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ORIGINAL PAPER

Cigarette smoking and risk of benign proliferative epithelial disorders of the breast in the Women's Health Initiative

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Abstract
Objective To investigate the association between cigarette smoking and risk of benign proliferative epithelial disorders (BPED) of the breast.
Methods We used data from an ancillary study of benign breast disease that is being conducted in the Women's Health Initiative randomized clinical trials among 68,132 postmenopausal women aged 50–79 at recruitment. After following the trial participants for an average of 7.8 years, we had ascertained 294 incident cases with atypical hyperplasia and 1,498 incident cases with non-atypical BPED of the breast. We used Cox proportional hazards models to estimate hazard ratios for the association between cigarette smoking and risk of BPED.
Results Smoking measures, including duration of smoking, intensity of smoking, pack-years of smoking, age at which smoking commenced, and years since quitting smoking, were not associated with risk of BPED overall or by histological subtypes.
Conclusion The null association between cigarette smoking and risk of BPED of the breast suggests that the carcinogenic and antiestrogenic effects of cigarette smoking on the breast might counterbalance each other and that cigarette smoking might have no overall effects on BPED of the breast among postmenopausal women.

Keywords Smoking · Risk · Benign proliferative epithelial disorders of the breast · Cohort study

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Introduction

A number of the carcinogens found in cigarette smoke can be stored in breast adipose tissue, and then metabolized and activated by human mammary epithelial cells [1, 2]. Experimental studies have demonstrated that these carcinogens [including polycyclic aromatic hydrocarbons and *N*-nitrosomines] are potential human breast carcinogens, and smoking-specific DNA adducts are more common in the breast tissue of smokers compared with nonsmokers [3–6]. Given this, it has been suggested that cigarette smoking might be a risk factor for breast cancer. In contrast, cigarette smoking also appears to have antiestrogenic effects, which might protect against breast cancer due to the fact that estrogen is a well-established risk factor

for breast cancer [7]. Hence, the association between cigarette smoking and breast cancer risk may depend upon the balance between these opposing effects. To date, the evidence overall suggests that cigarette smoking does not decrease breast cancer risk, and indeed suggests that long-term smoking may increase breast cancer risk [8]. This raises the possibility that cigarette smoking may also be associated with increased risk of benign proliferative epithelial disorders (BPED) of the breast, conditions which are possible precursors of breast cancer [9].

Only three epidemiological studies have investigated the association between cigarette smoking and risk of BPED of the breast. An early case–control study in Australia observed no difference in smoking history between cases with BPED and both clinic and community controls [10]. Similarly, no difference in smoking history was found between women with BPED and women whose biopsy showed no evidence of epithelial proliferation in a nested case–control study in Canada [11]. Moreover, the Canadian National Breast Screening Study provided little evidence that cigarette smoking was related to BPED of the breast [12]. However, these studies were subject to certain limitations such as incomplete ascertainment of cases, selection bias in the case–control studies, and relatively small sample sizes. These limitations suggest the need for large prospective studies among screened populations, in which selection bias and incomplete ascertainment of cases can be minimized [12].

We examined the association between cigarette smoking and risk of BPED of the breast using cases ascertained in the Women's Health Initiative (WHI) clinical trial study population as part of an ancillary study of BPED. In this setting, both selection bias and incomplete ascertainment of cases were minimized due to the prospective design and by the regular physical exams and mammograms undergone by study participants.

Materials and methods

Study population

The WHI randomized clinical trials comprise several overlapping components including two postmenopausal hormone trials (for women with and without prior hysterectomy), a dietary modification trial, and a calcium-vitamin D trial. The trials were conducted among 68,132 postmenopausal women aged 50–79 at enrollment and randomized between 1993 and 1998 at 40 clinics across the United States. The study design, implementation, and characteristics of study population have been described in detail elsewhere [13–16]. Women in the hormone trials had annual clinical breast exams and mammograms, while women in the dietary modification trial had biennial mammograms. Study participants in the calcium–vitamin D trial were recruited from the participants who were either in one of the hormone trials or in the dietary modification trial.

