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Original Contribution

Interaction Between Smoking and Obesity and the Risk of Developing Breast Cancer Among Postmenopausal Women

The Women's Health Initiative Observational Study

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Obesity is a well-established risk factor for postmenopausal breast cancer. Recent studies suggest that smoking increases the risk of breast cancer. However, the effect of co-occurrence of smoking and obesity on breast cancer risk remains unclear. A total of 76,628 women aged 50–79 years enrolled in the Women's Health Initiative Observational Study were followed through August 14, 2009. Cox proportional hazards regression models were used to estimate hazard ratios and 95% confidence intervals. Over an average 10.3 years of follow-up, 3,378 incident cases of invasive breast cancer were identified. The effect of smoking on the risk of developing invasive breast cancer was modified significantly by obesity status among postmenopausal women, regardless of whether the obesity status was defined by body mass index ($P_{interaction} = 0.01$) or waist circumference ($P_{interaction} = 0.02$). A significant association between smoking and breast cancer risk was noted in nonobese women (hazard ratio = 1.25, 95% confidence interval: 1.05, 1.47) but not in obese women (hazard ratio = 0.96, 95% confidence interval: 0.69, 1.34). In conclusion, this study suggests that the effect of smoking exposure on breast cancer risk was modified by obesity among postmenopausal women. The modification effect did not differ by general versus abdominal obesity.

breast neoplasms; obesity; risk factors; smoking

Abbreviations: CI, confidence interval; WHI, Women's Health Initiative.

Breast cancer is the most common type of cancer among women worldwide. Recent cohort studies suggest that smoking increases the risk of breast cancer, especially among women who smoked cigarettes for a long period of time and/or who started smoking at a young age (1–5). These associations have been further confirmed in postmenopausal women in our large prospective study (6). Obesity is a well-established risk factor for postmenopausal breast cancer. Elevated serum estrogen levels, as well as enhanced local production of estrogen, have been considered primary mediators of the mechanism by which body weight promotes breast cancer development in postmenopausal women (7–10).

There is a complex relation among smoking, weight, and fat distribution (11). On the one hand, smoking may lead to weight loss by increasing the metabolic rate (12–14), decreasing metabolic efficiency, or decreasing caloric absorption (15), which may help prevent the effect of obesity in increasing breast cancer risk in postmenopausal women. On the other hand, there is increasing evidence that smoking is associated with a more metabolically adverse fat distribution profile, with higher central adiposity (16, 17), which may lead to an increased risk of breast cancer. Thus, the effect of smoking on risk of breast cancer may be modified by obesity, and the modification effect may differ depending on whether obesity is defined by body weight or body shape.

In the prospective Women's Health Initiative (WHI) Observational Study, detailed information regarding breast cancer risk factors and smoking exposure was collected, along with

measurements of weight, height, and waist circumference. In our previous work, we observed an overall relation between smoking and breast cancer risk (6), with 9% (95% confidence interval (CI): 2, 17) increased risk of breast cancer among former smokers and 16% (95% CI: 0, 34) increased risk among current smokers compared with women who had never smoked. Significantly higher breast cancer risk was observed in smokers with high intensity and duration of smoking, as well as with initiation of smoking in the teenage years. In the present study, we used WHI data to assess if the effect of smoking on risk of breast cancer was modified by obesity among postmenopausal women, and if the modification effect differed by different definitions of obesity.

MATERIALS AND METHODS

Women's Health Initiative

The WHI is an ongoing, ethnically and geographically diverse, multicenter clinical trial and observational study designed to address major causes of morbidity and mortality in postmenopausal women (18). Briefly, a total of 161,808 women aged 50–79 years were recruited at 40 clinical centers throughout the United States. Recruitment began on September 1, 1993, and ended on December 31, 1998. Details of the scientific rationale, eligibility requirements, and baseline characteristics of the participants in the WHI have been published elsewhere (19, 20). The WHI Observational Study included 93,676 women who were screened for the clinical trials but proved to be ineligible or unwilling to participate or were recruited through a direct invitation to participate in the Observational Study. The study was overseen by institutional review boards at all 40 clinical centers and at the coordinating center, as well as by a data and safety monitoring board. All participants in the WHI gave informed consent and were followed prospectively.

