throughout the trial; annual or biennial mammography was a required trial protocol element, thus minimizing ascertainment bias; and breast cancer outcomes (including details on breast cancer characteristics: tumor hormone receptor status, histologic characteristics, nodal involvement, tumor grade, and disease stage) were adjudicated by physician adjudicators. In this context, BMI was positively associated with

Table 2. Overall and Tumor Specific Incidence of Invasive Breast Cancer and Other Breast Cancer Outcomes (No., Annualized %) and Multivariable[a] Adjusted HRs by Baseline BMI in the WHI Clinical Trial

Cancer	Normal, <25	Overweight, 25 to <30	HR (95% CI)	Obese, Grade I, 30 to <35	HR (95% CI)	Obese, Grade 2 + 3, ≥35	HR (95% CI)	*P* Value[b]
All invasive breast cancer	823 (0.37)	1183 (0.41)	1.17 (1.06-1.29)	828 (0.47)	1.37 (1.23-1.53)	554 (0.51)	1.58 (1.40-1.79)	<.001
Receptor status								
ER+/PR+	489 (0.22)	734 (0.25)	1.21 (1.07-1.37)	544 (0.31)	1.52 (1.33-1.74)	376 (0.35)	1.86 (1.60-2.17)	<.001
ER+/PR−	125 (0.06)	169 (0.06)	1.07 (0.83-1.38)	97 (0.05)	1.09 (0.82-1.45)	61 (0.06)	1.01 (0.71-1.44)	
ER−/PR−	112 (0.05)	156 (0.05)	1.22 (0.93-1.60)	93 (0.05)	1.15 (0.84-1.57)	54 (0.05)	1.15 (0.79-1.67)	
HER2								
Positive	95 (0.04)	143 (0.05)	1.31 (0.99-1.74)	103 (0.06)	1.59 (1.17-2.17)	57 (0.05)	1.37 (0.94-2.00)	.52
Negative	494 (0.22)	715 (0.25)	1.17 (1.04-1.33)	493 (0.28)	1.36 (1.18-1.56)	347 (0.32)	1.72 (1.47-2.01)	
Triple negative								
Yes	60 (0.03)	84 (0.03)	1.23 (0.86-1.77)	40 (0.02)	0.90 (0.57-1.41)	33 (0.03)	1.42 (0.89-2.28)	.12
No	517 (0.23)	753 (0.26)	1.19 (1.05-1.34)	542 (0.30)	1.45 (1.27-1.66)	365 (0.34)	1.71 (1.46-1.99)	
Tumor size, cm								
<1	232 (0.10)	321 (0.11)	1.20 (1.00-1.45)	219 (0.12)	1.35 (1.10-1.66)	145 (0.13)	1.58 (1.25-1.99)	.02
1 to <2	333 (0.15)	461 (0.16)	1.09 (0.93-1.26)	328 (0.18)	1.32 (1.12-1.56)	189 (0.17)	1.29 (1.06-1.58)	
≥2	187 (0.08)	303 (0.10)	1.34 (1.09-1.63)	206 (0.12)	1.55 (1.25-1.93)	163 (0.15)	2.12 (1.67-2.69)	
Positive lymph node								
Yes	168 (0.08)	245 (0.08)	1.22 (0.98-1.52)	184 (0.10)	1.50 (1.19-1.89)	138 (0.13)	1.89 (1.46-2.45)	.06
No	579 (0.26)	825 (0.28)	1.16 (1.03-1.30)	547 (0.31)	1.31 (1.15-1.49)	345 (0.32)	1.45 (1.25-1.68)	
Histologic type								
Ductal	521 (0.23)	759 (0.26)	1.20 (1.06-1.35)	554 (0.31)	1.48 (1.29-1.69)	349 (0.32)	1.56 (1.34-1.83)	.92
Lobular	69 (0.03)	130 (0.04)	1.41 (1.03-1.93)	63 (0.04)	1.07 (0.73-1.57)	62 (0.06)	1.90 (1.29-2.80)	
Ductal and lobular	126 (0.06)	139 (0.05)	0.95 (0.73-1.23)	109 (0.06)	1.28 (0.97-1.70)	66 (0.06)	1.35 (0.97-1.88)	
Other	102 (0.05)	153 (0.05)	1.17 (0.89-1.54)	95 (0.05)	1.17 (0.86-1.59)	70 (0.06)	1.72 (1.24-2.40)	
Grade								
Well differentiated	237 (0.11)	302 (0.10)	1.02 (0.85-1.23)	192 (0.11)	1.12 (0.91-1.38)	127 (0.12)	1.30 (1.03-1.65)	.14
Moderately differentiated	312 (0.14)	457 (0.16)	1.21 (1.03-1.42)	337 (0.19)	1.50 (1.27-1.79)	214 (0.20)	1.66 (1.33-2.02)	
Poorly differentiated	216 (0.10)	299 (0.10)	1.13 (0.93-1.36)	204 (0.11)	1.29 (1.04-1.59)	142 (0.13)	1.58 (1.25-2.00)	
Stage								
Local	622 (0.28)	902 (0.31)	1.17 (1.05-1.31)	602 (0.34)	1.33 (1.17-1.51)	383 (0.35)	1.48 (1.28-1.72)	.05
Regional/distant	187 (0.08)	271 (0.09)	1.21 (0.99-1.49)	206 (0.12)	1.51 (1.21-1.89)	156 (0.14)	1.94 (1.52-2.47)	
Other cancer outcomes								
In situ breast cancer	230 (0.10)	305 (0.10)	1.00 (0.83-1.21)	178 (0.10)	0.96 (0.77-1.19)	129 (0.12)	1.32 (1.03-1.68)	.12
Total breast cancer	1038 (0.47)	1471 (0.51)	1.13 (1.04-1.24)	996 (0.56)	1.29 (1.17-1.42)	671 (0.62)	1.52 (1.36-1.70)	<.001
Breast cancer deaths	64 (0.03)	82 (0.03)	0.93 (0.65-1.34)	61 (0.03)	1.08 (0.72-1.62)	67 (0.05)	2.25 (1.51-3.36)	<.001
Deaths after breast cancer	137 (0.06)	185 (0.06)	1.12 (0.87-1.44)	147 (0.07)	1.37 (1.04-1.79)	120 (0.10)	2.11 (1.57-2.84)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ER, estrogen receptor; HR, hazard ratio; PR, progestin receptor; +, positive; −, negative.