Case ascertainment

Every six months, all participants completed medical history update questionnaires which sought information on breast procedures (open surgical biopsy or core needle biopsy). Medical record and pathology reports were routinely collected for women reporting either invasive or non-invasive breast cancer diagnosis. In the Benign Breast Disease Ancillary Study, which was conducted in all clinical centers participating the WHI clinical trials, those women who had undergone a breast biopsy were contacted and asked to provide consent for review of the histological sections resulting from the biopsy. For those women who provided consent, the histological sections were sought from the appropriate hospital or clinic. 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 one biopsy). Histological sections were obtained for 4,225 of the 4,325 biopsies and reviewed by the study pathologist. The ancillary study was approved by the appropriate Institutional Review Boards, and informed consent was obtained from all study participants.

Histopathology

The histological sections were reviewed without knowledge of randomization groups or of other exposure information. They were classified according to the scheme employed by Page, which has been described in detail elsewhere [17]. Briefly, use of this scheme entailed us making an evaluation of the presence of epithelial proliferation and the presence of atypia in those with a benign proliferative epithelial disorder. For participants who had had multiple biopsies during the follow-up period, the earliest biopsy with a diagnosis of BPED of the breast was used as the end-point of interest and any biopsies performed afterwards were not taken into consideration. In addition, histological sections were evaluated for the presence/absence of fibroadenoma, sclerosing adenosis, and micropapilloma.

Case definition

Cases were defined as women with an incident benign proliferative epithelial disorder of the breast (with or without atypia) that arose during follow-up in the WHI clinical trials. 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 further 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 (including cigarette smoking), reproductive history, hormone use, medical history, family history, and dietary intake. Regarding cigarette smoking, participants were first asked whether or not they had ever smoked at least 100 cigarettes. Women who had smoked were then asked age at which they started smoking regularly, how many cigarettes they usually smoked per day, and how many years they had smoked regularly. If women were former smokers, they were asked age at which they had ceased smoking. Pack-years of smoking were calculated by multiplying the mid-point of the smoking duration category for an individual by the mid-point of the smoking intensity category for the same individual and then dividing by 20. For former smokers, years since cessation of smoking were calculated by subtracting the mid-point of age category at which smoking ceased from age at recruitment.

Statistical analysis

Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence limits (CLs) for the association between cigarette smoking and risk of BPED. For these analyses, cases contributed person-time to the study from their date of enrollment until the date of diagnosis of their BPED, 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 date of ceasing to be at risk of developing BPED (e.g., due to the development of breast cancer or due to a bilateral prophylactic mastectomy), whichever came first. We evaluated risk of BPED in association with smoking status (never, former, current), duration of smoking (years), intensity of smoking (cigarettes per day), pack-years of smoking, age at which smoking started, and years since quitting smoking. In multivariate analyses, we controlled for age at recruitment (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 physical exams during follow-up period (continuous), and frequency of mammograms during follow-up period (continuous). We further controlled for age at menarche (<12, 12, 13, 14+), age at menopause (<46, 46–50, 51–55, 56+, with a separate category for missing), number of live births (0, 1–2, 3–4, 5+), years of oral contraceptive (OC) use (0, >0–1, >1–4, >4–8, >8), years of postmenopausal hormone use (0, >0 to <5, 5 to <10, 10 to <15, 15+), body mass index (BMI) (continuous), and family history of breast cancer (yes or no, with a separate category for missing) to assess potential confounding effects by these factors. To explore the etiological difference between non-atypical BPED and atypical hyperplasia, we investigated their associations with cigarette smoking separately. For tests of trend in risk across successive levels of categorical variables, we assigned the categories their ordinal number and then fitted the assigned value of each risk factor as a continuous variable in the risk models. We then evaluated the statistical significance of the corresponding coefficient using the Wald test [18]. Tests for interaction were based on the likelihood ratio tests comparing models with or without product terms representing the variables of interest. The likelihood ratio test that all of the interaction parameters were 0 was conducted by referring 2* the absolute difference in the log likelihoods of models with or without interaction terms to the X^2 distribution on degrees of freedom equal to the number of interaction parameters. 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) during the follow-up period. The annual incidence rate of BPED of the breast was 339/100,000. The characteristics of cases of BPED of the breast and non-cases are summarized in Table 1.

