## Original Contribution

# Hormone Therapy and Young-Onset Breast Cancer

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Estrogen plus progestin hormone therapy (HT) is associated with an increased risk of postmenopausal breast cancer, but few studies have examined the impact of HT use on the risk of breast cancer in younger women. We assessed the association between estrogen plus progestin HT or unopposed estrogen HT and young-onset breast cancer using data from the Two Sister Study (2008–2010), a sister-matched study of 1,419 cases diagnosed with breast cancer before the age of 50 years and 1,665 controls. We assessed exposures up to a family-specific index age to ensure comparable opportunities for exposures and used propensity scores to control for birth cohort effects on HT use. Ever HT use was uncommon (7% and 11% in cases and controls, respectively). Use of estrogen plus progestin was not associated with an increased risk of young-onset breast cancer (odds ratio = 0.80, 95% confidence interval: 0.41, 1.59). Unopposed estrogen use was inversely associated with the risk of young-onset breast cancer (odds ratio = 0.58, 95% confidence interval: 0.34, 0.99). Duration of use, age at first use, and recency of use did not modify these associations.

hormone therapy; propensity score; young-onset breast cancer

Abbreviations: CI, confidence interval; E-HT, unopposed estrogen hormone therapy; EP-HT, combined estrogen and progestin hormone therapy; HT, hormone therapy; P-HT, progestin alone hormone therapy; WHI, Women's Health Initiative.

Breast cancer is the leading contributor to cancer incidence in women in the United States, with an estimated 232,340 new invasive and 64,640 new in situ breast cancer cases in 2013 (1). Although incidence increases with age, approximately 25% of diagnoses occur before the age of 50 years (2).

There are some etiologic and clinical differences between young-onset and older-onset breast cancer. For example, obesity is associated with reduced risk before but not after menopause (3–5), and later age at menarche might be a stronger risk factor for premenopausal breast cancer than for postmenopausal breast cancer (6–8). Younger cases tend to present with a higher histological grade and more advanced stage than later-onset cases and are more likely to have triple-negative or human epidermal growth factor receptor-2–positive cancer (9, 10).

Hormone therapy (HT) comprises estrogen and/or progestin/progesterone usually taken in the form of pills or patches. Women take HT for a range of indications, including but not limited to relief of menopausal symptoms, replacement of hormone levels after oophorectomy, migraine prevention, or osteoporosis prevention. Although most users are peri- or postmenopausal, there is some use among young or premenopausal women.

In many observational studies and randomized controlled trials, it has been reported that postmenopausal women treated with combined estrogen and progestin HT (EP-HT) experience an increased risk of breast cancer (11–21). In particular, in the Women's Health Initiative (WHI) (21), investigators found that postmenopausal women randomized to EP-HT had a hazard ratio of 1.26 (95% confidence interval (CI): 1.00, 1.59) for breast cancer relative to placebo users. Longer durations of EP-HT may further increase risk, although these associations seem to dissipate once treatment ends (11–13, 15, 18–21).

The effects of unopposed estrogen therapy (E-HT), which is contraindicated in women with intact uteri because of the risk of endometrial cancer (22), are less clear (11, 12, 15–20).

*Am J Epidemiol.* 2015;181(10):799–807

**Table 1.** Characteristics of Participants at Index Age in the Sister Study (2003–2009) and Two Sister Study (2008–2010)