[a] Analyses were adjusted for age, race/ethnicity, education, parity, age at first birth, bilateral oophorectomy, family history of breast cancer, estrogen-alone use and duration, estrogen and progesterone use and duration, smoking status, diabetes mellitus, alcohol consumption, and stratified by baseline age group, HT trial randomization group, dietary trial randomization group, hysterectomy status, Calcium/Vitamin D Randomized Trial randomization group (time-dependent) and extended follow-up (time-dependent).

[b] Corresponds to a trend test for the main effect of BMI on invasive breast cancer or other breast cancer end points, or a test of heterogeneity for trends between BMI and invasive breast cancer subtypes.

Table 3. Invasive Breast Cancer Incidence and Multivariable[a] Adjusted HR Associated With Weight Change[b] by Baseline BMI Subgroups in the WHI Clinical Trial

Characteristic	Main Effect	BMI Subgroup			
		Normal (<25)	Overweight (25-<30)	Obese, Grade 1 (30 to <35)	Obese, Grade 2 + 3 (≥35)
>5% Weight loss					
No. %	628 (0.44)	106 (0.36)	221 (0.43)	161 (0.44)	140 (0.52)
HR (95% CI)	1.00 (0.89-1.12)	1.03 (0.81-1.32)	1.05 (0.87-1.27)	0.92 (0.74-1.14)	0.99 (0.77-1.27)
2%-5% Weight loss					
No. %	460 (0.44)	104 (0.37)	168 (0.44)	107 (0.45)	81 (0.56)
HR (95% CI)	1.07 (0.95-1.21)	1.02 (0.80-1.31)	1.17 (0.96-1.43)	1.01 (0.79-1.29)	1.03 (0.76-1.40)
Weight stable,[c] within ±2%					
No. %	1065 (0.38)	259 (0.32)	367 (0.37)	265 (0.43)	174 (0.45)
2%-5% Weight gain					
No. %	546 (0.46)	136 (0.38)	194 (0.44)	135 (0.54)	81 (0.61)
HR (95% CI)	1.09 (0.97-1.23)	1.04 (0.82-1.30)	1.09 (0.90-1.32)	1.15 (0.91-1.45)	1.15 (0.85-1.55)
>5% Weight gain					
No. %	689 (0.46)	218 (0.46)	233 (0.41)	160 (0.52)	78 (0.50)
HR (95% CI)	1.12 (1.00-1.25)	1.36 (1.11-1.65)	0.98 (0.81-1.18)	1.14 (0.92-1.42)	1.00 (0.74-1.34)
P value[d]	.08	.05	.05	.05	.05

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HR, hazard ratio; WHI; Women's Health Initiative.

