Review

Cigarette Smoking and the Risk of Breast Cancer in Women: A Review of the Literature

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Abstract

Animal experiments and *in vitro* studies have shown that compounds found in tobacco smoke, such as polycyclic hydrocarbons, aromatic amines, and *N*-nitrosamines, may induce mammary tumors. The findings of smoking-specific DNA adducts and *p53* gene mutations in the breast tissue of smokers also support the biological plausibility of a positive association between cigarette smoking and breast cancer, as does the detection of carcinogenic activity in breast fluid. However, epidemiological studies conducted over the past few decades have variably shown positive, inverse, or null associations. To help reconcile the discrepant findings, epidemiologists have paid increasing attention to measures of exposure to tobacco smoke that might be of the greatest etiological importance, to aspects of the smoker that might modify the association between smoking and breast cancer risk, and to the potentially different associations that might exist with different types of breast tumors, such as those with and without estrogen or progesterone receptors. Overall, the results of these studies suggest that smoking probably does not decrease the risk and indeed suggest that there may be an increased breast cancer risk with smoking of long duration, smoking before a first full-term pregnancy, and passive smoking. These findings require confirmation in future studies, as do suggestions of increased risk among women with certain genotypes.

Introduction

Breast cancer is the most commonly diagnosed neoplasm among women worldwide, with annual incidence rates ranging from 11.8 per 100,000 in Eastern China to 86.3 per 100,000 in North America (1). In the United States, breast cancer incidence rates have been rising slowly for the past two decades (2). The severalfold difference in incidence rates between high-incidence and low-incidence regions and changes in incidence rates over time and among migrants (3–7) suggest that environmental factors can influence breast cancer risk. Of the identified environmental factors with potential relevance to breast cancer, one of the most widely studied has been tobacco smoke. Tobacco smoking is among the leading preventable risk factors for cancer in general (8, 9), including several cancers that occur at sites that are not in direct contact with tobacco smoke, such as cancers of the bladder (10–12) and pancreas (10, 13).

Carcinogens found in tobacco smoke pass through the alveolar membrane (14) and into the blood stream, by means of which they may be transported to the breast via plasma lipoproteins (15, 16). That potential breast carcinogens in tobacco smoke can be taken up and metabolized in humans is suggested by studies showing that urinary excretion levels of such compounds vary among individuals according to their smoking habits (17). Due to the fact that they are lipophilic, tobacco-related carcinogens can be stored in breast adipose tissue (18, 19) and then metabolized and activated by human mammary epithelial cells (20). Experimental studies have indicated that tobacco smoke contains potential human breast carcinogens [including PAHs,[2] aromatic amines, and *N*-nitrosamines (9, 10, 21, 22)], and the higher prevalence of smoking-specific DNA adducts and *p53* gene mutations found in the breast tissue of smokers compared with that in nonsmokers (23–29) supports the biological plausibility of a positive association between cigarette smoking and breast cancer risk. However, epidemiological studies have variably shown positive, inverse, or null associations (30).

Several explanations for the lack of consistency in previous studies have been suggested. Included among these is the possibility that the observed associations are not causal (30), in which case chance or bias might have driven some of the previous findings in either direction from the null. Another possible explanation for the discrepant findings includes the postulated "antiestrogenic" effect of cigarette smoking (31); estrogen is a known risk factor for breast cancer (32). Studies that have shown smoking to be associated with increased risk of osteoporosis (33, 34), an earlier age at natural menopause (31), and attenuated effects of hormone replacement therapy (34) suggest an antiestrogenic effect of smoking. Because an antiestrogenic effect of cigarette smoking may vary according to factors such as exogenous hormone use, menopausal status, and relative body weight (33, 35, 36), it is possible that the magnitude and direction of the association of breast cancer observed with cigarette smoking vary with the characteristics of the study population. However, circulating levels of estrogen among current smokers often do not differ from those among former smokers or nonsmokers (37–44). It is also possible that some of the many smoking exposure measures used in previous studies have not adequately captured the relevant exposure. For exam-

[2] The abbreviations used are: PAH, polycyclic aromatic hydrocarbon; NAT, *N*-acetyltransferase; CYP, cytochrome P450; GST, glutathione *S*-transferase; ER, estrogen receptor; PR, progesterone receptor; 16α-OHE1, 16-α-hydroxyestrone; 2-OHE1, 2-hydroxyestrone; BP, benzo(*a*)pyrene.

ple, if a long induction period, perhaps as long as 30–40 years, separates breast cancer initiation due to smoking and its clinical manifestation, as has been hypothesized for colorectal cancer (45), measures such as "ever" or "current" smokers might fail to reflect an underlying association with very long duration.

