

Cigarette smoking and breast cancer risk among young women (United States)

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Objectives: To evaluate whether heavy cigarette smoking as a teenager or long-term smoking increases breast cancer risk or, alternatively, whether smoking acts as an anti-estrogen and reduces risk.

Methods: Data from a multi-center, population-based, case-control study among women under age 55 were analyzed.

Results: Among women under age 45, there was a modest inverse relation with current (OR = 0.82, 95% CI = 0.67, 1.01) but not past (OR = 0.99, 95% CI = 0.81, 1.21) smoking. Odds ratios were decreased for current smokers who began at an early age (0.59 for ≤ 15 , 95% CI = 0.41, 0.85) or continued for long periods of time (0.70 for >21 years, 95% CI = 0.52, 0.94). In subgroup analyses, reduced odds ratios were observed among current smokers who were ever users of oral contraceptives (0.79, 95% CI = 0.63, 0.98), were in the lowest quartile of adult body size (0.53, 95% CI = 0.34, 0.81), or never or infrequently drank alcohol (0.68, 95% CI = 0.47, 0.98). Among women ages 45-54, there was little evidence for an association with smoking.

Conclusions: These results suggest that breast cancer risk among women under age 45 may be reduced among current smokers who began smoking at an early age, or long-term smokers, but require confirmation from other studies. *Cancer Causes and Control*, 1998, 9, 583-590

Key words: Breast neoplasms, cigarette smoking.

Introduction

Although many epidemiologic studies have not found an association between breast cancer risk and cigarette smoking,¹ several investigators²⁻⁵ have hypothesized that smoking may have anti-estrogenic as well as carcinogenic potential that masks any clear association in an individual study or produces heterogeneous results across studies. For example, a few studies report that

risk may be increased among heavy smokers who began smoking at an early age^{6,7} or among women who smoked for many years.^{3,7-9} Alternatively, investigators have suggested that because smoking has anti-estrogenic properties,¹⁰⁻¹² smokers may have a reduced risk of breast cancer. If there is a dual effect of smoking on breast cancer development, then it may become appar-

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ent when subjects are categorized by hormone receptor status of the breast tumor,⁴ by menopausal status, or by some other estrogen-related characteristic. This study was undertaken to evaluate these possibilities using data from a large multi-center, population-based, case-control study of young women.

Materials and methods

The Women's Interview Study of Health was conducted to determine whether long-term oral contraceptive use, adolescent diet, life-time use of alcohol, and other factors are associated with breast cancer risk among younger women. The study methods, which were approved by the participating institutions human subjects review boards, have been previously described.^{13,14} Cases were women who were newly diagnosed with *in situ* or invasive breast cancer between May 1, 1990, and December 31, 1992, under 45 years of age at diagnosis and residents of five counties in central New Jersey, the three-county area surrounding Seattle, WA, or under age 55 years at diagnosis and residents of the metropolitan area of Atlanta, GA. (The age range in Atlanta was expanded to permit examination of age-specific effects.) Controls were women identified through random digit dialing (RDD),¹⁵ and frequency matched to the expected distribution of cases by 5-year age group and geographic area.

The in-person, structured questionnaire averaged 70 minutes, and assessed menstrual, reproductive, and contraceptive histories; exogenous hormone use; medical history; family history of cancer; alcohol use; adolescent diet; cigarette smoking; and demographic characteristics. After completion of the questionnaire, the respondent completed a food frequency questionnaire. In addition, the trained interviewer obtained measures of height and weight along with other anthropometric indices. Increased risks were noted among women who were oral contraceptive users, alcohol users, had never breast fed, had a late age at first birth, an early age at menarche, a previous breast biopsy, a first degree relative with breast cancer, and a low body mass.^{13,14,16,17}

Study participants included 2,199 breast cancer cases (86.4 percent of eligible women) and 2,009 controls (78.1 percent of eligible women). With the response to the RDD telephone screener taken into account, the overall response rate among control women was 70.7 percent (screener rate times the interview response rate). Non-response among all women was primarily due to subject refusal (6.4 percent for cases and 18.5 percent for controls) and, among cases, physician refusal (5.4 percent). For comparability between cases and controls, we excluded 29 case women without a telephone at the

time of diagnosis and 19 control women who had been previously diagnosed with breast cancer.