| Characteristic | Sister Study Baseline[a] (n = 15,527) | | Two Sister Controls (n = 1,665) | | Two Sister Cases (n = 1,419) | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Index age, years | | | | | | |
| <40 | 3,657 | 24 | 334 | 20 | 296 | 21 |
| 40–44 | 5,396 | 35 | 602 | 36 | 496 | 35 |
| ≥45 | 6,474 | 42 | 729 | 44 | 627 | 44 |
| Race[b] | | | | | | |
| Non-Hispanic white | 12,646 | 81 | 1,485 | 89 | 1,252 | 88 |
| Black | 1,515 | 10 | 73 | 4 | 70 | 5 |
| Hispanic | 940 | 6 | 63 | 4 | 57 | 4 |
| Other | 422 | 3 | 43 | 3 | 40 | 3 |
| Relative birth order among included sisters | | | | | | |
| First (oldest) | | | 915 | 55 | 527 | 37 |
| Second | | | 606 | 36 | 792 | 56 |
| Third or younger | | | 144 | 9 | 100 | 7 |
| Educational level[c] | | | | | | |
| Less than a college degree | 4,854 | 31 | 436 | 30 | 387 | 27 |
| Associate, technical, or bachelor's degree | 7,084 | 46 | 776 | 46 | 678 | 48 |
| Master's or doctoral degree | 3,584 | 23 | 393 | 24 | 354 | 25 |
| Age at menarche, years[d] | | | | | | |
| <12 | 2,943 | 19 | 276 | 17 | 268 | 19 |
| 12–13 | 8,742 | 56 | 953 | 57 | 833 | 59 |
| ≥14 | 3,830 | 25 | 435 | 26 | 318 | 22 |
| Parity[e] | | | | | | |
| 0 births | 3,636 | 23 | 357 | 21 | 303 | 21 |
| 1 births | 2,598 | 17 | 259 | 16 | 226 | 16 |
| 2 births | 5,791 | 37 | 617 | 37 | 553 | 39 |
| ≥3 births | 3,502 | 23 | 431 | 26 | 337 | 24 |
| Age at which first term (≥37 weeks) pregnancy ended, years[f] | | | | | | |
| <25 | 4,678 | 41 | 470 | 37 | 328 | 31 |
| 25–29 | 3,766 | 33 | 459 | 36 | 396 | 37 |
| 30–34 | 2,164 | 19 | 235 | 19 | 255 | 24 |
| ≥35 | 837 | 7 | 102 | 8 | 87 | 8 |

**Table continues**

In a second WHI trial restricted to women who were 50–79 years of age with no uterus, those randomized to E-HT were less likely to develop breast cancer than were controls who took placebos (hazard ratio = 0.77, 95% CI: 0.62, 0.95) (23). Few studies have examined progestin alone (P-HT), but some have suggested an increased risk (11, 15, 18, 24).

The association between HT and breast cancer in young women has been examined in several studies (7, 25–31), but only 2 studies (29, 30) differentiated between types of HT. Shantakumar et al. (30) found odds ratios of 3.51 (95% CI: 1.45, 8.49) and 1.17 (95% CI: 0.23, 5.88) for the associations of premenopausal breast cancer with use of EP-HT and E-HT, respectively. Palmer et al. (29) found weak evidence

that women under 50 years of age who took E-HT for at least 5 years had increased risk of breast cancer (relative risk = 1.6, 95% CI: 0.3, 8.5). We used data from the Two Sister Study, a sister-matched case-control study, to examine whether use of HT (EP-HT, E-HT, and P-HT) is a risk factor for young-onset breast cancer.

## METHODS

### Study sample

The Two Sister Study is a sister-matched case-control study of young-onset breast cancer. Control sisters were recruited

**Table 1.**   Continued

| Characteristic | Sister Study Baseline[a] (n = 15,527) | | Two Sister Controls (n = 1,665) | | Two Sister Cases (n = 1,419) | |
|---|---|---|---|---|---|---|
| | No. | % | No. | % | No. | % |
| Average body mass index from ages 30 to 39 years[g] | | | | | | |
| <25.0 | 10,959 | 71 | 1,206 | 72 | 1,032 | 73 |
| 25.0–29.9 | 2,951 | 19 | 311 | 19 | 283 | 20 |
| ≥30.0 | 1,536 | 10 | 144 | 9 | 98 | 7 |
| Use of hormonal birth control[h] | | | | | | |
| None | 1,712 | 11 | 160 | 10 | 129 | 9 |
| Used 1–6 years before index age | 4,070 | 26 | 472 | 28 | 427 | 30 |
| Used >6 years before index age | 9,660 | 62 | 1,026 | 62 | 854 | 61 |
| Menopausal status at index age[i] | | | | | | |
| Premenopausal | 12,852 | 83 | 1,391 | 84 | 1,239 | 87 |
| Postmenopausal, age at menopause <41 years | 754 | 5 | 74 | 4 | 28 | 2 |
| Postmenopausal, age at menopause ≥41 years | 723 | 5 | 67 | 4 | 56 | 4 |
| Hysterectomy with retained ovarian tissue | 1,179 | 8 | 131 | 8 | 96 | 7 |
| Had menopausal symptoms at index age[j] | 4,077 | 27 | 448 | 27 | 256 | 18 |
| Surgical status at index age[k] | | | | | | |
| None | 13,397 | 86 | 1,439 | 86 | 1,282 | 88 |
| Hysterectomy only | 1,188 | 8 | 132 | 8 | 96 | 7 |
| Oophorectomy only | 21 | 0 | 2 | 0 | 1 | 0 |
| Hysterectomy and oophorectomy | 907 | 6 | 91 | 5 | 39 | 3 |
| Visited dentist in past 12 months[l] | 13,182 | 85 | 1,454 | 87 | 1,218 | 86 |
| Recall time >5 years[m] | 6,726 | 43 | 535 | 32 | 255 | 18 |

[a] Limited to women with a sister who was diagnosed before 50 years age and who had a recall time of less than 10 years. The mean age for included participants in the Sister Study was 47.1 years (range, 35.1–59.8 years).