The most recent comprehensive review of the literature on smoking and the risk of breast cancer (30) included studies published during and before 1992, and at least 67 studies have been published subsequently (25, 46–111). Therefore, to update the previous review, we obtained and reviewed the reports of all relevant epidemiological studies through Medline, Cancerlit, and the references cited in articles published in English. As in that review (30), we excluded studies of prevalent breast cancer (82, 112–116), which are subject to bias from factors related to the survival of those with the disease, studies with insufficient detail [*e.g.,* lacking confidence intervals, number of exposed cases, or definition of the reference category (74, 86, 87, 98, 100, 102, 103, 107, 113, 115, 117–136)], and case-control studies in which patients with smoking-related diagnoses were included in the control series (114, 132, 137–151). In addition, we focused on studies that examined quantitative smoking measures, and therefore we have excluded studies that examined qualitative measures of smoking, such as "ever/never" and "current/former/never" (52, 54, 59, 65, 75, 80, 81, 83, 85, 89, 91–93, 101, 104–106, 108, 152–158). With the measure "ever smoked," for example, it is not clear when the exposure occurred, for how long, or at what intensity. This is essentially true of the "former smoker" as well; from this measure, it is known only that the individual was not smoking at the time of the interview. As for the term "current smoker," the intensity and duration of the exposure are also unknown. Given the rapid rise in smoking prevalence among women since the 1950s, at least in North America (159), the percentage of long-term smokers among "current smokers" is likely to vary across populations and within populations over time; thus, the same qualitative measures are not necessarily comparable across studies. Therefore, published studies have paid increasing attention to measures of exposure to tobacco smoke that might be of the greatest etiological importance, such as smoking duration, intensity, and pack-years (the product of intensity and duration), as well as to aspects of the smoker (such as genotype) that might modify the association between smoking and breast cancer risk. Increasing attention also has been paid to the potentially different associations that might exist with different types of breast tumors, such as those with and without ERs or PRs, and to the associations between cigarette smoking and markers of breast cancer risk (such as mammographic density) and putative breast cancer precursor lesions (various types of benign breast disease). Environmental tobacco smoke (or passive smoking) has also been investigated recently, not only with respect to its association with breast cancer risk but also with regard to how it might influence the association observed with active cigarette smoking.

A Note on the Analysis of Cigarette Smoking. Qualitative measures of smoking have been used in most previous studies of breast cancer risk. Quantitative measures of smoking frequency (cigarettes/day), duration (years smoked), the product of smoking frequency and duration (pack-years), latency (years since smoking commenced), and recency (years since smoking ceased) have been used more frequently in recent years, although use of these measures remains sporadic, and rarely have most or all of these measures been examined in the same study. The fact that the various smoking measures are correlated with each other (160, 161) complicates the differentiation of their independent effects. For example, smokers of high intensity tend to be smokers of long duration, and the latter tend also to have commenced smoking at an early age. In such instances, to examine their independent effects, one can attempt to mutually adjust for various smoking measures in multivariate models or examine a particular smoking measure over strata of another. Pack-years, a potentially useful combined measure of smoking intensity and duration, has conceptual limitations, because 20 pack-years can accrue by smoking two packets of cigarettes per day for 10 years, for example, or by smoking a half of a packet of cigarettes per day for 40 years.

Tobacco smoke contains many potentially harmful substance (9, 10) that may act differently and at different stages in breast cancer development. Comparison of the associations of different smoking measures with respect to breast cancer risk may help not only to determine the most relevant measures with regard to risk but also to discern the various stages of breast cancer development that smoking might influence. For example, if a carcinogen acts early in cancer development, its association with cancer risk will be characterized by a relatively long latency period (160, 161). However, smoking measures that do not allow examination of a long latency period or studies in which participants have an insufficiently long interval between smoking initiation and cancer development would result in weaker or null associations with that smoking measure. In contrast, the association with risk of a carcinogen that acts late in cancer development would tend toward the null with increasing years since cessation of exposure to that carcinogen (160, 161). The latter would be true whether the carcinogen was associated with breast cancer risk positively or inversely. If there were an initiating effect at smoking commencement that was followed in time by an antiestrogenic effect, for example after menopause, then measures such as duration of smoking, years since smoking commencement, and pack-years might capture the two opposing effects in the same individuals, to some extent underestimating the magnitude of both. If such were the case, the examination of various smoking measures within the same study, including time since quitting, over strata defined by age or menopausal status, might provide further insight into the nature of the association between cigarette smoking and breast cancer. Unfortunately, the number of studies that examined a wide range of smoking measures is small. Comparisons among studies are complicated further by other methodological considerations, including the dearth of very long-term smokers in earlier studies, the examination of populations with varying age ranges and other factors that might modify the association between smoking and breast cancer (or capture different underlying effects of smoking), and varying degrees of attention to confounding and measurement error.

As with time since smoking commencement and time since cessation of smoking, the examination of smoking intensity may also lead to inferences regarding the stages of cancer development that smoking may influence. In a prospective cohort study among male British doctors, (162) for example, the quadratic increase in lung cancer risk observed with each cigarette smoked per day led to speculation that smoking acts at two independent stages in the carcinogenic process (initiation and promotion). Examinations of smoking intensity have also been used to quantify the excess relative and absolute risks at specific levels of exposure, to identify potential thresholds at which risk due to smoking begins to increase, and even to help make inferences regarding the causal nature of the association. In the latter instance, causality has been thought to be more likely when dose-risk trends have been demonstrated.

First author, study year	Study design	No. of cases/controls (or no. in cohort)	Benign breast disease	Comparison	OR (95% CI)[a]
Rohan, 1999 (170)	Cohort	691/56,837	Benign proliferative epithelial disorders of the breast	>27.5 pack-years *vs.* never smoked	0.9 (0.7–1.2)[b]
Rohan, 1999 (169)	Cohort	222/56,837	Fibroadenoma	>27.5 pack-years *vs.* never smoked	0.7 (0.4–1.1)
Dziewulska-Bokiniec, 1995 (167)	Case-Control	160/160	Fibroadenoma, dysplasia, fibrocystic disease, others	20+ years duration of smoking *vs.* never	0.8 (0.1–3.4)
Yu, 1992 (172)	Case-Control	117/117	Fibroadenoma	16+ years duration smoking *vs.* nonsmoker	0.6 (0.3–1.4)[c]
Parazzini, 1991 (171)	Case-Control	288/291	Dysplasia and benign tumors	20+ years duration of smoking *vs.* never	1.3 (0.7–2.6)[d]
Rohan, 1989 (168)	Case-Control	383/383	Benign proliferative epithelial disorders of the breast	Current smokers w/15+ pack-years *vs.* never smokers	0.6 (0.3–1.1)[e]

