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Menstrual and reproductive history, postmenopausal hormone use, and risk of benign proliferative epithelial disorders of the breast: a cohort study

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Abstract Menstrual and reproductive history and postmenopausal hormone use are well-established risk factors for breast cancer. However, previous studies that have assessed these factors in association with risk of benign proliferative epithelial disorders (BPED) of the breast, putative precursors of breast cancer, have yielded inconsistent findings. To investigate these associations, we conducted a cohort study among 68,132 postmenopausal women enrolled in the Women's Health Initiative randomized clinical trials. Women were prospectively followed and those reporting an open surgical biopsy or a core needle biopsy had histological sections obtained for centralized pathology review. Over an average of 7.8 years of follow-up, we identified 1,792 women with BPED of the breast. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence limits (CLs) for the associations of interest. Menstrual and reproductive histories were not associated with risk of BPED of the breast, overall or by histological subtype. Women who had used postmenopausal hormones for 15 years or more had a two-fold increase in risk of BPED of the breast compared to women who had never used postmenopausal hormones (HR = 2.03 95% CL = 1.73, 2.38) and the increase in risk was observed for both BPED of the breast without atypia and for atypical hyperplasia. Furthermore, the risk of BPED of the breast decreased with time since cessation of use so that there was essentially no increase in risk 5 or more years after ending use (HR for stopping ≥5 years earlier = 0.96, 95%CL = 0.79, 1.16; HR for stopping <5 years earlier = 1.32, 95% CL = 1.08,1.61).

Keywords Menstrual history · Reproductive history · Postmenopausal hormone use · Benign proliferative epithelial disorders of the breast

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Introduction

Benign breast disease consists of many histological entities, which can be broadly categorized into two major groups: non-proliferative benign breast disease and benign proliferative epithelial disorders (BPED) of the breast with or without atypia [1]. Women with BPED of the breast are at increased risk of developing subsequent breast cancer, whereas those with non-proliferative benign changes are not [1]. The estimated relative risks are 1.5–2.0 for BPED without atypia and 4–5 for BPED with atypia (atypical hyperplasia), respectively [2]. Along with epidemiological observations, experimental studies suggest that non-atypical proliferative changes and atypical hyperplasia represent successive steps preceding the development of breast cancer in situ and then invasive carcinoma of the breast [3].

If BPED of the breast are precursors of breast cancer, then risk factors for the former should be a subset of those for the latter [1]. In fact, previous studies that have assessed the

etiology of BPED of the breast have mainly focused on well-established or suspected risk factors for breast cancer. Among the latter are menstrual and reproductive factors and exogenous hormone use, reflecting the strong evidence in support of a hormonal etiology for breast cancer [4]. However, the results of previous studies of these factors in relation to risk of BPED have not been consistent [5–16]. The discrepancies may reflect the fact that some of previous studies were limited by small sample sizes, selection bias due to use of the case-control design, potential residual confounding, and incomplete ascertainment of cases with BPED of the breast. These limitations suggest that large prospective studies in regularly screened populations are warranted to further elucidate the etiology of BPED of the breast. However, there have been very few such prospective studies to date [14, 15].

Given these considerations, we investigated menstrual and reproductive history and postmenopausal hormone use in association with risk of BPED of the breast and its histological subtypes in the Women's Health Initiative (WHI) clinical trials, by building upon an ongoing ancillary study of benign proliferative epithelial disorders of the breast. In this study, bias was minimized due to the prospective design and to the regular physical exams and mammograms undergone by the study participants. We will address oral contraceptive use in relation to risk of BPED in a separate manuscript.

