Published in final edited form as:

Breast Cancer Res Treat. 2008 May ; 109(1): 101–111. doi:10.1007/s10549-007-9629-1.

Active and passive smoking, *IL6*, *ESR1*, and breast cancer risk

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Abstract

We evaluated the association between smoking and risk of breast cancer in non-Hispanic white (NHW) and Hispanic or American Indian (HAI) women living in the Southwestern United States. Data on lifetime exposure to active and passive smoke data were available from 1527 NHW cases and 1601 NHW controls; 798 HAI cases and 924 HAI controls. Interleukin 6 (*IL6*) and Estrogen Receptor alpha (*ESR1*) polymorphisms were assessed in conjunction with smoking. Pack-years of smoking (≥ 15) were associated with increased risk of pre-menopausal breast cancer among NHW women (OR 1.6, 95% CI 1.1–2.4). Passive smoke increased risk of pre-menopausal breast cancer for HAI women (OR 1.9, 95% CI 1.1–3.1 everyone; OR 2.3, 95% CI 1.2–4.5 nonsmokers). HAI pre-menopausal women who were exposed to 10+ h of passive smoke per week and had the rs2069832 *IL6* GG genotype had over a fourfold increased risk of breast cancer (OR 4.4, 95% CI 1.5–12.8; *P* for interaction 0.01). Those with the *ESR1* Xba1 AA genotype had a threefold increased risk of breast cancer if they smoked ≥ 15 pack-years relative to non-smokers (*P* interaction 0.01). These data suggest that breast cancer risk is associated with active and passive smoking.

Keywords

Breast cancer; Cigarette smoke; *ESR1*; *IL6*; Hispanic; Passive smoking

Introduction

Data suggest an increased risk of breast cancer among cigarette smokers [1–3]. While tobacco smoke has an antiestrogenic effect [3], carcinogens in tobacco smoke may alter breast cancer risk through other mechanisms since tobacco mutagens are found in breast fluid [4]. It has been hypothesized that some combination of hormonal and mutagenic exposures exist and that the anti-estrogenic effects of cigarette smoke are offset by carcinogenic damage to breast tissue [3]. This damage from cigarette smoke has been further hypothesized to vary by time of exposure and breast tissue susceptibility [3]. Since full differentiation of breast tissue takes place after first full-term pregnancy, it has been proposed that the greatest carcinogenic damage to breast tissue from cigarette smoke would occur between menarche and first full-term pregnancy [3]. In support of this hypothesis, several studies have shown that early exposure to cigarette smoke is associated with the greatest breast cancer risk [3,5,6].

Environmental tobacco smoke, or passive smoking or side-stream smoke, also has been associated with breast cancer [2]. It is unclear if the same mechanisms are operational for active and passive smoking. Side-stream smoke contains higher concentrations of many components such as carbon monoxide, carbon dioxide, *N*-nitrosamines, nicotine, and benzene [2,7]. Vapor-phase particulates from side-stream smoke have been shown to be absorbed more quickly into blood and lymph systems than particulate-phase constituents found in mainstream smoke [7]. In contrast to active smoking, data suggest there are limited anti-estrogenic effects associated with passive smoking [7].

Genetic susceptibility may help explain the association between breast cancer and cigarette smoking. Studies have examined genes that regulate metabolizing enzymes such as *NAT2* and *CYP1A1* [2,5,8–10]. Other genes such as *MnSOD* have been examined because it may influence susceptibility to cigarette smoking because of their influence on oxidative stress [11,12]. However given the general null findings from the majority of these studies, it is possible that other genes involved in other pathways may be important in defining the cigarette smoking risk with breast cancer. Smoking is associated with increased serum levels of the cytokine IL-6 and C-reactive protein (CRP) [13]. Several small case-control studies have suggested serum IL-6 is increased in women with breast cancer [14]. Recently, Il'yasova et al. [15] reported increased serum CRP was associated with incident breast cancer in a cohort of post-menopausal women. Polymorphisms in the *IL6* gene promoter, –572G/C and the –174G/C, have been reported to be related to levels of circulating CRP [16] and to breast cancer [17].

