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Hormone Replacement Therapy, Family History, and Breast Cancer Risk Among Postmenopausal Women

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Abstract

Background—Evidence is mixed regarding how familial predisposition to breast cancer affects the relation between hormone replacement therapy and risk of postmenopausal breast cancer. We investigated whether the risk difference for invasive breast cancer attributable to estrogen plus progesterone replacement therapy is greater among women with a first-degree family history of the disease.

Methods—This study is a longitudinal follow-up of 16,608 postmenopausal women aged 50–79 years who were enrolled between 1993 and 2002 in the Women's Health Initiative randomized trial of estrogen plus progesterone replacement therapy versus placebo.

Results—Three hundred forty-nine cases of invasive breast cancer occurred during a mean follow-up period of 5.6 years. The invasive breast cancer risk difference attributable to the hormone therapy was 0.007 among women with first-degree family history and 0.005 among the others, resulting in a negligible interaction contrast (IC = 0.002; 95% confidence interval = −0.014 to 0.018). The interaction contrast restricted to estrogen-receptor-positive invasive breast cancers was also negligible (IC = −0.006; 95% CI = −0.021 to 0.008).

Conclusion—Family history and estrogen plus progesterone replacement therapy have independent and noninteracting effects on the risk of invasive breast cancer among participants in the Women's Health Initiative randomized trial.

Family history[1-3] and estrogen replacement therapy[4-12] each demonstrate an independent association with the incidence of breast cancer among postmenopausal women. Earlier studies suggested that longer exposure to endogenous estrogens was more strongly associated with breast cancer risk among women having a family history of breast cancer.[13] Family history and estrogen risk potentially share biologic pathways of effect.[14]

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It remains unresolved as to whether familial predisposition to breast cancer enhances the carcinogenic effects of estrogen. Several studies have observed a stronger association between estrogen and breast cancer among women with a family history.[7-11,15] Others, however, have failed to observe this interaction.[12,16-18] Some of this discrepancy might have arisen because of differences in the definitions of interaction, the classification of family history, and residual confounding.

Women's knowledge about their own family history can influence their decisions about use of estrogen therapy.[19] The Women's Health Initiative randomized placebo-controlled trial of estrogen plus progesterone hormone replacement therapy eliminates the link between family history and decisions about estrogen use. This advantage allows direct evaluation of a potential interaction between family history and hormone therapy on breast cancer incidence.

METHODS

Design

We analyzed data from the Women's Health Initiative randomized trial of estrogen plus progesterone replacement therapy versus placebo, which began in 1993 and enrolled 16,608 postmenopausal women. Women were instructed to stop study medications on 8 July 2002 after the Data Safety and Monitoring Board determined that this hormone therapy did not provide net benefit as measured by a global index of outcomes (coronary heart disease, invasive breast cancer, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, hip fracture, and death due to other causes).[20]

Exposure and covariate information were obtained via baseline questionnaires, blood analysis, and anthropomorphic measurements. Each participant was contacted every 6 months to identify hospitalizations or diagnoses of diseases pertinent to the trial, including breast cancer. All invasive breast cancer diagnoses were confirmed by a centralized team of trained adjudicators via pathology reports. More details of the Women's Health Initiative design are described elsewhere.[21]

Participants

Postmenopausal women were recruited from populations of women living near the 40 Women's Health Initiative Clinical Centers across the United States. The most common method of recruitment was mass mailing to targeted groups. Women were eligible for participation if they met all of the following conditions: they were between the ages of 50 and 79 years at the time of enrollment (1993–1998); they were postmenopausal; they had not been diagnosed with any invasive cancer during the 10 years before enrollment; they had no personal history of breast, endometrial, or melanoma skin cancer; they had no breast, cervical, or endometrial cancers diagnosed at baseline screening; they had no medical conditions likely resulting in a life expectancy of fewer than 3 years; they had no conditions that made longitudinal participation unlikely (eg, dementia, alcoholism, or major mental illness); they had no conditions placing them at high risk for thromboembolic disease (eg, severe hypertension, severe blood clotting disorder, and myocardial infarction or stoke within the past 6 months); and they were not already participating in another clinical trial.