Table 1 Characteristics of cases of BPED and non-cases

	n (%)	
	Cases of BPED	Non-cases
Total number	1,792	66,340
Age at baseline		
50–54	285 (15.9)	8,905 (13.4)
55–59	422 (23.6)	14,241 (21.5)
60–64	475 (26.5)	16,377 (24.7)
65–69	362 (20.2)	14,175 (21.4)
70–74	199 (11.1)	9,065 (13.6)
75–79	49 (2.7)	3,577 (5.4)
Region of residence		
Northeast	391 (21.8)	15,249 (23.0)
South	446 (24.9)	17,014 (25.7)
Midwest	467 (26.1)	14,489 (21.8)
West	488 (27.2)	19,588 (29.5)
Ethnicity		
Non-Hispanic White	1,522 (84.9)	53,998 (81.4)
Black/African American	138 (7.7)	6,850 (10.3)
Hispanic/Latino	50 (2.8)	2,839 (4.3)
Other	75 (4.2)	2,510 (3.8)
Missing	7 (0.4)	143 (0.2)
BMI		
<25	534 (29.8)	18,003 (27.1)
25 to <30	646 (36.0)	23,559 (35.5)
30+	605 (33.8)	24,448 (36.9)
Missing	7 (0.4)	330 (0.5)
Family history of breast cancer		
No	1,344 (75.0)	51,823 (78.1)
Yes	356 (19.9)	10,926 (16.5)
Missing	92 (5.1)	3,591 (5.4)
Age at menarche		
<12	380 (21.2)	14,459 (21.8)
12	489 (27.3)	17,212 (25.9)
13	530 (29.6)	18,988 (28.6)
14+	388 (21.6)	15,448 (23.3)
Missing	5 (0.3)	233 (0.4)
Age at menopause		
≤40	308 (17.2)	10,096 (15.2)
41–45	233 (13.0)	8,681 (13.1)
46–50	398 (22.2)	16,127 (24.3)
51–55	422 (23.6)	15,780 (23.8)
56+	167 (9.3)	5,474 (8.3)
Missing	264 (14.7)	10,182 (15.3)
Years of OC use		
0	905 (50.5)	37,703 (56.8)
>0–1	255 (14.2)	8,749 (13.2)
>1–4	214 (12.0)	6,801 (10.3)
>4–8	192 (10.7)	5,910 (8.9)
>8	224 (12.5)	7,157 (10.8)
Missing	2 (0.1)	20 (0.0)
Years of postmenopausal hormone use		
0	637 (35.5)	32,227 (48.6)
>0 to <5	428 (23.9)	14,705 (22.2)
5 to <10	273 (15.2)	7,469 (11.2)
10 to <15	211 (11.8)	5,283 (8.0)
15+	243 (13.6)	6,655 (10.0)
Missing	0 (0.0)	1 (0.0)
Number of live births		
0	178 (9.9)	7,161 (10.8)
1–2	635 (35.4)	21,540 (32.5)
3–4	741 (41.4)	26,708 (40.3)
5+	234 (13.1)	10,575 (15.9)
Missing	4 (0.2)	356 (0.5)
Annual frequency of breast exams[a]		
Median (interquartile range)	0.6 (0.2–1.0)	0.6 (0.3–1.0)
Annual frequency of mammograms[a]		
Median (interquartile range)	0.7 (0.3–1.0)	0.8 (0.4–1.0)

[a] Truncated at the time of diagnosis in the cases

Compared with non-cases, cases were younger and more likely to reside in Midwest, be non-Hispanic White, have a BMI less than 30 kg/m^2, and have a family history of breast cancer. Regarding menstrual, reproductive, and hormonal histories, although cases and non-cases had similar ages at menarche and menopause, cases had used oral contraceptives and postmenopausal hormones for longer than non-cases and had had fewer live births than non-cases. Furthermore, cases and non-cases had similar annual frequencies of breast exams and mammograms.