Table 1   Studies of cigarette smoking and benign breast disease

[a] OR, odds ratio; CI, confidence interval.
[b] Results were similar when nonatypical cases were examined separately; the OR for atypical cases (>15 pack-years *versus* never smokers) was 1.3 (0.7–2.5).
[c] The results presented are based on population controls. The OR for biopsy controls was 1.3 (0.6–2.6).
[d] The results presented are for total cases and controls; the results were similar for dysplasia and benign tumors when analyzed separately.
[e] The OR when 192 biopsy controls were used instead of 383 community controls was 1.7 (0.7–4.2); the OR (current smokers *versus* never) for women with severe atypia was 2.3 (0.9–6.1).

Epidemiological Studies of Cigarette Smoking and Benign Breast Disease

Studies of an exposure such as cigarette smoking and the risk of a condition known to be a precursor to a disease, especially a disease that develops after a considerable latency period, may provide insight into the association between the exposure and the disease itself. For example, smoking has been associated consistently with precursors of colorectal cancer, namely, colorectal adenomas, even though its association with colorectal cancer itself has not been consistent (45). Because most colorectal cancers develop from adenomas (163), either the positive association with adenomas stems from bias, such as that which would occur if smokers were more likely to undergo endoscopy, or smoking acts early in the cancer process, but not later. Under the latter circumstance, the association with cancer may not be detected because a study is conducted before sufficient time has elapsed between smoking initiation and cancer development; indeed, investigators have recently hypothesized that a very long induction period (an estimated 35 years) separates colorectal cancer initiation due to smoking and its clinical manifestations, and it is only in studies conducted recently that a consistent association between cigarette smoking and colorectal cancer risk has become evident (45).

Women with benign breast disease are at increased risk of developing subsequent breast cancer (164). However, benign breast disease is a heterogeneous condition consisting of many histological entities (165), and risk varies by histological subcategory, at least some of which might represent precursors of breast cancer (164). Indeed, one model of the natural history of breast cancer posits that it develops as a result of the progression of breast tissue through specific histological forms of benign breast disease (166). Essentially, according to this model, nonatypical proliferative changes and proliferative disease with atypia represent successive steps preceding the development of *in situ* cancer and then invasive carcinoma. Therefore, studies of smoking and the various conditions that mark this progression may help to elucidate the role of smoking in breast cancer etiology.

Epidemiological studies of smoking and benign breast disease are few in number (167–172), and to date, they have shown no clear association (Table 1). Moreover, in addition to the lack of consistently defined smoking measures, perhaps the greatest limitation of these studies is the lack of consistency in defining the outcome of interest. With regard to the latter, studies have variably examined fibroadenoma, benign cystic breast disease, and other conditions, often combined into a single outcome (167). The two studies that examined fibroadenoma only (169, 172) showed a tendency toward a small decreased risk among smokers. Similarly, two studies that examined benign proliferative epithelial disorders of the breast (168, 170), a putative precursor of breast cancer (164), also found no clear association with either smoking duration or pack-years of smoking.

In summary, studies to date have provided little support for an association between cigarette smoking and risk of benign breast disease, either overall or for specific types of benign breast disease, such as fibrocystic breast disease, fibroadenoma, dysplasia, and benign proliferative epithelial disorders. However, given the heterogeneity of benign breast disease and the paucity of studies that have examined specific forms of this condition, additional studies that pay attention to the methodological challenges that this issue presents (*e.g.,* case definition and control selection) are warranted.

Studies of Cigarette Smoking and Breast Density

Mammographic density refers to the relative amount and configuration of breast tissue as it appears on a mammogram, with fat appearing dark (radiolucent), and epithelial and stromal tissues appearing light [radiodense (173)]. Mammographic density can be classified according to Wolfe patterns (a visual parenchymal method), the percentage of dense area in the breast, or the degree of density in dense areas of the breast (95). Studies have consistently shown that women with a large proportion of dense tissue in the breast are at severalfold greater risk of breast cancer than women with a relatively small proportion of dense breast tissue (173, 174). Two studies of cigarette smoking and mammographically defined breast density have been conducted, including a case-control study of high risk (P2/DY) parenchymal patterns nested within the European Prospective Investigation of Cancer (EPIC) cohort study (96) and a cross-sectional analysis of percentage of breast density in a cohort of family members of women with breast cancer (97). Both of these studies showed lower measures of breast density in current smokers than in nonsmokers. Because exposure to estrogen has been associated positively with breast density, the results of these studies are consistent with an antiestrogenic effect of cigarette smoking.

Epidemiological Studies of Cigarette Smoking and Breast Cancer

Case-Control Studies

The majority of studies on cigarette smoking and breast cancer risk published to date have used the case-control design. Case-control studies can be divided roughly into three categories: (*a*) hospital-based; (*b*) screening-based; and (*c*) population-based. Ensuring that the selection of control subjects is independent of the exposure of interest is particularly challenging in a hospital setting, where many conditions (or hospitalization for those conditions) may be related to smoking. For example, several studies of smoking and breast cancer risk included colorectal cancer cases in the control group (175–177) because this cancer was formerly believed to be unrelated to smoking. More recently (as indicated earlier), several studies in men have suggested that smoking may indeed be associated with increased colorectal cancer risk, but only several decades after smoking commencement (45). If the association between smoking and breast cancer risk is also characterized by a long induction period, then the inclusion of colorectal cancer patients in the control group might mask the association of breast cancer risk with smoking duration and years since commencement of smoking. However, the association between smoking and colon cancer among women remains unclear (178), especially in studies conducted before 1990 (45); therefore, the results of the three studies that have included colorectal cancer cases in their control series are discussed below. Population-based case-control studies are not plagued by this problem, but participation rates among controls might be lower than those in hospital-based case-control studies.

