Unopposed Estrogen Therapy and the Risk of Invasive Breast Cancer

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Background: Although short-term unopposed estrogen use does not seem to increase breast cancer risk, the effect of longer-term estrogen use remains unclear. We sought to assess the relationship between longer-term use of unopposed estrogen and the risk of invasive breast cancer over an extended follow-up period.

Methods: Within the Nurses' Health Study, a prospective cohort study, we observed 11 508 postmenopausal women who had a hysterectomy and reported information on estrogen use at baseline (1980). The study population was expanded every 2 years to include women who subsequently became postmenopausal and had a hysterectomy, so that 28 835 women were included in the final follow-up period (2000-2002). Estrogen use was assessed from self-reported data on biennial questionnaires. The main outcome was invasive breast cancer.

Results: A total of 934 invasive breast cancers were included in the analysis. Breast cancer risk increased with duration of unopposed estrogen use among longer-term users with the highest risk seen in cancers positive for estrogen receptor (ER+) and progesterone receptor (PR+). The multivariate relative risks (RRs) and 95% confidence intervals (CIs) for breast cancer with current use of unopposed estrogen for less than 5 years, 5 to 9.9 years, 10 to 14.9 years, 15 to 19.9 years, and 20 years or longer were, respectively, 0.96 (95% CI, 0.75-1.22), 0.90 (95% CI, 0.73-1.12), 1.06 (95% CI, 0.87-1.30), 1.18 (95% CI, 0.95-1.48), and 1.42 (95% CI, 1.13-1.77) (*P* for trend <.001). The risk of ER+/PR+ breast cancers was noted to be statistically significant after 15 years of current use (RR, 1.48; 95% CI, 1.05-2.07).

Conclusion: Users of unopposed estrogen were at increased risk of breast cancer but only after longer-term use.

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MULTIPLE OBSERVATIONAL studies have shown that postmenopausal hormone therapy (PMH) increases the risk of breast cancer, although much of the increase has been attributed to combination estrogen and progestin.[1,2] The Women's Health Initiative (WHI),[3] a large randomized trial evaluating the effect of PMH on the risk of chronic disease, recently released their results on the use of unopposed estrogen therapy (ET). With an average follow-up of 6.8 years, the hazard ratio for breast cancer among women randomized to ET was 0.77 (adjusted confidence interval [CI], 0.59-1.01) compared with placebo. However, uncertainty remains regarding the effect of longer-term ET on breast cancer risk and whether the effect varies by factors such as age or body mass index (BMI). Therefore, we have evaluated the association of longer-term ET and breast cancer in a large cohort of postmenopausal women.

METHODS

The Nurses' Health Study (NHS)[4] cohort was established in 1976, when 121 700 female registered nurses aged 30 to 55 years completed a baseline questionnaire including items on risk factors for cancer and cardiovascular disease. Every 2 years, follow-up questionnaires have been mailed to update risk factor information and disease development. The institutional review board of the Brigham and Women's Hospital approved the study protocol. The NHS population was predominantly white (84.1% white, 1.6% African American, 0.7% Hispanic, 0.9% Asian, and 12.7% other or unknown), reflecting the demographics of registered nurses in the United States in 1976. Participation has been extremely high with 6% of person-time lost to follow-up. Because we routinely searched the National Death Index for nonresponders, mortality identification for the entire cohort was at least 98%.[5] To control for risk factors including alcohol consumption, our analysis was limited to 98 462 postmenopausal women who completed the baseline dietary questionnaire in 1980. Dietary ques-

tionnaires were updated in 1984, 1986, 1988, 1990, 1994, and 1998.