Overall, risk of BPED of the breast was not associated with any of the smoking measures examined, including smoking status, duration of smoking, intensity of smoking, pack-years of smoking, age at which smoking commenced, and years since quitting smoking, after adjustment for age at baseline, ethnicity, region of residence, randomization groups, and frequency of physical exams and mammograms (Table 2). Further adjustment for age at menarche, age at menopause, number of live births, duration of OC use, duration of postmenopausal hormone use, BMI, and family history of breast cancer did not affect the aforementioned hazard ratio estimates appreciably. In addition, exclusion from the analyses of participants who had had a breast biopsy or needle aspiration before randomization, exclusion from the analysis of cases who were diagnosed with BPED within one year after enrollment, and inclusion of patients with fibroadenoma, sclerosing adenosis, and micropapilloma in the case group did not affect the hazard ratio estimates for smoking measures and risk of BPED substantially (data not shown).

We observed no associations between cigarette smoking and risk of non-atypical BPED and atypical hyperplasia, when these two case groups were analyzed separately (Table 3). We also observed no associations between cigarette smoking and BPED of the breast within strata defined by ethnicity, randomization assignment, age at menarche, age at menopause, number of live births, duration of OC use, duration of

Table 2 Association between cigarette smoking and risk of BPED of the breast

Smoking history	No. of cases	Person-years of follow-up	HR (95% CL)	
			Model 1[a]	Model 2[b]
Never smoked	913	268,684	1.0	1.0
Ever smoked	861	256,975	0.99 (0.90, 1.09)	0.97 (0.88, 1.08)
Ex-smoker	732	213,719	1.02 (0.92, 1.12)	1.00 (0.90, 1.11)
Current smoker	124	41,118	0.87 (0.72, 1.06)	0.84 (0.69, 1.02)
Years of smoking				
0	913	268,684	1.0	1.0
>0–9	203	58,213	1.00 (0.86, 1.17)	0.98 (0.83, 1.14)
10–19	200	53,589	1.08 (0.93, 1.26)	1.06 (0.91, 1.25)
20–29	171	54,674	0.92 (0.78, 1.09)	0.92 (0.78, 1.09)
30–39	147	48,105	0.91 (0.76, 1.08)	0.89 (0.75, 1.07)
40+	101	32,504	0.99 (0.80, 1.22)	0.96 (0.77, 1.18)
p (trend)			0.39	0.26
Cigarettes/day				
0	913	268,684	1.0	1.0
>0–4	179	55,089	0.98 (0.83, 1.15)	0.95 (0.80, 1.12)
5–14	262	78,554	1.00 (0.87, 1.15)	0.98 (0.85, 1.13)
15–24	223	69,259	0.94 (0.81, 1.09)	0.92 (0.79, 1.07)
25+	156	42,545	1.05 (0.88, 1.24)	1.05 (0.88, 1.25)
p (trend)			0.92	0.76
Pack-years of smoking				
0	913	268,684	1.0	1.0
>0–10	348	100,257	1.02 (0.90, 1.16)	1.00 (0.88, 1.13)
>10–20	150	46,691	0.95 (0.80, 1.13)	0.91 (0.76, 1.09)
>20–30	105	32,458	0.96 (0.78, 1.17)	0.95 (0.77, 1.17)
>30–40	84	24,534	0.98 (0.78, 1.23)	0.98 (0.78, 1.23)
>40	124	39,569	0.94 (0.78, 1.13)	0.94 (0.77, 1.14)
p (trend)			0.43	0.38
Age started smoking				
Never smoked	913	268,684	1.0	1.0
25+	102	33,172	0.98 (0.80, 1.20)	0.96 (0.78, 1.18)
20–24	255	76,976	0.99 (0.87, 1.14)	0.96 (0.83, 1.11)
15–19	449	127,626	1.02 (0.91, 1.14)	1.01 (0.90, 1.13)
<15	52	18,185	0.81 (0.61, 1.07)	0.82 (0.62, 1.09)
p (trend)			0.74	0.59
Years since quitting smoking				
Never smoked	913	268,684	1.0	1.0
>30	160	50,107	0.98 (0.83, 1.16)	0.95 (0.80, 1.13)
>20–30	206	51,481	1.16 (1.00, 1.35)	1.14 (0.98, 1.34)
>10–20	199	54,732	1.08 (0.93, 1.26)	1.06 (0.90, 1.24)
>0–10	133	45,103	0.85 (0.70, 1.02)	0.84 (0.69, 1.01)
p (trend)			0.79	0.57

