Weight Gain, Body Mass Index, Hormone Replacement Therapy, and Postmenopausal Breast Cancer in a Large Prospective Study

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Abstract

Excess adiposity and hormone replacement therapy (HRT) are important contributors to postmenopausal breast cancer risk. HRT has been shown to modify the association between body weight and breast cancer risk, although few studies are sufficiently large to examine the risk of breast cancer associated with body mass index (BMI) and weight gain separately among current HRT users and nonusers. This study includes 1,934 incident breast cancer cases occurring among 62,756 postmenopausal women in the Cancer Prevention Study-II Nutrition Cohort. Age-adjusted incidence rates were calculated, and Cox proportional hazards models were used to examine the association of BMI and adult weight gain (since age 18 years) with breast cancer risk stratified by HRT use. Total adult weight gain strongly predicted breast cancer risk among former and never HRT users (P for trend < 0.0001). Weight gain of 21–30 pounds was associated with a rate ratio of 1.4 (95% confidence interval 1.1–1.8); rates doubled among women gaining >70 pounds compared with women who maintained their weight within 5 pounds of their weight at age 18. After accounting for weight gain, neither recent BMI nor BMI at age 18 were independent predictors of risk. Among current HRT users, no association was seen between breast cancer and either BMI or weight gain. Adult weight gain is strongly associated with postmenopausal breast cancer only among non-HRT users in this study. These data illustrate the importance of examining breast cancer risk factors separately by HRT use; the effects of other risk factors may be attenuated or obscured among women taking HRT.

Introduction

Adiposity is one of the few modifiable risk factors for breast cancer and has been the subject of extensive study (1). Among premenopausal women, high body mass index (BMI), and other measures of adiposity are associated with a reduced risk of breast cancer. This phenomenon likely results from an increased frequency of annovulatory cycles that lead to lower levels of serum estradiol and progesterone among young obese women (2). In postmenopausal women, circulating estrogens are derived largely from extraglandular aromatization of plasma androstenedione to estrone in the adipose tissue. Thus, estrogen production in postmenopausal women is directly correlated with body weight (3). Obesity also is associated with decreased sex hormone binding globulin production and increased proportions of free and albumin-bound estrogens, resulting in more biologically active estrogen in circulation.

Hormone replacement therapy (HRT) provides an exogenous source of circulating hormones in postmenopausal women. Breast cancer risk is higher among women who take HRT (particularly the combination of estrogen plus progesterone) than in women who do not take hormones in both observational studies (4, 5) and a clinical trial (6). Furthermore, HRT use has been shown to modify the association between body weight and postmenopausal breast cancer risk. A statistical interaction between HRT use and BMI for postmenopausal breast cancer risk was first demonstrated in a cohort study by Huang *et al.* (7). Most subsequent studies have supported these findings (4, 8–10), although three large studies have observed no statistically significant interaction between HRT use and BMI (11–13) despite some attenuation of the positive association among women who reported HRT use.

The Cancer Prevention Study (CPS)-II Nutrition Cohort is sufficiently large to examine the risk of breast cancer associated with BMI and weight gain separately among women taking HRT and those not using HRT. Our analysis examines the risk of incident breast cancer in relation to reported BMI at age 18 years, BMI in 1992 (up to 7 years before breast cancer diagnosis), and weight gain between these two time periods among 62,756 postmenopausal women.

Materials and Methods

Study Cohort. Women in this analysis were drawn from the 97,786 female participants in the CPS-II Nutrition Cohort, a prospective study of cancer incidence and mortality among United States men and women established in 1992, as described in detail elsewhere (14). The Nutrition Cohort is a subgroup of the ~1.2 million participants in CPS-II, a prospective study of cancer mortality established by the American Cancer Society in 1982. Nutrition Cohort participants were recruited from original members of the CPS-II cohort who resided in 21 states and were ages 50–74 years in 1992. Participants completed a mailed self-administered questionnaire that included a food frequency diet assessment and information on demographic, medical, behavioral, environmental, and occupational factors. Follow-up questionnaires were sent to all living cohort members from September 1997 to August 1999 and again from September 1999 to August 2001 to update exposure information and to ascertain newly diagnosed cancers. The response

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rate for both of the follow-up questionnaires (after multiple mailings) was at least 90%.

