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CIGARETTE SMOKING AND BREAST CANCER[1]

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To investigate the relationship of smoking to breast cancer risk, the authors conducted a case-control study involving 1,547 patients and 1,930 controls identified between 1973 and 1980 through a nationwide screening program. There was no evidence that smoking affected risk (relative risk (RR) = 1.2), nor were there any apparent relationships with more detailed exposure measures. No substantial variations in risk were noted by menopausal status; in particular, there was no support for the notion that smoking is associated with a reduced risk among naturally menopausal women (RR = 1.1). In addition, the data provided no general evidence that smokers experience an earlier menopause than nonsmokers, even when heavy smoking was considered. Evaluation of a number of sources of confounding and effect modification failed to alter the conclusion that smoking status does not appear to alter breast cancer risk among this population.

breast neoplasms; menopause; risk; smoking

Epidemiologic data strongly support an association of cigarette smoking with an early natural menopause (1). This has provoked interest in the role of smoking on breast cancer, since earlier ages at menopause have been related to substantial risk reductions. Further stimulation for the issue has recently been provided by findings that urinary levels of endogenous estrogens are about 30 per cent lower in smokers than in nonsmokers during the luteal phase of the menstrual cycle (2).

Recent epidemiologic studies of the relationship of smoking to breast cancer risk, however, have provided conflicting results. A recent review of the literature on the topic (1) revealed that approximately half of the published results of case-control studies showed lower breast cancer risks for smokers, while the remaining studies showed no alteration in risk. Similar difficulties existed in the interpretation of results from cohort studies. In addition, there is some evidence from both epidemiologic (3) and laboratory (4) studies that cigarette smoke might actually have an adverse effect on breast tissue.

In an effort to investigate further the relationship of smoking to breast cancer risk, we examined the issue using data from a recently completed case-control study

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among participants in a multicenter breast cancer screening program. Since this study involved the collection of detailed smoking data, as well as extensive information on other breast cancer risk factors, a thorough examination of the role of confounding influences and effect modifications was made possible.

MATERIALS AND METHODS

Subjects for this case-control study comprised participants in the Breast Cancer Detection Demonstration Project, a multicenter breast cancer screening program involving over 280,000 women at 29 widely dispersed centers. This program, jointly sponsored by the American Cancer Society and the National Cancer Institute, recruited women between 1973 and 1975 for a five-year program of annual breast examinations by the combined modalities of clinical examination, mammography, and thermography.

Previous publications (5, 6) have described the methodology of an initial case-control study conducted among women whose breast cancer was detected during the first several years of screening (July 1973 through May 1977). An extension of the study, which involved the addition of a number of questions on smoking status to the questionnaire, enabled this issue to be pursued among the breast cancer cases diagnosed during the latter three years of screening (through November 1980). Control subjects for these cases were chosen from women who had not received either a recommendation for biopsy or a biopsy during the course of screening participation. Controls were stratified to the cases on center, race (white, black, Oriental, other), age (same five-year group), time of entry (same six-month period), and length of continuation in the program (controls had to have had at least as many years of screening as the cases).

During this extension of the original study, home interviews were obtained from 1,799 cases (74.4 per cent of eligible subjects) and 2,208 controls (89.9 per cent). The major reason for nonresponse was death of the study subjects (17.3 per cent among cases vs. 2.3 per cent among controls); additional reasons included inability to locate or inaccessibility of subjects for conducting interviews (1.3 per cent vs. 1.2 per cent), refusals (5.5 per cent vs. 5.7 per cent), and miscellaneous (1.4 per cent vs. 0.7 per cent).

Questions on smoking elicited information regarding whether subjects had ever smoked a total of 100 or more cigarettes in their lifetime and, if so, the age at which they started smoking; whether smoking habits were current; total years smoked; and average number of cigarettes smoked per day.

A total of 73 cases and 28 controls reported a history of breast cancer prior to entering the Project and were excluded from the present analysis. We also restricted analysis to white subjects (87 per cent of the entire study population). The final study groups consisted of 1,547 cases and 1,930 controls.