Because cigarette smoke is thought to be anti-estrogenic, it is possible that the estrogen receptor gene alpha, (*ESR1*) may regulate susceptibility to breast cancer when exposed to cigarette smoke. The three most widely studied polymorphisms of the *ESR1*, the PvuII 397T > C, the XbaI (351A > G) restriction fragment length polymorphisms, both located in intron 1, and the TA repeat within the promoter region of the gene, are in linkage disequilibrium [18,19]. These polymorphisms have been examined with breast cancer risk [20–23] as well as with other conditions that have been linked to estrogen [19,24,25] with mixed results.

In this study we examine the associations between both active and passive cigarette smoking exposure among non-Hispanic white (NHW) and Hispanic/AI women enrolled in the 4–Corners Breast Cancer Study. Associations are assessed by menopausal status. We evaluated the interaction between exposure to either active or passive cigarette smoke and *IL6* and

ESR1 polymorphisms to gain additional insight into mechanisms involved in these associations.

Methods

Study participants were women living in a seven-county area of Arizona, or the states of Colorado, New Mexico, or Utah at the time of diagnosis or selection; American Indian women living on reservations were not eligible. Study hypotheses focused specifically on breast cancer in Hispanic and American Indian women, therefore sampling was stratified on ethnicity to select these women in larger proportion than their representation in the population. All Hispanic and American Indian women between the ages of 25 and 79 who were diagnosed with breast cancer during the study period were eligible. An age-matched sample of NHW women were randomly selected on a 1:1 ratio to the distribution of Hispanic cases in Arizona and Colorado; at a 4:1 ratio to the distribution of Hispanic cases in Utah; all Hispanic and non-Hispanic cases age 50 and under in New Mexico; and a 1:1 ratio for women over 50 in New Mexico. The GUESS program (Generally Useful Ethnic Search System) was used along with the census Spanish surname list to initially identify women who were potentially Hispanic [26,27]. Hispanic ethnicity was verified by self-report at the time of the interview. A detailed description of study methods and response rates has been published and are briefly described below [28].

Cases were histologically confirmed in situ and invasive breast cancer (ICDO sites C50.0–C50.6 and C50.8–C50.9) diagnosed between October 1999 and May 2004. State tumor registries were used to initially identify and confirm case eligibility. Of cases identified, 873 Hispanic/AI, and 1683 NHW women participated (68% of women contacted). Of these cases, 798 Hispanic/AI, and 1527 NHW women were diagnosed with first primary breast cancer and 576 Hispanic/AI, and 1177 NHW cases had DNA available for analyses [29].

Controls were selected from the target populations to match ethnicity and 5-year age distribution of cases. In Arizona and Colorado, participants under 65 were randomly selected from a commercial mailing list; in New Mexico and Utah controls under 65 years were randomly selected from driver's license lists. In all states, women 65 years and older were randomly selected from Center for Medicare Services lists. Of controls identified, 935 Hispanic/AI, and 1671 NHW women participated (42% of participants contacted) of which 728 Hispanic/AI, and 1330 NHW controls had DNA available for analyses.

All women identified were screened for eligibility prior to study enrollment. As part of the screening, women were asked to self-identify their race and ethnicity. Women initially identified as being Hispanic who did not self-identify as Hispanic/AI were ineligible for the study. If a respondent described herself as belonging to more than one race or ethnic group, all were recorded. All participants signed informed a written consent prior to participation; the study was approved by the Institutional Review Board for Human Subjects at each institution.

Diet and lifestyle data were collected by trained and certified interviewers using an interviewer-administered computerized questionnaire. The referent period was the year prior to diagnosis for cases or selection for controls. Respondents were given the option of having the interview administered in either English or Spanish. The questionnaire included information about medical history, reproductive history, family history, dietary data using an extensive diet history questionnaire that was modified to incorporate foods commonly eaten in the Southwestern United States [30], physical activity using a questionnaire modified from the Cross Cultural Activity Participation Survey [31], tobacco use, medication use, diabetes history, and weight history. BMI was calculated as kilograms(kg)/meters(m)². Women were asked to "best describe your menstrual status on (referent date)" by selecting responses from a card; this information was used to define individual menopausal status.

