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The relationship between various measures of cigarette smoking and risk of breast cancer among older women 65–79 years of age (United States)

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Abstract

Results from studies evaluating the relationship between cigarette smoking and breast cancer have been inconsistent. Though most studies have found that smoking does not alter risk, others have observed both increased and decreased risks associated with smoking. The reasons for these inconsistencies are unclear, but they may be related to differences in study populations, designs, and exposure definitions. In particular, this relationship may vary by age, and few studies have focused on older women many of whom have smoked for very long durations. We conducted a population-based case–control study (975 cases/1007 controls) of women 65–79 years of age in western Washington State. Women who were current smokers, smoked for ≥40 years, had ≥11 pack-years of lifetime smoking, or started smoking before their first full-term birth each had 30–40% elevated risks of breast cancer ($p < 0.05$). Recency, length, and intensity of smoking are all associated with modest increased risks of breast cancer. A further understanding of the timing of smoking, and its interaction with other factors, may enhance our knowledge of whether and by what mechanisms smoking alters breast cancer risk.

Introduction

A recent pooled analysis of 53 observational studies that evaluated the relationship between cigarette smoking and breast cancer reported that ever smokers did not have an altered risk of breast cancer compared with never smokers, though some of the studies included in the analysis found smoking to be associated with an increased risk of breast cancer and others found it to be associated with a reduced risk [1]. These inconsistencies may be the result of variations in study design in terms of the ranges of age groups and diagnosis years included, as well as of measuring and reporting exposures in different ways. For example, few studies have focused on older postmenopausal women, many of whom have smoked for substantially longer durations than younger women. In addition, one of the limitations of the pooled analysis was that only ever *versus* never and current *versus* former smoking could be assessed, but factors such as duration, timing, and intensity of smoking could not.

Several studies suggest that these measures of smoking may be important. For example, a meta-analysis observed positive dose-response relationships between number of cigarettes smoked and duration of smoking and risk of breast cancer, and that breast cancer risk increases the younger women start smoking [2]. In addition, a recent study that stratified risk by menopausal status reported that among postmenopausal women, current smokers, smokers with a $\geqslant 11$ pack-year history of smoking, smokers who started smoking before the age of 20, and smokers who started smoking 5 years or more before their first pregnancy had 13–29% greater risks of breast cancer compared to never smokers [3]. Similarly, recently published results from a cohort of 30–50-year olds suggest that long durations, early initiation, and greater intensities of smoking are all positively related to breast cancer risk [4]. In their recent

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review of this literature Terry and Rohan concluded that despite being evaluated in several epidemiologic studies, the relationship between smoking and breast cancer is still unclear. They argued that further investigations of recent results indicating that long durations of smoking and smoking initiated before a woman's first full-term pregnancy are associated with elevated risks of breast cancer are warranted [5]. Thus, there is a clearly a need for additional studies aimed at clarifying these associations; particularly for the purpose of investigating the role of smoking duration, timing, and intensity, and also to evaluate possible interactions with other known breast cancer risk factors. In addition, no studies have explored this association in a population consisting exclusively of older postmenopausal women. Such an investigation is needed because many women in this age range have smoked for very long durations, and because risk factors for breast cancer vary by age. For example, while age at menarche, parity, and breast feeding are well established risk factors for postmenopausal breast cancer, we have found that among women 65 to 79 years of age these factors are not related to breast cancer risk [6]. Thus, the etiology of breast cancer among older postmenopausal women may differ in several respects from that of younger women.

Using data from a population-based case–control study of breast cancer, we assessed the relations between various measures of cigarette smoking and risk of invasive breast cancer among women 65 to 79 years of age. We also evaluated interactions between smoking and other breast cancer risk factors, and the relationship between smoking and different types of breast cancer (based on hormone receptor status and histology) to further our understanding of the mechanisms underlying the potential association between smoking and breast cancer.

Methods

We conducted a population-based case–control study of women 65 to 79 years of age living in the three county Seattle-Puget Sound metropolitan area. The study's protocol was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board, and written informed consent was obtained from all study subjects before each interview. The methods of this study have been described in detail elsewhere [7].

Cases

Women aged 65 to 79 years with no history of *in situ* or invasive breast cancer when diagnosed with invasive breast cancer between 1 April 1997 and 31 May 1999, were eligible as cases. The Cancer Surveillance System (CSS), the population-based tumor registry that serves the Seattle-Puget Sound region of Washington State and participates in the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, was used to identify cases. In order to be eligible for the study, all cases had to live in King, Pierce, or Snohomish counties and have a Health Care Financing Administration (HCFA) record, since these records were used to identify controls. Of the 1210 eligible cases identified, 975 (80.6%) were interviewed.

Information on hormone receptor status and tumor histology was ascertained from CSS, which abstracts data on tumor characteristics from medical records and pathology reports from institutions serving the area. CSS classifies estrogen receptor (ER) and progesterone receptor (PR) status as positive, negative, borderline, not assessed, or unknown based on information abstracted from medical records. The 75 (7.7%) cases with an ER and/or PR status that was borderline, not assessed, or unknown were excluded from our analyses by hormone receptor status. In our analyses we considered joint ER/PR status, which inluded 646 ER+/PR+ cases, 147 ER+/PR− cases, and 101 ER−/PR− cases. Since there were only six ER−/PR+ cases we were unable to analyze this group separately. CSS classifies histology using the International Classification of Diseases for Oncology (ICD-O) codes, and we divided cases into two groups with code 8500 used to define the invasive ductal carcinoma (IDC) cases (n = 656) and codes 8520 and 8522 used to define invasive lobular carcinoma (ILC) cases (n = 196). The 123 women with other breast cancer histologies were excluded from our analyses by histologic type.