We excluded from the analysis women who were lost to follow-up from baseline in 1992 through August 31, 1999 (n = 4,394). We also excluded participants who reported prevalent breast or other cancer at baseline, except nonmelanoma skin cancer (n = 11,908), or who did not specify their menopausal status (n = 646), or were pre- or perimenopausal (n = 4,451) in 1992. We excluded participants with extreme values for height, weight, or BMI (those below the 0.1 percentile and above the 99.9 percentile) or with unknown height or weight (n = 3,294). We also excluded women who reported net weight loss of >5 pounds since age 18 years (n = 3,829) because the relationship between breast cancer and weight loss may be very different than with weight gain. Finally, we excluded women who reported HRT use, but did not specify the type of use, and women who had missing or invalid HRT use responses (n = 6,485). After all exclusions, the final analytic cohort consisted of 62,756 postmenopausal women who were cancer free at baseline in 1992 and who had complete information on height, weight, and HRT use. Most participants were white (98%), middle-aged, or elderly (mean age 62.7 ± 6.1 years), and educated (31% college graduates).

Case Ascertainment. We documented 1934 incident cases of breast cancer diagnosed between enrollment in 1992 and August 31, 1999. Of these, 1761 were identified by self-report on the 1997–1999 follow-up questionnaire or the 1999–2001 follow-up questionnaire and subsequently verified by obtaining medical records or through linkage with state registries when complete medical records could not be obtained (14). Eighty self-reported cases for which medical verification could not be obtained were also included because previous work linking cohort members to state cancer registries indicated that the ability of our respondents to accurately report a past diagnosis of cancer is high (sensitivity = 0.93, specificity > 0.99 for report of any cancer; Ref. 15). An additional 59 women identified using the National Death Index (16) for whom the death certificate listed breast cancer as a primary or contributory cause of death (International Classification of Diseases, Ninth Revision, codes 174.0–174.9) were included as interval deaths. Forty-four of the 59 interval deaths were subsequently verified. Finally, 34 cases of breast cancer were not reported as breast cancer but were identified during confirmation of another reported cancer.

Anthropometric Measures. On the baseline questionnaire in 1992, participants were asked to report their height, current weight, and weight at age 18 years. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). We used different categories for BMI at age 18 years and BMI in 1992. BMI at age 18 years was categorized into <18.5, 18.5 to <20.0 (the referent category), 20.0 to <22.0, 22.0 to <25.0, 25.0 to <27.0, and ≥27.0 kg/m^2. BMI in 1992 was categorized into <22.0 (the referent category), 22.0 to <25.0, 25.0 to <27.0, 27.0 to <30.0, 30.0 to <35.0 and ≥35.0 kg/m^2. Total adult weight change (from age 18 years to 1992) was calculated from reported weight at age 18 years and the current weight on the 1992 baseline questionnaire and categorized as weight maintenance (−5 to 5 pounds; the referent category), or weight gain of 6–10, 11–20, 21–30, 31–40, 41–50, 51–60, 61–70, and >70 pounds.

HRT Use. On the baseline questionnaire, women were asked, "Have you ever used female hormones (other than oral contraceptives) for relief of menopausal symptoms, irregular periods, or prevention of disease such as bone loss?" Women who responded "yes" were subsequently asked about current use, type and duration of hormone used longest, and type and duration of hormone used most recently. The types of hormones included oral, patch, and vaginal preparations. Use of both estrogen only and combination estrogen and progesterone formulations was determined. However, estrogen only and combination estrogen and progesterone users were combined in this analysis because the rate ratio (RR) estimates for BMI and weight gain were similar in the two groups.

Statistical Analysis. We calculated age-adjusted breast cancer incidence rates for categories of BMI and weight gain standardized to the age distribution of women in the CPS-II Nutrition Cohort.