Exposure Definition

Women randomized to the treatment arm were defined as exposed. All analyses were completed using an intention-to-treat paradigm. Family history was defined at the time of the baseline assessment as the presence or absence of breast cancer ever diagnosed in a first-degree family member (ie, a full parent, full sibling, or child).

Outcome Definition

Cases were defined as those women diagnosed with invasive breast cancer before 8 July 2002. No invasive breast cancers were first identified upon a participant's death.

We also considered estrogen receptor positive (ER+) invasive breast cancer as a secondary outcome. Estrogen receptor expression was determined for 89% of cases. Approximately half of the remaining 11% had no assay for estrogen receptor expression and the status of others was unknown.

Covariate Measurement

Each of the following self-reported variables was obtained at baseline: age; household income; educational level; menstrual history; reproductive history; personal history of breast biopsies; exercise regimen; usual intake of fruits, vegetables, and alcoholic beverages; and smoking history. Height and weight were measured at baseline in light clothing without shoes.

Definition of Interaction

Both family history and estrogen use are causally related to invasive breast cancer.[1-3,5,20,22] We examined interaction as departure from the sum of their independent effects using the following formula:

$$\left(R_{FH=1,EP=1} - R_{FH=1,EP=0}\right) - \left(R_{FH=1,EP=1} - R_{FH=0,EP=0}\right) = IC;$$

where IC is the interaction contrast; IC >0 indicates superadditivity, and IC <0 indicates subadditivity; FH indicates first-degree family history (1 = yes and 0 = no); and EP indicates estrogen plus progesterone hormone replacement therapy (1 = EP and 0 = placebo).

Analyses

We assessed the frequency and distribution of each study variable within the full study population and within the 4 subcohorts defined by family history and hormone therapy (FH_1EP_1, FH_1EP_0, FH_0EP_1, and FH_0EP_0). For each subcohort, we calculated the risk of invasive breast cancer ($R_{FH=x,EP=y}$) and ER+ invasive breast cancer during the study period.

If factors that confound or modify the relation between hormone therapy and invasive breast cancer are unevenly distributed among women with and without a family history, this imbalance would bias our effect estimates. In previous reports from this clinical trial, the following factors appeared to modify the association between treatment and breast cancer incidence: current smoking, obesity, and history of estrogen plus progesterone replacement therapy use.[4] Therefore, we evaluated whether any of these 3 factors was associated with family history. For those factors associated with family history, we addressed potential confounding of the interaction contrast by calculating the contrast restricted to the strata without the potential confounding factor(s). In addition, we repeated the interaction calculation for ER+ breast cancer risk. This study was approved by the Memorial Hospital Committee for the use of Human Subjects in Research (Pawtucket, RI).

RESULTS

Table 1 describes the characteristics of the 16,608 women in this study. We observed 349 cases of invasive breast cancer and 270 cases of ER+ invasive breast cancer during a mean follow-up period of 5.6 years (range: 0.02–8.6 years, standard deviation = 1.3 years). Fifty-one percent were randomized to receive estrogen plus progesterone replacement therapy. A first degree

family history of breast cancer at baseline was reported by 12% of the study population. Within strata of family history, the demographic and covariate characteristics did not differ substantially between women randomized to receive the hormonal therapy and those who received the placebo.

Table 2 shows the risks of invasive breast cancer for the FH_1EP_1, FH_1EP_0, FH_0EP_1, and FH_0EP_0 subcohorts. The interaction contrast (IC) of 0.002 (95% confidence interval [CI] = −0.014 to 0.018) was equivalent to only 12% of the risk in the doubly unexposed group, thus demonstrating a negligible departure from the predicted additive effects of family history and hormone therapy on invasive breast cancer. We observe a negligible degree of subadditive interaction for the risk of ER+ invasive breast cancers (IC = −0.006 [−0.021 to 0.008]). IC calculations using rates yield similar results. When considering lifetime hormone replacement therapy as the exposure metric (which breaks the randomization), there were similarly negligible ICs.