Methods

Study population

Our investigation was conducted in the WHI randomized clinical trials which comprised two postmenopausal hormone trials, a dietary modification trial, and a calcium-vitamin D supplementation trial [17]. Participants in the calcium-vitamin D supplementation trial were enrolled from those women who were either in the postmenopausal hormone trials or in the dietary modification trial, or both. The trials involved 68,132 postmenopausal women who were recruited and randomized during 1993 and 1998 in 40 U.S. clinic centers. The study design, implementation, and characteristics of the study populations have been documented in detail elsewhere [17–20]. Women in the postmenopausal hormone trials underwent annual clinical breast exams and mammograms, while women in the dietary modification trial underwent biennial mammograms. Women with a self-reported history of benign breast disease were not excluded from the study.

Case ascertainment

The trial participants completed medical history update questionnaires every 6 months. The questionnaires asked the participants to report breast exams, mammograms, and tests of breast tissue or fluid for disease. In the ongoing ancillary study, women who had undergone a breast procedure (open surgical biopsy or core needle biopsy) were asked to provide consent for retrieval of the histological sections resulting from the procedures, and the sections then underwent centralized histological review. As of September 2005, 4,531 surgical or core needle biopsies had been performed among the trial participants, and consent from participants had been obtained for 4,325 biopsies (some participants had had more than 1 biopsy). Among those 4,325 biopsies, 4,225 were obtained and reviewed by the study pathologist.

Histopathology

The histological sections were reviewed by the study pathologist without knowledge of randomization assignment in the clinical trials and other exposure information. They were assessed for the presence of benign proliferative epithelial disorders and these lesions were further characterized according to the presence or absence of atypia [21]. In addition, histological sections were assessed for the presence of fibroadenoma, sclerosing adenosis, and micropapilloma.

Case definition

Cases were defined as women who were diagnosed with an incident BPED of the breast during the follow-up period. As of September 2005, a total of 1,792 incident cases of BPED of the breast had been identified among the trial participants after an average of 7.8 years of follow-up. The cases were categorized into two groups: women with non-atypical epithelial proliferation (BPED without atypia) and women with atypical hyperplasia (BPED with atypia). Of the 1,792 cases, 294 had atypical hyperplasia and 1,498 had a non-atypical form of BPED of the breast.

Exposure assessment

Upon enrollment, all WHI clinical trial participants completed a series of questionnaires which sought information on demographic characteristics, personal habits, menstrual and reproductive history, exogenous hormone use, medical history, and family history of cancer. The menstrual history variables included age at menarche, age at menopause, and years with menstrual periods, while the reproductive history variables included parity, age at first full-term pregnancy, history of stillbirths and spontaneous miscarriages, breast-feeding history, and history of bilateral oophorectomy. With regard to postmenopausal hormone (PMH) use, data were collected on use status (never, former, current),

duration of PMH use, age at which PMH use started, age at which PMH use stopped, and years since last use of PMHs.

Statistical analysis

Cox proportional hazards models (using time-on-study as the time scale) were used to estimate hazard ratios (HRs) and 95% confidence limits (CLs) for risk of BPED of the breast, overall and by histological subtype, in association with the exposures of interest. Cases contributed person-time to the study from their date of enrollment until the date of BPED diagnosis, and non-cases (participants who were censored) contributed person-time from their date of enrollment until the end of follow-up, date of death, date of withdrawal from the study, or the date on which they ceased to be at risk of developing BPED of the breast (e.g., due to the development of breast cancer or due to a bilateral prophylactic mastectomy), whichever came first.

In multivariate analyses, we controlled for age at baseline (continuous), ethnicity (non-Hispanic white, black/African American, Hispanic/Latino, and other ethnic groups), region of residence (Northeast, South, West, and Midwest), randomization groups (categorical), frequency of breast exams during follow-up (continuous), and frequency of mammograms during follow-up (continuous). For each of the exposures of interest, we also further controlled for well-established risk factors for breast cancer to assess their potential confounding effects. These factors included some of the exposures of interest, namely, age (years) at menarche (<12, 12, 13, 14+), age (years) at menopause (<41, 41–45, 46–50, 51–55, 56+, with a separate category for missing), parity (0, 1–2, 3–4, 5+), age at first full-term pregnancy (nulliparous, <20, 20–24, 25–29, 30+), years of oral contraceptive use (0, >0–1, >1–5, >5), and years of postmenopausal hormone use (0, >0–<5, 5–<10, 10–<15, 15+), as well as body mass index (continuous), history of benign breast disease (yes vs. no), and family history of breast cancer (yes vs. no). We did not control for tobacco smoking, alcohol drinking, and folate intake in multivariate analyses because these factors were not associated with risk of BPED of the breast in this population [22, 23].