Controls

Controls from the general population were identified using HCFA records and were frequency matched on age (in five-year groups) to cases. They were eligible for this study if they had no prior history of in situ or invasive breast cancer and were residents of King, Pierce, or Snohomish counties. Of the 1365 eligible women selected as controls, 1007 (73.8%) were interviewed.

Data collection

Subjects were interviewed in person and almost all interviews were conducted in the subjects' home. They were asked about a variety of factors including: menstrual, contraceptive, and reproductive histories; use of postmenopausal hormones (including both unopposed estrogen and combined estrogen/progestin regimens);

body size; alcohol use; demographic information; and medical history, including family history of cancer. Our questioning was limited to exposures that occurred before each subject's reference date. The reference date used for cases was their breast cancer diagnosis date. Controls were assigned reference years so that the distribution of control reference years was similar to that of the case diagnosis years to assure similar information quality. Reference months were then randomly assigned to controls.

Information on lifetime cigarette smoking before diagnosis/reference date was also collected. Women were classified as never smokers if they reported never smoking or smoking less than 100 cigarettes over their lifetime. Women who smoked 100 or more cigarettes over their lifetime were classified as ever smokers and were asked about the ages when they started smoking and when they last smoked, about the durations of any periods of time when they did not smoke, and about their average smoking intensity (number of cigarettes per day, week, month, or year). A life events calendar was used to enhance recall of times when patterns of cigarette smoking may have changed. These data were used to categorize smokers based on their recency of smoking, in which former smokers were defined as ever smokers who reported no smoking during the year before reference date, and current smokers were defined as ever smokers who did report smoking during this year. In addition, these data were used to compute each smoker's lifetime pack years of smoking (number of years she smoked the equivalent of one pack [20 cigarettes] per day for a year long period), the average number of cigarettes she smoked per day, and the years since she quit if she was a former smoker. Among smokers who were parous, we also evaluated their age of smoking initiation in relation to their age at their first full-term birth.

The data we collected on alcohol use was limited to consumption within the 20 years before diagnosis/reference date and is described in more detail elsewhere [8]. Briefly, alcohol drinkers were defined as women who reported that they had consumed at least 12 beverages containing alcohol during the past 20 years and had consumed at least one alcohol-containing beverage a month for six months or more during the past 20 years. Never drinkers over the past 20 years were women who reported consuming less than 12 beverages containing alcohol during the past 20 years, consumed less than one alcohol-containing beverage a month during the past 20 years, or who consumed more than one alcohol-containing beverage a month for less than six months during the past 20 years. Women who consumed more than these amounts were classified as ever users of alcohol, and they were asked separate questions about how many units of 12-ounce bottles or cans of beer, four-ounce glasses of wine, and 1.5-ounce shots of liquor they consumed per day, week, month, or year, and how their pattern of use of each of these types of alcohol changed over the past 20 years. Based on this information, cumulative intake of alcohol over the 20 years prior to reference date was calculated and then this total was divided into a daily alcohol intake over this period.

Statistical analysis

We compared all breast cancer cases to controls using unconditional logistic regression [9]. We compared cases with different hormone receptor profiles to controls, and ILC and IDC cases to controls, using polytomous logistic regression [10]. Both statistical approaches were used to calculate odds ratios (ORs) as an estimate of the relative risk and to compute 95% confidence intervals (CIs). Each measure of smoking evaluated was modeled independently of one another given that these measures were highly correlated. All analyses were adjusted for age and reference year because controls were matched to cases on these factors. Never smokers served as the reference group in all analyses. We tested for trends across categories of appropriate smoking variables by treating these variables as continuous in the analyses including the never smokers category. All statistical tests performed were two-sided.

The following variables (using the following categories) were evaluated as potential confounders and effect modifiers: education (less than high school, high school graduate, some college, college graduate or higher); annual household income (< \$15,000, \$15,000–\$24,999, \$25,000–\$49,999, ≥\$50,000); type of menopause (natural, induced, simple hysterectomy [hysterectomy without a bilateral oophorectomy]); age at menopause (five-year categories, note: women with an unknown age at menopause, including all women who had a simple hysterectomy, were excluded when this variable was assessed as a confounder); parity (parous/nulliparous); age at first full-term (> 26 weeks) pregnancy (14–19, 20–24, 25–29, ≥30 years); first-degree family history of breast cancer (yes/no); body mass index (BMI, kg/m^2) five years before reference date (quartiles of control population); ever use of unopposed estrogen menopausal hormones (never, ever for ≥ six months or longer, ever for six months to 4.9 years, and ever for ≥ five years); ever use of combined estrogen/progestin menopausal hormones (never, ever for ≥ six months or longer, ever for six months to 4.9 years, and ever for ≥ five years); and average grams of alcohol consumption per day over the 20 years before reference date (none,

< 1.5, 1.5–4.9, 5.0–14.9, 15.0–29.9, and ≥30.0). Only adjustment for alcohol use, use of menopausal hormones, and BMI changed the risk estimates of the odds ratios of interest by more than ten percent. Therefore, all analyses were adjusted for age, reference year, alcohol use, ever use of menopausal hormones, and BMI. Since the Collaborative Group on Hormonal Factors in Breast Cancer reported that alcohol use has an important effect on the relationship between smoking and breast cancer [1], we stratified our analyses on whether women were never users of alcohol or consumed less than or more than the mean amount of alcohol consumed by the controls in our study who were alcohol consumers (8.2 g/day). Further, given that use of menopausal hormones confounded the relationship between smoking and breast cancer, we explored whether or not use of hormones altered this relationship through stratified analyses. Likelihood ratio testing was used to evaluate whether or not each of these variables was a statistically significant ($p < 0.05$) effect modifier of the relationship between smoking and breast cancer.