[b] Data were missing for 4 Sister Study participants and 1 control.

[c] Data were missing for 5 Sister Study participants.

[d] Data were missing for 12 Sister Study participants and 1 control.

[e] Data were missing for 1 control.

[f] Data were missing for 4,082 Sister Study participants, 399 Two Sister Study controls, and 353 Two Sister Study cases.

[g] Data were missing for 81 Sister Study participants, 4 Two Sister Study controls, and Two Sister Study 6 cases. Body mass index was measured as weight (kg)/height (m)$^2$.

[h] Data were missing for 39 Sister Study participants, 6 Two Sister Study controls, and 8 Two Sister Study cases.

[i] Data were missing for 19 Sister Study participants and 2 controls.

[j] Data were missing for 243 Sister Study participants, 7 Two Sister Study controls, and 4 Two Sister Study cases.

[k] Data were missing for 14 Sister Study participants, 1 Two Sister Study control, and 1 Two Sister Study case.

[l] Data were missing for 3 Sister Study participants.

[m] Recall time was defined as the difference in years between interview age and index age.

from the Sister Study, a prospective cohort study of 50,884 women without breast cancer who had a full or half sister who had been diagnosed with breast cancer. Sister Study participants who were 35–74 years of age and lived in the United States or Puerto Rico were enrolled between 2003 and 2009.

Between 2008 and 2010, we invited affected full sisters (cases) to participate in the Two Sister Study if they had been diagnosed with breast cancer within the past 4 years and before 50 years of age. We enrolled 1,422 cases and 1,689 controls. We excluded control sisters who were more than 7 years younger than their case sisters if an older control sister had also been interviewed (n = 19). We also excluded 5 women

who were originally enrolled as controls but went on to be diagnosed with breast cancer at a younger age than their case sister. Three cases with no remaining eligible control sisters then had to be excluded. This left 1,419 eligible cases and 1,665 eligible controls in the Two Sister Study sample.

All participants provided written or verbal consent and completed computer-assisted telephone interviews, which included questions about reproductive history, health conditions, and lifestyle factors (32–36). To ensure similar accrual times for medical and exposure histories, all sisters in a family were assigned the same index age, which was the minimum of the age of the case at diagnosis and the age(s) of her control sister(s) at

**Table 2.** Odds Ratios for the Association Between Hormone Therapy and the Risk of Young-Onset Breast Cancer in the Two Sister Study, 2008–2010