The results of case-control studies of cigarette smoking and breast cancer risk are reviewed in the next three subsections. The results of two hospital-based studies, (57, 179) one screening-based study, (180), and six population-based case-control studies (60, 68–71, 181) that did not provide summary measures of association for the entire study population are discussed later in sections devoted to risk in specific population subgroups (see Tables 6, 8, and 9).

Hospital-based Case-Control Studies. The results of five hospital-based case-control studies of cigarette smoking and breast cancer risk are shown in Table 2 (49, 175–177, 182). All but one (182) of these studies examined categories of smoking frequency (*i.e.,* intensity), and they essentially found no association with risk. Two of these studies, one in the United States (175) and one in Italy (49), also examined categories of smoking duration and categories of age at commencement of cigarette smoking. In the former (175), a statistically nonsignificant 70% increased risk was observed with smoking of 40 years or more. That study also found a statistically nonsignificant 140% increased risk with smoking commencement before age 14 years. The remainder of the studies showed essentially no association with smoking duration (49), pack-years (182), or age at smoking commencement (49). It is perhaps noteworthy that (as mentioned earlier) three (175–177) of the five hospital-based case-control studies included colorectal cancer cases in the control group, although there is no clear pattern to indicate bias resulting from this inclusion. In each of these studies, control groups were comprised of women with medical conditions that were judged by the investigators to be unrelated to cigarette smoking.

Screening-based Case-Control Studies. Studies in screened populations, in which cases (and usually controls) are identified through breast cancer screening initiatives or referrals, are considered to have attributes that both predispose to and miti-

Table 2 Hospital-based case-control studies of cigarette smoking and breast cancer risk

First author, study year	Years of data collection	No. of cases/controls	Age range (yrs)	Smoking frequency (cigarettes/day) Comparison	OR (95% CI)[a]	Smoking duration (yrs) Comparison	OR (95% CI)	Pack-years (packs/day × years) Comparison	OR (95% CI)	Age smoking commenced (yrs) Comparison	OR (95% CI)
Braga, 1996 (49)	1991–1994	2569/2588	20–74	25+ vs. never	1.2 (0.8–1.7)	30+ vs. never	1.0 (0.8–1.2)			<16 vs. never	1.0 (0.8–7.1)
Palmer, 1991 (175)	1982–1986	1955/805	30–69	35+ vs. never	1.1 (0.7–1.8)	40+ vs. never[b]	1.7 (0.9–3.3)			<14 vs. never	2.4 (0.9–4.4)
Stockwell, 1987 (177)	1981	5246/3921	<50–75	>40 vs. non-smokers	1.3 (1.0–1.8)						
Rosenberg, 1984 (176)	1976–1982	2160/717	30–69	25+ vs. never	1.1 (0.8–1.6)						
Baron, 1986 (182)	1957–1965	1741/2128	40–89					15+ vs. never	0.9 (0.8–1.1)		

[a] OR, odds ratio; CI, confidence interval.
[b] Analysis was limited to smokers of 25 cigarettes/day or more.

Table 3 Screening-based case-control studies of cigarette smoking and breast cancer risk

First author, study year	Years of data collection	No. of cases/controls	Age range (yrs)	Smoking frequency (cigarettes/day)		Smoking duration (yrs)	
				Comparison	OR (95% CI)[a]	Comparison	OR (95% CI)
Delfino, 2000 (53)	1996–1998	113/278	20–74	>25 *vs.* never	0.5 (0.2–1.4)	>26 *vs.* never	0.7 (0.3–1.6)
Bennicke, 1995 (48)[b]	1989–1991	230/3010	29–80+			31+ *vs.* never	1.6 (1.1–2.2)
Meara, 1989 (179)	1980–1984	118/118	45–69	15+ *vs.* never	2.9 (1.2–7.3)		

[a] OR, odds ratio; CI, confidence interval.
[b] This study examined women referred to a hospital-based department of radiology for mammography.

gate against the possibility of obtaining biased results. On the one hand, women who are referred for breast cancer screening are not necessarily representative of the general population, thereby reducing the generalizability of the study's findings. Furthermore, similarities in the characteristics of those who are screened might reduce the range of exposure in the study population, for example, if smokers are less likely to be referred for screening. On the other hand, these similarities might also reduce the potential for bias, for example, by providing a measure of control for factors related to their selection for screening.

The results of three screening-based case-control studies are shown in Table 3. The most recent of these studies (53), which was also the smallest in terms of the number of cases analyzed, found statistically nonsignificant decreased risks with smoking of >26 years' duration and, separately, with smoking ≥25 cigarettes/day. In contrast, a study of comparable size (179) found a statistically significant 190% increased risk in association with smoking ≥15 cigarettes/day but did not examine other quantitative measures of smoking. The largest of the three studies (48) found a statistically significant 60% increased risk with smoking 31 years or more. It is important to note that these studies included cancers detected on initial screening (48, 53, 179, 180), which may introduce bias if risk factors for these cancers differ from those that would have been detected during follow-up.