Results

Controls were more likely than cases to be non-white, but were similar with respect to their income distribution (Table 1). Compared to controls, cases were somewhat less likely to have an induced menopause and to be in the lowest quartile of BMI, and were somewhat more likely to have had a simple hysterectomy, to have a first degree family history of breast cancer, to have used both unopposed estrogen and combined estrogen/progestin menopausal hormones, and to consume ≥30.0 g of alcohol per day. Compared to controls who were never smokers, controls who were ever smokers were somewhat more likely to have a lower income, a natural menopause, a first-degree family history of breast cancer, a lower BMI, and to have not used menopausal hormones. The most striking difference between controls who were never smokers *versus* ever smokers was in their use of alcohol. Compared to never smokers, ever smokers were less likely to never have used alcohol (39.6% *versus* 63.6%) and more likely to have consumed an average of ≥30.0 g/day of alcohol over their lifetimes (7.9% *versus* 1.5%).

Ever smokers had a 1.3-fold (95% CI: 1.0–1.5) increased risk of breast cancer (Table 2). Current smoking was more strongly associated with breast cancer risk (OR = 1.4, 95% CI: 1.0–1.9) than was former smoking (OR = 1.2, 95% CI: 1.0–1.5). Women who smoked for 40 years or longer had a 1.4-fold (95% CI: 1.1–1.7) increased risk of breast cancer (p for trend = 0.006). Women with eleven or more pack years of smoking had 30–40% elevated risks of breast cancer (p for trend = 0.009). There was also a suggestion that the younger women started smoking the greater their risk of breast cancer (p for trend = 0.028). In addition, women who started smoking before their first full-term birth had a greater risk of breast cancer (OR = 1.3, 95% CI: 1.0–1.6) than did those who started smoking after their first full-term birth (OR = 1.1, 95% CI: 0.8–1.5). Among former smokers, risk of breast cancer increased as the number of years since women quit smoking decreased (p for trend = 0.014).

Alcohol use was not observed to be an effect modifier of the relationship between various measures of smoking and breast cancer risk as risks were similar across women who never used alcohol, women who consumed < 8.2g/day of alcohol, and women who consumed ≥8.2 g/day of alcohol (Table 3). While not reaching statistical significance based on likelihood ratio testing, there was a suggestion that the relationship between smoking (including ever smoking, recency of smoking, and lifetime pack years of smoking) and breast cancer risk was modified by the use of combined estrogen/progestin menopausal hormones, but not by the use of unopposed estrogen menopausal hormones (Table 4). For example, current smokers who never used menopausal hormones had a 1.6-fold (95% CI: 0.9–2.6) increased risk of breast cancer, current smokers who used unopposed estrogen had a 1.3-fold (95% CI: 0.8–2.1) increased risk of breast cancer, but current smokers who used estrogen/progestin had a 3.4-fold (95% CI: 1.6–7.3) increased risk.

Associations between smoking and breast cancer also appeared to vary somewhat by the ER/PR status of the tumor (Table 5). Compared to never smokers, current smokers had an elevated risk of ER+/PR− breast cancers (OR = 2.3; 95% CI: 1.4–4.0), but not of ER+/PR+ (OR = 1.1; 95% CI: 0.8–1.6) or ER−/PR− (OR = 1.2; 95% CI: 0.5–2.4) breast cancers. However, there was less variation in the risk of breast cancers with different ER/PR profiles across the other measures of smoking. Additionally, no appreciable differences in risks associated with the various measures of smoking that we evaluated were observed across women with ductal compared to lobular breast carcinomas.

Discussion

The Collaborative Group on Hormonal Factors in Breast Cancer observed that neither ever or current smoking is related to breast cancer risk [1]. However,

Table 1. Distribution of demographic and known risk factors for breast cancer among 975 breast cancer cases and 1007 controls