For tests of trend in risk across successive levels of categorical variables, we assigned the categories their ordinal number and then fitted the resulting variable as a continuous variable in the models. We then evaluated the statistical significance of the corresponding coefficient using the Wald test [24]. To assess etiological differences between non-atypical BPED and atypical hyperplasia, we examined their associations with exposures of interest separately. All statistical analyses were performed in SAS 9.1 (SAS Institute, Cary, NC). *P*-values were two-sided.

Results

We followed the cohort of 68,132 postmenopausal women for an average of 7.8 years and identified 1,792 incident cases of BPED of the breast (294 with atypia and 1,498 without atypia). The estimated incidence rate of BPED of the breast was 339/100,000 per year. Compared with non-cases, cases were younger, were more likely to be non-Hispanic white and to reside in the Midwest (data not shown). Furthermore, cases had had fewer breast exams and mammograms than non-cases, which was due to the fact that cases were on average followed for a shorter period of time than non-cases (data not shown).

BPED of the breast, either overall or by specific histological subtypes, were not associated with age at menarche, age at menopause, and total years with menstrual periods in multivariate models with adjustment for age, ethnicity, region of residence, randomization assignment, and frequency of physical exams and mammograms (Table 1). Further adjustment for reproductive history, exogenous hormone use, body mass index, family history of breast cancer, and history of benign breast disease in multivariate models did not change the results appreciably (data not shown).

There was little association between risk of BPED of the breast, overall and for its histological subtypes, and parity, age at first full-term pregnancy, history of stillbirths and miscarriages, and breastfeeding (Table 2). Further control for menstrual history, exogenous hormone use, body mass index, family history of breast cancer, and history of benign breast disease did not change the aforementioned estimates substantially. In multivariate models, a history of bilateral oophorectomy was positively associated with BPED of the breast overall and with non-atypical BPED of the breast, but not with atypical hyperplasia. However, the positive associations for BPED overall and for non-atypical BPED disappeared after further adjustment for postmenopausal hormone use. Additional control for menstrual history, OC use, body mass index, family history of breast cancer, and history of benign breast disease in multivariate models did not further change the estimates appreciably.

Positive trends with risk of BPED of the breast were observed for duration of PMH use, age at which PMH use started, and age at which PMH use stopped (Table 3). Women who had used PMH for 15 years or more had a two-fold increase in risk of BPED of the breast compared to women who had never used PMH (HR = 2.03 95% CL = 1.73, 2.38). The risk of BPED of the breast decreased gradually after women stopped using PMH over the time and disappeared after women had stopped using PMH for 5 years or more (HR for stopping ≥5 years earlier = 0.96, 95% CL = 0.79, 1.16; HR for stopping