Population-based Case-Control Studies. The results of 16 population-based case-control studies of the association between cigarette smoking and breast cancer risk (47, 56, 61, 64, 66, 67, 73, 90, 175, 183–189) are summarized in Table 4. Two of these studies (184, 186) do not strictly meet the definition of population-based studies because not all of the cases occurring in the catchment area were included. However, these two studies are essentially "population-based" in that controls were selected from the communities that largely gave rise to the cases. These studies are listed in reverse chronological order according to the calendar years in which smoking was assessed, given that the more recent the assessment of smoking, the greater the likelihood of being able to examine risk in association with smoking of very long duration. Eleven of these studies (47, 56, 61, 64, 66, 175, 183, 184, 187–189) examined smoking of 20 years' duration or more, and three of these studies (61, 64, 66) found a statistically significant positive association with breast cancer risk. Two of the three latter studies (64, 66) had the most recent assessment of smoking exposure (both used data from the Carolina Breast Cancer Study; the former examined smoking during adolescence, and the latter examined lifelong smoking). The remainder of the studies did not show clear positive associations with smoking duration, frequency, pack-years, or age at smoking commencement.

Cohort Studies

Although the problems of unbiased selection and recall are minimized or avoided by using the prospective cohort study design, cohort studies are not without limitations. For example, changes in smoking habits during follow-up can lead to misclassification of the exposure if, as has generally been the case, exposure is not updated after the baseline assessment. Such exposure misclassification, occurring before disease occurrence, would tend to be nondifferential with respect to the outcome, with bias toward the null being the most likely consequence (190). Cohort studies can also be compromised by losses to follow-up, where the resulting bias can be toward or away from the null when the losses are differential with respect to exposure and disease.

The results of 12 cohort studies that have examined the association between cigarette smoking and breast cancer risk (51, 58, 63, 76, 79, 84, 191–196) are shown in Table 5. Of these studies, two found statistically significant positive associations with high levels of smoking intensity and smoking duration (51, 195), pack-years (195), and early ages at smoking commencement (51). These two studies were among those with the most recent assessment of smoking habits, perhaps indicating an increasing number of long-term smokers in the studied populations. The American Cancer Society's Cancer Prevention Study II (51) found that smoking for 40 years or longer was associated with a 40% increase in the risk of fatal breast cancer after adjustment for alcohol consumption and other potentially confounding variables. However, studies of breast cancer mortality may be biased if smoking is related to factors that influence survival, such as delays in diagnosis and treatment. In the Canadian National Breast Screening Study (195), smoking of 40 years' duration or more was positively associated with breast cancer risk, especially among women who also smoked a packet of cigarettes per day or more. However, women who had smoked at high intensity but for <30 years were not at altered risk. The majority of the remaining studies did not show clear associations between smoking intensity, duration, pack-years, or age at smoking commencement and breast cancer risk. However, as with the case-control studies, most relative risk estimates were at unity or above.

Studies in Specific Subgroups

The association between cigarette smoking and breast cancer risk has sometimes been more or less evident in certain subgroups of the studied populations, subgroups defined by factors such as menopausal status, age (*e.g.,* youth or adulthood), whether or when a woman had children, or certain genotypes. Such effect modification might reflect differences in the biological parameters underlying the association or methodological factors such as differences that occur by chance or with the varying prevalence of confounding variables. It is also possible that effect modification reflects differences in the opportunities

Table 4 Population-based case-control studies of cigarette smoking and breast cancer risk