Characteristic	Cases (n = 975)		Controls (n = 1007)		Controls: Never smokers (n = 523)		Controls: Ever smokers (n = 484)	
	N	%	N	%	N	%	N	%
Reference age, years								
65–69	300	31	330	33	178	34	152	31
70–74	381	39	381	38	190	36	191	40
75–79	294	30	296	29	155	30	141	29
Race								
White	929	95	925	92	477	91	448	93
Black	16	2	37	4	18	3	19	4
Asian/Pacific Islander	19	2	29	3	20	4	9	2
Other/unknown	11	1	16	2	8	2	8	2
Income								
< $15,000	177	21	191	22	87	19	104	24
$15–25,000	198	24	214	24	108	24	106	25
$25–50,000	296	36	296	34	153	34	143	33
≥$50,000	159	19	180	20	102	23	78	18
Missing	145		126		73		53	
Parity								
Nulliparous	88	9	94	9	47	9	47	10
Parous	887	91	913	91	476	91	437	90
Age at first birth, years								
14–19	152	17	187	21	99	21	88	20
20–24	432	49	435	48	221	47	214	49
25–29	206	23	205	23	106	22	99	23
≥30	93	11	85	9	49	10	36	8
Missing	92		95		48		47	
Type of menopause								
Natural	583	61	607	62	302	59	305	64
Induced	129	14	148	15	73	14	75	16
Simple hysterectomy	237	25	231	22	137	27	94	20
Missing	26		21		11		10	
First degree family history of breast cancer								
No	703	77	771	83	412	84	359	82
Yes	208	23	159	17	78	16	81	18
Missing	64		77		33		44	
Body mass index, quartiles, kg/m^2								
< 23.33	209	22	261	27	130	26	131	29
23.33–26.20	240	26	241	25	129	26	112	24
26.21–30.11	245	26	230	24	118	23	112	24
≥30.12	245	26	231	24	127	25	104	23
Missing	36		44		19		25	
Ever use of unopposed estrogen menopausal hormones								
Never user	284	38	339	42	170	40	169	44
Ever user	455	62	466	58	253	60	213	56
6 mos–5 yrs	112	15	144	18	76	17	68	16
≥5 yrs	343	46	322	40	177	39	145	34
Ever use of combined estrogen/progestin menopausal hormones								
Never user	284	55	339	67	170	65	169	69
Ever user	232	45	165	33	90	35	75	31
6 mos–5 yrs	65	13	60	12	31	11	29	10
≥5 yrs	167	32	105	21	59	20	46	16
Average daily alcohol intake, grams/day								
None	461	48	518	52	327	63	191	40
< 1.5	60	6	59	6	35	7	24	5
1.5–4.9	129	13	122	12	53	10	69	14
5.0–14.9	161	17	167	17	75	14	92	19
15.0–29.9	96	10	92	9	24	5	68	14
≥30.0	63	7	46	5	8	2	38	8
Missing	5		3		1		2	

Table 2. Relationship between various measures of smoking and breast cancer risk

Factor	Cases N = 975		Controls N = 1007		OR[a]	95% CI	*p*-Value for trend[b]
	N	%	N	%			
Ever smoked[c]							
Never	432	46	504	52	1.0	ref	
Ever	507	54	459	48	1.3	1.0-1.5[d]	
Recency of smoking							
Never smoked	432	46	504	52	1.0	ref	
Former	384	41	351	36	1.2	1.0–1.5	
<20 pack years	147	16	157	16	1.1	0.8–1.4	
≥20 pack years	234	25	193	20	1.3	1.1–1.7[d]	
Current	123	13	108	11	1.4	1.0–1.9[d]	
<20 pack years	14	1	12	1	1.3	0.6–3.0	
≥20 pack years	109	12	96	10	1.4	1.0–2.0[d]	
Number of years smoked							
0	432	46	504	52	1.0	ref	
<20	105	11	111	12	1.0	0.8–1.4	
20–39	169	18	149	16	1.3	1.0–1.7	
≥40	231	25	198	21	1.4	1.1–1.7[d]	0.006
Lifetime pack years of smoking							
Never smoked	432	46	504	52	1.0	ref	
<11	96	10	111	12	1.0	0.7–1.3	
11–27	139	15	113	12	1.4	1.1–1.9[d]	
28–52	141	15	120	13	1.3	1.0–1.8[d]	
≥53	128	14	114	12	1.3	1.0–1.7	0.009
Smoking intensity, average number of cigarettes per day							
Never smoked	432	46	504	52	1.0	ref	
<10	136	15	122	13	1.3	1.0–1.7	
10–19	153	16	128	13	1.3	1.0–1.7	
≥20	214	23	208	22	1.2	0.9–1.5	0.057
Age of smoking initiation, years							
Never smoked	432	46	504	52	1.0	ref	
≥20	223	24	202	21	1.2	1.0–1.6	
<20	284	30	257	27	1.3	1.0–1.6[d]	0.028
Smoking initiation in relation to age at first full-term birth (FFB) among parous women only							
Never smoked (and parous)	399	47	461	53	1.0	ref	
Smoked pre-partum	365	43	324	37	1.3	1.0–1.6[d]	
Started <5 yrs before 1st FFB	178	21	154	18	1.3	1.0–1.7	
Started ≥5 yrs before 1st FFB	187	22	170	19	1.2	1.0–1.6	
Smoked post-partum only	94	11	91	10	1.1	0.8–1.5	
Years since quitting smoking							
Never smoked	432	46	504	52	1.0	ref	
≥20	174	21	174	20	1.1	0.8–1.4	
10–19	97	12	94	11	1.1	0.8–1.6	
<10	112	14	82	10	1.5	1.1–2.1[d]	0.014

[a] Odds ratios (OR) are adjusted for age (65–69, 70–74, and 75–79), reference year (categorical), grams/day of alcohol use (none, <1.5, 1.5–4.9, 5.0–14.9, 15.0–29.9, and ≥30.0), ever use of postmenopausal hormones (never/ever), and body mass index (quartiles).

[b] Trend tests between levels of smoking categories including never smokers.

[c] Ever smokers were women who reported ever smoking a total of 100 cigarettes or more in their lifetime.