[a] Analyses were adjusted for age, race/ethnicity, education, parity, age at first birth, bilateral oophorectomy, family history of breast cancer, estrogen-alone use and duration, estrogen and progesterone use and duration, smoking status, diabetes mellitus, alcohol consumption, baseline BMI group, and stratified by baseline age group, hormone therapy trial randomization group, dietary trial randomization group, hysterectomy status, Calcium/Vitamin D Randomized Trial randomization group (time-dependent), and extended follow-up (time-dependent).

[b] Percentage change from baseline (annual visit minus baseline), divided by baseline × 100, and included as a time-dependent variable.

[c] Referent group.

[d] *P* values correspond to the statistical significance of a 1-df test of trend for the main effect of weight change, or a 3-df test of the interaction between weight change and BMI subgroup.

increased risk of invasive breast cancer (*P* < .001). We observed a strong linear trend in which the risk progressively increased across the BMI categories. The strongest associations were observed for women with a BMI higher than 35.0; these women had a 58% increased risk of invasive breast cancer compared with women with a BMI lower than 25.0 . Breast cancer deaths were also more than 2-fold higher among those with grade 2 plus 3 obesity compared with those with normal BMI.

Obesity was associated with breast cancer characteristics, including tumor size, lymph node positivity, and regional and/or distant stage at diagnosis. In addition, women with estrogen receptor- and progesterone receptor-positive tumors who were obese, grade 1, or obese, grade 2 plus 3, had 52% and 86% increased risk of breast cancer, respectively, compared with women with normal BMI, respectively. The growth of estrogen receptor-positive tumors are under estrogen influence,[17,18] and estrogen levels are higher in overweight and obese postmenopausal women owing to the aromatization of androstenedione and testosterone to estrogens in adipose tissue.[19,20] Furthermore, obese individuals have larger and more abundant adipose tissue cells than those of normal weight, and these women typically have greater endogenous synthesis of estrogens in their adipose tissue. Leptin may also increase estrogen levels,[21] and while leptin data are not available for study participants, leptin levels are higher in overweight and obese individuals than in those of normal weight.[22,23] These biological relationships of BMI and altered hormone and cytokine profiles and the potential causal relationships with breast cancer risk are supported by our data showing a strong linear relationship between baseline BMI and both estradiol and estrone levels and are consistent with findings of a previous report[24] on the role of serum hormone and breast carcinogenesis.

The WHI clinical trial results differ from findings in the National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (NSABP P-1) and the Study of Tamoxifen and Raloxifene (STAR).[25-28] In contrast to the findings of the WHI clinical trial reported herein, the NSABP P-1 and STAR results showed a modest but nonsignificant, increased risk for postmenopausal breast cancer (relative risk [RR], 1.14; 95% CI, 0.94-1.38) for women with a BMI of at least 30.0 compared with women with a BMI lower than 25.0.[25] Similar to the WHI clinical trial , the NSABP P-1 trials had baseline breast cancer risk assessment, baseline and serial mammography, and adjudicated breast cancer outcomes. However, the NSABP P-1 results are not directly comparable with those reported herein because nearly 75% of NSABP P-1 participants were randomized to tamoxifen or raloxifene, agents that decrease breast cancer incidence by almost 50%.[26-28] As a result, there were fewer than 3200 postmenopausal women who were randomized to placebo for whom findings could reasonably be compared with those in the WHI clinical trial . The HRs for breast cancer risk in obese, grade 1, and obese, grade 2 plus 3, NSABP P-1 postmenopausal-placebo participants were 1.77 and 1.28, respectively (*P* = .36). However, the limited sample size precludes reliable generation of information regarding BMI influence on

Table 4. Invasive Breast Cancer Incidence (No., Annualized %) and Multivariable Adjusted HR (95% CI) Associated With Baseline BMI by Select Baseline Age, Race/Ethnicity, and Postmenopausal Hormone Use in the WHI Clinical Trial