Cox proportional hazards modeling was used to examine the association of BMI and weight gain with breast cancer incidence while adjusting for each other and for other potential risk factors. All models were stratified on single year of age at enrollment. Potential confounders included in multivariate models were age at menarche (<12, 12, 13, ≥14 years, or unknown), age at menopause (<45, 45 to <50, 50 to <54, ≥54 years, or unknown), number of live births (nulliparous, 1–2, ≥3 births), age at first live birth (nulliparous, <20, 20–24, 25–29, ≥30 years, or unknown), oral contraceptive use (ever, never, or unknown), family history of breast cancer in mother or sister (yes or no), personal history of breast cysts (yes or no), screening mammography (within the last year, not within the last year, or unknown), height (<63, 63 to <65, 65 to <67, ≥67 inches) education (less than high school, high school graduate, some college, or college graduate), recreational physical activity (at baseline; Ref. 17) as assessed by metabolic equivalents of energy expenditure units (METS) for exercise (Ref. 18; MET-h/week <7, 7 to <15, 15 to <25.5, ≥25.5, or unknown), alcohol use (none, <1, 1, or ≥1 drink/day, or unknown), and race (white, black, or other).

To test for effect modification by the potential confounders described above and by attained age, interaction terms between total adult weight gain (age 18 years to 1992), BMI in 1992, and BMI at age 18 years as categorical variables, and each of the other risk factors were included in multivariate models. We evaluated the significance of potential interactions and the proportional hazards assumption using the likelihood ratio test (19).

Results

The relationship between breast cancer risk and either BMI at baseline or weight gain since age 18 years was qualitatively different in women who reported current HRT use from those who reported no use or past use at baseline. We found strong statistical interaction between current HRT use and both BMI (P < 0.00001) and adult weight gain (P = 0.00008) but no evidence of statistical interaction between former and never HRT users with either BMI or weight gain. Consequently, all subsequent analyses separated current HRT users (n = 21,597; 752 cases) from former or never HRT users (n = 41,159; 1,182 cases). Former users made up 19% of the nonuser category, including 216 cases. Former users and never users were of similar age (average ages 64 and 63 years, respectively) and were slightly older than current HRT users (average age = 61 years). The median duration of use for former users was 2 years compared with 8 years for current users.

Baseline characteristics of the postmenopausal women in this cohort by HRT use and level of total weight change (age 18 years to age in 1992) are provided in Table 1. Compared with women who maintained their weight through adulthood, those

Table 1 Age-standardized baseline characteristics according to total weight gain (age 18 years to 1992) in Cancer Prevention Study-II Nutrition Survey cohort, 1992–1999

	Total adult weight gain (pounds)									
	Non-hormone replacement therapy users[a]					Current hormone replacement therapy users				
	−5 to 5	6–20	21–40	41–60	61+	−5 to 5	6–20	21–40	41–60	61+
n	4184	10571	13665	7726	5013	2768	6634	7123	3408	1664
Total weight gain[b]	0.9	14.0	30.8	50.2	79.9	1.0	13.7	30.4	49.8	77.7
Age in 1992	63.9	63.8	63.6	63.6	62.7	61.3	61.0	61.0	60.9	59.9
Body mass index 1992 (kg/m^2)[b,c]	21.5	23.1	25.6	28.8	33.8	21.2	22.7	25.2	28.3	33.2
Body mass index − Age 18 (kg/m^2)[b,c]	21.3	20.8	20.4	20.3	20.4	21.1	20.4	20.1	20.0	20.2
Age at menopause[b]	49.2	49.2	48.9	48.8	48.6	48.3	48.1	47.8	47.3	46.5
Recreational physical activity[d,e]										
METS 0 to <7	33.7	35.6	40.9	45.8	52.5	31.1	34.4	39.3	47.7	52.2
METS 7 to <15	31.6	32.8	32.2	31.2	28.6	32.8	35.0	33.6	31.4	30.6
METS 15 to <25.5	18.9	17.7	15.8	14.1	11.3	18.8	16.8	16.3	12.5	10.3
METS >25.5	14.2	12.6	9.6	7.3	5.8	16.4	12.9	9.7	7.2	5.5
Smoking[d]										
Never smoker	51.2	54.3	56.4	58.9	59.5	48.9	52.2	53.6	54.9	57.3
Current smoker	13.1	10.7	9.0	7.0	5.5	9.3	7.4	6.1	4.9	3.4
Former smoker	34.6	34.0	33.5	32.9	33.5	40.9	39.3	39.4	39.3	38.2
Alcohol use[d]										
Nondrinker	41.8	42.6	46.7	52.4	59.7	35.7	36.6	43.4	48.4	57.0
<1 drink/day	37.3	39.0	36.9	34.1	28.8	42.7	44.8	41.7	40.3	33.8
1 drink/day	10.7	9.1	7.2	5.0	3.0	13.1	10.5	7.3	4.8	3.6
>1 drink/day	6.0	5.4	4.6	3.7	2.7	5.6	5.8	4.9	3.3	2.3