[a] Adjusted for age at baseline, ethnicity, region of residence, randomization groups, and frequency of physical exams (number per year) and mammograms (number per year)

[b] Adjusted for covariates in model 1 and the following variables: age at menarche, age at menopause, number of live births, duration of OC use, duration of postmenopausal hormone use, BMI, and family history of breast cancer

postmenopausal hormone use, BMI, and family history of breast cancer (data not shown).

Discussion

The etiology of BPED of the breast is not well understood. Previous studies investigating the etiology of BPED have mainly focused on well-documented or suspected risk factors for breast cancer due to the fact that BPED are possible precursors of breast cancer [9]. Three published studies investigating cigarette smoking in relation to risk of BPED of the breast have uniformly shown null results [10–12]. Consistent with the previous studies, we observed no association between cigarette smoking and risk of BPED of the breast among postmenopausal women.

Cigarette smoking appears to have dual effects on the breast. On one hand, cigarette smoking has demonstrated carcinogenic effects on the breast in experimental studies, as smoke-specific DNA adducts and *p*53 gene mutations are more common in the breast tissue of smokers than that of nonsmokers [6, 19–21]. On the other hand, cigarette smoking may have antiestrogenic effects given that smokers have reduced bone density, an earlier age at natural menopause, and reduced urinary levels of estrogen [22–25]. It is conceivable that the effect of cigarette smoking on the breast might depend on the net balance between its carcinogenic effects and antiestrogenic effects [24]. The

Table 3 Associations between cigarette smoking and risk of non-atypical BPED and atypical hyperplasia