The following participants were excluded from the original WHI Observational Study cohort of 93,676: 12,075 women who had a history of cancer (except nonmelanoma skin cancer) at baseline; 443 women who had no follow-up time; and 4,530 women who had missing values of smoking status or anthropometric variables. This yielded a sample of 76,628 women for further analysis.

Measurement of exposures and confounders

In the WHI, detailed smoking information was collected at baseline, and smoking status was also updated annually. Ever smokers were defined as having smoked at least 100 cigarettes during their entire life. In our data, 6% of women were current smokers and 94% were nonsmokers (53% never smokers and 41% former smokers) at baseline. Over 6 years of follow-up (from enrollment to the end of the main study period), about 60% of smokers continued to smoke, and 99% of nonsmokers remained never smokers or were abstinent. Because smoking status changed in few women and changed predominantly from current smokers to former smokers during the period of observation, we used only the smoking exposure information collected at baseline.

Information on smoking included smoking status (never, former, and current), and women who were current or former smokers were also asked the age of smoking initiation, the number of cigarettes smoked per day, and the duration of smoking in years. Among former smokers, age at quitting smoking was also collected. Pack-years of smoking were calculated by multiplying the total years of smoking by the number of cigarettes smoked per day divided by 20. During the baseline clinic visit, trained and certified staff performed anthropometric measurements, including height, weight, and hip and waist circumferences. Body mass index was calculated (weight (kg)/height $(m)^2$). Waist circumference at the natural waist or narrowest part of the body was measured to the nearest 0.1 cm.

The potential confounders used in multivariable analyses were measured at baseline, including age at enrollment ($<$55, 55–59, 60–64, 65–69, 70–74, $\geq$75 years); ethnicity (American Indian or Alaska Native, Asian or Pacific Islander, black or African American, Hispanic/Latino, non-Hispanic white, and other); education (high school or less, some college/technical training, college or some postcollege, and master's degree or higher); body mass index ($<$18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, $\geq$40); physical activity (metabolic equivalent tasks (METs) per week: $<$5, 5–$<$10, 10–$<$20, 20–$<$30, $\geq$30); alcohol intake (nondrinker, past drinker, $<$1 drink/month, 1 drink/month–$<$1 drink/week, 1–$<$7 drinks/week, $\geq$7 drinks/week); parity (never pregnant, never had term pregnancy, 1, 2, 3, 4, $\geq$5); family history of breast cancer (yes/no); history of hormone therapy use (none, estrogen alone, estrogen and progestin, mixed); age at menarche ($<$12, 12–13, 14–15, $\geq$16 years); age at first livebirth (never had term pregnancy, $<$20 years, 20–29 years; $\geq$30 years); and having had mammography during the last 2 years (yes, no).

Follow-up and ascertainment of cases

Initial reports of cancer were ascertained by annual self-administered questionnaires, and all self-reports of breast cancer were confirmed by review of medical records, including pathology reports (if a biopsy or resection was done). The breast cancer cases were then coded by an experienced Surveillance, Epidemiology, and End Results (SEER) coder in accordance with program coding guidelines (21). Primary site and histology were coded by using the *International Classification of Diseases for Oncology,* Second Edition (ICD-O-2). The completion rate of annual questionnaires was 93%–96% through 2005—the end of the main study period. Since then, about 73% of Observational Study women continued an extension study until 2009. Among those women who agreed to the extension, completion of annual follow-up forms was 96% among women who remained alive. As of August 14, 2009, with an average 10.3 years of follow-up, 3,378 incident cases of invasive breast cancer (2,506 among nonobese women and 872 among obese women) had been identified.

Statistical analysis

All participants were followed up from the date of enrollment until the date of invasive breast cancer diagnosis, date of death, loss to follow-up (including nonparticipation in the extension), or August 14, 2009, whichever occurred first.