| Hormone Therapy | Controls (*n* = 1,665) | | Cases (*n* = 1,419) | | Crude[a] | | Multivariate-Adjusted[a,b] | | Propensity Score–Adjusted[a,c] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| Hormone therapy used[d] | | | | | | | | | | |
| None | 1,466 | 88 | 1,316 | 93 | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent |
| Unopposed estrogen | 115 | 7 | 50 | 4 | 0.42 | 0.29, 0.62 | 0.56 | 0.33, 0.93 | 0.58 | 0.34, 0.99 |
| Estrogen plus progestin | 56 | 3 | 25 | 2 | 0.41 | 0.24, 0.70 | 0.61 | 0.32, 1.15 | 0.80 | 0.41, 1.59 |
| Progestin alone | 23 | 1 | 20 | 1 | 1.24 | 0.66, 2.35 | 1.42 | 0.73, 2.78 | 1.51 | 0.76, 3.00 |
| Duration of use[d,e] | | | | | | | | | | |
| Never | 1,466 | 90 | 1,316 | 95 | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent |
| Unopposed estrogen | | | | | | | | | | |
| ≤2 years | 57 | 3 | 25 | 2 | 0.45 | 0.26, 0.77 | 0.59 | 0.32, 1.09 | 0.59 | 0.32, 1.08 |
| >2 years | 58 | 4 | 25 | 2 | 0.39 | 0.22, 0.68 | 0.39 | 0.15, 1.04 | 0.53 | 0.19, 1.49 |
| Estrogen plus progestin | | | | | | | | | | |
| ≤2 years | 26 | 2 | 14 | 1 | 0.59 | 0.29, 1.24 | 0.90 | 0.40, 2.03 | 1.30 | 0.55, 3.10 |
| >2 years | 30 | 2 | 11 | 1 | 0.27 | 0.12, 0.62 | 0.38 | 0.14, 1.01 | 0.48 | 0.17, 1.37 |
| Age at first use[d,e] | | | | | | | | | | |
| Never | 1,466 | 90 | 1,316 | 95 | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent |
| Unopposed estrogen | | | | | | | | | | |
| <40 years | 66 | 4 | 22 | 2 | 0.33 | 0.19, 0.56 | 0.49 | 0.25, 1.00 | 0.50 | 0.25, 1.02 |
| ≥40 years | 49 | 3 | 28 | 2 | 0.54 | 0.31, 0.94 | 0.61 | 0.30, 1.23 | 0.63 | 0.31, 1.28 |
| Estrogen plus progestin | | | | | | | | | | |
| <40 years | 21 | 1 | 10 | 1 | 0.40 | 0.17, 0.98 | 0.53 | 0.19, 1.51 | 0.64 | 0.22, 1.86 |
| ≥40 years | 35 | 2 | 15 | 1 | 0.40 | 0.20, 0.81 | 0.66 | 0.30, 1.43 | | |
| Menopausal status at first use[d,f] | | | | | | | | | | |
| Never | 1,466 | 89 | 1,316 | 94 | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent |
| Unopposed estrogen | | | | | | | | | | |
| Premenopausal | 64 | 4 | 29 | 2 | 0.41 | 0.25, 0.69 | 0.53 | 0.30, 0.93 | 0.52 | 0.29, 0.95 |
| Postmenopausal | 51 | 3 | 21 | 2 | 0.42 | 0.23, 0.75 | 0.47 | 0.12, 1.82 | 0.60 | 0.16, 2.32 |
| Estrogen plus progestin | | | | | | | | | | |
| Premenopausal | 40 | 2 | 23 | 2 | 0.63 | 0.36, 1.10 | 0.82 | 0.43, 1.56 | 0.97 | 0.49, 1.91 |
| Postmenopausal | 18 | 1 | 4 | 0 | N/A[g] | N/A[g] | N/A[g] | N/A[g] | N/A[g] | N/A[g] |

**Table continues**

completion of the baseline interview. The institutional review board of the National Institute of Environmental Health Sciences approved both studies, as did the Copernicus Group.

Cases included both invasive and in situ cancers. At baseline, participants reported whether they had ever used any form of HT. HT users were further questioned about type of therapy and ages at which they started and stopped. Using this information, we reconstructed each participant's exposure history. Women who reported using HT via patches, pills, injections, or other oral administrations (e.g., lozenges or tablets) were considered users. Pill or patch use was most common (91%). Women who exclusively used creams, suppositories, or gels were considered nonusers (*n* = 5).

Women who had used EP-HT were classified as EP-HT users even if they had used E-HT (*n* = 14) or P-HT (*n* = 3) at another time. Those who had used E-HT and P-HT at different times were classified as E-HT users (*n* = 5). If the index

age was equal to the case's age at diagnosis, we reset the index age to 1 year younger for all sisters in the family. This was done to allow for latencies in effects.

HT users were further subdivided according to duration of use (<2 years vs. ≥2 years), age at first use (<40 years vs. ≥40 years), and timing of first use relative to menopause. We also considered recency of use, including use in the year before the index age (0–4 vs. ≥5 years prior). Cutpoints were selected to ensure roughly equal numbers for each category. There were too few P-HT users to permit further stratification.

Women who had had both ovaries removed or who had not had a menstrual period in the preceding 12 months were considered to be postmenopausal. Women who were still menstruating, currently pregnant, or currently breastfeeding were considered premenopausal, as were women who had been pregnant within 1 year of their reported last menstrual period (*n* = 6). Women who were premenopausal but who had undergone