Women were asked if they ever smoked 100 or more cigarettes in their life, the years started and stopped smoking, and the usual amount smoked in a day. We also collected exposure to second-hand smoke including the number of hours per week exposed both in and out of the house during the referent year and at ages 15, 30, and 50. We created a variable that captured long-term exposure to passive smoke that categorized the level of exposure (none, low, high) based on average exposure at ages 15, 30 and referent year for pre- and peri-menopausal women and at ages 15, 30, and 50 for post-menopausal women.

DNA was extracted for 76.6% of participants in Arizona, 74.8% of participants in Colorado, 75% percent of participants in New Mexico and 93.6% of participants in Utah who were willing to provide a blood sample. Five *IL6* markers were genotyped using TaqMan-based assays as previously described [17]. These markers were rs1800797 (-596A/G); rs1800796 (-572 G/C, also known as -634C/G); rs1800795 (-174G/C); rs2069832 (G/A, intron +180 of exon 2); and rs2069849 (C/T coding exon 5). The 351A > G XbaI polymorphism of the *ESR1* gene was evaluated by PCR amplifying as previously described [32]. The 'X' or A allele was cut yielding bands of 148 bp and 198 bp, whereas the 'X' or G allele remained uncut and resulted in a band of 346 bp as modified from van Meurs et al.[19].

Statistical methods

SAS statistical package, version 9.1 (Cary, NC, 2002) was used. Women reporting AI were combined with women reporting Hispanic ethnicity for analyses. Analyses were restricted to women with a first primary breast cancer. Multivariable logistic regression models were used to estimate relative risk for disease. Exposure to cigarette smoke was categorized as never, former, and current, as well as pack-years smoked, age first smoked, and if started smoking prior to first pregnancy. Passive (second-hand) smoking was assessed as total number of hours per week exposed during the referent year, and at ages 50, 30, and 15; long-term exposure (none, low, and high as previously defined) based on average exposure from each of these time periods. Associations were stratified by menopausal status. Since recent exposure to hormones among post-menopausal women did not influence results, data are presented for all post-menopausal women adjusted for recent estrogen exposure. Adjustment variables in logistic regression models included age, center, parity, BMI, long-term physical activity, and average alcohol intake at ages 30, 50 and during the referent year for women 30 or older and alcohol intake during the referent year for women less than 30. These factors were shown to significantly influence risk estimates in this study population. Long-term physical activity was based on MET hours per week of moderate and vigorous activity reported at ages 15, 30, 50, and during the referent year. Adjustment for other factors such as age at menarche, age at first birth, oral contraceptive use, and age at menopause did not alter findings. To test for linear trend, exposure variables were included as continuous in logistic models and significance was assessed by likelihood ratio testing with models without the exposure. We evaluated the interaction between active and passive cigarette smoking and *IL6* and *ESR1* polymorphisms. For *IL6*, we present results for one of the five polymorphisms previously examined [17], since associations with breast cancer were similar and three markers (rs1800797, rs1800795, and rs2069832), were in pair-wise linkage disequilibrium (LD) (absolute value of Lewontin's D' statistic >0.90). Markers rs1800796, and rs2069849, not in LD for NHW controls but in pair-wise LD with the other markers, did not interact with smoking or passive smoking and are not shown. Interaction was assessed by the Wald χ^2 -test of significance for the multiplicative interaction term. *IL6*, rs2069832, and *ESR1* were assessed using a dominant model because of relatively few individuals homozygous for the minor allele. Independent associations of *IL6*, and *ESR1* with breast have been described in previous publications [17,32].

Results

The majority of both NHW and Hispanic/AI women reported never having smoked cigarettes with between 12.1% and 13.4% of women reporting being a current cigarette smoker (Table 1). The age distribution of starting to smoke cigarettes was similar for NHW and HAI women.

Significant associations between smoking and breast cancer risk were limited to pre- peri-menopausal NHW who ever smoked (OR 1.3, 95% CI 1.0–1.7), who reported smoking more than 15 pack-years (OR 1.6, 95% CI 1.1–2.4), and who started smoking before their first pregnancy (OR 1.4, 95% CI 1.03–1.9) (Table 2). Smoking cigarettes did not alter breast cancer risk among Hispanic/AI women or among post-menopausal women. Other indicators of cigarette exposure such as cigarettes per day or total years smoked did not yield results different from those observed for pack-years smoked.