The association between smoking and breast cancer was assessed by stratification on obesity status defined by body

mass index (normal: <25 kg/m^2; overweight: 25–<30 kg/m^2; obese: ≥ 30 kg/m^2). Because the results for overweight and normal women were similar, they were combined in the tables. In addition, studies have shown that waist circumference may be a more sensitive measure of relative disease risk than is body mass index among postmenopausal women (22, 23). We further defined obesity status by waist circumference (nonobese: waist, <88 cm; obese: waist, ≥ 88 cm) (24) and waist/hip ratio (nonobese: waist/hip ratio, <0.85; obese: waist/hip ratio, ≥ 0.85). In addition, we also performed analyses stratified by body mass index at age 18 (with cutpoints at 21 kg/m^2 and 23 kg/m^2).

Cox proportional hazards regression models were used to estimate hazard ratios and 95% confidence intervals, with adjustment for the potential confounders specified earlier (refer to "Measurement of Exposures and Confounders" above). Tests for trend were performed by using the ordered category as a continuous variable in the proportional hazard model. Interactions between obesity status and different metrics of smoking were tested by entering multiplicative interaction terms into the model. The proportionality assumption was satisfied for all exposure variables of interest and potential confounding variables based on graphs of scaled Schoenfeld residuals (25).

We performed several sensitivity analyses to confirm our results. First, we excluded the first 2 years of follow-up, because undiagnosed breast cancer could have affected weight at enrollment. Second, we performed the analyses using only breast cancers ascertained during the main study period through March 31, 2005, because smoking and/or obesity may have affected women's willingness to participate in the extension study. To check the assumption of nondifferential follow-up, we looked at nonparticipation in the extension study by smoking and obesity status. Third, we performed the analysis by using total non-breast cancer mortality as the outcome, to determine whether mortality could have been a competing outcome for obese women or smokers.

All statistical analyses were conducted by using SAS, version 9.0, software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Baseline characteristics of the study subjects by smoking status and obesity status are shown in Table 1. Compared with nonobese women, slightly few obese women were current smokers (6.6% vs. 5.5%) and more were former smokers (40.6% vs. 42.5%). Among nonobese women, compared with women who were never smokers, women who were current smokers were significantly more likely to have the following characteristics: younger age, lower body mass index, lower physical activity, less likely to be white, non-Hispanic ethnicity, lower educational level, younger age at menarche, less use of estrogen plus progesterone hormone therapy, nulliparity, younger age at first livebirth, heavier alcohol intake, lower family history of breast cancer, and less likely to have had mammography within 2 years. Among obese women, the pattern was similar when comparing women who were current smokers with women who were never smokers, with the exceptions that there were no differences in body mass index or age at menarche. In addition, there was no significant difference in the distribution of breast cancer hormone receptor status in either nonobese women or obese women (Table 1).

In multivariable analyses, the risk of breast cancer associated with different metrics of active smoking stratified by general obesity (defined by body mass index of ≥ 30 kg/m^2) is presented in Table 2. In the nonobese group, an elevated risk of breast cancer associated with smoking persisted after adjustment for other known breast cancer risk factors. Compared with never smokers, former smokers and current smokers had elevated breast cancer risks of 15% (95% CI: 5, 25) and 25% (95% CI: 5, 47), respectively. The risk of breast cancer was positively associated with smoking intensity, smoking duration, and pack-years of cigarette smoking and inversely associated with age at smoking initiation and the years since quitting smoking for former smokers.

In contrast, we did not observe any significant association between breast cancer and different metrics of smoking among obese women. The association of smoking with the risk of breast cancer was significantly different by obesity status, including ever smoking ($P = 0.01$), smoking status (never, former, and current) ($P = 0.047$), average number of cigarettes per day ($P = 0.03$), smoking duration ($P = 0.03$), and pack-years of cigarette smoking ($P = 0.005$).