First author, study year	Years of data collection	No. of cases/ controls	Age range (yrs)	Smoking frequency (cigarettes/day)		Smoking duration (yrs)		Pack-years (packs/day × years)		Age smoking commenced (yrs)	
				Comparison	OR (95% CI)[a]	Comparison	OR (95% CI)	Comparison	OR (95% CI)	Comparison	OR (95% CI)
Marcus, 2000 (64)	1993–1996	864/790	20–74	20+ vs. never	1.1 (0.9–1.4)	20+ vs. never	1.3 (1.1–1.8)			<15 vs. never	1.5 (0.9–2.5)
Millikan, 1998 (66)	1993–1995	498/473	20–74	>20 vs. never	1.1 (0.7–1.7)	20+ vs. never	1.6 (1.1–2.3)				
Morabia, 1996 (67)	1992–1993	244/1032	30–74	20+ vs. never	4.6 (2.2–9.7)			20+ vs. never	2.9 (1.4–6.0)		
Gammon, 1998 (56)[b]	1990–1992	1645/1497	<45	>20 vs. never	1.0 (0.7–1.4)	>21 vs. never	0.7 (0.5–0.9)	>20 vs. never	0.8 (0.6–1.1)	≤15 vs. never	0.6 (0.4–0.9)
Baron, 1996 (47)	1988–1991	6888/9529	<75	>40 vs. never	1.1 (0.8–1.5)	50+ vs. never	1.1 (0.8–1.4)			≤15 vs. never	1.0 (0.8–1.3)
Lash, 1999 (61)	1983–1986	266/765	<50–80	20+ vs. never	1.6 (0.6–4.3)	40+ vs. never	2.4 (1.1–5.5)			<17 vs. never	2.4 (0.8–7.2)
Adami, 1988 (183)	1984–1985	422/527	<45	20+ vs. never	1.1 (0.7–1.8)	20+ vs. never	1.2 (0.8–1.7)			<15 vs. never	1.3 (0.7–2.5)
Palmer, 1991 (175)	1982–1986	607/1214	35–69	25–34 vs. never	1.5 (0.9–2.5)	40+ vs. never[c]	1.0 (0.5–2.1)			<14 vs. never	1.9 (0.9–4.4)
Ewertz, 1993, 1990 (94, 189)	1983–1984	623/578	25–69	20+ vs. never	0.8 (0.6–1.0)	30+ vs. never	1.0 (0.7–1.5)			<15 vs. never	0.9 (0.4–1.8)
Smith, 1994 (73)	1982–1985	755/755	<36	16+ vs. never	1.1 (0.8–1.5)	10+ vs. never	1.0 (0.8–1.2)	10+ vs. never	1.0 (0.8–1.4)	<16 vs. never	1.1 (0.8–1.4)
Rohan, 1989 (185)	1982–1984	451/451	20–74	>15 vs. never	1.6 (1.0–2.6)			25+ vs. never	1.6 (1.0–2.5)		
Field, 1992 (184)	1982–1984	1617/1617	20–79	>40 vs. never	1.2 (0.7–2.0)	40+ vs. never	1.2 (0.7–2.0)	40+ vs. never	1.1 (0.8–1.4)	<20 vs. never	1.0 (0.9–1.2)
Mayberry, 1994 (90)	1980–1982	148/167	20–54					11+ vs. none	1.1 (0.6–1.9)		
Chu, 1990 (188)	1980–1982	4720/4682	20–54	25+ vs. never	1.2 (1.1–1.4)	30+ vs. never	1.1 (0.9–1.3)	40+ vs. never	1.1 (0.9–1.4)	<17 vs. never	1.1 (1.0–1.2)
O'Connell, 1987 (186)	1977–1978	276/1519	20–54	>20 vs. never	0.6 (0.3–1.1)						
Stroup, 1987 (187)[d]	1959–1960	4720/4682	20–54	25+ vs. never	1.2 (1.0–1.4)	30+ vs. never	1.1 (1.0–1.3)			<15 vs. never	1.1 (0.9–1.4)

[a] OR, odds ratio; CI, confidence interval.
[b] Results presented are for current smokers. Results for former smokers showed statistically non-significant positive associations with smoking.
[c] The analysis was limited to smokers of 25 or more cigarettes/day.
[d] Results presented are for current smokers. Results for former smokers were similar.

Table 5 Prospective cohort studies of cigarette smoking and breast cancer risk

First author, study year	Years of data collection	No. of cases/no. in cohort	Age range (yrs)	Smoking frequency (cigarettes/day)		Smoking duration (yrs)		Pack-years (packs/day × years)		Age smoking commenced (yrs)	
				Comparison	RR (95% CI)[a]	Comparison	RR (95% CI)	Comparison	RR (95% CI)	Comparison	RR (95% CI)
Zheng, 1999 (76)	1986	273/657	55–69	15+ vs. none[b]	1.1 (0.7–1.6)						
Calle, 1994 (51)[c]	1982–1986	800/604412	30–70+	40+ vs. never	1.7 (1.2–2.6)	40+ vs. never	1.4 (1.1–1.8)			<16 vs. never	1.6 (1.2–2.2)
Terry, 2002 (195)	1980–1985	2552/89835	40–59	40+ vs. never	1.3 (1.1–1.7)	40+ vs. never	1.6 (1.2–2.2)	40+ vs. never	1.4 (1.2–1.6)	<16 vs. never	1.1 (0.9–1.4)
Egan, 2002 (84)	1982	3140/78206	36–61			40+ vs. never	1.1 (0.9–1.2)			<17 vs. never	1.2 (1.0–1.4)
Manjer, 2001 (63)	1974–1992	268/10902	25–75	20+ vs. never	1.3 (1.0–1.8)						
Vatten, 1990 (196)	1974–1978	242/24329	35–51	10+ vs. none	0.9 (0.6–1.2)						
Hiatt, 1988 (194)	1979–1984	303/68674		40+ vs. never	1.2 (0.5–2.8)						
Hunter, 1997 (58)	1976	466/466[d]	30–55	15+ vs. never[e]	1.6 (1.0–2.4)			30+ vs. never	1.3 (0.9–1.9)		
London, 1989 (192)	1976	1788/117557	30–55	25+ vs. never	1.0 (0.9–1.2)					<17 vs. never	1.1 (0.9–1.3)
Hiatt, 1986 (193)	1964–1972	1363/84172	20–84	"heavy" vs. never	1.2 (0.9–1.6)						
Schatzkin, 1989 (191)	1949–1988	143/2636	31–64	20+ vs. none	1.0 (0.6–1.7)						
Nordlund, 1997 (79)	1963	170/26000	18–69	16+ vs. never	1.1 (0.7–1.7)					<19 vs. never	1.2 (0.8–1.8)

RR, relative risk; CI, confidence interval.

[a] Results presented are for smokers of 25 years or longer.
[b] Results presented are for smokers of 25 years or longer.
[c] The endpoint examined was breast cancer mortality.
[d] This study was of nested case-control design (the numbers represent cases/controls).
[e] Results presented are for smoking 10 years prior to diagnosis (results for smoking at interview were essentially the same).

for exposure to cigarette smoke, such as those that might occur if postmenopausal women (by virtue of their age) were more likely than premenopausal women to have been exposed to cigarette smoke for 40 years or more. Nonetheless, studies that stratify results according to certain factors of interest may help to clarify the association between cigarette smoking and breast cancer risk and may ultimately help to reconcile the disparate findings noted earlier.