The interview included details of usual cigarette smoking habits including the age the respondent started and stopped smoking; total years smoked excluding years when the respondent did not smoke; and intensity of smoking (number of cigarettes smoked per day, week, or year). For these analyses, smoking histories were truncated at the reference date (date of the breast cancer diagnosis for cases or the date of the RDD telephone screener for controls). An ever smoker was defined as having ever smoked 100 cigarettes or more, and having ever smoked 1 cigarette or more per day for six months or longer. A current smoker was defined as smoking at the reference date, or stopped within the six months prior to the reference date. A past smoker was defined as having stopped smoking at least six months or more before the reference date.

Unconditional logistic regression was used to calculate the odds ratios (ORs) and corresponding 95 percent confidence intervals (CIs)¹⁸ for breast cancer in relation to cigarette smoking. All models that focused on women under age 45 years included as covariates the frequency-matched factors of geographic center and age; for models that included women under age 55 years from Atlanta only age but not geographic center was included.

Multivariate models¹⁸ were also used to adjust for potential confounding and to evaluate effect modification on a multiplicative scale. Factors evaluated as confounders included menopausal status (with post-menopause defined as no menstruation for six months or longer prior to the reference date); age at menarche; age at first birth; number of live births; number of miscarriages; number of induced abortions; ever breast fed; level of education; family income; marital status; race; body mass index (BMI, weight in kilograms/height in meters squared) at age 20; BMI as an adult; ever use of oral contraceptives; ever use of non-contraceptive hormones (with the reasons for use not specified); usual alcohol use (<7 drinks per week/7 + drinks per week/never or infrequent); caloric intake during past year; history of breast biopsy; and family history of breast cancer.

To explore possible dual effects of cigarette smoking on breast cancer risk, we hypothesized that these may become apparent among subgroups of women who may have lower or higher levels of estrogens (due to exogenous or endogenous sources), crudely indicated by estrogen-related characteristics. Thus, factors considered as possible effect modifiers were those with a hypothesized hormonal mechanism of action such as contraceptive and non-contraceptive hormone use, menopausal status, body size, and alcohol use.

Polytomous logistic regression¹⁸ was used to evaluate risk in relation to smoking with the cases categorized by hormone receptor status (ER+PR+/ER+PR-/ER-PR+/ER-PR-) and by stage of disease (*in situ*/local invasive/regional-distant invasive).

Results

Table 1 shows the odds ratios for breast cancer in relation to cigarette smoking among women 20 to 45 years of age in Atlanta, New Jersey, and Seattle. Age- and center-adjusted odds ratios revealed little or no relation between smoking and breast cancer. As shown in Table 1, alcohol had the largest confounding effect on the association, with other possible risk factors for breast cancer having only slight effect on the estimates. With adjustments made for possible confounding factors, the multivariate-adjusted odds ratio was slightly decreased among ever smokers (OR = 0.90, 95% CI = 0.76, 1.07). However, the reduction was apparent in current (0.82, 95% CI = 0.67, 1.01), but not past (0.99, 95% CI = 0.81, 1.21) smokers. When subjects were categorized by race or center, no substantial heterogeneity in the odds ratios was noted ($p > 0.05$).

Among Atlanta cases and controls who were 45 to 54 years of age ($n = 525$ and 489 , respectively), the multivariate-adjusted odds ratio varied only slightly among current smokers (0.91, 95% CI = 0.63, 1.31) and past smokers (1.05, 95% CI = 0.75, 1.46). The risk for smoking among women under age 45 in Atlanta (data not shown) was similar to the risk among all women under 45 shown in Table 1, including the risk reduction with current use.

Table 2 shows the odds ratios for breast cancer among women under age 45 in relation to various patterns of cigarette smoking among current and past smokers. Risk did not appear to vary with number of cigarettes smoked per day, pack-years of smoking, with years since stopped smoking, or years since first use. Risk was significantly reduced, however, among current smokers

who reported smoking for more than 21 years (OR = 0.70, 95% CI = 0.52, 0.94), but the corresponding risk among past smokers was not decreased (OR = 1.27, 95% CI = 0.58, 2.77). Also, the odds ratios were reduced for women who began smoking at age 15 years and younger among current (OR = 0.59, 95% CI = 0.41, 0.85) and past (OR = 0.76, 95% CI = 0.50, 1.15) smokers. Among women in Atlanta 45 to 54 years of age, there was no association between breast cancer risk and any pattern of cigarette smoking (data not shown).