[a] Combined former and never users.
[b] Means standardized to the age distribution of the analytic cohort.
[c] Body mass index [weight/(height^2)].
[d] Percentages adjusted to the age distribution of the analytic cohort.
[e] Physical activity as assessed by metabolic equivalents for energy expenditure unit (METS) for exercise.

with greatest weight gain had slightly lower BMI at age 18 years, earlier age at menopause, and less physical activity. Over one-half of women who gained >60 pounds in adulthood reported doing <7 h of physical activity/week compared with about one-third of women who had maintained their weight from age 18 years through adulthood. Women who maintained their weight through adulthood were more likely to be current smokers and consumed more alcohol than women who reported adult weight gain.

Table 2 shows age-standardized rates and RRs for incident breast cancer by BMI in 1992 stratified by HRT status. Among women of normal weight (BMI < 25.0 kg/m^2), age-standardized rates of breast cancer were higher in current HRT users than non-HRT users. The age-standardized rates increased among non-HRT users with increasing BMI, and BMI was strongly associated with increased postmenopausal breast cancer incidence when controlling for multiple risk factors and no other weight-related exposures (P for trend < 0.0001). However, when total adult weight gain was added to the multivariate model, the increased risk associated with BMI was attenuated and no longer an independent predictor of risk (P for trend = 0.11). Among women who were using HRT at baseline, increasing BMI was not associated with increased risk of breast cancer. Instead, the age-standardized rates and RRs declined with increasing BMI. This trend reached statistical significance only after adult weight gain was included in the multivariate model (P for trend = 0.002).

Total adult weight gain from age 18 years to 1992 was more strongly associated with breast cancer risk (Table 3) than was recent BMI (Table 2). As with BMI, the positive association was observed only among women not using HRT. Furthermore, the association between adult weight gain and breast cancer risk remained statistically significant in analyses controlling for current BMI among non-HRT users (Table 3). Weight gain of 21–30 pounds was associated with an approximate 40% increase in incidence (RR = 1.42, 95% confidence interval 1.10–1.83), and risk was doubled among women gaining >70 pounds during adulthood compared with women with a ≤5 pounds fluctuation in their weight since age 18 years. Adult weight gain was not associated with increased risk of breast cancer among women using HRT at baseline, nor was there any suggestion of a decreased risk (P for trend = 0.53, Table 3). Among women who had gained ≤20 pounds in adulthood, age-standardized rates were markedly higher in current HRT users than in nonusers, reflecting the increased risk of breast cancer associated with HRT among leaner women (9).

We found no overall association of BMI at age 18 years and postmenopausal breast cancer in multivariate adjusted models (P for trend = 0.83). Rates were similar between women with BMI at age 18 years of ≥27.0 kg/m^2 and those with BMI at age 18 years between 18.5 and 20.0 kg/m^2 (RR 0.95; 95% confidence interval 0.67–1.35). Including adult weight gain in the multivariate model did not change the RR estimates. We also examined whether the adverse effect of total weight gain in women from age 18 years to 1992 on postmenopausal breast cancer risk was influenced by the BMI at age 18 years. In stratified analysis, total adult weight gain among non-HRT users increased postmenopausal breast cancer risk, regardless of BMI at age 18 years (data not shown).

With the exception of HRT use, we found no statistically significant interactions between total weight gain and other covariates included in our multivariate models. We also observed no evidence of effect modification by attained age.