Table 1 Association between menstrual history and risk of BPED of the breast

	Person-years	# of cases			HR (95% CL)[a]		
		All	Nonatypia	Atypia	BPED overall	Non-atypical BPED	Atypical hyperplasia
Age at menarche							
<12	115,033	380	323	57	1.0	1.0	1.0
12	137,530	489	417	72	1.08 (0.95, 1.24)	1.09 (0.94, 1.26)	1.08 (0.76, 1.52)
13	151,872	530	434	96	1.06 (0.93, 1.21)	1.02 (0.88, 1.18)	1.29 (0.93, 1.80)
14+	122,988	388	320	68	0.98 (0.85, 1.13)	0.94 (0.81, 1.10)	1.17 (0.82, 1.66)
P trend					0.66	0.31	0.23
Age at menopause[b]							
≤40	78,480	308	272	36	1.0	1.0	1.0
41–45	67,243	233	193	40	0.89 (0.75, 1.07)	0.84 (0.69, 1.01)	1.33 (0.85, 2.10)
46–50	125,996	398	326	72	0.81 (0.69, 0.94)	0.75 (0.63, 0.88)	1.27 (0.84, 1.91)
51–55	123,143	422	353	69	0.87 (0.74, 1.02)	0.82 (0.69, 0.97)	1.23 (0.80, 1.87)
56+	42,047	167	142	25	1.03 (0.85, 1.25)	0.99 (0.80, 1.22)	1.33 (0.79, 2.25)
P trend					0.63	0.35	0.38
Total years with menstrual periods[b]							
<30	94,818	369	321	48	1.0	1.0	1.0
30–<35	79,999	264	217	47	0.85 (0.73, 1.00)	0.80 (0.67, 0.96)	1.18 (0.79, 1.78)
35–<40	137,640	426	353	73	0.79 (0.68, 0.92)	0.75 (0.64, 0.88)	1.04 (0.71, 1.52)
40+	123,856	465	392	73	0.97 (0.84, 1.12)	0.94 (0.80, 1.10)	1.17 (0.80, 1.71)
P trend					0.66	0.46	0.58

[a] Adjusted for age at baseline, ethnicity, region of residence, randomization assignment, and frequency of physical exams and mammograms

[b] Approximately 15% of the participants had missing data

<5 years earlier = 1.32, 95% CL = 1.08,1.61). The association with duration and recency of PMH use was similar for non-atypical BPED of the breast and atypical hyperplasia, although numbers of cases in some categories of the latter were limited.

Both unopposed estrogen and estrogen given in conjunction with progesterone were associated with an increased risk of BPED of the breast and its histological subtypes (Table 4). However, the associations appeared stronger for estrogen and progesterone combined than for unopposed estrogen, especially with respect to atypical hyperplasia. Further control for well-established breast cancer risk factors including menstrual history, reproductive factors, OC use, body mass index, family history of breast cancer, and history of benign breast disease in multivariate models did not change the estimated hazard ratios for various PMH measures substantially. Moreover, with mutual control for using unopposed estrogen and using estrogen in conjugation with progesterone, years since last use of unopposed estrogen were not associated with risk of BPED of the breast, while an association was observed for years since last use of estrogen and progesterone combined (Stopping ≥15 years earlier = 1.50, 95% CL = 0.80, 2.80; Stopping <15 years earlier = 2.21, 95% CL = 1.83, 2.67).

Discussion

Both endogenous levels of sex hormones [25] and exogenous hormone use [26, 27] have been associated with an increased risk of breast cancer among postmenopausal women. These epidemiological observations are consistent with experimental evidence linking estrogen and/or progesterone with increased proliferation of mammary epithelial tissue [4]. The increased proliferation associated with estrogen and/or progesterone is potentially relevant to BPED of the breast. A recent study [28] among postmenopausal women associated serum concentrations of estrogens with an increased risk of breast hyperplasia when non-proliferative changes of the breast were used as a reference group (bioavailable estradiol, highest vs. lowest quartile: OR = 4.3, 95% CL = 1.9, 9.5). Proliferative benign breast lesions express estrogen and progesterone receptors [29, 30], and treatment with tamoxifen, a selective estrogen receptor modulator, was associated with a reduced incidence of BPED of the breast with or without atypia in the Breast Cancer Prevention Trial [31].