Having a first-degree family history was modestly associated with a lower prevalence of current smoking (odds ratio [OR] = 0.90 [95% CI = 0.76 to 1.06]). Family history was not associated with obesity or a history of estrogen plus progesterone replacement therapy use. Results were nearly identical regardless of whether women smoked at enrollment—among nonsmokers the IC for invasive breast cancer was 0.002 (CI = −0.016 to 0.020) and for ER+ invasive breast cancer was −0.007 (−0.023 to 0.009), while among current smokers the IC for all invasive breast cancer was −0.004 (CI = −0.043 to 0.035) and IC for ER+ invasive breast cancer was −0.007 (CI = −0.040 to 0.026). IC estimates among current smokers at enrollment, however, were based upon only 30 cases of incident invasive breast cancer, 19 of which were ER+.

DISCUSSION

We assessed interaction between the additive effects of family history and estrogen plus progesterone replacement therapy on the risk of breast cancer. We find no important interaction.

Previous studies have examined interaction as a departure from multiplicativity. Two studies provide data about stratum-specific absolute risks, from which we can assess departure from additivity. Olsson et al[12] examined interaction among a cohort of 29,508 Swedish women aged 25–65 years. They defined estrogen replacement use as ever versus never and did not provide a definition of breast cancer family history. Reanalysis of their published data yields an interaction contrast of 0.005, similar to the small IC in our data.

Sellers et al[18] conducted a follow-up study among 35,919 women aged 55–69 years. They defined family history as any breast cancer ever diagnosed in a mother, sister, or daughter, and estrogen replacement use as ever versus never. From these data, we estimate an interaction contrast of 0.007, which is also similar to the clinically insignificant IC in our study.

The other published works on this topic were based on case-control study designs,[7-11, 15-17] for which stratum-specific absolute risks are not observed. Nevertheless, we can evaluate departures from additivity by assessing the relative excess risk for interaction (RERI).[23] Four studies provided enough data for us to estimate the RERI. For each study, we classified estrogen replacement use as ever versus never, and family history as present or absent, based upon breast cancer in a mother or sister. The resulting RERI values for these 4 studies are 0.58 (Pesch et al[15]), 0.60 (Magnusson et al[16]), 0.20 (Newcomb et al[10]), and 0.94 (Nomura et al[11]). There are no established standards for a clinically meaningful RERI. We propose that a RERI that exceeds half the risk in the doubly unexposed (ie, RERI >0.50) implies a potentially important degree of interaction. Although the data of Magnusson et al showed a RERI above this

threshold, their data demonstrated no departure from multiplicative effects and thus Magnusson et al concluded that no interaction existed.

The RERI for our study (0.12) is lower than that observed by others. It is possible that the categorization of estrogen replacement therapy as ever versus never (as in all of the studies to which we compare our results) influences the estimates of interaction. The Pesch et al[15] data allow for categorization by current versus not current, which comes closer to the definitions in the present study. Such reclassification strongly reduces the RERI estimate (0.02), thus supporting the potential for estrogen exposure categorization to explain the higher estimates among earlier studies. A second potential explanation is that our estimates of the other studies' IC or RERI are based on unadjusted data extracted from the published results. None of these studies randomized estrogen replacement as in the present study. Thus, confounding remains a potentially important factor in explaining the discrepancy between the present findings and previously reported results. For these reasons, we believe that the evidence from the extant literature does not substantially challenge our conclusion of an absence of interaction between estrogen plus progesterone replacement therapy and family history on the incidence of breast cancer.