Characteristic	Normal, <25	Overweight, 25 to <30	HR (95% CI)	Obese, Grade 1, 30 to <35	HR (95% CI)	Obese, Grade 2 + 3, ≥35	HR (95% CI)	*P* Value[a]
Main effect	823 (0.37)	1183 (0.41)	1.17 (1.06-1.29)	828 (0.47)	1.37 (1.23-1.53)	554 (0.51)	1.58 (1.40-1.79)	**<.001**
Age at screening, y								
50-59	312 (0.37)	375 (0.37)	1.02 (0.87-1.20)	265 (0.41)	1.24 (1.04-1.48)	191 (0.43)	1.33 (1.09-1.62)	
60-69	353 (0.37)	566 (0.42)	1.26 (1.09-1.45)	401 (0.48)	1.41 (1.20-1.66)	280 (0.55)	1.73 (1.45-2.07)	**.05**
70-79	158 (0.37)	242 (0.45)	1.29 (1.03-1.62)	162 (0.55)	1.64 (1.28-2.10)	83 (0.65)	1.75 (1.27-2.42)	
Race/ethnicity								
White	743 (0.38)	1025 (0.42)	1.18 (1.06-1.31)	704 (0.50)	1.39 (1.24-1.56)	435 (0.53)	1.56 (1.36-1.78)	
Black	34 (0.34)	87 (0.35)	0.87 (0.56-1.36)	81 (0.36)	0.98 (0.63-1.53)	82 (0.41)	1.15 (0.74-1.80)	**.34**
Other	46 (0.26)	71 (0.31)	1.15 (0.76-1.73)	43 (0.32)	1.23 (0.77-1.97)	37 (0.50)	2.20 (1.36-3.55)	
With uterus[b]	576 (0.40)	776 (0.46)	1.20 (1.07-1.35)	487 (0.50)	1.35 (1.18-1.54)	308 (0.54)	1.52 (1.30-1.77)	**<.001**
Never used E + P	227 (0.37)	326 (0.40)	1.14 (0.95-1.37)	221 (0.44)	1.29 (1.05-1.59)	164 (0.51)	1.46 (1.17-1.83)	
Past E + P use	33 (0.25)	54 (0.38)	1.57 (0.98-2.51)	33 (0.44)	1.64 (0.97-2.78)	20 (0.49)	1.84 (0.97-3.48)	.78
Current E + P use	316 (0.46)	396 (0.54)	1.21 (1.03-1.42)	233 (0.59)	1.36 (1.13-1.64)	124 (0.60)	1.53 (1.22-1.91)	
Without uterus[c]	247 (0.31)	407 (0.33)	1.09 (0.91-1.30)	341 (0.42)	1.40 (1.16-1.69)	246 (0.48)	1.62 (1.32-2.00)	**<.001**
Never used E alone	36 (0.23)	97 (0.34)	1.66 (1.06-2.60)	99 (0.45)	2.16 (1.38-3.39)	84 (0.54)	2.63 (1.65-4.18)	
Past E-alone use	39 (0.33)	62 (0.31)	0.85 (0.55-1.31)	52 (0.39)	1.05 (0.67-1.64)	41 (0.46)	1.32 (0.82-2.12)	.11
Current E-alone use	171 (0.33)	248 (0.34)	1.05 (0.84-1.30)	190 (0.42)	1.35 (1.07-1.71)	121 (0.45)	1.47 (1.12-1.92)	