[d] $p < 0.05$.

consistent with several more recent studies that evaluated more detailed aspects of smoking history [2–4], we found that various measures of smoking exposure are related to risk of breast cancer within our population of older postmenopausal women. Specifically, we observed that women who were current smokers, smoked

Table 3. Relationship between smoking and breast cancer stratified by alcohol use

	Cases N = 975		Controls N = 1007		OR[a]	95% CI	*p*-Value for interaction
	N	%	N	%			
Ever smoked[b]							
Never users of alcohol							
Never	265	60	315	64	1.0	ref	
Ever	175	40	179	36	1.2	0.9–1.5	
Consumers of <8.2 g/day of alcohol							
Never	100	42	116	49	1.0	ref	
Ever	139	58	119	51	1.4	1.0–2.0	
Consumers of ≥8.2 g/day of alcohol							
Never	67	26	72	31	1.0	ref	
Ever	188	74	159	69	1.3	0.9–1.9	0.7542
Recency of smoking							
Never users of alcohol							
Never	265	60	315	64	1.0	ref	
Former	136	31	143	29	1.1	0.8–1.5	
Current	39	9	36	7	1.5	0.9–2.5	
Consumers of <8.2 g/day of alcohol							
Never	100	42	116	49	1.0	ref	
Former	111	46	91	39	1.4	1.0–2.1	
Current	28	12	28	12	1.3	0.7–2.3	
Consumers of ≥8.2 g/day of alcohol							
Never	67	26	72	31	1.0	ref	
Former	133	52	116	50	1.2	0.8–1.9	
Current	55	22	43	19	1.5	0.9–2.5	0.8309
Lifetime pack years of smoking							
Never users of alcohol							
Never	265	60	315	64	1.0	ref	
<20	62	14	72	15	1.0	0.7–1.5	
≥20	111	25	106	22	1.3	0.9–1.8	
Consumers of <8.2 g/day of alcohol							
Never	100	42	116	49	1.0	ref	
<20	48	20	48	20	1.2	0.7–1.9	
≥20	90	38	71	30	1.5	1.0–2.3[c]	
Consumers of ≥8.2 g/day of alcohol							
Never	67	26	72	31	1.0	ref	
<20	50	20	49	21	1.1	0.7–1.9	
≥20	138	54	110	48	1.4	0.9–2.1	0.9713

[a] Odds ratios (OR) are adjusted for age (65–69, 70–74, and 75–79), reference year (categorical), ever use of postmenopausal hormones (never/ever), and BMI (quartiles).

[b] Ever smokers were women who reported ever smoking a total of 100 cigarettes or more in their lifetime.

[c] $p < 0.05$.

for ≥40 years, had ≥11 pack-years of lifetime smoking, or started smoking before their first full-term birth each had small elevations in their risks of breast cancer.

Before interpreting these findings certain limitations of our study should be acknowledged. We interviewed only 80.6% of all eligible cases and 73.8% of all eligible controls. Our results could be biased if the women we were unable to interview differed from those who did participate with regard to their smoking history. For example, smoking status is related to socioeconomic status (SES), and here we did observe that ever smokers tended to have lower incomes compared to never smokers among our controls. It is noteworthy though that overall the cases and controls in this study had a similar income distribution, so at least with respect to SES, our control group is unlikely to include an over-representation of non-smokers that would bias our results away from the null. We also relied on participants' recall of their smoking history. However, in the pooled analysis of 53 studies evaluating the association between smoking and breast cancer, the risk of breast

Table 4. Relationship between smoking and breast cancer stratified by menopausal hormone use

	Cases N = 975		Controls N = 1007		OR[a]	95% CI	*p*-Value for interaction
	N	%	N	%			
Ever smoked[b]							
Never users of menopausal hormones							
Never	112	42	159	51	1.0	ref	
Ever	155	58	154	49	1.4	1.0–2.0[c]	
Ever users of unopposed estrogen therapy							
Never	221	20	247	55	1.0	ref	
Ever	220	50	205	45	1.1	0.9–1.5	0.3689
Ever users of combined estrogen and progestin therapy							
Never	95	41	88	54	1.0	ref	
Ever	136	59	74	46	1.8	1.2–2.7[c]	0.5111
Recency of smoking							
Never users of menopausal hormones							
Never	112	42	159	51	1.0	ref	
Former	111	42	106	34	1.4	0.9–2.0	
Current	44	17	48	15	1.6	0.9–2.6	
Ever users of unopposed estrogen therapy							
Never	221	20	247	55	1.0	ref	
Former	168	38	162	36	1.1	0.8–1.5	
Current	52	12	43	10	1.3	0.8–2.1	0.5833
Ever users of combined estrogen and progestin therapy							
Never	95	41	88	54	1.0	ref	
Former	101	44	64	40	1.5	1.0–2.3	
Current	35	15	10	6	3.4	1.6–7.3[c]	0.1520
Lifetime pack years of smoking							
Never users of menopausal hormones							
Never	112	42	159	51	1.0	ref	
<20	47	18	55	18	1.1	0.7–1.8	
≥20	107	40	99	32	1.6	1.1–2.3[c]	
Ever users of unopposed estrogen therapy							
Never	221	20	247	55	1.0	ref	
<20	75	17	79	18	1.0	0.7–1.5	
≥20	145	33	125	28	1.2	0.9–1.7	0.7003
Ever users of combined estrogen and progestin therapy							
Never	95	41	88	54	1.0	ref	
<20	46	20	33	20	1.3	0.8–2.3	
≥20	90	39	41	25	2.1	1.3–3.5[c]	0.6859

[a] Odds ratios (OR) are adjusted for age (65–69, 70–74, and 75–79), reference year (categorical), grams/day of alcohol use (none, <1.5, 1.5–4.9, 5.0–14.9, 15.0–29.9, and ≥30.0), and BMI (quartiles).