Our study has limitations. First, this study had both a short period of exposure to hormone treatment and a short follow-up period. It is possible that longer exposure and longer follow-up would demonstrate a different association between postmenopausal hormonal therapy and breast cancer, and be characterized by more interaction between this therapy and family history. The extant literature is inconsistent regarding a dose-dependent relation between duration of estrogen use and breast cancer risk.[6-10,12,24-26] Second, family history is measured only at baseline in the Women's Health Initiative. It is likely that some women categorized as not having a family history became aware of such a history during the follow-up period. If the occurrence of a new family history influenced the woman's adherence to the trial medication or led to more frequent self-examinations for breast lumps, then this misclassification could be differential and dependent. This misclassification would bias the hormonal therapy risk difference estimate among the family history negative group in an unpredictable direction, thus causing unpredictable bias of the IC. Nevertheless, we expect that the opportunity to influence the diagnosis of breast cancer either by study adherence or by detection behavior is low, given the small group of women likely to be misclassified with regard to family history and the short interval of follow-up. Therefore, we expect that any bias due to misclassification of family history is unlikely to have substantial impact on the observed interaction contrast. Finally, the Women's Health Initiative trial population represents a more educated and a somewhat healthier population with fewer racial minorities than the US population as a whole. While this is likely to influence the absolute rates of breast cancer, it is unknown how these differences might influence the interaction between family history and estrogen plus progesterone replacement therapy exposure on breast cancer. We posit that the biology of unrepresented groups is likely to be sufficiently similar as to yield similar conclusions. However, this remains to be examined.

Our study has unique and important strengths. First, this study takes advantage of randomized hormonal treatment. Prior work demonstrates that family history influences postmenopausal women's choices to use estrogen,[19] creating an important degree of confounding when examining the potential interaction between these 2 clinically-important breast cancer risk factors. Thus, randomized hormonal therapy allows a better estimate of the individual—and combined—effects of hormones and family history on breast cancer risk. Second, our approach to interaction on the additive scale provides clinically useful information for postmenopausal women and their physicians who are considering the use of postmenopausal hormonal therapy. Since family history is immutable and taking hormones is a personal choice having potential

clinical benefits, the absolute risks associated with choosing hormone therapy can help women decide whether the incremental breast cancer risk is acceptable.

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TABLE 1

Description of Study Sample: Postmenopausal Women With an Intact Uterus (Age: 50–79 Years) Enrolled in the Women's Health Initiative Randomized Trial of Estrogen Plus Progesterone Replacement Therapy (1993–1998)

		First-degree Family History			
		Yes		No	
Variable	**Full Sample (n = 16,608)**	**EP (n = 1009)**	**Placebo (n = 895)**	**EP (n = 7497)**	**Placebo (n = 7207)**
Invasive breast cancers; no.	349	35	25	164	125
Woman-years; no.	92,292	5596	4900	41,998	39,798
	No. (%)	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**
Age (years)					
50–59	5522 (33)	281 (28)	264 (30)	2558 (34)	2419 (34)
60–69	7510 (45)	464 (46)	399 (45)	3389 (45)	3258 (45)
70–79	3576 (22)	264 (26)	232 (26)	1550 (21)	1530 (21)
Ethnicity					
Hispanic	888 (5)	40 (4)	32 (4)	432 (6)	384 (5)
Black	1124 (7)	45 (5)	51 (6)	504 (7)	524 (7)
White, non-Hispanic	13,945 (84)	886 (88)	784 (88)	6254 (84)	6021 (84)
Other	610 (4)	36 (4)	23 (3)	291 (4)	260 (4)
Educational attainment					
<High school graduate	1114 (7)	67 (7)	43 (5)	508 (7)	496 (7)
High school graduate	3222 (20)	194 (19)	188 (21)	1420 (19)	1420 (20)
Some college	6415 (39)	384 (38)	348 (39)	2972 (40)	2711 (38)
Collage graduate	5753 (35)	359 (36)	308 (35)	2556 (35)	2530 (35)
Household income <$35,000	7521 (47)	508 (52)	453 (52)	3827 (53)	3768 (54)
BMI (m/kg^2)					
Underweight (<18.5)	57 (<1)	5 (<1)	4 (<1)	17 (<1)	31 (<1)
Normal (18.5–24.9)	5004 (30)	295 (29)	277 (31)	2263 (30)	2169 (30)
Overweight (25–29.9)	5831 (35)	346 (34)	317 (35)	2649 (35)	2519 (35)
Obese (≥30)	5643 (34)	362 (36)	296 (33)	2539 (34)	2446 (34)
Diet					
Fruit ≥1.5 servings/day	8453 (51)	527 (52)	466 (52)	3777 (51)	3683 (51)