**Table 2.**   Continued

| Hormone Therapy | Controls (*n* = 1,665) | | Cases (*n* = 1,419) | | Crude[a] | | Multivariate-Adjusted[a,b] | | Propensity Score–Adjusted[a,c] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| Recency of use, relative to index age[h] | | | | | | | | | | |
| Never | 1,450 | 89 | 1,308 | 92 | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent |
| Unopposed estrogen | | | | | | | | | | |
|   0–4 years before | 89 | 5 | 34 | 2 | 0.41 | 0.26, 0.64 | 0.56 | 0.28, 1.10 | 0.58 | 0.28, 1.20 |
|   ≥5 years before | 31 | 2 | 21 | 2 | 0.49 | 0.25, 0.97 | 0.59 | 0.29, 1.23 | 0.62 | 0.30, 1.30 |
| Estrogen plus progestin | | | | | | | | | | |
|   0–4 years before | 45 | 3 | 17 | 1 | 0.32 | 0.16, 0.62 | 0.49 | 0.23, 1.05 | 1.12 | 0.47, 2.66 |
|   ≥5 years before | 21 | 1 | 10 | 1 | 0.48 | 0.21, 1.11 | 0.50 | 0.20, 1.25 | 0.52 | 0.21, 1.33 |

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] The odds ratios compare users of a particular agent to those who never used hormone therapy; each type of hormone therapy was assessed in a separate conditional logistic regression model.

[b] Adjusted for birth order (ordinal), menopausal status (premenopausal, postmenopausal and <41 years of age, or postmenopausal and ≥41 years of age), menopausal symptoms (ever or never), hysterectomy/oophorectomy status (no surgery, oophorectomy with or without hysterectomy, or hysterectomy only), and recall time (>5 years vs. ≤5 years).

[c] Hormone therapy status was modeled as a 4-level, polytomous variable in Sister Study participants who had a sister diagnosed with breast cancer before the age of 50 years and within 10 years of the interview date. The following variables were included in the model: menopausal status (premenopausal, postmenopausal, age at menopause <41 years, postmenopausal, or age at menopause ≥41 years), restricted cubic spline for year of menopause (centered at 2002) times menopausal status, restricted cubic spline for age in 2002, hysterectomy/oophorectomy status, race (white vs. nonwhite), menopausal symptoms (ever or never), recent dental visit (yes or no), recall time (>5 years or ≤5 years between interview age and index age), parity (yes or no), and age at menarche (<13 years of age versus ≥13 years of age). All time-related variables were assessed as of the index age or 1 year before the case sister's diagnosis age, whichever came first. The outcome model estimated the association between hormone therapy and case status in the Two Sisters sample after adjustment for birth order and propensity score (as a restricted cubic spline). Estrogen plus progestin models were also adjusted for dental visit and menopausal status. Unopposed estrogen models were also adjusted for surgical status and race.

[d] Hormone therapy use in participants in the Two Sister Study was assessed as of the index age or 1 year before the case sister's age at diagnosis, whichever came first. Sister Study participants were assessed as of their index age (minimum of their interview date and their affected sister's age at diagnosis). Data on hormone therapy use were missing for 5 controls and 8 cases.

[e] Data were missing for 23 controls and 20 cases.

[f] Data were missing for 21 controls and 18 cases.

[g] There were too few subjects to estimate the effect.

[h] Data were missing for 22 controls and 19 cases.

hysterectomy with retention of ovarian tissue were categorized separately. If HT users were missing data for menopausal status and age at menopause, we assumed that they took HT before menopause (*n* = 10).

**Propensity scores**

Because controls were up to 74 years of age at interview and cases were at most 54 years of age at interview, more than half of cases (61%) were younger than their control sister(s). The mean age was identical for the 2 groups (47.3 years), but controls were between 35 and 67 years of age at interview, whereas cases were between 31 and 54 years of age. Consequently, cases and controls could systematically differ in their propensity for exposures if there was a birth cohort effect.

After the release of the initial WHI trial results in 2002, HT use declined dramatically in the United States. In 1999–2000, 38% of women aged 50–59 years reported current HT use (35), but by 2003–2004, prevalence of use had fallen to 19%. By 2009–2010, it dropped below 7%. Because 10% of control sisters and no case sisters had reached the age of 50 years before 2002 when HT use was widespread, bias was a concern

(21, 35). We used propensity score methods to adjust for differential opportunity for HT use.

A propensity score is a probability of an exposure given individual characteristics (36). If accurately modeled, one can adjust for many confounders and obtain a less-biased estimate of the effect of an exposure on an outcome by including the propensity scores in a multivariate regression model.

Månsson et al. (36) demonstrated that in a case-control setting, the best possible propensity score is one modeled using data from the source population. We used a subcohort of the Sister Study as a proxy for the Two Sister Study source population and modeled each participant's propensity for use of EP-HT, E-HT, or P-HT. The subcohort included Sister Study participants who had a sister diagnosed before 50 years of age and who had less than a 10-year gap between interview age and index age, which was again defined as the minimum of the sister's diagnosis age and the participant's age at completion of the computer-assisted telephone interview. A total of 15,527 Sister Study participants met these criteria, including 1,488 who were also serving as controls in the Two Sister Study.