Exposure to passive smoke increased risk of breast cancer among pre- and peri-menopausal Hispanic/AI women (OR 1.9, 95% CI 1.1–3.1 among smokers and non-smokers; OR 2.3, 95% CI 1.2–4.5 among never smokers) (Table 3). Among pre- and peri-menopausal Hispanic/AI women, exposure to more than 10 h of passive smoke per week was associated with significant increased breast cancer risk at age 30 (OR 2.2 95% CI 1.2–3.9, *P*-linear trend 0.01) as well as during the referent year. Passive smoke exposure at age 15 was not associated with increased breast cancer risk. Among NHW or post-menopausal women, passive smoke exposure was not associated with increased risk of breast cancer at any age.

Among pre- peri-menopausal Hispanic/AI women who did not smoke cigarettes, we observed an interaction for both the *IL6* rs1800795 (–174 5' promoter, data not shown) and the rs2069832 (intron +180 of exon 2) polymorphisms (Table 4). Among these women, having the GG *IL6* genotype was associated with increased risk when exposed to passive smoke while having the GC/CC or GA/AA genotypes was not associated with increased risk in the presence of passive smoke. Regardless of smoking history, the GG genotype was associated with an increase risk of breast cancer among Hispanic/AI women who were exposed to >10 h/week of tobacco smoke. Similar trends were observed for NHW women although the *P*-value for interaction did not reach statistical significance. Association of the most common haplotype (wildtype alleles at all five *IL6* markers), with an estimated population frequency of around 50%, was consistent with genotype associations for rs1800795, and rs2069832; evaluation of haplotype risks for *IL6* markers in high LD and smoking (data not shown) were not informative beyond the genotype associations. There were no significant interactions between *IL6* genotype and passive smoking among post-menopausal women.

The association between exposure to tobacco smoke (active and passive) and breast cancer risk by *ESR1* Xba1 polymorphism status showed significant associations but were limited to NHW women (Table 5). Among pre- peri-menopausal women a significant increased risk was observed for women who smoked >15 cigarettes pack-years and had the xx genotype (OR 2.9, 95% CI 1.3–6.4). Among post-menopausal women there was a significant/borderline significant interaction between *ESR1* Xba1 polymorphism and pack-years smoked among NHW (OR 1.4, 95% CI 1.0–2.1; *P*-interaction 0.04). The *ESR1* Xba1 polymorphism was not associated with passive smoking.

We evaluated the associations between active and passive smoking and ER tumor status. Among HAI women, lifetime exposure to passive smoke resulted in an 80% greater risk of an ER- breast tumor (*P*-trend with increasing exposure 0.04) as compared to a 30% increased risk for an ER + tumor (*P*-trend with increasing exposure 0.30). Other associations were similar for ER + and ER- tumors.

Discussion

Findings from this study indicate that active and passive smoking are associated with increased risk of breast cancer among pre- and peri-menopausal women. The associations appear to vary by ethnicity; genetic susceptibility may explain ethnic differences in risk.

As shown in other studies, cigarette smoking had a greater influence on breast cancer risk among women diagnosed at a young age or prior to menopause [3,5]. Although this finding is not universal, the magnitude of the association usually has been reported as being in the range of 1.3–1.7 [1,3,6,33], which is comparable to the 1.4–1.6 reported in this study. It is believed that breast tissue is at greatest risk to carcinogen exposure prior to first pregnancy [34,35]. While we observed an increased risk from cigarette smoking among women diagnosed prior to menopause, risk was not limited to women who started to smoke prior to first pregnancy as has been reported in some [6,36] but not all studies [1,37]. Likewise, as reported by others [33], we observed a stronger risk associated with starting to smoke when older rather than prior to age 18. Our data corroborate the findings of others of a dose-response breast cancer risk with increasing pack-years smoked [1,38].

Our data from Hispanic/AI women support previously detected associations of breast cancer with passive smoking. Several studies have shown an increased risk of breast cancer associated with exposure to passive smoke with risk estimates generally around 1.6 [3,33], and in some instances stronger associations for passive than for active smoking [33]. In the present study, the strength of the association as reflected by the OR was stronger for passive smoking than for active smoking. The association was strongest among those women who did not smoke cigarettes. The timing of exposure appeared to be important, in that more recent exposure had a greater risk than exposure at age 15. Others have reported stronger effects for passive smoking exposure when older rather than around age 15 [33].