Variable	Full Sample (n = 16,608)	First-degree Family History: Yes — EP (n = 1009)	First-degree Family History: Yes — Placebo (n = 895)	First-degree Family History: No — EP (n = 7497)	First-degree Family History: No — Placebo (n = 7207)
Vegetables ≥2 servings/day	7469 (45)	491 (49)	420 (47)	3294 (44)	3264 (45)
Walking ≥10 minutes episode (days/week)					
<1	7498 (45)	433 (43)	417 (47)	3386 (45)	3262 (45)
1–2	4185 (25)	265 (26)	229 (26)	1890 (25)	1801 (25)
≥3	4852 (29)	308 (31)	247 (28)	2188 (29)	2109 (29)
Smoking status					
Current	1718 (10)	95 (9)	87 (10)	785 (11)	751 (11)
Former	6519 (40)	388 (39)	357 (40)	2974 (40)	2800 (39)
Never	8177 (50)	519 (52)	439 (50)	3659 (49)	3560 (50)
Alcohol (drinks/week)					
<1	4717 (29)	304 (30)	242 (27)	2095 (28)	2076 (29)
1–6	9657 (59)	577 (58)	534 (60)	4417 (59)	4129 (58)
≥7	2095 (13)	120 (12)	114 (13)	927 (12)	934 (13)
Previous breast biopsies					
0	12,618 (83)	708 (78)	668 (80)	5632 (84)	5610 (84)
1	1928 (13)	157 (17)	128 (15)	799 (12)	844 (13)
≥2	578 (4)	39 (4)	44 (5)	251 (4)	244 (4)
Age at menarche <12 years	7631 (46)	495 (49)	387 (43)	3371 (45)	3378 (47)
Number of term pregnancies					
0	1688 (10)	95 (9)	90 (10)	761 (10)	742 (10)
1–2	8939 (54)	522 (52)	455 (51)	4096 (55)	3866 (54)
≥3	5903 (36)	390 (39)	348 (39)	2601 (35)	2564 (36)
Age at first birth ≥30 (among parous women)	1344 (10)	85 (10)	62 (9)	638 (11)	559 (10)
Breast-fed >6 months (among parous women)	4669 (32)	272 (30)	261 (33)	2141 (32)	1995 (31)
EP use prior to enrollment	4310 (26)	266 (26)	249 (28)	1963 (26)	1832 (25)

EP indicates estrogen plus progesterone replacement therapy.

TABLE 2

Interaction Between Family History (FH) and Estrogen Plus Progesterone (EP) on the Risk of Invasive Breast Cancer

	Strata of Family History by Estrogen Plus Progesterone Replacement			
	FH_1EP_1	FH_1EP_0	FH_0EP_1	FH_0EP_0
No. cases	35	25	164	125
No. women	1009	895	7497	7207
Risk	0.035	0.028	0.022	0.017
Interaction contrast (IC)	$= (R_{FH = 1, EP = 1} - R_{FH = 1, EP = 0}) - (R_{FH = 0, EP = 1} - R_{FH = 0, EP = 0})$ = (0.035 – 0.028) – (0.022 – 0.017) = 0.002 (95% CI = −0.014 to 0.018)			