The propensity score model incorporated potential confounders of the relationship between HT and breast cancer,

as well as well-established risk factors for breast cancer (37). Web Appendix 1 and Web Tables 1 and 2 (available at http://aje.oxfordjournals.org/) provide a more detailed discussion of the variables included in the model and how the propensity score was applied. We also include descriptions of the observed propensity score distributions (Web Tables 3–6, Web Figures 1–3).

Briefly, we used unconditional polytomous logistic regression to model the probabilities of EP-HT, E-HT, or P-HT use versus never use within the Sister Study subcohort and then applied the fitted propensity model to participants in the Two Sister Study and calculated 3 estimated probabilities for each individual. These probabilities were used to estimate each participant's conditional probability for all 3 types of HT use given her individual characteristics. We used likelihood ratio tests to assess the fit of the propensity model and to identify covariates that were insufficiently balanced across treatment groups (Web Table 6) (38).

### Statistical analysis

We estimated crude and adjusted odds ratios and 95% confidence intervals for the associations of each type of HT with breast cancer risk in the Two Sister Study using conditional logistic regression. Nonusers served as the common reference group for each analysis. Adjusted models included birth order (an ordinal variable, with the oldest sister assigned a value of 1), menopausal status (premenopausal, postmenopausal and <41 years of age, or postmenopausal and ≥41 years of age), presence of menopausal symptoms (yes or no), hysterectomy/oophorectomy status (no surgery, oophorectomy with or without hysterectomy, or hysterectomy), and length of recall (>5 years vs. ≤5 years between a woman's interview age and HT exposure assessment age). We adjusted for relative birth order to account for the possibility that older siblings influence their younger siblings' HT use and the fact that cases in the Two Sister Study were usually younger than their control sister(s). We also generated a third set of conditional odds ratios and 95% confidence intervals that included any insufficiently balanced covariates and propensity score as a restricted cubic spline. We compared users of each HT type to nonusers separately, using the propensity score specific to the treatment category of interest.

### Sensitivity analyses

To further minimize possible bias due to a birth cohort effect, we conducted additional analyses using a restricted study sample. The restricted sample included sister pairs born less than 5 years apart (1,085 controls and 974 cases). The subcohort of Sister Study participants used to derive the propensity score included only those with the same birth years as those in the restricted sample (1951–1975; $n = 16,201$). We also examined whether oophorectomy status modified the association between HT and young-onset breast cancer.

### RESULTS

Most participants in the Two Sister Study were white, well-educated, premenopausal at the index age, and nonobese and had good access to health care (Table 1). Controls were more likely to have had hysterectomies, hysterectomies with bilateral oophorectomies, and menopausal symptoms. The selected Sister Study subcohort used for assessing propensities was very similar to Two Sister Study controls.

E-HT was the most common type of HT used, followed by EP-HT, though HT use was low overall. More controls than cases reported using HT, and the crude odds ratios for breast cancer were less than 1 for every HT category except P-HT (Table 2). Multivariate-adjusted odds ratios were closer to the null but still less than 1.

Although we did not ask women to specify why they used HT, results from the Two Sister Study and the Sister Study propensity score model (Web Tables 1 and 2) showed that participants who experienced early menopause, underwent bilateral oophorectomy, or had menopausal symptoms or recent visits to the dentist had a high probability of taking EP-HT. Having menopausal symptoms was also associated with E-HT use. Other strong predictors of E-HT use included hysterectomy, bilateral oophorectomy, and early menopause. Because women with a longer recall period (>5 years) were less likely to report taking HT before their index age, we adjusted for recall time using the propensity score model.

EP-HT use was not strongly associated with young-onset breast cancer (odds ratio = 0.80, 95% CI: 0.41, 1.59; Table 2) in the model adjusted for propensity score. Use for more than 2 years was associated with reduced relative risk, but the numbers were small and the confidence intervals were wide. Adjustment for recency of use and age at first use did not measurably modify the associations. E-HT use was inversely associated with young-onset breast cancer (propensity score odds ratio = 0.58, 95% CI: 0.34, 0.99; Table 2). Adjustment for duration of use, age at first use, menopausal status at first use, and recency of use did not appear to modify the association. P-HT use was associated with a statistically nonsignificant increased risk of young-onset breast cancer in the propensity score–adjusted model (odds ratio = 1.51, 95% CI: 0.76, 3.00).