It has been hypothesized that cigarette smoke modulates breast cancer risk through its anti-estrogenic effect [3]. It has been shown that cigarette smoke increases the 2-OHE1 form of estrogen rather than the 16 α OHE-1 form of estrogen [3]; the 2-OHE-1 form of estrogen has been shown to decrease mammary cell proliferation thereby reducing risk of breast cancer. However, the literature suggests increased risk rather than decreased breast cancer risk [3]. Several studies have shown that cigarette smoking is associated with ER negative tumors [39,40] further suggesting an estrogen-related mechanism. Our data show only slightly stronger associations for lifetime exposure to passive smoke and an increased risk of ER- versus ER+ tumors. This increased risk is seen only for Hispanic/AI women. Since cigarette smoking influences many hormones in addition to estrogen, the association between active and passive smoking and breast cancer among pre-menopausal women could involve a variety of hormones [41].

Our data suggest possible different mechanisms between active and passive exposure to cigarette smoke. Active, but not passive cigarette smoke interacted with *ESR1*, suggesting involvement with an estrogen-related pathway. It has been stated that the anti-estrogenic effect of passive smoke is less than that of active smoking [7]. In contrast, *IL6* interacted with passive smoking, suggesting involvement of inflammation in response to mutagens is stronger from exposure to passive rather than active smoke, although there are limited data examining inflammation-related pathways and breast cancer. However, some but not all studies show that *NAT2*, *CYP1A1*, and *MnSOD* alter smoking-related breast cancer risk [5,12,42–47].

The greatest risk associated with cigarette smoke exposure and breast cancer was seen for pre- and peri-menopausal women. Active smoking appeared to influence risk the most among NHW women while exposure to passive smoke appeared to have a greater effect among Hispanic/AI women. The reasons for this are not clear but could be from unidentified or unmeasured

pattern of smoking, types of cigarettes used, genetic factors that differ by ethnicity and influence risk, or chance. While these differences could also stem from recall bias or selection bias given less than optimal response rates, these differences do not exist for post-menopausal women, suggesting that bias is not the contributing factor. It is possible that Hispanic/AI woman had different patterns of cigarette exposure throughout their lives, or that exposure to cigarette smoke differed because of different brands or smoking practices. It also is possible that other unidentified characteristics of these women may have affected susceptibility to tobacco smoke differently among NHW and Hispanic/AI women. Of interest is one study that showed that slow *N*-acetylators are more susceptible to active smoke and rapid acetylators are more susceptible to passive smoke [9,46], suggesting that heterocyclic amines rather than PAHs may be the relevant carcinogen in tobacco smoke [2]. Data show that 32% of Hispanic people are slow acetylators compared to 60% of NHW individuals [48]. Possibly the *NAT2* genotype influences these ethnic differences in associations between breast cancer and cigarettes smoking.

Although this is one of the largest studies to examine the association between active and passive smoking in Hispanic women, there are limitations. First, response rates were low especially among Hispanic controls. However, response rates were similar for pre- and post-menopausal women; therefore seeing an association only among pre-menopausal women is less likely to be from response rates. Participants were asked to recall their exposure to other people's tobacco smoke, which could be perceived differently and therefore recalled inaccurately. We lack detail as to type or brand of active and passive cigarette smoke exposure which could influence associations. We were able to adjust for potential confounding factors such as alcohol intake, body size, activity patterns, and parity that could bias associations.

In summary our findings corroborate those by others that smoking cigarettes or being exposed to cigarette smoke by others increases risk of pre-menopausal breast cancer. Our data suggest that this risk may be influenced by underlying genetic susceptibility and that mechanisms involving both estrogen and inflammation may be important in defining risk. Differences observed by ethnicity may reflect additional underlying genetic susceptibility to cigarettes and patterns of actual and passive smoke.

Acknowledgements

This study was funded by CA 078682, CA 078762, CA078552, CA078802. This research was supported by the Utah Cancer Registry, which is funded by Contract #N01-PC-67000 from the National Cancer Institute, with additional support from the State of Utah Department of Health, the New Mexico Tumor Registry and the Arizona and Colorado cancer registries, funded by the Centers for Disease Control and Prevention National Program of Cancer Registries and additional state support. We would like to acknowledge the contributions of Roger Edwards, Jennifer Herrick, Leslie Palmer, Betsy Risendal, Tara Patton, Jason Witter, and Kelly May to this study. The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official view of the National Cancer Institute.