To compare median ages at menopause between smokers and nonsmokers, we used a standard life table approach (7), accumulating the experience of both premenopausal women (who contributed women-years until the age of breast cancer diagnosis) and naturally menopausal women.

For evaluating effects of an exposure factor, the measure of association used was the relative risk (RR), as estimated by the odds ratio. Confounding variables were evaluated by stratified techniques, deriving maximum likelihood estimates of combined ratios and 95 per cent confidence intervals (CI) (8). For multiple levels of exposure, significance was assessed by a one-tailed linear trend test (9). We employed logistic regression, utilizing a disease probability model (10), to control simultaneously for numerous potential confounding variables.

RESULTS

Table 1 examines various characteristics of smoking related to risk of breast cancer. A total of 47.8 per cent of the cases and

TABLE 1

Relative risks of breast cancer, by smoking history, Breast Cancer Detection Demonstration Project, 1973–1980*

	Cases	Controls	Relative risk	95% confidence interval
Nonsmoker	805	1,090	1.00	
Smoker	739	838	1.20	1.0–1.4
Current	351	413	1.18	0.9–1.4
Noncurrent	385	424	1.24	1.0–1.5
Years smoked				
<10	111	110	1.40	1.0–1.9
10–19	142	165	1.19	0.9–1.5
20–29	216	255	1.17	0.9–1.4
30–39	169	205	1.13	0.9–1.4
40+	96	101	1.26	0.9–1.7
χ_1 for linear trend			1.98	$p = 0.02$
No. of cigarettes/day				
<10	208	248	1.15	0.9–1.4
10–19	184	179	1.41	1.1–1.8
20–29	207	248	1.15	0.9–1.4
30–39	64	72	1.24	0.9–1.8
40+	74	89	1.15	0.8–1.6
χ_1 for linear trend			2.02	$p = 0.2$
Age at start of smoking (years)				
<17	190	206	1.30	1.0–1.6
17–19	249	267	1.29	1.0–1.6
20–22	147	177	1.14	0.9–1.5
23+	151	187	1.10	0.9–1.4

* Relative risks are adjusted for ages at diagnosis. Unknowns are excluded from analysis.

43.4 per cent of the controls reported ever having smoked 100 or more cigarettes in their lifetime, resulting in a relative risk of 1.2 (95 per cent CI 1.0–1.4). There was little variation in risk according to whether the women were current or noncurrent smokers. Although there were significant trends in risk with years smoked and number of cigarettes smoked per day, this primarily reflected a difference in risk between smokers and nonsmokers rather than a true trend with varying levels of smoking. Women who started smoking prior to age 17 were at highest risk (RR = 1.3), but examination of finer age categories (including those who began smoking prior to age 16) revealed no distinctive trends.

Since it has been suggested that smokers might have an earlier menopause than nonsmokers (1), we next examined effects of smoking according to menopausal status. As shown in table 2, there was no substantial difference in the risks associated with ever smoking for premenopausal women (RR = 1.3), naturally menopausal women (RR = 1.1), and surgically menopausal women (RR = 1.3). This remained true even when currency of smoking (as shown) or more detailed measures of smoking were considered. In addition, we found no evidence in the data that smoking substantially reduced the age at natural menopause, with the median ages at menopause among controls being 50.6 for nonsmokers and 50.5 for ever smokers. Similarly, there was no evidence that heavily exposed controls experienced a significantly earlier menopause, with the median ages at menopause being 50.4 for current smokers, 50.1 for smokers of 40 or more years, 50.7 for those smoking 30 or more cigarettes per day, and 51.3 for those who first started smoking prior to age 17. Thus, adjustment for age at menopause resulted in only minor alterations in the previously observed relative risks.