We also assessed the risk of breast cancer associated with different metrics of active smoking stratified by abdominal obesity (defined by waist, ≥ 88 cm) (Table 3). Overall, the results were similar to the findings stratified by general obesity defined by body mass index. A significant association between smoking and breast cancer risk was observed among non-abdominally obese women but not among abdominally obese women. Significant interactions were detected for abdominal obesity status with ever smoking ($P = 0.02$), the age at smoking initiation ($P = 0.03$), average number of cigarettes per day ($P = 0.045$), and smoking duration ($P = 0.009$) (Table 3). Similar results were observed when abdominal obesity was defined as a waist/hip ratio of >0.85 (data not shown). We also performed analyses stratified by body mass index at age 18 years (with cutpoints at 21 kg/m^2 and 23 kg/m^2) and did not observe significant interaction between smoking and body mass index at age 18 years on the risk of invasive breast cancer. The hazard ratios of breast cancer risk associated with ever smoking were 1.16 (95% CI: 1.06, 1.26) among women who had a body mass index at age 18 years of <21 kg/m^2 and 1.02 (95% CI: 0.90, 1.15) among women who had a body mass index at age 18 years of ≥ 21 kg/m^2. The hazard ratios of breast cancer risk associated with ever smoking were 1.08 (95% CI: 1.01, 1.17) among women who had a body mass index at age 18 years of <23 kg/m^2 and 1.27 (95% CI: 1.04, 1.54) among women who had a body mass index at age 18 years of ≥ 23 kg/m^2.

In order to minimize the possibility of reverse causation (i.e., that some women with undiagnosed breast cancer may have lost enough weight to become nonobese), we performed all analyses after excluding the first 2 years of follow-up. The results were similar to those based on the whole data set (data not shown).

Among all living participants, the participation rates in the extension were 71.2%, 74.8%, and 64.4% for never, former, and current smokers, respectively, and they were 74.3% and 66.1% for nonobese women and obese women, respectively.

Table 1. Baseline Characteristics of 76,628 Postmenopausal Women by Smoking Status and Obesity Status, the Women's Health Initiative Observational Study, United States, 1993–1998[a]

Variable	Nonobese									*P* Value[b]
	Never Smoked			Past Smoker			Current Smoker			
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	
Total no. of women	30,471	52.82		23,423	40.60		3,798	6.58		
Age at baseline, years			63.87 (7.51)			63.43 (7.27)			61.95 (7.08)	<0.0,001
Body mass index, kg/m^2			24.56 (2.95)			24.71 (2.85)			24.24 (3.05)	<0.0001
Physical activity, METs/week			14.78 (14.64)			16.45 (15.09)			10.46 (12.50)	<0.0001
White, non-Hispanic ethnicity	25,149	82.53		20,899	89.22		3,090	81.36		<0.0001
College graduate or above education	13,727	45.05		10,935	46.68		1,269	33.41		<0.0001
Age at menarche (<12 years)	2,987	9.80		2,335	9.97		431	11.35		0.02
Hormone therapy use										<0.0001
Estrogen alone	9,412	30.89		7,207	30.77		1,178	31.02		
Estrogen plus progestin	7,456	24.47		6,660	28.43		797	20.98		
Mixed use	1,981	6.50		1,760	7.51		194	5.11		
Parity (nulliparous)	3,963	13.01		2,939	12.55		505	13.30		<0.0001
Age at first livebirth (≥30 years)	2,488	8.17		1,792	7.65		237	6.24		<0.0001
Alcohol intake (≥7 drinks/week)	2,629	8.63		4,707	20.10		826	21.75		<0.0001
Family history of breast cancer (yes)	5,504	18.06		4,258	18.18		626	16.48		0.02
Mammogram within 2 years (yes)	25,805	84.69		20,365	86.94		2,763	72.75		<0.0001
Breast cancer cases	1,210	3.97		1,133	4.84		163	4.29		0.43
ER+/PR+	747	61.74		713	62.93		113	69.33		
ER+/PR−	167	13.80		170	15.00		17	10.43		
ER−/PR+	20	1.65		16	1.41		0	0.00		
ER−/PR−	157	12.98		138	12.18		19	11.66		
Unknown	119	9.83		96	8.47		14	8.59		

Table continues

This implies that current smoking and obesity were associated with nonparticipation in the extension study. In order to assess the impact of this differential participation to the extension study, we examined the breast cancer cases ascertained as of March 31, 2005. The point estimates of the hazard ratios were similar, although the confidence intervals were wider because of the smaller number of breast cancer cases; the results are shown in Web Table 1 and Web Table 2 , which appear on the *Journal*'s Web site (http://aje.oxfordjournals.org).