Menopausal Status. Given the reduction in circulating estrogen levels that occurs after menopause, one might speculate that any antiestrogenic effects of smoking might then be relatively smaller, with consequent differences between menopausal strata in the association between cigarette smoking and breast cancer risk. Although plasma levels of estrogens have not been associated with smoking in either pre- or postmenopausal women in several studies, (37–39), statistically nonsignificant reductions in estrone and estradiol levels in current smokers compared with former smokers or never smokers have been noted among postmenopausal women using hormone replacement therapy (34, 36). Nevertheless, most of the studies that have examined cigarette smoking in relation to breast cancer risk among both premenopausal and postmenopausal women have not shown meaningful differences in risk according to menopausal status (Table 6). There appears to be little support for an inverse association in either group of women, with most of these studies showing some degree of increased risk with high intensity or long duration of smoking, regardless of menopausal status (47, 57, 60, 66, 129, 175, 185, 193).

Smoking in Very Young Women. Exposure to ionizing radiation from the atomic bombs blasts over Hiroshima and Nagasaki was found to induce an especially high risk of breast cancer among adolescent females [aged 10–19 years at exposure (197)]. That observation raises the possibility that the adolescent breast may also be sensitive to the DNA-damaging effects of other exposures. Therefore, it is possible that the genotoxic compounds contained in tobacco smoke may be particularly hazardous to youthful smokers, for example, women who commence smoking in their teens. Of the 15 studies that examined breast cancer risk in relation to smoking commencement at such young ages [47, 49, 51, 61, 64, 73, 84, 129, 175, 183, 184, 188, 189, 192, 195 (Tables 2, 4, and 5)], most have found no clear association or statistically nonsignificant weak to moderate positive associations, with the greatest increase in risk being observed among women who started smoking in their mid-teens or earlier. Although the increased risks observed in association with young age at commencement were generally not as large as those observed for smoking of long duration, there have been few attempts to disentangle the effects of these two measures, at least in part because of the difficulty of examining highly correlated measures concurrently.

Smoking before or after a First Full-term Pregnancy. A relatively early age at first full-term pregnancy has been associated with reduced breast cancer risk (198), hypothetically due to terminal differentiation of the breast epithelium that occurs late in the first trimester. It has been suggested that in the early stages of pregnancy, when growth-promoting hormone levels are high [but before terminal differentiation (199)], the breast may be particularly susceptible to the cancer-promoting chemicals in tobacco smoke. The potential importance of cigarette smoking before a first full-term pregnancy was first studied in a population-based case-control study in Sweden (183), which found no clear association (Table 7). More recently, a case-control study nested within the Nurses' Health Study (58) found that 5 years' duration of smoking or longer before a first

Table 6 Studies of cigarette smoking and breast cancer risk according to menopausal status

First author, study year	Study design	No. of cases/controls (or no. in cohort)	Comparison categories	Comparison	Premenopausal (or age ≥ 50)	OR (95% CI)	Postmenopausal (or age ≥ 50)	OR (95% CI)
Baron, 1996 (47)	Population case-control	6888/9529	Pre/postmenopausal	30–40 years' duration vs. never	Premenopausal	1.3 (0.9–1.9)	Postmenopausal	1.1 (1.0–1.2)
Brownson, 1988 (180)	Screening case-control	456/1693	Pre/postmenopausal	15+ years' duration vs. never	Premenopausal	1.8 (0.9–3.7)	Postmenopausal	0.9 (0.6–1.4)
Chu, 1990 (188)	Population case-control	4720/4682	Pre/postmenopausal	40+ pack-years vs. never smoked	Premenopausal	1.5 (1.0–2.3)	Postmenopausal	1.0 (0.7–1.6)
Hirose, 1995 (57)	Hospital case-control	711/17205	Pre/postmenopausal	10+ cigarettes/day vs. nonsmokers	Premenopausal	1.3 (1.0–1.7)	Postmenopausal	1.1 (0.8–1.6)
Johnson, 2000 (60)	Population case-control	869/909	Pre/postmenopausal	Highest years smoked[a] vs. never	Premenopausal	2.1 (0.9–4.7)	Postmenopausal	1.7 (1.1–2.7)
London, 1989 (192)	Prospective cohort	1788/117557	Pre/postmenopausal	25+ cigarettes/day vs. nonsmokers	Premenopausal	1.0 (0.8–1.3)	Postmenopausal	1.1 (0.8–1.4)
Meara, 1989 (179)	Hospital case-control	998/998	Age 25–44/age 45–69	15+ cigarettes/day vs. never	Age 25–44	1.2 (0.7–1.8)	Age 45–69	0.8 (0.6–1.1)
Millikan, 1998 (66)	Population case-control	497/472	Pre/postmenopausal	>20 years' duration vs. never	Premenopausal	1.4 (0.8–2.6)	Postmenopausal	1.7 (1.1–2.6)
Palmer, 1991 (175)	Population case-control	607/1214	Age 30-49/age 50-69	35+ cigarettes/day vs. never	Age 30–49	1.9 (1.0–3.7)	Age 50–69	0.9 (0.4–2.1)
Pawlega, 1992 (181)	Population case-control	127/250	Age 35-49/age 50-75+	20+ years' duration vs. never	Age 35–49	0.5 (0.1–2.3)	Age 50–75+	1.5 (0.7–3.2)
Ranstam, 1995 (70)	Population case-control	388/448	Pre/postmenopausal	11+ cigarettes/day vs. never	Premenopausal	1.2 (0.7–2.1)	Postmenopausal	0.8 (0.4–1.6)
Rautalahti, 1993 (71)	Population case-control	67/157	Pre/postmenopausal	15+ cigarettes/day vs. nonsmokers	Premenopausal	2.6 (0.8–8.1)	Postmenopausal	0.9 (0.2–3.7)
Rohan, 1989 (185)	Population case-control	426/420	Pre/postmenopausal	Highest pack-years[b] vs. never	Premenopausal	1.6 (0.7–3.8)	Postmenopausal	1.6 (0.9–2.8)