[b] Ever smokers were women who reported ever smoking a total of 100 cigarettes or more in their lifetime.

[c] $p < 0.05$.

cancer associated with ever smoking when the cohort studies were pooled was similar to the risk obtained when the case–control studies were pooled [1], suggesting that the impact of recall bias in case–control studies of smoking and breast cancer is limited. Additionally, we did not test all tumors for hormone receptor status or conduct independent pathology reviews in a centralized manner. Instead we relied on the assessments made by the numerous pathologists and laboratories serving the Seattle-Puget Sound area. Misclassification of hormone receptor status and tumor histology may have resulted.

A strength of this study is that it included a unique population of older women. Previous studies have not focused exclusively on older women, so in this study we were able to assess both the risk of breast cancer among smokers specific to this age group, and to evaluate risks associated with very long smoking durations. Consistent with several recent studies, we observed that more detailed information about smoking history, beyond ever smoking or current smoking, is important to consider when evaluating the association between smoking and breast cancer. For example, in terms of pack year

Table 5. Relationship between smoking and risk of breast cancer by ER/PR status and histologic type

Factor	ER+/PR+ N = 646		ER+/PR− N = 147		ER−/PR− N = 101		Ductal N = 656		Lobular N = 196	
	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI	OR[a]	95% CI
Ever smoker[b]										
No	1.0	ref	1.0	ref	1.0	ref	1.0	ref	1.0	ref
Yes	1.2	1.0–1.5	1.3	0.9–1.9	1.3	0.8–2.0	1.3	1.1–1.6[c]	1.2	0.9–1.7
Recency of smoking										
Never	1.0	ref	1.0	ref	1.0	ref	1.0	ref	1.0	ref
Former	1.2	1.0–1.5	1.1	0.7–1.5	1.3	0.8–2.1	1.3	1.0–1.6[c]	1.2	0.8–1.6
Current	1.1	0.8–1.6	2.3	1.4–4.0[c]	1.2	0.5–2.4	1.5	1.0–2.0[c]	1.3	0.8–2.2
Number of years smoked										
0	1.0	ref	1.0	ref	1.0	ref	1.0	ref	1.0	ref
<20	1.0	0.7–1.4	1.0	0.5–1.8	1.4	0.7–2.6	1.1	0.8–1.5	0.9	0.5–1.5
20–39	1.3	1.0–1.8	1.0	0.6–1.8	1.2	0.6–2.2	1.3	1.0–1.8	1.4	0.9–2.2
≥40	1.2	0.9–1.6	1.6	1.0–2.5[c]	1.4	0.8–2.4	1.4	1.1–1.8[c]	1.2	0.8–1.8
Lifetime pack years of smoking										
0	1.0	ref	1.0	ref	1.0	ref	1.0	ref	1.0	ref
<20	1.1	0.8–1.4	1.0	0.6–1.7	1.3	0.7–2.2	1.1	0.9–1.5	1.0	0.6–1.5
≥20	1.3	1.0–1.6[c]	1.4	0.9–2.1	1.3	0.8–2.2	1.4	1.1–1.8[c]	1.3	0.9–1.9
Smoking intensity (average number of cigarettes per day)										
Never	1.0	ref	1.0	ref	1.0	ref	1.0	ref	1.0	ref
<10	1.3	0.9–1.7	1.2	0.7-2.1	1.0	0.5–2.0	1.3	0.9–1.8	1.2	0.7–1.9
10–19	1.2	0.9–1.6	1.3	0.8–2.2	2.0	1.1–3.5[c]	1.5	1.1–2.0[c]	1.0	0.6–1.7
≥20	1.2	0.9–1.5	1.2	0.7–1.9	1.1	0.6–2.0	1.1	0.9–1.5	1.3	0.9–2.0
Age of smoking initiation										
Never	1.0	ref	1.0	ref	1.0	ref	1.0	ref	1.0	ref
≥20	1.1	0.9–1.5	1.5	1.0–2.4	1.3	0.7–2.2	1.3	1.0–1.6	1.1	0.8–1.7
<20	1.3	1.0–1.6	1.1	0.6–1.6	1.3	0.8–2.2	1.3	1.0–1.7[c]	1.2	0.8–1.8
Smoking initiation in relation to age at first full-term birth										
Never and parous	1.0	ref	1.0	ref	1.0	ref	1.0	ref	1.0	ref
Smoked pre-partum	1.2	1.0–1.5	1.2	0.8–1.8	1.6	1.0–2.6	1.1	0.8–1.6	1.0	0.5–1.8
Smoked post-partum only	1.1	0.7–1.5	1.5	0.8–2.7	0.7	0.3–1.8	1.3	1.0–1.6[c]	1.3	0.9–1.9
Years since quitting smoking										
Never	1.0	ref	1.0	ref	1.0	ref	1.0	ref	1.0	ref
≥20	1.1	0.8–1.4	1.0	0.6–1.7	1.1	0.6–2.1	1.1	0.8–1.5	1.1	0.7-1.6
10–19	1.2	0.9–1.7	0.9	0.5–1.8	1.1	0.5–2.4	1.3	0.9–1.8	1.1	0.7–2.0
<9	1.5	1.1–2.1[c]	1.3	0.6–2.5	2.0	1.0–3.8[c]	1.5	1.1–2.2[c]	1.4	0.8–2.5

[a] Odds ratios (OR) are adjusted for age (65–69, 70–74, and 75–79), reference year (categorical), grams/day of alcohol use (none, <1.5, 1.5–4.9, 5.0–14.9, 15.0–29.9, and ≥30.0), ever use of postmenopausal hormones (never/ever), and BMI (quartiles).