Because we observed that the mean age of death from any other cause among obese smoking women was 69.6 years versus 77.0 years in nonobese never smokers, we evaluated the influence of competing risk on our results by examining all metrics of smoking in relation to the competing risk of death from any cause other than invasive breast cancer, stratified by obesity status. We found the hazard ratios for the competing risk of non-breast cancer mortality associated with smoking was stronger in nonobese women than in obese women for most smoking metrics; the results are shown in Web Table 3 and Web Table 4.

DISCUSSION

Our large prospective study revealed that the effect of smoking on the risk of developing invasive breast cancer was significantly modified by obesity status among postmenopausal women, regardless of whether the obesity status was defined by body mass index or waist circumference. A significant association between smoking and breast cancer risk was noted only among nonobese women but not in obese women.

The overall relation between smoking and breast cancer risk observed in our previous study (6) is consistent with those in most recent studies, which show a magnitude of risk elevation around 20%–50% for women who smoked cigarettes for a long period of time and/or who started smoking at a young age (1–4, 26–28). A recent report from a Canadian panel of

Table 1. Continued

Variable	Obese									*P* Value[b]
	Never Smoked			Past Smoker			Current Smoker			
	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	
Total no. of women	9,852	52.03		8,045	42.49		1,039	5.49		
Age at baseline, years			63.25 (7.18)			62.68 (6.95)			59.92 (6.52)	<0.0001
Body mass index, kg/m^2			35.00 (5.13)			35.29 (5.35)			35.09 (5.52)	0.001
Physical activity, METs/week			9.16 (11.80)			9.91 (11.95)				<0.0001
White, non-Hispanic ethnicity	7,445	75.57		6,391	79.44		687	66.12		<0.0001
College graduate or above education	3,111	31.58		2,719	33.80		272	26.18		<0.0001
Age at menarche (<12 years)	1,636	16.61		1,306	16.23		176	16.94		0.2
Hormone therapy use										<0.0001
Estrogen alone	3,115	31.62		2,518	31.30		296	28.49		
Estrogen plus progestin	1,511	15.34		1,519	18.88		155	14.92		
Mixed use	421	4.27		386	4.80		28	2.69		
Parity (nulliparous)	1,062	10.78		949	11.80		136	13.09		<0.0001
Age at first livebirth (≥30 years)	659	6.69		537	6.67		49	4.72		<0.0001
Alcohol intake (≥7 drinks/week)	419	4.25		783	9.73		104	10.01		<0.0001
Family history of breast cancer (yes)	1,695	17.20		1,373	17.07		154	14.82		0.06
Mammogram within 2 years (yes)	7,797	79.14		6,559	81.53		749	72.09		<0.0001
Breast cancer cases	458	4.65		374	4.65		40	385		0.09
ER+/PR+	285	62.23		250	66.84		23	57.50		
ER+/PR−	40	8.73		33	8.82		3	7.50		
ER−/PR+	1	0.22		7	1.87		0	0.00		
ER−/PR−	76	16.59		44	11.76		6	15.00		
Unknown	56	12.23		40	10.70		8	20.00		

Abbreviations: ER+, estrogen receptor positive; ER−, estrogen receptor negative; MET, metabolic equivalent task; PR+, progesterone receptor positive; PR−, progesterone receptor negative; SD, standard deviation.

[a] "Obese" here was defined as body mass index ≥30. Overall, all variables listed in this table were significantly different between obese women and nonobese women.

[b] The chi-square test was used to test the difference between cases and noncases for categorical variables, and the analysis of variance test was used for continuous variables.

experts (29) reviewed the extensive new research in this area and concluded that the relations between active smoking and both pre- and postmenopausal breast cancer are consistent with causality, on the basis of the weight of evidence from epidemiologic and toxicologic studies and on an understanding of biologic mechanisms. This represented a reversal of the view espoused by earlier systematic reviews, which had concluded that there was no overall association between active smoking and breast cancer risk (30–32).