In the study reported here, we investigated BPED of the breast in association both with menstrual and reproductive history, which might reflect exposure of the breast to endogenous hormones, and with use of postmenopausal

Table 2 Association between reproductive history and risk of BPED of the breast

	Person-years	# of cases			HR (95% CL)[a]		
		All	Nonatypia	Atypia	BPED overall	Non-atypical BPED	Atypical hyperplasia
Parity							
Nulliparous	56,120	175	142	33	1.0	1.0	1.0
1–2	167,736	618	521	97	1.18 (0.99, 1.39)	1.22 (1.01, 1.47)	0.99 (0.67, 1.47)
3–4	214,171	737	611	126	1.10 (0.94, 1.30)	1.12 (0.94, 1.35)	1.02 (0.69, 1.49)
5+	88,448	258	222	36	0.96 (0.79, 1.16)	1.01 (0.82, 1.25)	0.72 (0.45, 1.17)
P trend					0.21	0.38	0.26
Age at first full-term pregnancy							
Nulliparous	56,120	175	142	33	1.0	1.0	1.0
30+	36,525	132	105	27	1.19 (0.95, 1.49)	1.16 (0.90, 1.50)	1.32 (0.79, 2.19)
25–29	105,260	388	330	58	1.20 (1.00, 1.43)	1.25 (1.02, 1.52)	0.97 (0.63, 1.48)
20–24	205,107	706	586	120	1.09 (0.92, 1.28)	1.11 (0.92, 1.33)	1.00 (0.68, 1.47)
<20	77,458	265	228	37	1.09 (0.90, 1.32)	1.16 (0.94, 1.43)	0.81 (0.50, 1.30)
P trend					0.87	0.50	0.27
Ever had stillbirths							
Never	456,891	1,567	1,314	253	1.0	1.0	1.0
Ever	22,913	87	71	16	1.18 (0.95, 1.47)	1.15 (0.90, 1.46)	1.36 (0.82, 2.25)
Number of spontaneous miscarriages							
0	316,720	1,079	912	167	1.0	1.0	1.0
1	107,607	373	311	62	1.03 (0.91, 1.16)	1.01 (0.89, 1.15)	1.10 (0.83, 1.48)
2+	57,720	208	168	40	1.10 (0.95, 1.28)	1.05 (0.89, 1.24)	1.36 (0.96, 1.93)
P trend					0.22	0.57	0.087
Months of breastfeeding							
0	251,133	828	696	132	1.0	1.0	1.0
1–6	136,223	464	380	84	1.05 (0.94, 1.18)	1.02 (0.90, 1.15)	1.21 (0.92, 1.60)
7–12	58,606	211	180	31	1.08 (0.93, 1.26)	1.10 (0.93, 1.29)	1.01 (0.69, 1.50)
13–23	46,268	176	149	27	1.15 (0.97, 1.35)	1.15 (0.96, 1.38)	1.11 (0.73, 1.68)
24+	30,637	100	82	18	0.98 (0.79, 1.20)	0.95 (0.75, 1.19)	1.13 (0.69, 1.85)
P trend					0.30	0.38	0.56
Ever had bilateral oophorectomy							
No	418,167	1,384	1,145	239	1.0	1.0	1.0
Yes, model 1[a]	98,009	377	327	50	1.16 (1.03, 1.30)	1.21 (1.07, 1.38)	0.88 (0.64, 1.21)
Yes, model 2[b]	98,009	377	327	50	0.99 (0.87, 1.12)	1.03 (0.90, 1.19)	0.78 (0.56, 1.09)

[a] Adjusted for age at baseline, ethnicity, region of residence, randomization assignment, and frequency of physical exams and mammograms

[b] Further adjustment for postmenopausal hormone use

hormones use. The main finding of our study was that PMH use was associated with an approximately two-fold increased risk of BPED of the breast. In addition to duration of PMH use, recency of PMH use showed a strong association with risk of BPED of the breast. The effect of PMH use disappeared after women had stopped using PMHs for 5 years or more, similar to epidemiological observations for breast cancer [26]. Moreover, our data suggest estrogen and progesterone combined are more strongly associated with risk of BPED of the breast than unopposed estrogens. This is in accordance with the epidemiological observations for breast cancer [27, 32] and the experimental evidence that estrogen given in conjunction with progesterone induces greater breast cell proliferation than estrogen alone in postmenopausal macaques [33].