The analysis was limited to postmenopausal women who had a hysterectomy. Women who did not have a hysterectomy but used unopposed estrogen were excluded from the main analysis because for most of the follow-up period, the standard of care was to add progestin for a woman with an intact uterus. A woman began contributing person-time from the time she first reported hysterectomy with bilateral oophorectomy. Women who underwent natural menopause and subsequently had a hysterectomy began contributing person-time from the time of surgery. Women who reported that their menses ended after hysterectomy without bilateral oophorectomy were considered hormonally premenopausal and were thus excluded from the analysis until the age at which natural menopause had occurred in 90% of the cohort (54 years for current cigarette smokers and 56 years for nonsmokers), at which time they were considered postmenopausal and began contributing person-time. Self-report of natural menopause and extent of ovarian surgery has been shown to be highly accurate and reproducible in this cohort.[6] Menopausal status was updated every 2 years and the cohort was expanded to include women who subsequently underwent a hysterectomy and became menopausal. For the main analysis, 11 508 women met these criteria and entered the initial follow-up period (1980-1982); 28 835 women were included in the last follow-up period (2000-2002). In a secondary analysis, the NHS population was analyzed using the same eligibility criteria as the WHI[3]: each woman who had a hysterectomy before age 50 years began contributing person-time to the analysis beginning from the time that she turned 50, and women who had a hysterectomy after age 50 years began contributing person-time at the time of the hysterectomy.

We defined ET as the use of oral unopposed conjugated estrogen therapy. Most women in this cohort who had a hysterectomy used ET. The few women who used other types of PMH (eg, other types of estrogen) were analyzed separately. Because the effect of ET on breast cancer risk is stronger with current use, past ET users were considered separately from current users and will be reported in a future report. The methodologic issues regarding reasons for stopping ET (eg, diagnosis of breast cancer) among past users require different analytic approaches that would detract from the focus of this study on the effect of current ET use. Current ET users were then categorized by duration of use. Use of PMH (never, past, or current) reported on a questionnaire was used prospectively to define the subsequent 2-year period. Women missing information on PMH use on a specific questionnaire were excluded from the analysis for the subsequent 2-year period but reentered the analysis the next time PMH information was complete. Approximately 15% of person-time within the study population was excluded due to missing information on PMH exposure.

The primary end point was the diagnosis of invasive breast cancer. Carcinomas in situ were censored in the main analysis. On each questionnaire, we asked whether breast cancer had been diagnosed and, if so, the date of diagnosis. We asked all women who reported breast cancer (or next of kin for those who died) for permission to review the pertinent medical records for confirmation. We also searched the National Death Index for breast cancer deaths among women who did not respond to the questionnaires, which accounted for less than 1% of confirmed breast cancer cases. Pathology reports or cancer registry data were obtained in 95% of the cases. Physicians without data on the subjects' ET use abstracted the hormone receptor information from the records. Tumors classified as borderline positive for estrogen receptor (ER) or progesterone receptor (PR) were considered to be ER+ or PR+ in the analyses. Tumors with mixed ER/PR status (eg, ER+/PR– and ER–/PR+) were excluded from the analyses by ER/PR status where we included only ER+/PR+ and ER–/PR– tumors. About 84% of the cancers with pathology reports had both ER and PR status. Data on tumor size and stage will be presented in a separate report. Follow-up of the study cohort for identification of breast cancer was estimated to be 95% complete.

The follow-up period for this analysis began in 1980 and terminated with the diagnosis of any type of cancer (including in situ breast cancer), death, or June 1, 2002, whichever came first. Follow-up was censored at the time of in situ disease, since the main risk of breast cancer for those subjects would be driven most strongly by the in situ disease rather than other exogenous or endogenous factors, and the effect of exogenous or endogenous factors on breast cancer recurrence may differ from their effects on breast cancer incidence. Use of ET at the time of each biennial questionnaire was used to define exposure prospectively during the subsequent 2-year period. Cox proportional hazards models were used to compute age-adjusted and multivariate-adjusted relative risks (RRs) and 95% CIs. Covariates in the model were chosen because of clinical relevance and/or potential for confounding within our cohort and included age, age at menopause, age at menarche, age at first birth and parity, BMI (calculated as weight in kilograms divided by the square of height in meters), family history of breast cancer in a first-degree relative, average daily alcohol consumption, questionnaire cycle, and history of benign breast disease. Interactions were evaluated using a Wald test with a cross-product interaction term. Tests for trend for duration of ET use were calculated using a continuous variable for ET duration. All analyses were performed using SAS software, version 8.0 (SAS Inc, Cary, NC). A 2-sided *P* value of less than .05 was used to determine statistical significance. To determine whether higher rates of screening could contribute to an increased breast cancer detection rate among current ET users compared with never users, we also performed analyses limited to women who had a recent screening mammogram or clinical breast examination.