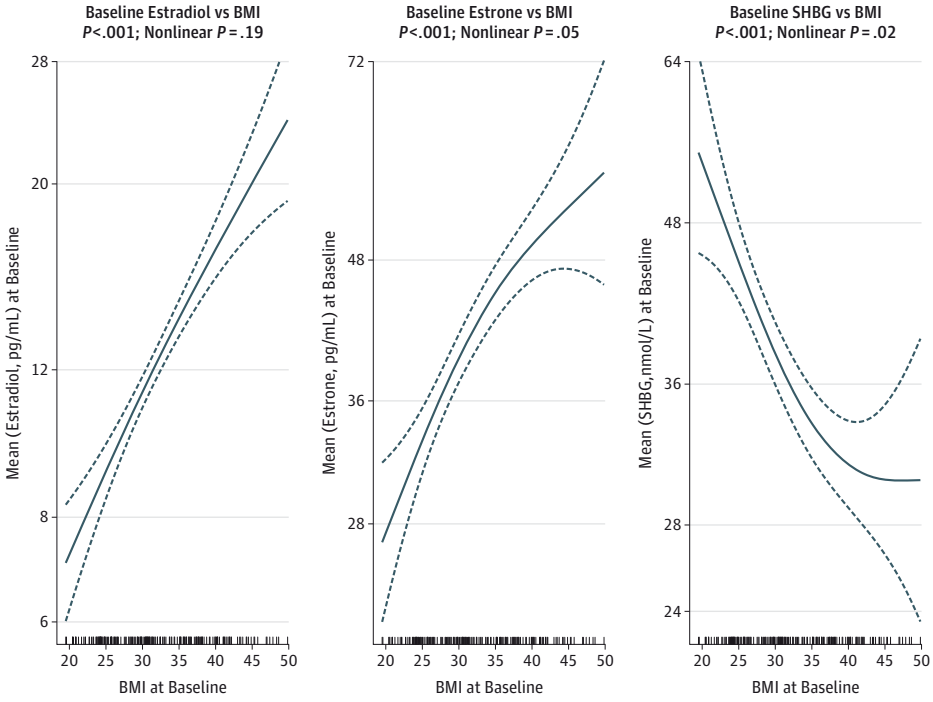
Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); E, estrogen; HR, hazard ratio; P, progesterone; WHI; Women's Health Initiative.

[a] *P* values (in bold) correspond to the statistical significance of a 1-df test of trend for the main effect of BMI on invasive breast cancer risk in the full cohort, or by cohorts defined by baseline hysterectomy status. The remaining *P* values correspond to tests of interaction within their respective cohorts.

[b] Includes only participants who reported not having had a hysterectomy and were randomized to any WHI clinical trial (n = 38 981).

[c] Includes only participants who reported having had a hysterectomy and were randomized to any WHI clinical trial (n = 28 158).

Figure. Baseline Measurements of Estradiol, Estrone, and the Protein SHBG vs BMI at Baseline



Solid curves indicates means; dashed curves, 95% CIs. BMI indicates body mass index, calculated as weight in kilograms divided by height in meters squared; SHBG, sex hormone binding globulin.

breast cancer risk in women not receiving these effective chemoprevention agents.

Several observational studies have reported that the relationship between obesity and breast cancer risk is modified by postmenopausal HT use.[29-32] Huang et al[30] found that higher vs lower BMI was associated with an increased postmenopausal breast cancer risk (RR, 1.59; 95% CI, 1.09-2.32; $P < .001$ for trend), except among current and past HT users. Subsequent observational studies from the Carolina Breast Cancer Study,[31] a follow-up analysis from the Nurses' Health Study,[29] the Breast Cancer Surveillance Consortium,[32] the WHI Observational Study,[33] and others[34-37] have similarly reported apparent effect modification of the obesity-breast cancer relationship by HT use. Many investigators reporting interactions of HT and obesity in relation to breast cancer risk have posited that HT use obscures the effects of obesity, particularly in relation to their effects on circulating hormone levels. To our knowledge, a biological mechanism to explain these associations has not been identified nor have results been confirmed with evidence from randomized clinical trials. Of note, 2 previous reports[38,39] from the WHI clinical trial did not find an interaction between BMI and CEE alone or CEE plus MPA, and in this report we found no effect modification, and similar directions of associations were observed across BMI categories for never, past, and current HT use. While we did find attenuations of the risk estimates for ever-users of estrogen alone among women with a prior hysterectomy, the association between obesity and breast cancer remained. Differences in findings may be due to observational studies' reliance on self-reported height, weight, and HT and may be subject to mammography screening and ascertainment bias when outcomes are collected by self-report. Notably, there are higher rates of routine screening mammograms for women receiving postmenopausal HT; the larger detection rates from screening mammograms could introduce bias in the observational studies if obese women underwent screening mammography at a different rate than women of normal weight.[40]

The WHI clinical trial findings of consistent dose-response risks across the BMI categories regardless of postmenopausal HT use have clinical implications. One report[32] suggested that since the obesity-breast cancer risk was attenuated or not observed among HT users, obese women may benefit from HT use because they observed no excess breast cancer risk for these women. However, the preponderance of evidence suggests that postmenopausal HT is not beneficial for multiple health outcomes, including breast cancer, and the risks outweigh the benefits.[41]