[b] Ever smokers were women who reported ever smoking a total of 100 cigarettes or more in their lifetime.

[c] $p < 0.05$.

history of smoking, which is a measure that takes into account both intensity and duration of smoking, we observed that women with an eleven or more pack year history of smoking have an elevated risk of breast cancer. This is consistent with previous studies that evaluated breast cancer risk among postmenopausal women, including all four of the cohort studies [3, 4, 11, 12] that evaluated pack year history and three [13–15] of the five [16, 17] population-based case–control studies.

We also observed that timing of smoking initiation is related to breast cancer risk as women who started smoking before their first full-term birth had a greater risk of breast cancer than did women who started smoking after their first full-term birth. Few studies have evaluated this aspect of smoking. Of those that consisted primarily of postmenopausal breast cancer cases, three cohort studies [4, 10, 18] and one case–control study [19] found that women who started smoking before their first pregnancy, particular five or more years before this pregnancy, had an elevated risk of breast cancer. However, one cohort study [20] and three case–control studies [21–23] that also evaluated

this relationship did not. In addition, a meta-analysis of studies of smoking and breast cancer found that risk of breast cancer increased the earlier women started smoking, with those who started smoking as teenagers having a 14% elevated risk of breast cancer compared to never smokers [2]. Timing of smoking initiation has been hypothesized to be related to breast cancer risk because the nulliparous breast is thought to be more susceptible to carcinogens than is the parous breast. Our results do add to the limited evidence suggesting that timing of smoking initiation, particularly in relation to first pregnancy, is related to breast cancer risk.

Our results also indicate that the elevated risk of breast cancer that smokers experience declines as the number of years since smoking cessation increases. Again, few studies have evaluated this relationship in postmenopausal women and results are inconsistent. Three studies of predominantly postmenopausal women observed no relationship between years since quitting smoking and breast cancer risk [3, 12, 18], though two studies did [13, 24]. Whether or not women who have stopped smoking for a particular period of time have a risk of breast cancer that has returned to their baseline remains unclear, warranting further studies.

In the Collaborative Group on Hormonal Factors in Breast Cancer pooled analysis, the association between smoking and breast cancer was strongly confounded by alcohol use. Here we also found alcohol use to be a confounder of this relationship, but not to be an effect modifier, as the risks associated with ever smoking, recency of smoking, and lifetime pack years of smoking were similar across women who never used alcohol, who consumed <8.2 g/day of alcohol, or who consumed ≥ 8.2 g/day of alcohol. Thus, the association between smoking and breast cancer appears to be independent of alcohol use among this population of older postmenopausal women.

There was some non-statistically significant evidence of an interaction between smoking and use of combined estrogen/progestin postmenopausal hormones with respect to breast cancer risk. Ever smokers, current smokers, or smokers with a ≥ 20 pack-year history who had also ever used combined estrogen/progestin hormonal therapy had higher risks of breast cancer compared to women who never used menopausal hormones or who had ever used unopposed estrogen. To our knowledge, such an interaction has not been previously reported and thus requires confirmation. A possible biologic basis for this interaction is unclear, though one study did report that smokers who received estrogen replacement therapy had elevated levels of specific carcinogenic catecholestrogens compared to non-smokers who took menopausal estrogen therapy [25].

A few studies have also evaluated the relationship between smoking and risk of breast cancer by hormone receptor status. One large cohort study found that smoking increased risk of ER+ but not ER− breast cancers [26], but two other studies found that smoking was associated with a greater risk of ER− than ER+ breast cancer [27, 28]. One of these studies also evaluated PR status and found no difference in the association of smoking with PR+ compared to PR− tumors [27]. Here we observed little variation in the association between smoking and risk or breast cancer by joint ER/PR status. The one exception was that current smokers had a 2.3-fold elevated risk of ER+/PR− breast cancer, but not of ER+/PR+ or ER−/PR− tumors. Thus, overall there is a lack of clear evidence that smoking is related to breast cancers with particular ER/PR profiles. Risk factors for breast cancer have also been shown to vary by histologic type, as numerous differences between lobular and ductal carcinomas have been observed [6–8]. However, here we found that the association between smoking and ductal carcinoma did not differ from the association between smoking and lobular carcinoma.

In summary we observed that in a population of postmenopausal women 65–79 years of age, women who were current smokers, smoked for 40 years or longer, had 11 or more pack-years of lifetime smoking, smoked an average of ten or more cigarettes per day, or started smoking before age 20 each had 30–40% elevated risks of breast cancer. The biologic plausibility of these associations is enhanced by the consistent dose-response relationships observed between these measures of smoking and breast cancer risk. Such dose-response relationships were also recently reported in a cohort of women 30–50 years of age [4]. Because our study focused exclusively on older postmenopausal women, the results are not directly comparable to those of previous studies that have evaluated various aspects of smoking exposure. However, our findings are generally consistent with the results of these prior studies. We also found that risk of breast cancer tended to decline as the number of years since quitting smoking increased. Continued efforts to promote smoking cessation are certainly warranted regardless of smoking's possible association with breast cancer, though a growing body of evidence does suggest that breast cancer may be an additional risk to add to the long list of adverse outcomes related to smoking.