RESULTS

Table 1 lists the demographic characteristics of the study population in 1990, which was chosen as a representative point since the population for analysis was expanded from 1980 to include women who subsequently became postmenopausal. In 1990, breast cancer risk factors varied both by use or never use of ET as well as duration of use. In several categories, including age and age at menopause, women who never used ET were similar to those who used ET for longer than 10 years but differed from those who currently used ET for less than 10 years. Never users differed from all current ET users in that they were less likely to have history of benign breast disease or to have undergone screening within the past 2 years and more likely to have a family history of breast cancer. Women who used ET for longer than 10 years were thinner and more likely than other women to have had a bilateral salphingo-oophorectomy, which would be associated with a decreased risk of breast cancer, but were more likely to be nulliparous. Age at menarche and alcohol consumption were similar across the groups.

Tables 2, **3**, and **4** list the multivariate RRs for current ET users compared with women who never used any type of PMH. A total of 934 invasive breast cancers (226

Table 1. Demographic Characteristics of the Study Population in 1990*

Characteristic	Never Used ET (n = 3288)	Duration of Current ET Use in 1990, y		
		<5 (n = 3255)	5-10 (n = 5006)	>10 (n = 4492)
Mean age, y	61.7	55.9	58.1	61.5
Mean age at menarche, y	11.8	12.4	12.4	12.4
Mean age at menopause, y	41.3	45.9	44.8	40.4
Type of uterine surgery				
Before natural menopause—hysterectomy with bilateral salpingo-oophorectomy	30.9	36.3	49.1	65.8
Before natural menopause—hysterectomy with or without unilateral salpingo-oophorectomy	52.7	46.6	37.3	29.5
After menopause—hysterectomy with any type of ovarian surgery	11.7	16.7	13.0	4.1
Nulliparous	5.6	4.6	6.5	10.1
BMI ≥25	58.0	47.3	46.1	43.0
History of benign breast disease	11.3	17.7	18.0	20.4
Family history of breast cancer	10.2	8.5	8.1	8.5
Mammogram and/or clinical breast examination in past 2 y	60.8	79.1	78.1	78.3
Alcohol consumption, g/d				
Mean	4.1	4.6	4.5	5.1
Median	0.9	1.0	1.1	0.9

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); ET, unopposed estrogen therapy.
*Unless otherwise noted, data are presented as percentage of study subjects.

Table 2. Risk of Invasive Breast Cancer by Duration of ET Use Among All Postmenopausal Women Who Had Undergone Hysterectomy and Those With ER+/PR+ Cancers Only*

ET Use and Duration, y	All Postmenopausal Women Who Had Undergone Hysterectomy				ER+/PR+ Cancers Only			
	All		Screened Cohort†		All		Screened Cohort†	
	Cases	Risk	Cases	Risk	Cases	Risk	Cases	Risk
Never	226	1.00	104	1.00	87	1.00	48	1.00
Current								
<5	99	0.96 (0.75-1.22)	59	1.06 (0.76-1.47)	38	1.00 (0.67-1.49)	26	1.04 (0.64-1.70)
5-9.9	145	0.90 (0.73-1.12)	95	0.91 (0.68-1.21)	70	1.19 (0.86-1.66)	50	1.08 (0.72-1.62)
10-14.9	190	1.06 (0.87-1.30)	141	1.11 (0.85-1.44)	85	1.27 (0.93-1.73)	77	1.29 (0.89-1.86)
15-19.9	129	1.18 (0.95-1.48)	95	1.19 (0.89-1.58)	61	1.48 (1.05-2.07)	58	1.50 (1.02-2.21)
≥20	145	1.42 (1.13-1.77)	127	1.58 (1.20-2.07)	69	1.73 (1.24-2.43)	74	1.83 (1.25-2.68)
P for trend for current use		<.001		<.001		<.001		<.001