One intriguing finding was that women in the WHI clinical trial who began the study with a BMI lower than 25.0 and gained more than 5% of body weight over the follow-up period had a breast cancer HR of 1.36 (95% CI, 1.1-1.65) compared with women of stable weight. After menopause, the breast tissue evolves toward a higher adipose content. Breast tissue adipocytes serve as a source of inflammatory cytokines as well as local estrogen production.[19,20] It is possible that a weight gain–induced sudden and steep rise in breast adipocytes and exposure to cytokines and estrogens could explain why women of normal weight who gained more than 5% bodyweight had an increased risk for breast cancer compared with women of stable weight. These results suggest that prevention of weight gain may be an important public health strategy for reducing breast cancer risk.

In contrast, women who were overweight or obese at baseline had no change in risk by weight gain or loss during follow-up relative to weight stability. It is important to note that the WHI clinical trial was not a weight loss trial, and the weight change data we present may reflect both intentional and unintentional weight loss. Well-designed clinical trials are needed to definitively test whether weight loss and body composition changes in overweight and obese women or obesity prevention in women of normal weight will reduce breast cancer risk. In addition, it is not clear at what stage in life excess weight confers the greatest risk. For example, during adolescence and pregnancy, breast epithelial cells undergo rapid division and differentiation. It is possible that obesity superimposed on this rapid cell growth may set the stage for aberrant cell growth and biological susceptibility to breast cancer.[5,42] Another susceptible time point may be the menopause, when breast tissue is undergoing further changes.

Strengths of this WHI-CT report include the large sample size, standardized data collection, adjudicated breast cancers, protocol-required mammography, and limited loss to follow-up. Limitations include fewer participants of minority race/ethnic groups, lack of data on tumor molecular characteristics,[43] and fewer data on longer-term weight and body composition changes and inability to distinguish from unintentional weight loss. Death from breast cancer was not common, so the elevated mortality risk for women with grade 2 plus 3 obesity should be viewed with caution. Finally, we had insufficient power to examine risk for distant stage only owing to very few cases presenting with distant stage at diagnosis.

Conclusions

Obesity is associated with a dose-response increased postmenopausal breast cancer risk, particularly for estrogen receptor– and progesterone receptor–positive disease, but risk does not vary by HT use or race/ethnicity. These clinically meaningful findings support the need for trials clinical trials evaluating the role of obesity prevention and treatment on breast cancer risk.

ARTICLE INFORMATION

Accepted for Publication: April 24, 2015.

Published Online: June 11, 2015. doi:10.1001/jamaoncol.2015.1546.

Author Affiliations: Division of Public Health Sciences, Cancer Prevention Program, Fred Hutchinson Cancer Research Center, Seattle, Washington (Neuhouser, Aragaki, Prentice, Tinker, Anderson); Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts (Manson); Los Angeles Biomedical Research Institute at Harbor-UCLA, David Geffen School of Medicine, University of California, Los Angeles (Chlebowski); Department of Medicine, George Washington University School of Medicine, Washington, DC (Carty); Department of Epidemiology and Environmental Health, University at Buffalo, Buffalo, New York (Ochs-Balcom); Division of Health Promotion Sciences, University of Arizona, Tucson/Phoenix (Thomson); Division of Research, Kaiser Permanente, Oakland, California (Caan); Department of Obstetrics and Gynecology, University of North Carolina, Chapel Hill (Urrutia); Division of Reproductive Endocrinology and Fertility, University of Texas Health Science Center, San Antonio (Knudtson).

Author Contributions: Dr Neuhouser and Mr Aragaki had full access to the data and take full responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Neuhouser, Prentice, Manson, Thomson, Anderson.
Acquisition, analysis, or interpretation of data: Neuhouser, Aragaki, Prentice, Manson, Chlebowski, Carty, Ochs-Balcom, Caan, Tinker, Urrutia, Knudtson, Anderson.
Drafting of the manuscript: Neuhouser, Aragaki, Chlebowski, Thomson, Anderson.
Critical revision of the manuscript for important intellectual content: Neuhouser, Aragaki, Prentice, Manson, Carty, Ochs-Balcom, Caan, Tinker, Urrutia, Knudtson, Anderson.
Statistical analysis: Neuhouser, Aragaki, Prentice, Carty, Caan.
Obtained funding: Prentice.
Administrative, technical, or material support: Manson, Chlebowski, Thomson, Knudtson.
Study supervision: Neuhouser, Manson, Chlebowski, Ochs-Balcom, Anderson.