Whether breast cancer risk in relation to the age a woman first started smoking varied with smoking intensity was examined, as suggested by Palmer⁶. Little heterogeneity was noted. For example, among women under age 45 the odds ratio for starting smoking at age 15 years or younger was 0.62 (95% CI = 0.41, 0.93) for current smokers who smoked 20 or more cigarettes per day, and the corresponding odds ratio was 0.53 (95% CI = 0.27, 1.04) for those who smoked fewer than 20 cigarettes per day. In addition, among women ages 45 to 54 years the odds ratios associated with age at first use did not vary within strata of the number of cigarettes smoked per day (data not shown).

Table 3 shows the relation between cigarette smoking and breast cancer risk among women under age 45 years stratified by selected hormonally-related characteristics: menopausal status, oral contraceptive use, non-contraceptive hormone use, body size as an adult, and usual alcohol use. The odds ratio associated with current smoking appeared to be reduced among young women who had ever used oral contraceptives (0.79, 95% CI = 0.63, 0.98); had a low adult BMI (0.53 for the lowest quartile, 95% CI = 0.34, 0.81); or had never or infrequently drank alcohol (0.68, 95% CI = 0.47, 0.98). The apparent effect modification with oral contraceptive use, adult BMI, usual alcohol intake or other factors in Table 3 was not statistically significant ($p > 0.05$).

Among women 45 to 54 years of age in Atlanta, possible effect modification by menopausal status, oral

Table 1. Adjusted odds ratios (OR) and 95% confidence intervals (CI) for breast cancer in relation to cigarette smoking history among women under age 45 in Atlanta, New Jersey and Seattle, 1990-1992

	Controls ^a	Cases	Age- and center adjusted		Age-, center- and alcohol use-adjusted		Multivariate-adjusted	
			OR	95% CI	OR	95% CI	OR ^b	95% CI
Never smoked	817	913	1.00	—	1.00	—	1.00	—
Ever smoked	680	732	0.96	(0.83, 1.10)	0.90	(0.78, 1.05)	0.90	(0.76, 1.07)
Current smoked	370	370	0.90	(0.76, 1.07)	0.85	(0.71, 1.01)	0.82	(0.67, 1.01)
Past smoker	310	362	1.03	(0.86, 1.23)	0.97	(0.81, 1.17)	0.99	(0.81, 1.21)

^a 3 controls were missing information on smoking status.

^b Adjusted for age, center, usual alcohol consumption, parity, age at first birth, age at menarche, breastfeeding, abortion, miscarriage, menopausal status, ever married, education, income, race BMI at age 20, BMI as an adult, oral contraceptive use, non-contraceptive hormone use, caloric intake, history of breast biopsy, family history of breast cancer.

Table 2. Adjusted odds ratios (OR) and 95% confidence intervals (CI) for breast cancer in relation to patterns of cigarette smoking among women under age 45 in Atlanta, New Jersey and Seattle, 1990-1992