Abbreviations: BMI, body mass index; CI, confidence interval; ER+/PR+, positive for both estrogen and progesterone receptors; ET, unopposed estrogen therapy.
*All cases are reported as number of cases; risks are reported as multivariate relative risk (95% CI), controlled for age (continuous), age at menopause (continuous), age at menarche (continuous), BMI (quintiles), history of benign breast disease (yes or no), family history of breast cancer in first-degree relative (yes or no), average daily alcohol consumption (0, 0.5-5, 5-10, 10-20, or ≥20 g/d), parity/age at first birth (nulliparous; 1-2 children and age at first birth ≤22 years; 1-2 children and age at first birth 23-25 years; 1-2 children and age at first birth >25 years; ≥3 children and age at first birth ≤22 years; ≥3 children and age at first birth 23-25 years; ≥3 children and age at 1st birth >25 years).
†Screened cohort defined as those women starting in 1988 who reported either a screening mammogram or clinical breast examination in the previous 2 years. All cases before 1988 are excluded.

among women who never used hormones and 708 among current ET users) were diagnosed during 335 296 person-years of follow-up among postmenopausal women who had a hysterectomy. Only results for never and current users are reported. As stated in the "Methods" section, we do not report results for 351 cases among past users, which will be presented in a separate report. Among current ET users, there was a linear increase in breast cancer risk with increasing duration of ET use (*P* for trend <.001), although the relative risk did not become statistically significant until current use exceeded 20 years (RR, 1.42; 95% CI, 1.13-1.77) (Table 2). For women who currently used ET for less than 10 years, there did not seem to be an increased risk of breast cancer: RR, 0.96 (95% CI, 0.75-1.22) for less than 5 years and RR, 0.90; (95% CI, 0.73-1.12) for 5 to 9.9 years.

Table 3. Breast Cancer Risk by Duration of ET Use Stratified by BMI*

ET Use and Duration, y	BMI <25		BMI ≥25	
	Cases	Risk	Cases	Risk
Never	78	1.00	148	1.00
Current				
<5	45	1.03 (0.69-1.52)	54	0.96 (0.69-1.33)
5-9.9	78	1.17 (0.84-1.62)	66	0.74 (0.55-1.00)
10-14.9	94	1.18 (0.86-1.62)	94	0.97 (0.74-1.28)
15-19.9	66	1.36 (0.97-1.92)	63	1.11 (0.82-1.51)
≥20	80	1.77 (1.26-2.48)	65	1.25 (0.91-1.71)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); ET, unopposed estrogen therapy.
*All cases are reported as number of cases; risks are reported as multivariate relative risk (95% confidence interval), controlled for age (continuous), age at menopause (continuous), age at menarche (continuous), BMI (quintiles), history of benign breast disease (yes or no), family history of breast cancer in first-degree relative (yes or no), average daily alcohol consumption (0, 0.5-5, 5-10, 10-20, or ≥20 g/d), parity/age at first birth (nulliparous; 1-2 children and age at first birth ≤22 years; 1-2 children and age at first birth 23-25 years; 1-2 children and age at first birth >25 years; ≥3 children and age at first birth ≤22 years; ≥3 children and age at first birth 23-25 years; ≥3 children and age at 1st birth >25 years). $P = .10$ for interaction of BMI and duration of estrogen use.