The association between PMH use and BPED of the breast has not been well-studied among postmenopausal women. Published case-control studies have generally been limited by small sample sizes [7, 8], non-population-based study designs [5, 7, 8], and an inappropriate reference group [8]. Of these studies, one [7] observed an inverse association with risk of benign breast disease and the other two [5, 8] reported little association with BPED of the

Table 3 Association between postmenopausal hormone (PMH) use and risk of BPED of the breast

	Person-years	# of cases			HR (95% CL)		
		All	Nonatypia	atypia	BPED overall	Non-atypical BPED	Atypical hyperplasia
Status[a]							
Never	255,022	637	521	116	1.0	1.0	1.0
Past	93,092	259	223	36	1.14 (0.99, 1.33)	1.20 (1.02, 1.41)	0.89 (0.61, 1.30)
Current	180,717	894	752	142	2.13 (1.89, 2.40)	2.23 (1.95, 2.54)	1.71 (1.28, 2.27)
Duration (years) of PMH use[a]							
Never	255,022	637	521	116	1.0	1.0	1.0
>0–<5	119,614	428	361	67	1.41 (1.24, 1.60)	1.47 (1.28, 1.69)	1.16 (0.85, 1.59)
5–<10	60,652	273	235	38	1.77 (1.52, 2.06)	1.89 (1.60, 2.22)	1.27 (0.86, 1.87)
10–<15	41,995	211	178	33	2.06 (1.75, 2.43)	2.15 (1.80, 2.57)	1.67 (1.11, 2.50)
15+	51,926	243	203	40	2.03 (1.73, 2.38)	2.09 (1.75, 2.49)	1.78 (1.21, 2.63)
P trend					<0.0001	<0.0001	0.0009
Age started using PMH among users[b]							
<45	63,444	249	222	27	1.0	1.0	1.0
45–49	66,244	288	236	52	1.27 (1.05, 1.53)	1.15 (0.95, 1.41)	2.30 (1.38, 3.86)
50–54	84,331	373	304	69	1.41 (1.16, 1.71)	1.27 (1.03, 1.56)	2.69 (1.55, 4.68)
55+	60,178	245	215	30	1.61 (1.27, 2.04)	1.54 (1.20, 1.98)	2.23 (1.10, 4.54)
P trend					<0.0001	0.0007	0.022
Age stopped taking PMH among past users[b]							
<50	25,822	66	59	7	1.0	1.0	1.0
50–54	26,378	63	54	9	0.90 (0.63, 1.29)	0.87 (0.59, 1.27)	1.21 (0.44, 3.31)
55–59	20,476	60	52	8	1.14 (0.79, 1.64)	1.09 (0.74, 1.60)	1.73 (0.60, 5.00)
60+	20,415	70	58	12	1.56 (1.06, 2.29)	1.36 (0.90, 2.07)	4.16 (1.35, 12.81)
P trend					0.020	0.12	0.015
Years since stopped taking PMH[b]							
Never user	255,022	637	521	116	1.0	1.0	1.0
15+	30,274	64	60	4	0.88 (0.68, 1.14)	1.00 (0.76, 1.32)	0.31 (0.11, 0.84)
10–<15	9,694	24	23	1	1.00 (0.67, 1.51)	1.17 (0.77, 1.79)	0.23 (0.03, 1.67)
5–<10	15,684	43	36	7	1.08 (0.79, 1.47)	1.10 (0.78, 1.55)	0.97 (0.45, 2.10)
>0–<5	37,440	128	104	24	1.32 (1.08, 1.61)	1.31 (1.05, 1.63)	1.39 (0.87, 2.21)
Current user	180,717	894	752	142	1.99 (1.72, 2.30)	2.07 (1.76, 2.43)	1.64 (1.15, 2.34)
P trend					<0.0001	<0.0001	0.0051

[a] Adjusted for age at baseline, ethnicity, region of residence, randomization assignment, and frequency of physical exams and mammograms

[b] Further adjusted for duration (years) of PMH use

breast or fibrocystic breast disease with atypia. To date, only one cohort study has been published that assessed the association between PMH use and BPED of the breast. Consistent with our results, this cohort study [15] observed an increased risk of BPED of the breast in association with a long-term PMH use (8 years vs. never: RR = 1.70, 95% CL = 1.06, 2.72).