	Current smokers				Past smokers			
	Controls	Cases	OR ^a	95% CI	Controls	Cases	OR ^a	95% CI
Never smoker ^b	817	913	1.00	—	817	913	1.00	—
Age at first use								
≤15 years	98	79	0.59	(0.41, 0.85)	64	55	0.76	(0.50, 1.15)
16-17 years	82	79	0.79	(0.55, 1.13)	83	101	1.15	(0.82, 1.62)
18-19 years	90	111	0.98	(0.71, 1.36)	90	114	0.95	(0.69, 1.30)
20+ years	100	101	0.91	(0.66, 1.27)	73	92	1.03	(0.72, 1.48)
<i>p</i> -trend			0.14				0.92	
Years of use ^c								
≤8	36	21	0.63	(0.34, 1.15)	155	178	0.98	(0.76, 1.28)
9-14	76	82	0.98	(0.68, 1.41)	97	113	0.98	(0.71, 1.35)
15-21	122	134	0.92	(0.68, 1.23)	45	50	0.91	(0.57, 1.44)
>21	136	132	0.70	(0.52, 0.94)	12	20	1.27	(0.58, 2.77)
<i>p</i> -trend			0.06				0.95	
Cigarettes per day								
<10	72	58	0.69	(0.47, 1.02)	98	118	0.96	(0.70, 1.31)
10-19	90	97	0.91	(0.65, 1.28)	69	96	1.21	(0.84, 1.74)
20	135	128	0.78	(0.58, 1.04)	99	94	0.84	(0.61, 1.16)
>20	73	87	0.95	(0.66, 1.38)	44	54	1.05	(0.66, 1.68)
<i>p</i> -trend			0.22				0.87	
Pack-years ^c								
≤3.7	50	40	0.71	(0.44, 1.13)	121	152	1.03	(0.77, 1.37)
3.8-10	76	70	0.84	(0.57, 1.22)	96	98	0.92	(0.66, 1.27)
10.1-20	112	112	0.86	(0.63, 1.17)	68	69	0.86	(0.59, 1.26)
>20	132	147	0.84	(0.62, 1.12)	24	42	1.38	(0.78, 2.44)
<i>p</i> -trend			0.22				0.61	
Years since first use (latency)								
≤17	121	96	0.75	(0.54, 1.04)	76	77	1.03	(0.71, 1.50)
18-21	81	100	1.03	(0.73, 1.45)	88	93	0.87	(0.62, 1.22)
22-24	84	86	0.82	(0.57, 1.17)	82	91	0.81	(0.57, 1.16)
>24	84	88	0.74	(0.52, 1.06)	64	101	1.32	(0.91, 1.91)
<i>p</i> -trend			0.07				0.94	
Years since stopped smoking								
0.5-5					82	97	1.02	(0.73, 1.43)
6-10					85	88	0.95	(0.67, 1.34)
11-15					76	94	1.01	(0.70, 1.44)
>15					67	83	0.97	(0.67, 1.40)
<i>p</i> -trend							0.98	

^a Adjusted for age, center, usual alcohol consumption, parity, age at first birth, age at menarche, breastfeeding abortion, miscarriage, menopausal status, ever married, education, income race, BMI at age 20, BMI as an adult, oral contraceptive use, non-contraceptive hormone use, caloric intake, history of breast biopsy, family history of breast cancer.

^b Referent group for all comparisons.

^c One control was missing information on this variable.

contraceptive use, non-contraceptive hormone use, and alcohol use was not apparent; the odds ratios for women in all subgroups were close to unity (data not shown). Among women 45 to 54 in Atlanta the odds ratios (and 95% CI) in relation to current smoking stratified by the lowest to the highest quartile of BMI as an adult were 1.56 (0.66, 1.14), 1.21 (0.50, 2.90), 0.79 (0.35, 1.78), and 0.33 (0.14, 0.79). Thus, the inverse relation with smoking was observed within the highest quartile of BMI among women 45 to 54 years of age, and within the lowest quartile of BMI among women under age 45.

Categorizing cases by hormone receptor status revealed significant heterogeneity of effect among the youngest women. In women younger than age 45, the multivariate-adjusted odds ratios for current smoking were 1.06 (95% CI = 0.84, 1.34) for cases with breast tumors that were ER + PR+; 0.36 (95% CI = 0.19, 0.69) for ER+PR-; 0.88 (95% CI = 0.54, 1.41) for ER-PR+; and 1.02 (95% CI = 0.77, 1.34) for ER-PR-. In Atlanta, women aged 45 to 54 there was no substantial variation from the null value with cases categorized by receptor status, although Atlanta women

Table 3. Adjusted odds ratios (OR) and 95% confidence intervals (CI) for breast cancer in relation to cigarette smoking stratified by menopausal status, use of oral contraceptives, use of non-contraceptive hormones, body mass index (BMI) as an adult, or usual alcohol use among women under age 45 in Atlanta, New Jersey and Seattle, 1990-1992