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Table 1

Study population characteristics

	NHW			p ^a	Hispanic/AI			p ^a	p ^b	
	Cases				Controls					
	N	(%)	(%)		N	(%)	(%)			
Center	AZ	232	15.2	305	19.1	169	21.2	208	22.5	<.01
	CO	318	20.8	301	18.8	165	20.7	201	21.8	
	NM	645	42.2	618	38.6	362	45.4	324	35.1	
	UT	332	21.7	377	23.5	102	12.8	191	20.7	
	Menopausal Status ^c									
	Pre/Peri	538	35.3	492	30.8	333	41.8	333	36.2	<.01
	Post, Recent ^d	127	8.3	98	6.1	63	7.9	65	7.1	
	Post, Not Recent	859	56.4	1010	63.1	400	50.3	522	56.7	
	Smoking Status ^e									
	Never	839	55.0	939	58.9	527	66.3	600	65.4	0.20
Age Started Smoking	Former	482	31.6	452	28.4	172	21.6	202	22.0	
	Current	204	13.4	203	12.7	96	12.1	116	12.6	
	Age Started Smoking									
	Age ≥ 20	221	32.2	187	28.5	100	37.3	126	39.6	0.78
	Age 17–19	254	37.0	259	39.5	80	29.9	86	27.0	
	Age ≤16	211	30.8	209	31.9	88	32.8	106	33.3	
	IL6 rs2069832 (intron 2 +180)									
	GG	426	36.5	406	30.7	384	67.0	457	62.9	0.02
	GA	545	46.7	660	49.8	161	28.1	241	33.2	
	AA	197	16.9	258	19.5	28	4.9	28	3.9	
ESR1 XbaI A/G	Xx	492	42.3	564	42.5	287	50.0	351	48.4	0.93
	XX	528	45.4	600	45.2	235	40.9	313	43.2	
	XX	143	12.3	164	12.3	52	9.1	61	8.4	
	Mean		SD	Mean	SD	Mean	SD	Mean	SD	
	Age	55.3	11.1	56.4	12.2	52.2	11.2	54.5	12.1	p ^a <.01
	Passive Smoking (hr/wk)									
	Referent	6.1	20.3	5.6	19.5	8.7	21.7	6.8	19.3	0.58
	Age 15	21.6	31.8	21.9	33.2	13.4	22.4	16.1	28.4	0.39
	Age 30	21.9	34.1	22.3	34.9	14.4	25.0	15.5	29.1	0.86
	Age 50	9.4	26.1	9.9	26.2	6.2	18.5	6.8	19.8	0.14

^aComparison of cases and controls within ethnic groups; p-values for frequencies, chi-square test; for means Wilcoxon's rank-sum test