It is biologically plausible that some constituents of tobacco may have a direct and/or indirect influence on the carcinogenic process leading to breast cancer. Human biomarker studies have strongly suggested that breast tissue is a target for the carcinogenic effects of tobacco smoke (33). Studies have also found that tobacco smoke-specific DNA adducts are more common in the breast tissue of smokers than in that of nonsmokers (34–36). The detection of *p53* gene mutations in the breast tissue of smokers also supports the biologic plausibility of a positive association between cigarette smoking and breast cancer (33).

Our study is the first prospective study to examine the interaction among smoking, obesity, and the risk of breast cancer among postmenopausal women. We observed a significantly increased risk of breast cancer associated with smoking amount and duration among nonobese women. The mechanism behind this relation may be mainly due to the

Table 2. Hazard Ratios and 95% Confidence Intervals for Invasive Breast Cancer Incidence Associated With Smoking Status Among 76,628 Postmenopausal Women by Obesity Status, the Women's Health Initiative Observational Study, United States, 1993–2009[a]

Exposure	Nonobese			Obese			$P_{interaction}$
	No. of Cases	Multi-adjusted HR[b]	95% CI	No. of Cases	Multi-adjusted HR[b]	95% CI	
Smoking history							
Never smokers	1,210	1.00	Referent	458	1.00	Referent	
Ever smokers	1,296	1.16	1.07, 1.26	414	0.96	0.84, 1.10	0.01
Smoking status							0.047
Former smokers	1,133	1.15	1.05, 1.25	374	0.96	0.83, 1.11	
Current smokers	163	1.25	1.05, 1.47	40	0.96	0.69, 1.34	
Age at smoking initiation, years							0.10
<20	747	1.19	1.08, 1.31	245	1.00	0.85, 1.18	
20–24	422	1.15	1.03, 1.29	119	0.92	0.75, 1.14	
≥25	127	1.03	0.86, 1.24	50	0.88	0.66, 1.18	
P_{trend}		0.0002			0.73		
Average no. of cigarettes/day							0.03
<15	708	1.13	1.03, 1.25	212	0.97	0.82, 1.15	
≥15	588	1.20	1.08, 1.33	202	0.95	0.80, 1.13	
P_{trend}		0.0003			0.54		
Total no. of smoking years							0.03
<10	288	1.02	0.90, 1.16	96	0.96	0.77, 1.20	
10–29	588	1.16	1.05, 1.28	174	0.91	0.76, 1.09	
30–49	370	1.25	1.11, 1.41	138	1.07	0.88, 1.30	
≥50	50	1.62	1.22, 2.17	6	0.62	0.28, 1.40	
P_{trend}		<0.0001			0.76		
No. of smoking pack-years							0.005
<10	517	1.05	0.95, 1.17	170	1.01	0.84, 1.21	
10–<30	463	1.31	1.17, 1.46	112	0.86	0.69, 1.06	
30–<50	174	1.14	0.97, 1.34	60	0.87	0.66, 1.15	
≥50	142	1.20	1.00, 1.43	72	1.15	0.89, 1.48	
P_{trend}		0.0001			0.84		
Years since quit smoking (former smokers)							0.6
<10	201	1.25	1.08, 1.46	77	0.94	0.73, 1.20	
10–<20	284	1.18	1.03, 1.35	108	1.02	0.82, 1.26	
20–<30	278	1.11	0.97, 1.27	83	0.94	0.74, 1.19	
≥30	303	1.14	1.00, 1.29	86	0.95	0.75, 1.20	
P_{trend}		0.0005			0.69		

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] "Obese" here was defined as body mass index ≥30.

[b] The adjusted variables in all multi-adjusted models included age (<55, 55–59, 60–64, 65–69, 70–74, ≥75 years), race (American Indian or Alaska Native, Asian or Pacific Islander, black or African American, Hispanic/Latino, non-Hispanic white, and other), education (high school or less, some college/technical training, college or some postcollege, and master's degree or higher), family history of cancer (yes/no), age at menarche (<12, 12–13, 14–15, ≥16 years), age at first livebirth (never had term pregnancy, <20, 20–29, ≥30 years), hormone use (no, estrogen alone, estrogen and progestin, mixed), parity (never pregnant, never had term pregnancy, 1, 2, 3, 4, ≥5), alcohol intake (nondrinker, past drinker, <1 drink/month, 1 drink/month–<1 drink/week, 1–<7 drinks/week, ≥7 drinks/week), body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, ≥40), physical activity (metabolic equivalent tasks/week: <5, 5–<10, 10–<20, 20–<30, ≥30), and mammography during the last 2 years (yes/no). The P_{trend} test included the reference group.