When we restricted the analysis to sister pairs with an age difference of less than 5 years (Table 3), the findings were less precise but qualitatively similar. The odds ratio for EP-HT exceeded 1 but the confidence interval was wide. There was no evidence of an interaction between HT use and oophorectomy status ($P = 0.86$ and $0.50$ for E-HT and EP-HT, respectively; Web Table 7).

### DISCUSSION

Our results suggest that neither EP-HT nor E-HT increase the risk of young-onset breast cancer and that E-HT might be associated with a reduced risk. Although the low rate of P-HT usage resulted in imprecise estimates, we also found some evidence that P-HT use increased the risk of young-onset breast cancer.

Our finding that E-HT use is associated with a decreased risk of young-onset breast cancer is consistent with the WHI findings for postmenopausal breast cancer (24). Although Shantakumar et al. (30) and Palmer et al. (29) previously found evidence that E-HT use increased the risk of young-onset disease, the estimates from both studies were highly imprecise (3 and 9 E-HT users, respectively).

**Table 3.**   Adjusted Odds Ratios for the Association Between Hormone Therapy and Young-Onset Breast Cancer When Analysis Is Restricted to Sister Pairs With an Age Difference of 5 Years or Less, Two Sister Study, 2008–2010[a]

| Hormone Therapy Use[a] | Controls (n = 1,085) | | Cases (n = 974) | | Crude[b] | | Multivariate-Adjusted[b,c] | | Propensity Score–Adjusted[b,d] | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No. | % | No. | % | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| Never | 964 | 89 | 901 | 93 | 1.00 | Referent | 1.00 | Referent | 1.00 | Referent |
| Unopposed estrogen | 76 | 7 | 34 | 4 | 0.44 | 0.27, 0.69 | 0.61 | 0.33, 1.12 | 0.60 | 0.32, 1.15 |
| Estrogen plus progestin | 28 | 3 | 21 | 2 | 0.65 | 0.33, 1.25 | 0.95 | 0.45, 2.03 | 1.12 | 0.49, 2.56 |
| Progestin alone | 15 | 1 | 13 | 1 | 1.16 | 0.53, 2.52 | 1.26 | 0.57, 2.78 | 1.11 | 0.50, 2.47 |

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Hormone therapy use in participants in the Two Sister Study was assessed as of the index age or 1 year before the case sister's age at diagnosis, whichever came first. Sister Study participants were assessed as of their index age (minimum of their interview date and their affected sister's age at diagnosis). Data on hormone therapy use were missing for 2 controls and 5 cases in this restricted analysis.

[b] The odds ratios compare users of a particular agent to those who never used hormone therapy; each type of hormone therapy was assessed in a separate conditional logistic regression model.

[c] Adjusted for birth order (ordinal), menopausal status (premenopausal, postmenopausal and <41 years of age, or postmenopausal and ≥41 years of age), menopausal symptoms (ever or never), hysterectomy/oophorectomy status (no surgery, oophorectomy with or without hysterectomy, or hysterectomy only) and recall time (>5 years vs. ≤5 years).

[d] Hormone therapy status was modeled as a 4-level, polytomous variable in Sister Study participants who had a sister diagnosed with breast cancer before the age of 50 years and within 10 years of the interview date. The following variables were included in the model: menopausal status (premenopausal, postmenopausal, age at menopause <41 years, postmenopausal, or age at menopause ≥41 years), restricted cubic spline for year of menopause (centered at 2002) times menopausal status, restricted cubic spline for age in 2002, hysterectomy/oophorectomy status, race (white vs. nonwhite), menopausal symptoms (ever or never), recent dental visit (yes or no), recall time (>5 years or ≤5 years between interview age and index age), parity (yes or no), and age at menarche (<13 years of age versus ≥13 years of age). All time-related variables were assessed as of the index age or 1 year before the case sister's diagnosis age, whichever came first. The outcome model estimated the association between hormone therapy and case status in the Two Sisters sample after adjustment for birth order and propensity score (as a restricted cubic spline). Estrogen plus progestin models were also adjusted for dental visit and menopausal status. Unopposed estrogen models were also adjusted for surgical status and race.