TABLE 2

Relative risks of breast cancer, by currency of smoking habits and menopausal status, Breast Cancer Detection Demonstration Project, 1973–1980*

	Cases	Controls	Relative risk	95% confidence interval
Premenopausal				
Nonsmoker	213	268	1.00	
Smoker	234	235	1.26	0.9–1.6
Current	117	134	1.10	0.8–1.5
Noncurrent	116	101	1.44	1.0–2.0
Natural menopause				
Nonsmoker	346	464	1.00	
Smoker	268	354	1.06	0.8–1.3
Current	125	166	1.12	0.8–1.5
Noncurrent	142	188	1.05	0.8–1.4
Surgical menopause				
Nonsmoker	237	337	1.00	
Smoker	228	241	1.34	1.0–1.7
Current	103	109	1.33	0.9–1.9
Noncurrent	125	131	1.35	0.9–1.8
Total (adjusted)				
Nonsmoker	796	1,069	1.00	
Smoker	730	830	1.20	1.0–1.4
Current	345	409	1.17	0.9–1.4
Noncurrent	383	420	1.24	1.0–1.5

* Relative risks are adjusted for ages at diagnosis. Unknowns are excluded from analysis.

Among the naturally menopausal women, smoking associations were pursued further by cross-tabulating the various parameters. Included in this analysis was an examination of the combined effects of currency of smoking and years smoked (table 3), which, like the other cross-tabulations, showed no striking associations. None of the categories was associated with any substantial risk reduction; in fact, noncurrent smokers of 40 or more years were at a nonsignificantly elevated risk.

Given that it probably takes 10–15 years for any alterations in age at menopause to exert an effect on breast cancer risk (11), we examined further the effects of smoking according to ages at diagnosis as well as ages at menopause among the naturally menopausal women. Smoking was associated with a nonsignificant reduction in risk among women who developed breast cancer after age 65 (RR = 0.6, 95 per cent CI 0.4–1.0), but this did not appear to be the result of a difference in the ages at menopause between smokers and nonsmokers. Smokers diagnosed with breast cancer after age 65 had a median age at natural menopause of 49.4 years, a value nearly identical to that observed among nonsmokers (49.5 years). Current smokers, those smoking 40 or more years, those smoking 30 or more cigarettes per day, and those who first started smoking prior to age 17 demonstrated similar median ages at menopause (values among the older controls being 49.4, 49.7, 49.4, and 49.9 years, respectively). When attention was focused on the age at which 75 per cent of this older cohort became menopausal, rather than on the median, there was some indication of an earlier menopause for heavy smokers, since the associated values were 51.2 years for smokers of 40 or more years and 50.6 years for those smoking 30 or more cigarettes per day compared with 52.4 years for nonsmokers. These differences, however, were not sufficient to exert any substantial confounding effects on the smoking-associated risks, either among the older naturally menopausal women or among the other age

TABLE 3

Relative risks of breast cancer among naturally menopausal women, by currency of smoking and years smoked, Breast Cancer Detection Demonstration Project, 1973–1980*

Currency of smoking	Years of cigarette smoking				
	<10	10–19	20–29	30–39	40+
Current	1.07 (4)†	0.98 (8)	0.97 (26)	0.92 (40)	1.13 (47)
Noncurrent	1.12 (25)	0.79 (27)	1.03 (40)	0.87 (30)	1.82 (19)

* All risks are relative to nonsmokers (346 cases, 464 controls). Unknowns are excluded from analysis.
† Numbers of exposed cases are shown in parentheses.

TABLE 4

Relative risks of breast cancer among naturally menopausal women, by smoking history and ages at diagnosis, Breast Cancer Detection Demonstration Project, 1973–1980*

Smoking history	Ages at diagnosis (years)			
	<55	55–64	65+	Total
Ever smoked				
No	1.00 (48)†	1.00 (154)	1.00 (144)	1.00 (346)
Yes	1.30 (66)	1.23 (153)	0.65 (49)	1.06 (268)
Current smoker				
No	1.55 (30)	1.16 (82)	0.61 (30)	1.03 (142)
Yes	1.17 (36)	1.32 (70)	0.73 (19)	1.13 (125)
Years smoked				
<10	2.26 (9)	1.40 (18)	0.38 (3)	1.27 (30)
10–19	1.10 (12)	1.06 (18)	0.41 (5)	0.90 (35)
20–29	1.36 (25)	1.21 (33)	0.76 (8)	1.17 (66)
30–39	1.27 (20)	0.90 (37)	0.93 (13)	0.98 (70)
40+	0.00 (0)	1.76 (46)	0.65 (20)	1.19 (66)
χ_1 for linear trend	0.71	1.48	−1.46	0.57
No. of cigarettes/day				
<10	2.25 (19)	1.27 (46)	0.53 (12)	1.17 (77)
10–19	1.56 (17)	1.58 (44)	0.60 (13)	1.25 (74)
20–29	0.90 (18)	0.81 (36)	0.60 (13)	0.77 (67)
30+	1.25 (12)	1.91 (27)	1.10 (11)	1.51 (50)
χ_1 for linear trend	0.11	1.14	−1.19	0.28
Age at start of smoking (years)				
<17	1.09 (13)	1.55 (52)	0.97 (8)	1.35 (73)
17–19	1.48 (25)	1.13 (38)	0.52 (10)	1.05 (73)
20–22	1.07 (12)	0.91 (23)	0.97 (16)	0.96 (51)
23+	1.54 (16)	1.30 (40)	0.44 (14)	1.00 (70)