	Current smokers				Past smokers			
	Controls	Cases	OR ^a	95% CI	Controls	Cases	OR ^a	95% CI
Menopausal status ^b								
Premenopausal								
Non-smoker	740	821	1.00				1.00	
Smoker	297	318	0.83	(0.67, 1.04)	270	334	1.04	(0.84, 1.28)
Postmenopausal								
Non-smoker	75	90	1.00				1.00	
Smoker	71	52	0.77	(0.42, 1.41)	39	28	0.61	(0.30, 1.25)
Oral contraceptive use								
Never used								
Non-smoker	169	141	1.00				1.00	
Smoker	56	52	1.18	(0.64, 2.15)	32	40	1.68	(0.90, 3.13)
Ever used								
Non-smoker	648	772	1.00				1.00	
Smoker	314	318	0.79	(0.63, 0.98)	278	322	0.93	(0.75, 1.15)
Non-contraceptive hormone use ^c								
Never used								
Non-smoker	759	853	1.00				1.00	
Smoker	321	338	0.83	(0.67, 1.03)	278	347	1.04	(0.84, 1.28)
Ever used								
Non-smoker	58	59	1.00				1.00	
Smoker	49	31	0.61	(0.28, 1.31)	32	15	0.42	(0.17, 1.02)
BMI ^d								
<22.01								
Non-smoker	179	282	1.00				1.00	
Smoker	93	98	0.53	(0.34, 0.81)	75	101	0.82	(0.55, 1.23)
≥22.01-<24.58								
Non-smoker	189	202	1.00				1.00	
Smoker	83	82	0.94	(0.60, 1.47)	78	91	1.12	(0.74, 1.70)
≥24.58-<28.93								
Non-smoker	184	202	1.00				1.00	
Smoker	95	104	0.96	(0.63, 1.44)	70	88	1.09	(0.72, 1.67)
≥28.93								
Non-smoker	200	195	1.00				1.00	
Smoker	83	77	1.03	(0.67, 1.57)	65	70	1.05	(0.68, 1.63)
Usual alcohol use ^e								
Never/infrequent								
Non-smoker	401	411	1.00				1.00	
Smoker	113	89	0.68	(0.47, 0.98)	61	69	1.11	(0.73, 1.69)
<7 drinks/week								
Non-smoker	356	424	1.00				1.00	
Smoker	188	183	0.78	(0.59, 1.04)	209	239	0.94	(0.73, 1.22)
≥7 drinks/week								
Non-smoker	60	77	1.00				1.00	
Smoker	67	98	1.21	(0.67, 2.19)	40	53	1.27	(0.67, 2.40)

^a Adjusted for age, center, usual alcohol consumption (except when stratified by this variable), parity, age at first birth, age at menarche, breastfeeding, abortion, miscarriage, menopausal status (except when stratified by this variable), ever married, education, income, race, BMI at age 20, BMI as an adult, oral contraceptive use (except when stratified by this variable), non-contraceptive hormone use (except when stratified by this variable), caloric intake, history of breast biopsy, family history of breast cancer.

^b 2 cases and 5 controls missing information.

^c 2 cases missing information.

^d 53 cases and 103 controls missing information.

^e 2 cases and 2 controls missing information.

under age 45 revealed the same pattern as all women under 45.

There was little variation in breast cancer risk in relation to smoking when cases were partitioned by stage of disease. For example, among current smokers under age 45 the odds ratios were 0.83 (95% CI = 0.56, 1.37) for *in situ* disease, 0.92 (95% CI = 0.73, 1.27) for local invasive, and 0.92 (95% CI = 0.71, 1.22) for regional-distant invasive cancer.

Discussion

Data analyzed from the Women's Interview Study of Health show a modest decrease in the breast cancer risk among women under age 45 in Atlanta, New Jersey, and Seattle in relation to current cigarette smoking, particularly among those who have smoked for a long duration, and among those who began to smoke at 15 years of age or younger. In addition, the risk reduction was pronounced in women under age 45 years who reported ever using oral contraceptives, had a low body size, or had used little or no alcohol, although none of these apparent interactions was statistically significant. A reduced risk was also evident among case women with tumors that were ER+PR-, but not among others. Among women ages 45 to 54 years in Atlanta, no consistent relation between smoking and breast cancer was observed.

These data reported here were collected as part of a large, population-based case-control study with uniform data collection procedures used across all three geographic locations. During the personal interview, detailed information was assessed for known and suspected risk factors for breast cancer, including a comprehensive measure of cigarette smoking. It is unlikely that any limitations in the data collection process were likely to produce an inverse association.