carcinogenic effects of tobacco smoking on the breast tissue as mentioned earlier. However, the lack of association between smoking and breast cancer risk among obese women is somewhat surprising. Because smoking and obesity are 2 leading causes of morbidity and mortality, the co-occurrence of smoking and obesity has substantial consequences for

Table 3. Hazard Ratios and 95% Confidence Intervals for Invasive Breast Cancer Incidence Associated With Smoking Status Among 76,628 Postmenopausal Women by Abdominal Obesity, the Women's Health Initiative Observational Study, United States, 1993–2009[a]

Exposure	Nonobesity			Obesity			$P_{interaction}$
	No. of Cases	Multi-adjusted HR[b]	95% CI	No. of Cases	Multi-adjusted HR[b]	95% CI	
Smoking history							
Never smokers	1,065	1.00	Referent	603	1.00	Referent	
Ever smokers	1,092	1.16	1.07, 1.27	618	1.01	0.89, 1.13	0.02
Smoking status							0.07
Former smokers	963	1.16	1.05, 1.27	544	1.00	0.88, 1.13	
Current smokers	129	1.21	1.00, 1.45	74	1.06	0.83, 1.36	
Age at smoking initiation, years							0.03
<20	646	1.23	1.11, 1.37	346	0.98	0.86, 1.13	
20–24	347	1.11	0.98, 1.26	194	1.05	0.89, 1.24	
≥25	99	0.96	0.78, 1.19	78	1.01	0.80, 1.29	
P_{trend}		0.0002			0.99		
Average no. of cigarettes/day							0.045
<15	609	1.12	1.01, 1.25	311	1.02	0.89, 1.18	
≥15	483	1.21	1.09, 1.36	307	0.99	0.86, 1.14	
P_{trend}		0.0005			0.95		
Total no. of smoking years							0.009
<10	257	1.02	0.89, 1.17	127	0.98	0.81, 1.19	
10–29	505	1.18	1.05, 1.31	257	0.95	0.81, 1.10	
30–49	290	1.24	1.08, 1.41	216	1.12	0.95, 1.31	
≥50	40	1.73	1.26, 2.39	16	0.86	0.52, 1.42	
P_{trend}		<0.0001			0.53		
No. of smoking pack-years							0.09
<10	462	1.07	0.95, 1.19	225	0.99	0.85, 1.16	
10–<30	382	1.29	1.14, 1.45	193	1.01	0.85, 1.19	
30–<50	141	1.15	0.97, 1.38	93	0.93	0.75, 1.17	
≥50	107	1.22	0.99, 1.49	107	1.12	0.91, 1.38	
P_{trend}		0.0004			0.59		
Years since quit smoking (former smokers)							0.5
<10	156	1.23	1.04, 1.46	122	0.94	0.73, 1.20	
10–<20	238	1.18	1.04, 1.39	154	1.02	0.82, 1.26	
20–<30	242	1.11	0.97, 1.28	119	0.94	0.74, 1.19	
≥30	263	1.13	0.98, 1.29	126	0.95	0.75, 1.20	
P_{trend}		0.002			0.78		

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a] "Abdominal obesity" was defined by waist circumference ≥88 cm.

[b] The adjusted variables in all multi-adjusted models included age (<55, 55–59, 60–64, 65–69, 70–74, ≥75), race (American Indian or Alaska Native, Asian or Pacific Islander, black or African American, Hispanic/Latino, non-Hispanic white, and other), education (high school or less, some college/technical training, college or some postcollege, and master's degree or higher), family history of cancer (yes/no), age at menarche (<12, 12–13, 14–15, ≥16 years), age at first livebirth (never had term pregnancy, <20, 20–29, ≥30 years), hormone use (no, estrogen alone, estrogen and progestin, mixed), parity (never pregnant, never had term pregnancy, 1, 2, 3, 4, ≥5), alcohol intake (nondrinker, past drinker, <1 drink/month, 1 drink/month–<1 drink/week, 1–<7 drinks/week, ≥7 drinks/week), body mass index (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, ≥40), physical activity (metabolic equivalent tasks/week: <5, 5–<10, 10–<20, 20–<30, ≥30), and mammography during the last 2 years (yes/no). The P_{trend} test included the reference group.