* Relative risks are adjusted for ages at menopause; total relative risks are additionally adjusted for ages at diagnosis. Unknowns are excluded from analysis.
† Numbers of exposed cases are shown in parentheses.

groups examined (table 4). Furthermore, the one group in whom smoking was associated with a low risk (those diagnosed after age 65) failed to show any evidence of dose-response relationships according to either years smoked, number of cigarettes smoked per day, or age at start of smoking.

Effects of smoking were also examined after adjustment for a number of potential confounding variables. In particular, there was concern about confounding effects of weight, since smokers have been shown to generally be lighter than nonsmokers (12). Although smokers were lighter than nonsmokers in the present study, there was no evidence that the effects of smoking were confounded by weight or Quetelet index (a measure of body mass) or by a variety of other demonstrated breast cancer risk factors, including age at menarche, age at first

TABLE 5

Relative risks of breast cancer associated with ever smoking, by selected risk factors, Breast Cancer Detection Demonstration Project, 1973–1980

Risk factors	Exposed cases	Exposed controls	Relative risk	95% confidence interval
Age at first livebirth (years)				
Nulliparous	127	139	0.99	0.7–1.4
<20	50	67	1.11	0.7–1.8
20–24	256	307	1.32	1.0–1.7
25–29	195	214	1.20	0.9–1.6
30+	106	109	1.11	0.8–1.6
Family history of breast cancer (first-degree relative)				
No	532	696	1.20	1.0–1.4
Yes	202	140	1.04	0.8–1.4
Previous biopsy for benign breast disease				
No	555	695	1.19	1.0–1.4
Yes	184	143	1.17	0.9–1.6
Weight (kg)				
<56.2	173	213	1.27	0.9–1.7
56.2–60.7	168	186	1.13	0.8–1.5
60.8–69.7	220	234	1.20	0.9–1.5
69.8+	155	191	1.18	0.9–1.6
Oral contraceptive use				
No	528	625	1.10	0.9–1.3
Yes	211	212	1.57	1.2–2.1
Menopausal hormone use				
No	418	499	1.03	0.9–1.2
Yes	320	339	1.50	1.2–1.9

livebirth, family history of breast cancer in a first-degree relative, history of benign breast biopsies, weight, and exogenous hormone use. In addition, none of these variables exerted any significant confounding effects among those experiencing a natural menopause. Furthermore, although numbers became sparse in the analyses, it did not appear as though any of these variables contributed to the nonsignificantly reduced risk among smokers who developed breast cancer after age 65.

Results from the stratified analyses were consistent with those derived from a multivariate approach, which adjusted simultaneously for a number of potential confounding factors. For example, the risks derived from a model that focused on the naturally menopausal women and included the variables of age, age at menopause, and weight were 1.04 for ever smokers, 1.12 for current smokers, 0.97 for noncurrent smokers, 1.01 for smokers of 30 or more years, 1.25 for those smoking 30 or more cigarettes per day, and 1.28 for women who started smoking prior to age 17. These estimates are similar to those presented in table 4.