^bComparison of cases and controls in combined ethnic groups

^cStatus at reference date

^dPost-menopausal 2 years of reference date

Table 2
Associations between active cigarette smoking and breast cancer^a

	NHW				P-trend	Hispanic /AI				P-trend
	Cases N	Controls N	OR	95% CI		Cases N	Controls N	OR	95% CI	
Pre- and Peri-menopausal Smoking Status ^b										
Never	313	327	1.0	—		232	232	1.0	—	
Ever	222	164	1.3	(1.0, 1.7)	0.04	97	98	1.1	(0.7, 1.5)	0.77
Former	148	105	1.4	(<1.0, 1.8)		67	61	1.1	(0.8, 1.7)	
Current	74	59	1.3	(0.9, 1.9)	0.09	30	37	0.9	(0.5, 1.6)	0.98
Pack Years										
Never<1	333	339	1.0	—		249	248	1.0	—	
1–15	126	106	1.1	(0.8, 1.6)		60	59	1.0	(0.7, 1.6)	
>15	76	45	1.6	(1.1, 2.4)	0.03	18	23	0.9	(0.5, 1.7)	0.88
Age Started Smoking										
Never	313	327	1.0	—		232	232	1.0	—	
Age ≥ 20	59	40	1.4	(0.9, 2.3)		30	33	1.1	(0.6, 1.9)	
Age 17–19	73	57	1.2	(0.8, 1.8)		29	24	1.1	(0.6, 1.9)	
Age ≤ 16	90	67	1.3	(0.9, 1.9)	0.08	38	41	1.0	(0.6, 1.7)	0.84
Smoked Before 1st Pregnancy										
Never	313	327	1.0	—		232	232	1.0	—	
No	22	18	1.2	(0.6, 2.4)		16	19	1.0	(0.5, 2.1)	
Yes	174	124	1.4	(1.0, 1.9)	0.03	74	68	1.1	(0.8, 1.7)	0.56
Post-menopausal Smoking Status ^b										
Never	516	597	1.0	—		286	355	1.0	—	
Ever	451	486	1.0	(0.9, 1.2)	0.77	164	214	1.0	(0.7, 1.3)	0.76
Former	324	345	1.1	(0.9, 1.3)		100	138	0.9	(0.7, 1.3)	
Current	127	141	1.0	(0.7, 1.3)	0.96	64	76	1.0	(0.7, 1.5)	0.84
Pack Years										
Never<1	532	616	1.0	—		301	366	1.0	—	
1–15	190	183	1.2	(0.9, 1.5)		79	126	0.7	(0.5, 1.0)	
>15	243	279	1.0	(0.8, 1.2)	0.90	67	76	1.2	(0.8, 1.7)	0.96
Age Started Smoking										
Never	516	597	1.0	—		286	355	1.0	—	
Age ≥ 20	158	146	1.2	(0.9, 1.6)		68	90	1.0	(0.7, 1.4)	
Age 17–19	177	200	1.0	(0.8, 1.2)		50	61	1.0	(0.7, 1.6)	
Age ≤ 16	116	140	0.9	(0.7, 1.2)	0.51	46	63	0.9	(0.6, 1.3)	0.65
Smoked Before 1st Pregnancy										
Never	516	599	1.0	—		287	355	1.0	—	
No	71	81	1.0	(0.7, 1.4)		51	58	1.2	(0.8, 1.8)	
Yes	334	371	1.0	(0.8, 1.3)	0.83	105	142	0.9	(0.7, 1.2)	0.66

^a Adjusted for age, center, BMI, aspirin/NSAIDs, parity, long-term alcohol use, long-term physical activity, and recent estrogen in post-menopausal women

^b Status at reference date

Table 3
Associations between passive smoking during reference period and breast cancer^a

Hours/Wk.	NHW			Hispanic/AI			p-trend
	Cases N	Controls N	OR	95% CI	Cases N	Controls N	
Pre- and Peri-Menopausal							
Everyone							
None	392	363	1.0	—	202	201	
1–10	86	76	1.0	(0.7, 1.4)	67	94	
>10	57	52	0.8	(0.5, 1.3)	60	35	0.11
Never Smokers							
None	254	276	1.0	—	155	154	
1–10	43	37	1.2	(0.7, 1.9)	43	62	
>10	16	14	1.2	(0.6, 2.7)	34	16	0.13
Postmenopausal Everyone							
None	718	818	1.0	—	294	372	
1–10	141	155	1.0	(0.7, 1.2)	81	113	
>10	108	112	1.0	(0.8, 1.4)	76	84	0.99
Never Smokers							
None	424	496	1.0	—	206	258	
1–10	67	71	1.0	(0.7, 1.5)	47	59	
>10	25	30	1.0	(0.6, 1.7)	33	38	0.96

^a Adjusted for age, center, BMI, aspirin/NSAIDs, parity, long-term alcohol use, long-term physical activity, cigarette pack years, and recent estrogen in postmenopausal women

Table 4

Interaction between passive smoking *IL6* G/A (rs2069832, intron 2 +180) and by menopause status^d