Discussion

In this large prospective study, total adult weight gain was strongly associated with breast cancer incidence in postmeno-

Table 2 Rate ratios (RR) of breast cancer incidence according to recent body mass index (BMI) in 1992 stratified by hormone replacement therapy (HRT) use in 1992 in the Cancer Prevention Study-II Nutrition Cohort, 1992–1999

	BMI 1992 (kg/m^2)						*P*
	<22.0	22.0 to <25.0	25.0 to <27.0	27.0 to <30	30.0 to <35.0	≥35.0	
Non-HRT users							
No. cases	187	304	182	233	204	72	
Age standardized rate	402.5	404.8	412.7	520.0	623.5	571.7	
Age-adjusted RR[a]	1.00	1.03	1.05	1.29	1.56	1.44	
95% CI		0.86–1.23	0.85–1.28	1.07–1.57	1.28–1.90	1.10–1.89	
Multivariate RR[b]	1.00	1.06	1.11	1.41	1.74	1.61	<0.0001
95% CI		0.88–1.27	0.91–1.36	1.16–1.71	1.42–2.13	1.22–2.12	
Multivariate RR[c]	1.00	1.00	1.00	1.22	1.35	1.08	0.11
95% CI		0.83–1.22	0.80–1.26	0.97–1.54	1.04–1.76	0.75–1.55	
Current HRT users							
No. cases	223	253	102	101	51	22	
Age standardized rate	697.6	587.6	472.3	577.9	456.8	621.1	
Age-adjusted RR[a]	1.00	0.85	0.69	0.78	0.64	0.96	
95% CI		0.71–1.02	0.55–0.87	0.62–0.99	0.47–0.87	0.62–1.49	
Multivariate RR[b]	1.00	0.89	0.74	0.86	0.72	1.09	0.12
95% CI		0.74–1.06	0.59–0.94	0.68–1.09	0.53–0.98	0.70–1.69	
Multivariate RR[c]	1.00	0.84	0.67	0.74	0.56	0.73	0.002
95% CI		0.69–1.01	0.52–0.87	0.56–0.97	0.40–0.80	0.45–1.21	

[a] RR adjusted for age at interview.
[b] RR adjusted for age at interview, age at menarche, age at menopause, number of live births, age at first live birth, oral contraceptive use, family history of breast cancer, history of breast cysts, history of mammography, height, education, physical activity, alcohol use, and race.
[c] RR adjusted for total adult weight gain (age 18 years to 1992) in addition to all covariates listed above.

pausal women who were not taking HRT. Among women using HRT, we found no increased risk associated with adult weight gain. After accounting for weight gain, neither recent BMI nor BMI at age 18 years predicted risk.

Most (1, 4, 7–10) but not all (11–13) previous studies have found that HRT use modifies the effect of body weight on risk of breast cancer. Our results closely parallel those recently published from the Women's Health Initiative Observational Study (8) and from a large population based case-control study (10) that also demonstrated strong effect modification of the association between breast cancer and body size by HRT use. In these two studies, risk of breast cancer was clearly elevated only among never HRT users with high adult BMI and weight gain. In contrast, two other recent studies, one large population-based case-control study (12) and one cohort study (11), did not observe statistically significant interaction between weight or BMI and HRT use on breast cancer risk, although risk was attenuated among hormone users in both studies.

That the association between weight gain and breast cancer in most studies is limited to women who do not have an

Table 3 Rate ratios (RR) of breast cancer incidence according to weight gain from age 18 years to 1992 stratified by hormone replacement therapy (HRT) use in 1992 in the Cancer Prevention Study-II Nutrition Cohort, 1992–1999

	Adult weight gain (in pounds) from age 18 years to 1992									*P*
	−5 to 5	6 to 10	11 to 20	21 to 30	31 to 40	41 to 50	51 to 60	61 to 70	71+	
Non-HRT users										
No. cases	96	78	170	218	169	153	92	81	125	
Age-standardized rate	371.4	378.7	375.1	472.4	432.1	546.0	475.2	640.2	708.7	
Age-adjusted RR[a]	1.00	1.06	1.01	1.30	1.18	1.46	1.30	1.80	1.92	
95% CI		0.79–1.43	0.79–1.30	1.02–1.65	0.92–1.52	1.13–1.89	0.98–1.73	1.34–2.43	1.47–2.51	
Multivariate RR[b]	1.00	1.07	1.03	1.34	1.24	1.55	1.39	1.96	2.08	<0.0001
95% CI		0.80–1.45	0.80–1.32	1.05–1.70	0.96–1.59	1.20–2.01	1.04–1.85	1.46–2.64	1.59–2.73	
Multivariate RR[c]	1.00	1.09	1.07	1.42	1.31	1.60	1.39	1.94	2.13	<0.0001
95% CI		0.81–1.47	0.83–1.38	1.10–1.83	0.99–1.72	1.20–2.13	1.00–1.93	1.37–2.75	1.50–3.01	
Current HRT users										
No. cases	109	81	173	125	109	65	37	19	34	
Age-standardized rate	636.7	608.9	649.9	548.3	532.7	528.8	521.7	486.2	693.1	
Age-adjusted RR[a]	1.00	1.00	0.98	0.80	0.90	0.79	0.74	0.68	1.00	
95% CI		0.75–1.33	0.77–1.25	0.62–1.04	0.69–1.17	0.58–1.08	0.51–1.08	0.42–1.10	0.68–1.47	
Multivariate RR[b]	1.00	1.01	1.00	0.84	0.96	0.85	0.82	0.73	1.11	0.35
95% CI		0.76–1.34	0.79–1.28	0.65–1.09	0.73–1.25	0.62–1.16	0.57–1.20	0.45–1.19	0.75–1.64	
Multivariate RR[c]	1.00	1.02	1.04	0.89	1.02	0.88	0.83	0.72	1.13	0.53
95% CI		0.77–1.36	0.81–1.33	0.68–1.17	0.76–1.36	0.63–1.24	0.55–1.25	0.43–1.21	0.72–1.76	