Two previous investigations^{19,20} that also focused on younger women observed a reduction in breast cancer risk with current smoking. These results have been attributed to bias resulting from use of hospital-based controls.^{12,20} However, an additional case-control study,²¹ which used community-based controls, and a cohort study of screenees²² have also reported an inverse association among heavy current smokers of all ages. Another cohort study²³ noted a decreased risk in exsmokers, but not current smokers. Ours is the only investigation to observe an apparent risk reduction in relation to current smoking, particularly among women who began smoking at an early age, or among long-term smokers.

Epidemiologic, clinical and laboratory data indicate that cigarette smoking has anti-estrogenic properties¹². For example, among premenopausal women, current

smokers have lower luteal phase urinary levels of estradiol than never smokers.^{24,25} In addition, current smokers as compared with nonsmokers have an earlier age at menopause,^{26,27} a reduced risk of endometrial cancer,^{28,29} and their use of hormone replacement does not decrease the risk of hip fractures.³⁰ These data suggest that any anti-estrogenic effects of smoking may be transitory, and thus current smokers, rather than past smokers, are more affected.

Some researchers have noted an increase in breast cancer risk with heavy smoking,²⁰ heavy smoking at an early age,^{6,7} or among long-term smokers.^{3,7-9,31,32} However, these associations were not confirmed in our data or by others.^{5,33-35} Investigators have also noted elevations in risk among other subgroups of women, such as premenopausal smokers,^{3,32} smokers younger than age 50,^{6,36} premenopausal exsmokers,³⁷ exsmokers under age 55,³⁸ or premenopausal smokers with high BMI,²² but again these particular subgroup observations were not apparent in our study or in others.^{5,33,34}

One previous investigation,³⁹ but not others,^{35,40,41} noted a nonsignificant increase in risk in relation to smoking for case women with ER- tumors, but not ER+ tumors. Also, one study⁴² observed an elevation in risk in PR+ tumors, but not PR- tumors. In our study there was little effect by hormone receptor status with one exception: cases under age 45 with ER+PR- tumors had a significantly lower risk associated with smoking. Breast cancers that are ER+ and PR+ are believed to be the most hormonally responsive, ER-PR- the least, and those that are ER/PR discordant to have an intermediate response.⁴³ Thus, there is no clear biologic rationale for our observation of a lower risk for intermediately responsive cancer among women under age 45 only. Given that no associations were noted in women aged 45 to 54 as well as the multiple comparisons in our analyses, chance is a likely explanation.

In a further attempt to explore the possible dual effects of cigarette smoking on breast cancer development, we determined breast cancer risk in relation to smoking among subgroups of women who may have particularly high or low levels of estrogen, roughly indicated by the presence or absence of selected estrogen-related characteristics. We observed no significant effect modification, but did note a more pronounced decrease in risk among women who were lean or who had used little or no alcohol. This may suggest that among women with lower levels of endogenous estrogen, anti-estrogenic effects of smoking may become more apparent.

Many investigators have reported that smoking does not affect breast cancer risk,^{5,29,33-35,44-52} including three previous studies that also focused on young women.^{45,48,52} However, there is sufficient heterogeneity of

results among studies to suggest additional research is required. One innovative strategy is to identify biologically distinct subgroups of women who may be at a particularly high risk. For example, Ambrosone and colleagues⁵³ partitioned women on genotype for NAT2, a metabolic enzyme that detoxifies constituents of cigarette smoke, and observed a fourfold increase in breast cancer risk among smokers who were identified as slow metabolizers. These results, however, have not been replicated.⁵⁴ In still another approach in examining a possible smoking-breast cancer association, a few investigators^{55,56} found that women with a history of passive smoking were at a modest increased risk of breast cancer, and then excluded these women from the referent group where an increase in risk with active smoking also became apparent. Others, however, have not found an association with passive smoking.^{45,57} Our study did not include information to enable us to explore either the effects of passive smoking or of NAT2.

In sum, data reported here suggest a modest inverse association between breast cancer risk in women under 45 years of age and current cigarette smoking, particularly among long-term smokers, and those who began smoking at an early age. This apparent anti-estrogenic effect of current smoking among younger women requires confirmation by others.

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