health (37, 38). We initially speculated that the null association among obese women might be attributable to reverse causation or competing risk (39, 40). However, this was not supported by additional analyses. In the Framingham Study, the life expectancy of obese smokers was more than 13 years less than that of normal-weight nonsmokers (41). We indirectly

assessed the influence of the competing risk on our results by estimating hazard ratios for that association of smoking and non-breast cancer mortality and comparing these in nonobese and obese women. The stronger association in nonobese women than in obese women suggests that the lack of association of smoking with breast cancer in obese women is unlikely to be explained by competing mortality risk.

One of the possible explanations for the lack of association between smoking and breast cancer risk among obese women may be due to an interaction between smoking and estrogen. Smoking has been reported to lower the level of estrogen (42), which is a primary mediator of the mechanism by which obesity promotes the risk of breast cancer development in postmenopausal women (7). The antiestrogenic effects associated with smoking may have counterbalanced the carcinogenic effects of tobacco smoking in the obese smokers compared with obese nonsmokers.

Another possible explanation is that obese smokers may have a different genetic profile from that of nonobese smokers. As is well known, smoking is generally associated with lower body weight, which may result from an increased metabolic rate, decreased metabolic efficiency, or lower caloric intake (14, 15). However, the women who became obese despite smoking may have better metabolism of tobacco-related toxins (including carcinogens) than lean smoking women (43). Studies have shown that the effect of smoking on breast cancer risk is modified by different genetic polymorphisms. In 1996, Ambrosone et al. (44) reported that *N*-acetyltransferase 2 gene (*NAT2*) slow acetylators compared with rapid acetylators who smoked had a significantly elevated risk of breast cancer among postmenopausal women. A similar study (45) also observed that polymorphisms in the *NAT2* gene may act differentially in modifying breast cancer risk associated with exposure to smoking. The heterogeneity in response to carcinogenic exposures could explain the null association between smoking and breast cancer among obese women if the *NAT2* slow acetylator status is more prevalent in lean smoking women than in obese smoking women. Unfortunately, we do not yet have the genetic data to test this hypothesis.

Strengths of our study include the prospective design, detailed information on potential confounders and, particularly, the large size of the cohort and the large number of cases, which enable us to look at the interaction. However, there are some limitations in our study as well. One is that we used only women's smoking status at baseline and did not account for small changes during follow-up, which may have caused some exposure misclassification among women who were current smokers at baseline and biased our results toward the null. However, on the basis of our data, only a few current smokers at baseline (2.4% of women) became former smokers during follow-up. This should have a minimal effect on our results, because all measures of smoking other than current smoking status were among ever smokers. In addition, this would not explain why the relation between smoking and the risk of breast cancer differed by obesity status. The anthropometric factors, including body mass index and waist circumference, were also based on measurements at baseline. Because postmenopausal women are likely to gain weight during follow-up, the lack of updating body mass index and waist circumference information during the follow-up may have led to some misclassification among the nonobese group. This may have caused our estimate of the association between smoking and breast cancer among the nonobese group to be more conservative. In addition, the WHI has a low rate of smoking relative to this age group in the general population (46); thus, it is possible that results could differ in populations that include more smokers.

In conclusion, our study supports the hypothesis that the effect of smoking exposure on breast cancer risk was modified by obesity among postmenopausal women and that the modification effect did not substantially differ by general versus abdominal obesity. The lack of association between smoking and breast cancer risk among obese women deserves further investigation. Future studies examining how genetic polymorphisms and other risk factors modify the effect of tobacco exposure on breast cancer risk are likely to help our understanding of this important women's health issue.

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A short list of WHI investigators is given in the Web Appendix, which appears on the *Journal*'s Web site (http://aje.oxfordjournals.org).

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