A final analysis examined effect modifications of smoking by selected risk factors (table 5). There were no substantial differences in the risk associated with smoking according to either age at first livebirth, family history of breast cancer in a first-degree relative, previous benign breast disease, or weight. Significantly elevated risks, however, were associated with smoking among both oral contraceptive users (RR = 1.6) and users of menopausal hormones (RR = 1.5). Further exploration of these excess risks failed to show linear relationships with more detailed measures of smoking, including years of smoking, with the risks associated with <10, 10–19, 20–29, and 30+ years of smoking being 1.3, 2.0,

1.7, and 1.2, respectively, for oral contraceptive users and 1.7, 1.2, 1.4, and 1.6, respectively, for menopausal hormone users. Analyses also demonstrated no evidence that breast cancer risk factors modified the effects of smoking among women with a natural menopause.

Discussion

This study failed to find that smoking is associated with a reduced risk of breast cancer, a finding consistent with a number of other studies (13–20). Our results, however, were in contrast with several studies that have suggested that smokers may be at a 20 per cent reduced risk relative to nonsmokers (21–26). We found no evidence for any protective effect of smoking; in fact, our results supported a slightly increased risk (RR = 1.2). This risk is nearly identical to that recently observed by Rosenberg et al. (20) in another large case-control study.

An explanation to those studies that have shown lowered breast cancer risks for smokers are observations that smoking is associated with earlier ages at natural menopause (12, 27–30). Thus, it is not surprising that we found no effect of smoking in our data, since smokers had a median age at natural menopause similar to that of nonsmokers. Also notable was the fact that heavy smokers showed no evidence of having experienced significantly earlier ages at menopause. In fact, the only group for whom there was evidence for an early menopause were long-term smokers, who exhibited only an eight-month earlier median age at menopause than nonsmokers. We cannot resolve our findings with studies that have found substantial effects of smoking on menstrual status, but these studies have generally shown that smokers reach menopause only a year earlier than nonsmokers, and the difference between the menopausal ages of smokers and nonsmokers has tended to be smaller in studies based on nonhospitalized populations.

If smoking was related to breast cancer risk through a mechanism of earlier menopause, one might suspect that any reduction in risk would be most profound among those women old enough to have experienced the 10- to 15-year latent period usually associated with age at menopause effects on breast cancer risk. We found that women over age 65 who reported heavy smoking histories did experience menopause slightly earlier than nonsmokers and that smoking was associated with a nonsignificantly reduced risk (RR = 0.6) among older subjects. This effect could not be attributed to age at menopause differences, however. In addition, the biologic plausibility of the association is questionable, since there were no linear relationships of risk with either years smoked, number of cigarettes smoked per day, or age at start of smoking. Thus, it seems likely that chance may explain the seemingly reduced risk associated with smoking observed among older women in this study.

We also found no general evidence in this study that the effects of smoking were modified by other breast cancer risk factors, a finding in agreement with that of Rosenberg et al. (20). Although there were statistically significant excess risks associated with ever smoking among oral contraceptive users (RR = 1.6) and users of menopausal hormones (RR = 1.5), neither association was supported by dose-response relationships with years of smoking, leading to questions regarding the reality of the excess risks.

Although this study failed to support the notion that smoking might reduce the risk of breast cancer, some attention needs to be given to certain methodological considerations. Although our study population represented a self-selected group of women, our results should not have been affected, since both cases and controls were ascertained similarly and without regard to smoking status. In addition, our results with respect to smoking are probably less biased than studies that have utilized hospitalized patients, which probably overestimate any reductions in risk associated with smoking. Of concern, however, was the fact that we had a larger proportion of

cases than controls who had died prior to being interviewed. Thus, if survival was better among smokers, our results would be biased toward overestimating smoking effects. Although the issue of breast cancer survival among smokers is not well studied, several studies have shown lower breast cancer mortality rates for smokers (16, 31). Others, however, have shown either no effect of smoking (32) or higher breast cancer mortality rates for smokers (33).

In sum, we found no evidence in the present study that smoking affords any protection against the development of breast cancer. Our results thus fail to support studies that have suggested that smokers may be at a 20 per cent lower risk than nonsmokers. The accepted explanation for this association, however, is that smokers experience an earlier average age at menopause, an observation that was not apparent in our data. We also found no evidence that certain subgroups of women were differentially affected by smoking, including older women, for whom smoking-induced ovarian changes should be most apparent.

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