Table 4. Risk of Invasive Breast Cancer by Duration of ET Use Among Women 50 Years or Older*

ET Use and Duration, y	All Women		Bilateral Oophorectomy†		Unilateral or No Oophorectomy†	
	Cases	Risk	Cases	Risk	Cases	Risk
Never	270	1.00	55	1.00	213	1.00
Current						
<5	114	0.99 (0.79-1.24)	28	0.71 (0.44-1.16)	85	1.07 (0.82-1.39)
5-9.9	148	0.87 (0.71-1.07)	54	0.83 (0.56-1.24)	80	0.81 (0.62-1.06)
10-14.9	191	1.05 (0.87-1.28)	81	1.15 (0.80-1.65)	96	0.99 (0.77-1.27)
15-19.9	130	1.19 (0.96-1.48)	67	1.28 (0.88-1.88)	58	1.18 (0.87-1.60)
≥20	145	1.41 (1.13-1.76)	80	1.71 (1.16-2.53)	65	1.41 (1.04-1.92)
P value for trend for current use		<.001		<.001		.04

Abbreviations: BMI, body mass index; CI, confidence interval; ET, unopposed estrogen therapy.
*All cases are reported as number of cases; risks are reported as multivariate relative risk (95% CI), controlled for age (continuous), age at menopause (continuous), age at menarche (continuous), BMI (quintiles), history of benign breast disease (yes or no), family history of breast cancer in first-degree relative (yes or no), average daily alcohol consumption (0, 0.5-5, 5-10, 10-20, or ≥20 g/d), parity/age at first birth (nulliparous; 1-2 children and age at first birth ≤22 years; 1-2 children and age at first birth 23-25 years; 1-2 children and age at first birth >25 years; ≥3 children and age at first birth ≤22 years; ≥3 children and age at first birth 23-25 years; ≥3 children and age at 1st birth >25 years).
†Thirty-six women whose extent of ovarian surgery was unknown were excluded from the analysis by extent of ovarian surgery.

Analyses were repeated limited to women who reported a mammogram or clinical breast examination within the past 2 years (Table 2). Data on screening were only available beginning with the 1988 questionnaire, so the analyses began in 1988 for the screened cohort. Results were similar, with a slightly stronger association (RR, 1.58; 95% CI, 1.20-2.07) for women who currently used ET for 20 years or longer.

As expected, the association with ET seemed stronger for ER+/PR+ cancers (RR, 1.73; 95% CI, 1.24-2.43) among current users for 20 years or longer (Table 2). The risk for ER+/PR+ cancers was elevated slightly sooner than for all breast cancers, although this could not be differentiated statistically. Associations with ER+/PR+ cancers were stronger among women who had a recent screening mammogram and/or clinical breast examination.

Since the influence of ET may be greater in leaner women who have lower endogenous estrogen levels than heavier women, analyses were repeated stratifying by BMI (Table 3). As hypothesized, the association with ET was seen mainly in postmenopausal women with BMI lower than 25, with an RR of 1.77 (95% CI, 1.26-2.48) found for current use for 20 years or longer compared with 1.25 (95% CI, 0.91-1.71) among women with BMI of 25 or higher who used ET for 20 years or longer, although the difference did not reach statistical significance ($P=.10$). Of note, the lower risk seen with 5 to 9.9 current years of ET use seemed to be limited to women with a BMI of 25 or higher (RR, 0.74; 95% CI, 0.55-1.00).

Current ET users were also more likely to have had a bilateral salpingo-oophorectomy and an earlier age at menopause and therefore may have lowered their breast cancer risk compared with never users. In analyses limited to women who underwent a hysterectomy with bilateral salpingo-oophorectomy, results were similar (Table 4).

Analysis was performed according to dose of estrogen, which was available for about 90% of women who reported current ET use. For this analysis, we excluded ET users whose estrogen dose was unknown. Power was limited by few women using 0.3 mg or at least 1.25 mg.

Nevertheless, there did not seem to be a strong dose-response relationship (data not shown).

To simulate the eligibility criteria of the WHI,[3] analyses were performed limited to women who were at least 50 years old and had undergone a hysterectomy, regardless of menopausal status (Table 4). Results were similar to those among postmenopausal women of all age groups. Consistent with the WHI, there was a statistically nonsignificant decrease in breast cancer risk among current ET users for 5 to 9.9 years (RR, 0.87; 95% CI, 0.71-1.07). Analyses were repeated limited to women older than 60 years and women who initiated ET after age 50 years with similar results (data not shown).