The few published studies [6, 8, 9, 11, 16] that have assessed menstrual and reproductive factors in association with risk of proliferative forms of benign breast disease have yielded inconsistent results. Some studies observed a positive association with a late age at menopause [6] and an inverse association with parity [9, 11], while others observed no association with age at menarche [6, 8, 11, 16], age at menopause [6, 8], parity [6, 8, 16], age at first live birth [6, 8, 9, 16], and breastfeeding [8, 11, 16]. Notably, these studies were generally subject to selection bias [6, 8], were underpowered due to small sample sizes [8, 9, 11, 16], and were not stratified on menopausal status [8, 9, 11, 16]. The association between risk of proliferative forms of benign breast disease and stillbirths, miscarriages, and bilateral oophorectomy was not investigated in these studies. In the study reported here, no associations with BPED of the breast and its histological subtypes were observed for menstrual and reproductive factors.

The strengths of our study include the large sample size, the prospective study design, essentially complete follow-up of the cohort, intensive breast exams and mammograms

Table 4 Associations between durations of unopposed estrogen and estrogen/ progesterone use and risk of BPED of the breast

	HR (95% CL)		
	BPED overall	Non-atypical BPED	Atypical hyperplasia
Duration (years) of unopposed estrogen use[a]			
0	1.0	1.0	1.0
>0–<5	1.25 (1.08, 1.43)	1.30 (1.12, 1.51)	1.01 (0.71, 1.43)
5–<10	1.57 (1.32, 1.87)	1.76 (1.47, 2.12)	0.75 (0.43, 1.30)
10–<15	1.43 (1.16, 1.76)	1.59 (1.27, 1.98)	0.75 (0.40, 1.44)
15+	1.93 (1.64, 2.28)	1.97 (1.64, 2.36)	1.77 (1.19, 2.65)
P trend	<0.0001	<0.0001	0.072
Duration (years) of estrogen/progesterone use[b]			
0	1.0	1.0	1.0
>0–<5	1.27 (1.10, 1.46)	1.29 (1.10, 1.50)	1.17 (0.82, 1.68)
5–<10	1.83 (1.54, 2.17)	1.76 (1.46, 2.13)	2.15 (1.46, 3.18)
10+	2.19 (1.82, 2.65)	2.12 (1.72, 2.61)	2.55 (1.65, 3.94)
P trend	<0.0001	<0.0001	<0.0001

[a] Adjusted for age at baseline, ethnicity, region of residence, randomization assignment, frequency of physical exams and mammograms, and duration of estrogen/progesterone use

[b] Adjusted for age at baseline, ethnicity, region of residence, randomization assignment, frequency of physical exams and mammograms, and duration of unopposed estrogen use

undergone by study participants, and comprehensive baseline data. By far, this is the largest study that has assessed risks of BPED of the breast and its histological subtypes in association with menstrual and reproductive history and exogenous hormone use. Selection bias is presumably minimal in our study due to the prospective study design and the essentially complete follow-up of the cohort. Furthermore, the trial participants underwent intensive breast exams and mammograms, which might have maximized the ascertainment of cases with BPED of the breast and consequently minimized selection bias. Indeed, the incidence rate of BPED of the breast in our cohort was much higher than previously reported [34], supportive of better case ascertainment in our study. Finally, to control for potential confounding, we adjusted for a wide range of potential BPED risk factors in multivariate analyses.

In conclusion, we observed that PMH use was associated with an increased risk of BPED of the breast overall, and by histological subtype. This finding raises the possibility that the association of postmenopausal hormone use with breast cancer risk might result from an increase in the risk of the putative precursors of breast cancer.

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Appendix

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