Smoking history	Non-atypical BPED		Atypical hyperplasia	
	No. of cases	HR (95% CL)[a]	No. of cases	HR (95% CL)[a]
Never smoked	772	1.0	141	1.0
Ever smoked	709	0.97 (0.87, 1.07)	152	1.11 (0.88, 1.40)
Ex-smoker	597	0.98 (0.88, 1.10)	135	1.19 (0.94, 1.51)
Current smoker	109	0.91 (0.74, 1.11)	15	0.68 (0.40, 1.16)
Years of smoking				
0	772	1.0	141	1.0
>0–9	165	0.96 (0.81, 1.14)	38	1.20 (0.84, 1.72)
10–19	167	1.08 (0.91, 1.27)	33	1.13 (0.77, 1.66)
20–29	138	0.89 (0.74, 1.06)	33	1.13 (0.77, 1.65)
30–39	124	0.91 (0.75, 1.10)	23	0.90 (0.58, 1.41)
40+	83	0.96 (0.77, 1.21)	18	1.14 (0.69, 1.87)
p (trend)		0.28		0.77
Cigarettes/day				
0	772	1.0	141	1.0
>0–4	152	0.98 (0.83, 1.17)	168	0.94 (0.62, 1.41)
5–14	212	0.96 (0.83, 1.12)	218	1.21 (0.88, 1.68)
15–24	174	0.87 (0.74, 1.02)	267	1.32 (0.95, 1.83)
25+	136	1.08 (0.90, 1.30)	287	0.86 (0.54, 1.37)
p (trend)		0.62		0.40
Pack-years of smoking				
0	772	1.0	141	1.0
>0–10	291	1.02 (0.89, 1.16)	57	1.07 (0.78, 1.45)
>10–20	121	0.91 (0.75, 1.10)	29	1.17 (0.78, 1.74)
>20–30	79	0.85 (0.68, 1.08)	26	1.51 (0.99, 2.30)
>30–40	73	1.01 (0.79, 1.29)	11	0.83 (0.45, 1.53)
>40	104	0.93 (0.76, 1.15)	20	0.98 (0.61, 1.56)
p (trend)		0.30		0.69
Age started smoking				
Never smoked	772	1.0	141	1.0
25+	81	0.92 (0.73, 1.15)	162	1.31 (0.82, 2.07)
20–24	209	0.96 (0.83, 1.12)	208	1.16 (0.83, 1.61)
15–19	375	1.01 (0.89, 1.15)	282	1.06 (0.80, 1.41)
<15	42	0.78 (0.57, 1.06)	292	0.98 (0.51, 1.86)
p (trend)		0.58		0.67
Years since quitting smoking				
Never smoked	772	1.0	141	1.0
>30	136	0.98 (0.82, 1.18)	24	0.95 (0.62, 1.47)
>20–30	168	1.13 (0.95, 1.33)	38	1.34 (0.94, 1.93)
>10–20	161	1.04 (0.88, 1.23)	38	1.33 (0.93, 1.90)
>0–10	103	0.78 (0.63, 0.96)	30	1.20 (0.81, 1.79)
p (trend)		0.28		0.081

[a] Adjusted for age at baseline, ethnicity, region of residence, randomization groups, and frequency of physical exams (number per year) and mammograms (number per year)

null association observed in our study suggests that the carcinogenic and antiestrogenic effects of cigarette smoking on the breast might counterbalance each other and that cigarette smoking might have no overall effects on BPED of the breast among postmenopausal women.

Among the strengths of our study are the large sample size, the prospective study design, essentially complete follow-up of the cohort, intensive breast exams and mammograms undergone by study participants, and comprehensive baseline data. By far, this is the largest study that has investigated the association between cigarette smoking and risk of BPED of the breast. Moreover, the prospective study design and the essentially complete follow-up of the cohort should have minimized selection bias. In the general population, an unknown proportion of women with BPED of the breast comes to clinical attention and proceeds to biopsy [26]. Therefore, studies conducted in the general population without extra effort to detect women with BPED of the breast might be subject to selection bias due to the fact that women with BPED who come to clinical attention may not represent all women with BPED in the population. In our study, participants underwent intensive breast exams and mammograms, which should have maximized the ascertainment of cases with BPED and consequently minimized selection bias. Indeed, the incidence rate of women with BPED in our cohort was much higher than previously reported [27], supportive of better case ascertainment in our study. In addition, information on cigarette

smoking and other factors was collected at baseline, which might have minimized recall bias. To minimize confounding, we controlled for potential risk factors for BPED of the breast in multivariate analyses.

A limitation of our study is that we did not collect updated information on smoking exposure during the follow-up period. Changes in smoking habits during follow-up could have lead to exposure misclassification. However, this might not be very problematic due to the fact that we followed a cohort of postmenopausal women, most of whom are unlikely to have changed their smoking habits during the follow-up period. Furthermore, due to the fact that our study was restricted among postmenopausal women aged 50 or above, the results reported here might not be generalizable to young or premenopausal women.

In summary, among this large cohort of postmenopausal women, we observed no association between cigarette smoking and risk of BPED of the breast, overall, or when examined by histological subtype.

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