COMMENT

Among women who used ET for less than 20 years, we did not observe a statistically significant increased risk of breast cancer overall. However, breast cancer risk was significantly elevated with longer durations of use, primarily for ER+/PR+ cancers. We also observed a stronger linear increase in risk of ER+/PR+ cancers with increasing duration of ET use. This is consistent with our previous findings and other studies showing that PMH was associated more strongly with the development of ER+/PR+ than ER–/PR– cancers.[7-13] Our research group has previously published on the relation between PMH and breast cancer within the NHS, but most of these analyses grouped together ET and combination regimens of estrogen and progesterone.[14,15] In 2000, our group published a log incidence model for cumulative lifetime breast cancer risk and estimated a 23% (95% CI, 6%-42%) increase in the cumulative incidence rate with 10 years of unopposed estrogen use, consistent with our current results.[16] At that time, we did not have sufficient power to investigate longer durations of ET use.

We did not observe a clear effect of dose but were limited by few women who used doses other than 0.625 mg. Many studies have evaluated the dose of estrogen in relation to changes in endometrial hyperplasia, lipids, and bone density. Rates of endometrial hyperplasia seemed lower with lower doses of estrogens,[17] but endometrial cancer risks were unchanged.[18,19] Improvements in bone density occurred with lower doses of estrogen, but the gain was greater with higher doses of estrogen.[20-22] The Million Women Study[2] did not observe a significant difference in breast cancer risk between women who used doses of 0.625 mg or smaller compared with those who used doses larger than 0.625 mg. However, they combined women who used the standard 0.625-mg dose with those who used lower doses, so the effect of conjugated equine estrogen doses other than 0.625 mg on breast cancer risk is still not known.

As in the WHI,[3] we also observed a statistically nonsignificant decrease in risk among women who currently used ET for 5 to 9.9 years limited to women with BMI of 25 or higher. It is possible that the lower risk was due to the protective effect of a bilateral oophorectomy and earlier age at menopause among current ET users or due to chance alone. The similarity between our results, the WHI (which had similar distributions for bilateral oophorectomy and ages at menopause between the placebo and ET arms), and another large prospective study[11] suggests that this possibility should be explored further.

The NHS is an observational study, and PMH use was not randomly assigned. Although current users were younger, thinner, and less likely to have a family history of breast cancer then never users, these factors would have led to a decreased risk of breast cancer in the current user group rather than the increased risk we observed. Higher mammography screening rates are also unlikely to explain the difference, since mammography rates were similar among the groups, and results were similar when limited to women undergoing regular screening. Given that all of the subjects were registered nurses, there would be less variation in socioeconomic status to cause significant confounding. Women who took ET for longer than 10 years may represent a somewhat different population, but their mammography patterns were similar to shorter-term current users and they were much more likely to have had a bilateral oophorectomy, neither of which would be associated with an increased risk of breast cancer. However, there could be uncontrolled confounders that separate out the longer-term users, although we controlled for most of the known breast cancer risk factors. Longer-term users were also more likely to have a history of benign breast disease, which was controlled for in the model, although there may be residual confounding by the type of benign breast disease. Finally, the increase in breast cancer risk with increasing duration of ET suggests a true biologic relationship.

Our results for current ET users for less than 10 years were consistent with those of the randomized WHI,[3] which had an average follow-up of 6.8 years.[3] Since treatment has been discontinued, the WHI will not be able to evaluate the effect of longer-term ET use on disease risk and we will need to rely on observational studies to evaluate this.

In conclusion, we found that ET was associated with an increased risk of breast cancer with longer-term use. This association seemed stronger in leaner women and for ER+/PR+ cancers. Although current use of ET for less than 10 years was not associated with a statistically significant increase in breast cancer risk, the WHI has shown an increased risk of stroke and deep-vein thrombosis in the same time period.[3] Women who take ET for prevention or treatment of osteoporosis typically require longer-term treatment and should thus explore other options, given the increased risk of breast cancer with longer-term use.

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