Genotype GG		Genotypes GA or AA			p ^d	Genotype GG			Genotypes GA or AA			p ^d
Cases N	Controls N	OR ^c	95% CI	Cases N		Controls N	OR ^c	95% CI	Cases N	Controls N	OR ^c	
All Postmenopausal Women												
9	100	200	1.0	—	197	199	1.0	—	343	456	0.8	(0.6, 1.0)
0	13	39	1.3	(0.6, 2.8)	39	43	0.8	(0.5, 1.4)	72	87	0.8	(0.5, 1.2)
7	8	24	1.5	(0.6, 3.7)	31	26	1.1	(0.6, 1.9)	43	63	0.6	(0.4, 1.0)
Breast Cancer												
8	106	52	1.0	—	141	174	1.0	—	70	105	0.8	(0.5, 1.1)
7	49	19	0.7	(0.4, 1.2)	36	53	0.8	(0.5, 1.3)	19	42	0.5	(0.3, 0.9)
1	17	10	2.3	(1.1, 4.6)	40	42	1.1	(0.7, 1.8)	17	21	1.0	(0.5, 1.9)
Never Smokers, Postmenopausal Women												
1	76	156	1.0	—	114	124	1.0	—	213	288	0.8	(0.6, 1.1)
1	5	19	1.9	(0.6, 6.1)	18	20	0.9	(0.5, 1.9)	33	38	0.9	(0.5, 1.6)
5	2	4	3.0	(0.6, 15.9)	8	11	0.8	(0.3, 2.1)	12	16	0.8	(0.4, 1.8)
Perimenopausal Women												
8	83	41	1.0	—	106	120	1.0	—	45	72	0.7	(0.4, 1.1)
5	30	12	0.7	(0.3, 1.4)	27	28	1.0	(0.5, 1.8)	8	22	0.3	(0.1, 0.8)
0	5	3	4.4	(1.5, 12.8)	17	23	0.8	(0.4, 1.7)	6	8	0.7	(0.2, 2.2)

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er, BMI, aspirin/NSAIDs, parity, long-term physical activity, cigarette pack years, and recent hormone exposure in postmenopausal women

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Table 5
Interaction between cigarette pack years or passive smoking and *ESR1* XbaI^a

	Genotype xx			Genotypes xX or XX			<i>p</i> ^b
	Cases N	Controls N	OR	95% CI	Cases N	Controls N	
Pre- and Peri-menopausal Cigarette Pack Years							
NHW							
Never/<1	104	129	1.0	—	148	157	
1–15	43	46	1.1	(0.7, 1.9)	52	42	0.15
>15	25	10	2.9	(1.3, 6.4)	33	28	
Hispanic/AI							
Never/<1	85	106	1.0	—	97	90	0.01
1–15	19	32	0.7	(0.4, 1.4)	23	18	
>15	7	3	3.0	(0.7, 12.5)	4	15	
Passive Smoking, Never Smokers (Hours/Wk.) ^c							
Non-Hispanic White							
None	80	105	1.0	—	115	129	0.29
1–10	13	14	1.1	(0.5, 2.5)	17	15	
>10	1	6	0.2	(0.0, 1.7)	9	7	
Hispanic/AI							
None	51	62	1.0	—	68	57	0.74
1–10	17	32	0.7	(0.3, 1.5)	11	19	
>10	10	5	2.4	(0.7, 8.1)	13	8	
Post-menopausal Cigarette Pack Years							
NHW							
Never/<1	164	227	1.0	—	256	300	0.04
1–15	60	61	1.4	(0.9, 2.1)	75	81	
>15	89	85	1.4	(1.0, 2.1)	98	141	
Hispanic/AI							
Never/<1	124	126	1.0	—	96	165	0.06
1–15	26	54	0.5	(0.3, 0.8)	32	48	
>15	21	23	1.1	(0.5, 2.0)	25	31	
Passive Smoking, Never Smokers (Hours/Wk.) ^c							
Non-Hispanic White							
None	129	177	1.0	—	207	249	0.62
1–10	21	30	0.9	(0.5, 1.6)	31	31	
>10	9	12	1.1	(0.4, 2.6)	11	15	
Hispanic/AI							
None	91	86	1.0	—	62	112	0.53
1–10	18	20	0.7	(0.4, 1.5)	18	31	
>10	11	16	0.7	(0.3, 1.7)	12	15	

^a Adjusted for age, center, BMI, aspirin/NSAIDs, parity, long-term alcohol use, long-term physical activity, and recent estrogen in post-menopausal women. Reference is homozygous wildtype and low-risk exposure

^b Multiplicative interaction term

^c Exposure during reference period