Conflict of Interest Disclosures: Dr Chlebowski has received speaker's fees and honorarium from Novartis; honorarium for advisory boards and consulting for Novartis, Novo Nordisk, Pfizer, Genetech, and Amgen. No other disclosures are reported.

Funding/Support: The Women's Health Initiative (WHI) programs are funded by the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health, US Department of Health and Human Services through contracts, HHSN268201100046C, HHSN268201100001C, HHSN268201100002C, HHSN268201100003C, HHSN268201100004C, and HHSN271201100004C.

Role of the Funder/Sponsor: The WHI project office at the NHLBI, which was the sponsor of WHI, had a role in the overall design and conduct of the WHI, but no direct role in this manuscript with regards to design, interpretation of the data, review and approval of the manuscript and decision to submit the manuscript for publication. Decisions concerning the above, as well as overall data collection, management, and analysis resided, with committees composed of WHI investigators and included NHLBI representatives.

Additional Information: A complete list of WHI investigators can be found at https://www.whi.org.

REFERENCES

1. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. *JAMA*. 2014;311(8):806-814.

2. World Cancer Research Fund. *American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington, DC: American Institute for Cancer Research; 2007.

3. Suzuki R, Orsini N, Saji S, Key TJ, Wolk A. Body weight and incidence of breast cancer defined by estrogen and progesterone receptor status: a meta-analysis. *Int J Cancer*. 2009;124(3):698-712.

4. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008; 371(9612):569-578.

5. Vrieling A, Buck K, Kaaks R, Chang-Claude J. Adult weight gain in relation to breast cancer risk by estrogen and progesterone receptor status: a meta-analysis. *Breast Cancer Res Treat*. 2010;123 (3):641-649.

6. Eheman C, Henley SJ, Ballard-Barbash R, et al. Annual report to the nation on the status of cancer, 1975-2008, featuring cancers associated with excess weight and lack of sufficient physical activity. *Cancer*. 2012;118(9):2338-2366.

7. Women's Health Initiative Study Group. Design of the Women's Health Initiative clinical trial and observational study. *Control Clin Trials*. 1998;19(1): 61-109.

8. Anderson GL, Manson J, Wallace R, et al. Implementation of the Women's Health Initiative study design. *Ann Epidemiol*. 2003;13(9)(suppl):S5-S17.

9. Edlefsen KL, Jackson RD, Prentice RL, et al. The effects of postmenopausal hormone therapy on serum estrogen, progesterone, and sex hormone-binding globulin levels in healthy postmenopausal women. *Menopause*. 2010;17(3): 622-629.

10. Curb JD, McTiernan A, Heckbert SR, et al; WHI Morbidity and Mortality Committee. Outcomes ascertainment and adjudication methods in the Women's Health Initiative. *Ann Epidemiol*. 2003;13 (9)(suppl):S122-S128.

11. Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women:

principal results From the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288(3):321-333.

12. 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*. 2006;295(6):629-642.

13. Beresford SA, Johnson KC, Ritenbaugh C, et al. Low-fat dietary pattern and risk of colorectal cancer: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295(6):643-654.

14. Howard BV, Van Horn L, Hsia J, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. *JAMA*. 2006;295(6):655-666.

15. Jackson RD, LaCroix AZ, Gass M, et al; Women's Health Initiative Investigators. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med*. 2006;354(7):669-683.

16. Hefti MM, Hu R, Knoblauch NW, et al. Estrogen receptor negative/progesterone receptor positive breast cancer is not a reproducible subtype. *Breast Cancer Res*. 2013;15(4):R68.

17. Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanisms of cancer development in obesity. *Nat Rev Cancer*. 2011;11(12):886-895.

18. Althuis MD, Fergenbaum JH, Garcia-Closas M, Brinton LA, Madigan MP, Sherman ME. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. *Cancer Epidemiol Biomarkers Prev*. 2004;13(10):1558-1568.

19. Goodwin PJ. Obesity and endocrine therapy: host factors and breast cancer outcome. *Breast*. 2013;22(suppl 2):S44-S47.

20. Morris PG, Hudis CA, Giri D, et al. Inflammation and increased aromatase expression occur in the breast tissue of obese women with breast cancer. *Cancer Prev Res (Phila)*. 2011;4(7):1021-1029.