Our results are also consistent with the analysis by Nelson et al. (28) of 40–49-year-old women, in which they reported that HT users who did not have a uterus ( probable E-HT users) had a reduced risk of young-onset breast cancer compared with former or never users and that HT users who did have a uterus ( probable EP-HT users) had risk similar to those of former or never users. However, both Chlebowski et al. (14) and Shantakumar et al. (30) reported elevated breast cancer risk with EP-HT use, and we had only limited power (approximately 43%) to detect a difference between the estimate of 1.26 reported in the WHI and our estimate of 0.8 (Web Appendix 2, Web Figure 4). No other studies have examined the relationship between P-HT and young-onset breast cancer, but several studies targeting older women also found evidence of increased risk (11, 15, 18, 22).

Although young women who take HT could be a medically distinct group, most of our HT users were in their 40s and thus likely to be perimenopausal. Nonetheless, use of hormones can serve as a surrogate for a range of treatment indications that are independently associated with a reduced risk of breast cancer, such as primary ovarian insufficiency, endogenous estrogen deficiency, gynecologic surgery, menopausal symptoms, or premature menopause (25, 39–43). Although we adjusted for these factors and tested for interaction by oophorectomy status, some residual confounding by indication may persist.

HT users might also be more likely to utilize the medical system in general. Although we did not have good information on mammography use before the index age, we adjusted for health care utilization using a recent dental visit as an indicator.

Any residual confounding due to surveillance bias would likely result in elevated estimates of breast cancer risk among HT users.

Menopausal status is a potential source of confounding in many existing studies of HT. For women at a given age, those who are premenopausal or perimenopausal are at greater risk of breast cancer, but they are less likely to be using HT than are postmenopausal women (12). In an attempt to minimize bias due to confounding by menopausal status, investigators might exclude premenopausal and perimenopausal women, women who have undergone a hysterectomy, and women who began HT before menopause (12, 14–16). However, because many women initiate HT after a hysterectomy or at the onset of menopausal symptoms, we felt that an investigation of the risk implications of HT in young women was of public health importance. By including pre- and postmenopausal women, we were also able to study associations with the timing of HT initiation, which may be key to identifying critical susceptibility periods. An additional strength of the Two Sister Study is the sister-matched design, which presumably controls for unmeasured confounders that are similar across sisters.

Study limitations include our small numbers of exposed women, possible healthy-participant bias, possible surveillance bias, and possible recall bias. Exact participation rates for the Two Sister Study are hard to establish, as some contacted cases might have elected not to contact us because they realized they were ineligible. Only a small fraction of participants were explicitly excluded because of death or poor health, and more than half of the identified cases participated. Although we cannot

exclude healthy-participant bias, the magnitude of such bias would be mitigated by the sister-matched design. As noted earlier, there might be some surveillance bias due to our inability to capture mammography usage around the index age. However, differential surveillance would presumably make HT users more likely to be diagnosed, with the implication that the use of HT could be even more protective than we estimated.

Recall bias may be present, because controls were more likely to have a large gap between their interview age and index age and those with longer recall periods were less likely to report HT use before their index age. We adjusted for recall time in both the multivariate and propensity score analyses, but residual confounding might exist. Nonetheless, because of their shorter recall times, we would expect cases to report HT use more often than controls, and therefore recall bias would not explain the evident protective association of E-HT use seen here. Our sensitivity analyses that excluded sister pairs with large age differences also served to reduce recall bias. The similarity of these results with the main findings suggests that recall bias was not influential.

The fact that control sisters tended to be slightly older than their case sisters is also a concern. Although this tendency helped ensure that controls were cancer-free at the age that their sister was diagnosed, it produced a potentially biasing birth cohort effect related to the sharply declining use of HT in the early 2000s. We controlled for this effect by adjusting for individualized propensity scores. Propensity scores are not typically applied to case-control studies, but we were able to model well-informed, stable propensity estimates by using a large subcohort of the Sister Study (36). This subcohort represents the source population for the Two Sister Study. We further equalized the opportunity for exposure by evaluating all covariates at an index age that occurred before either sister was diagnosed. The use of an index age both controlled for age and eliminated effects due to any behavioral changes brought about by having a sister diagnosed with breast cancer. We do acknowledge, however, that this novel application of propensity scores to a matched case-control study has not been validated.

To our knowledge, this is the largest study to examine the association between HT use and young-onset breast cancer and the first conducted in the post-WHI era. This research informs the trade-offs between risks and benefits of HT for young women, who might take it to help manage symptoms of early or surgically induced menopause. Our findings suggest that for women under 50 years of age, EP-HT use does not increase risk but that E-HT, indicated only for women who have undergone hysterectomy, might be associated with a reduced risk of young-onset breast cancer.

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