[a] RR adjusted for age at interview.
[b] RR adjusted for age at interview, age at menarche, age at menopause, number of live births, age at first live birth, oral contraceptive use, family history of breast cancer, history of breast cysts, history of mammography, height, education, physical activity, alcohol use, and race.
[c] RR adjusted for BMI in 1992 in addition to all covariates listed above.

exogenous source of hormones suggests that adiposity increases breast cancer risk entirely through its estrogenic effects. Lean women who are not using HRT have the lowest levels of circulating estrogens and the lowest risk of breast cancer. In HRT users, both lean and heavy women have high levels of circulating estrogens by virtue of their HRT use; against this background, the estrogenic effect of obesity is imperceptible and does not increase risk further.

In our study, BMI reported at baseline was highly correlated with total adult weight gain ($r = 0.82$). Despite this high correlation, adult weight gain was a much stronger predictor of breast cancer risk than was BMI when both variables were simultaneously included in the regression model. BMI reflects both lean body mass and adipose, whereas weight gain throughout adult life reflects primarily the accumulation of peripheral adipose tissue. Thus, weight gain may be a more precise measure of the relevant exposure (*e.g.*, adipose) than BMI. Other studies that have examined both adult weight gain and adult BMI in the same study population have found weight gain to be an equivalent (12, 20) or stronger (7, 21–23) predictor of postmenopausal breast cancer risk than recent BMI. However, at least one study reported that recent BMI was a stronger predictor of postmenopausal breast cancer risk than adult weight gain when both were included in the regression model (8).

We did not expect to find decreasing risk of breast cancer with increasing BMI among women who are currently using HRT, although this is not entirely inconsistent with previous studies (8, 10). Given that we did not observe a similar association with adult weight gain, we speculate that this finding may be due to chance.

Although a modest reduction in postmenopausal breast cancer risk has been observed with obesity in early adulthood (18–20 years) in most prospective studies (7, 8, 13, 24, 25), we found no association between BMI at age 18 years and postmenopausal breast cancer. Although we did not have sufficient power to examine the effects of obesity at age 18 years (0.5% had BMI > 30 kg/m^2 at age 18 years), we saw no increased or decreased risk of postmenopausal breast cancer among women with BMI > 27 kg/m^2 at age 18 years.

The primary strength of this study is its large, prospective design that gives us the ability to examine current HRT users separately from nonusers with adequate statistical power. The primary limitation of our study is the reliance on self-reported height and weight at only two time periods that spanned, on average, 45 years. Serial measures of weight from several other points in adulthood would have strengthened this study. In particular, information on weight at menopause would have allowed us to examine the effects of pre- and postmenopausal weight gain on breast cancer risk.

In summary, HRT use and the accumulation of adipose tissue are two important contributors to postmenopausal breast cancer risk. In our study, the association between adult weight gain and breast cancer risk was limited to women not currently taking HRT, and adult weight gain was a stronger predictor of risk than BMI. These data underscore the importance of examining breast cancer risk factors separately by HRT use because the effect of other risk factors, especially those that operate via estrogenic pathways, may be attenuated or obscured among women taking HRT.

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