21. Geisler J, Haynes B, Ekse D, Dowsett M, Lønning PE. Total body aromatization in postmenopausal breast cancer patients is strongly correlated to plasma leptin levels. *J Steroid Biochem Mol Biol*. 2007;104(1-2):27-34.

22. Harris RBS. Leptin: much more than a satiety signal. *Annu Rev Nutr*. 2000;20:45-75.

23. Hursting SD, Digiovanni J, Dannenberg AJ, et al. Obesity, energy balance, and cancer: new opportunities for prevention. *Cancer Prev Res (Phila)*. 2012;5(11):1260-1272.

24. Zhao S, Chlebowski RT, Anderson GL, et al. Sex hormone associations with breast cancer risk and the mediation of randomized trial postmenopausal hormone therapy effects. *Breast Cancer Res*. 2014;16(2):R30.

25. Cecchini RS, Costantino JP, Cauley JA, et al. Body mass index and the risk for developing invasive breast cancer among high-risk women in NSABP P-1 and STAR breast cancer prevention trials. *Cancer Prev Res (Phila)*. 2012;5(4):583-592.

26. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst*. 1998;90(18):1371-1388.

27. 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*. 2005;97(22):1652-1662.

28. Vogel VG, Costantino JP, Wickerham DL, et al; National Surgical Adjuvant Breast and Bowel Project (NSABP). Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA*. 2006;295(23):2727-2741.

29. Chen WY, Hankinson SE, Schnitt SJ, Rosner BA, Holmes MD, Colditz GA. Association of hormone replacement therapy to estrogen and progesterone receptor status in invasive breast carcinoma. *Cancer*. 2004;101(7):1490-1500.

30. Huang Z, Hankinson SE, Colditz GA, et al. Dual effects of weight and weight gain on breast cancer risk. *JAMA*. 1997;278(17):1407-1411.

31. Huang WY, Newman B, Millikan RC, Schell MJ, Hulka BS, Moorman PG. Hormone-related factors and risk of breast cancer in relation to estrogen receptor and progesterone receptor status. *Am J Epidemiol*. 2000;151(7):703-714.

32. Hou N, Hong S, Wang W, Olopade OI, Dignam JJ, Huo D. Hormone replacement therapy and breast cancer: heterogeneous risks by race, weight, and breast density. *J Natl Cancer Inst*. 2013;105(18):1365-1372.

33. Morimoto LM, White E, Chen Z, et al. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). *Cancer Causes Control*. 2002;13(8):741-751.

34. Li CI, Malone KE, Daling JR. Interactions between body mass index and hormone therapy and postmenopausal breast cancer risk (United States). *Cancer Causes Control*. 2006;17(5):695-703.

35. Munsell MF, Sprague BL, Berry DA, Chisholm G, Trentham-Dietz A. Body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status. *Epidemiol Rev*. 2014;36(1):114-136.

36. Brinton LA, Richesson D, Leitzmann MF, et al. Menopausal hormone therapy and breast cancer risk in the NIH-AARP Diet and Health Study Cohort. *Cancer Epidemiol Biomarkers Prev*. 2008;17(11):3150-3160.

37. Beral V, Reeves G, Bull D, Green J; Million Women Study Collaborators. Breast cancer risk in relation to the interval between menopause and starting hormone therapy. *J Natl Cancer Inst*. 2011;103(4):296-305.

38. 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*. 2012;13(5):476-486.

39. Chlebowski RT, Anderson GL, Gass M, et al; WHI Investigators. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. *JAMA*. 2010;304(15):1684-1692.

40. Anderson GL, Neuhouser ML. Obesity and the risk for premenopausal and postmenopausal breast cancer. *Cancer Prev Res (Phila)*. 2012;5(4):515-521.

41. 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*. 2013;310(13):1353-1368.

42. Feigelson HS, Jonas CR, Teras LR, Thun MJ, Calle EE. Weight gain, body mass index, hormone replacement therapy, and postmenopausal breast cancer in a large prospective study. *Cancer Epidemiol Biomarkers Prev*. 2004;13(2):220-224.

43. Caan BJ, Sweeney C, Habel LA, et al. Intrinsic subtypes from the PAM50 gene expression assay in a population-based breast cancer survivor cohort: prognostication of short- and long-term outcomes. *Cancer Epidemiol Biomarkers Prev*. 2014;23(5):725-734.