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References

1. Collaborative Group on Hormonal Factors in Breast Cancer (2002) Alcohol, tobacco and breast cancer – collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. *Brit J Cancer* 87: 1234–1245.
2. Khuder SA, Mutgi AB, Nugent S (2001) Smoking and breast cancer: a meta-analysis. *Rev Environ Hlth* 16: 253–261.
3. Reynolds P, Hurley S, Goldberg DE, *et al*. (2004) Active smoking, household passive smoking, and breast cancer: evidence from the California Teachers Study. *J Natl Cancer Inst* 96: 29–37.
4. Gram IT, Braaten T, Terry PD, *et al*. (2005) Breast cancer risk among women who start smoking as teenagers. *Cancer Epidemiol Biomarker Prev* 14: 61–66.
5. Terry PD, Rohan TE (2002) Cigarette smoking and the risk of breast cancer in women: a review of the literature. *Cancer Epidemiol Biomark Prev* 11: 953–971.
6. Li CI, Malone KE, Porter PL, Weiss NS, Tang MC, Daling JR (2003) Reproductive and anthropometric factors in relation to the risk of lobular and ductal breast carcinoma among women 65–79 years of age. *Int J Cancer* 107: 647–651.
7. Li CI, Malone KE, Porter PL, *et al*. (2003) Relationship between long durations and different regimens of hormone therapy and risk of breast cancer. *JAMA* 289: 3254–3263.
8. Li CI, Malone KE, Porter PL, Weiss NS, Tang MC, Daling JR (2003) The relationship between alcohol use and risk of breast cancer by histology and hormone receptor status among women 65–79 years of age. *Cancer Epidemiol Biomarker Prev* 12: 1061–1066.
9. Breslow NE, Day NE (1980) *The Analysis of Case–Control Studies*, Lyon, France: International Agency for Research on Cancer.
10. Begg CB, Gray R (1984) Calculation of polychotomous logistic regression parameters using individualized regressions. *Biometrika* 71: 11–18.
11. Hunter DJ, Hankinson SE, Hough H, *et al*. (1997) A prospective study of NAT2 acetylation genotype, cigarette smoking, and risk of breast cancer. *Carcinogenesis* 18: 2127–2132.
12. Terry PD, Miller AB, Rohan TE (2002) Smoking and breast cancer risk. *Int J Cancer* 100: 723–728.
13. Johnson KC, Hu J, Mao Y, The Canadian Cancer Registries Epidemiology Research Group (2000) Passive and active smoking and breast cancer risk in Canada, 1994–97. *Cancer Causes Control* 11: 211–221.
14. Rohan TE, Baron JA (1989) Cigarette smoking and breast cancer. *Am J Epidemiol* 129: 36–42.
15. Morabia A, Bernstein M, Heritier S, Khatchatrian N (1996) Relation of breast cancer with passive and active exposure to tobacco smoke. *Am J Epidemiol* 143: 918–928.
16. Chu SY, Stroup NE, Wingo PA, Lee NC, Peterson HB, Gwinn ML (1990) Cigarette smoking and the risk of breast cancer. *Am J Epidemiol* 131: 244–253.
17. Field NA, Baptiste MS, Nasca PC, Metzger BB (1992) Cigarette smoking and breast cancer. *Int J Epidemiol* 21: 842–848.
18. Egan KM, Stampfer MJ, Hunter D, *et al*. (2002) Active and passive smoking in breast cancer: prospective results from the Nurses' Health Study. *Epidemiology* 13: 138–145.
19. Lash TL, Aschengrau A (1999) Active and passive cigarette smoking and the occurrence of breast cancer. *Am J Epidemiol* 149: 5–12.
20. Lawlor DA, Ebrahim S, Smith GD (2004) Smoking before the birth of a first child is not associated with increased risk of breast cancer: findings from the British Women's Heart and Health Cohort Study and a meta-analysis. *Brit J Cancer* 91: 512–518.
21. Adami HO, Lund E, Bergstrom R, Meirik O (1988) Cigarette smoking, alcohol consumption and risk of breast cancer in young women. *Brit J Cancer* 58: 832–837.
22. Lash TL, Aschengrau A (2002) A null association between active or passive cigarette smoking and breast cancer risk. *Breast Cancer Res Treat* 75: 181–184.
23. Band PR, Le ND, Fang R, Deschamps M (2002) Carcinogenic and endocrine disrupting effects of cigarette smoke and risk of breast cancer. *Lancet* 360: 1044–1049.
24. Braga C, Negri E, La Vecchia C, Filiberti R, Franceschi S (1996) Cigarette smoking and the risk of breast cancer. *Eur J Cancer Prev* 5: 159–164.
25. Bernstein LM, Tsyrlina EV, Kolesnik OS, Gamajunova VB, Adlercreutz H (2000) Catecholestrogens excretion in smoking and non-smoking postmenopausal women receiving estrogen replacement therapy. *J Steroid Biochem Molec Biol* 72: 143–147.
26. London SJ, Colditz GA, Stampfer MJ, Willett WC, Rosner BA, Speizer FE (1989) Prospective study of smoking and the risk of breast cancer. *J Natl Cancer Inst* 81: 1625–1631.
27. Manjer J, Berglund G, Bondesson L, Garne JP, Janzon L, Malina J (2000) Breast cancer incidence in relation to smoking cessation. *Breast Cancer Res Treat* 61: 121–129.
28. Morabia A, Bernstein M, Ruiz J, Heritier S, Diebold Berger S, Borisch B (1998) Relation of smoking to breast cancer by estrogen receptor status. *Int J Cancer* 75: 339–342.