[a] 21+ years smoked (premenopausal women) and 35+ years smoked (postmenopausal women).
[b] > 10.75 pack-years (premenopausal women) and 25+ pack-years (postmenopausal women).

full-term pregnancy was associated with a slight increased risk of breast cancer overall and with a 50% increased risk among women with rapid *NAT2* acetylation genotype. In a subsequent analysis of the same cohort (84), smoking before a first childbirth was positively associated with risk, whereas smoking after a first childbirth was not. Overall, the results of the few studies of risk in association with the timing of smoking relative to a first pregnancy have been unclear, but they appear to suggest the greater susceptibility of breast tissue to the carcinogenic chemicals in tobacco smoke before rather than after terminal differentiation of breast epithelium.

NAT and Other Genotypes. The carcinogenic effects of compounds found in tobacco smoke have been hypothesized to be stronger or weaker according to genotypes that either biologically activate or detoxify those compounds in the human body (22). Thus, cancer risk is, at least in part, an integrated function of carcinogen exposure and polymorphisms in genes involved in carcinogen metabolism, including CYPs, catechol-*O*-methyltransferase, epoxide hydrolase, peroxidases, GSTs, NATs, and sulfotransferases (200).

Aromatic (and possibly heterocyclic) amines, constituents of tobacco smoke, can be detoxified or activated by NATs, including NAT1 and *NAT2*. Polymorphisms in these genes can give rise to fast and slow aceytlation genotypes that determine the rate of detoxification or activation of carcinogenic aryl or heterocyclic amine substrates (201). For example, most studies indicate that slow acetylators (particularly individuals homozygous for *NAT2* slow acetylator alleles) are at increased risk for arylamine-induced bladder cancer (202). However, whether this is true for breast cancer is unknown.

It is only recently that variation in genetic susceptibility to the effects of cigarette smoking on breast cancer risk has been examined. The first of these studies was a population-based case-control study of women in Western New York State published in 1996 (46). That study, together with a small number of subsequent studies (58, 66, 69, 110), examined risk associated with smoking according to *NAT2* genotypes (either rapid or slow acetylator status; Table 8). The Western New York State Study (46) found a statistically significant increased risk among heavy smokers compared with never smokers, but only among postmenopausal women who were slow acetylators. This finding suggests that rapid acetylators more efficiently detoxify the carcinogenic compounds in tobacco smoke (in other words, greater exposure to the activated compounds is likely in slow acetylators). The results of a recent study of aromatic-DNA adducts and *NAT2* polymorphisms in breast cancer patients tend to support this hypothesis, (203) because there was a higher frequency of smoking-related DNA adducts among women with slow rather than rapid *NAT2* acetylator genotypes. However, a case-control study nested within the Nurses' Health Study cohort (58) found no clear indication of effect modification in the association between cigarette smoking and breast cancer risk by *NAT2* acetylation genotype. Similarly, clear effect modification by *NAT2* genotype was not observed in the Carolina Breast Cancer Study (66), a population-based case-control study. Moreover, a population-based case-control study from Switzerland (69) found that smoking was associated with an increased breast cancer risk in all subgroups of women defined by *NAT2* genotype and menopausal status, but especially among postmenopausal women who were rapid acetylators. As has been noted (69), this finding raises the possibility that the carcinogenic substrate is not aromatic amines but heterocyclic amines because the latter are activated (and the former are detoxified) by *NAT2*. In this light,

Table 7   Studies of cigarette smoking before, during, and after a first full-term pregnancy, and breast cancer risk

First author, study year	Study design	No. of cases/controls (or no. in cohort)	Comparison	Before first birth OR (95% CI)[a]	After first birth OR (95% CI)
Egan, 2002 (84)	Cohort	3140/78206	5+ years before and 20+ years after *vs.* never	1.1 (1.0–1.3)[b]	1.0 (1.9–1.1)
Hunter, 1997 (58)	Cohort[c]	466/466	5+ years smoking duration *vs.* never	1.1 (0.8–1.6)	
Adami, 1988 (183)	Case-control	422/527	10+ years smoking duration *vs.* never	0.7 (0.3–1.4)	

[a] OR, odds ratio; CI, confidence interval.
[b] A statistically significant test of trend was reported.
[c] A nested case-control study. In this study, women with rapid *NAT2* acetylation genotype had a relative risk of 1.5 (0.9–2.6).

Table 8   Studies of cigarette smoking and breast cancer risk according to *NAT2* genotypes

First author, study year	Study design	No. of cases/controls (or no. in cohort)	Comparison	Premenopausal		Postmenopausal	
				NAT2 rapid OR (95% CI)[a]	*NAT2* slow OR (95% CI)	*NAT2* rapid OR (95% CI)	*NAT2* slow OR (95% CI)
Chang-Claude, 2002 (110)	Case-control[b]	422/887	20+ years' duration active *vs.* never	1.2 (0.6–2.4)	1.8 (1.1–3.2)[c]		
			21+ years' duration passive *vs.* never	2.9 (1.1–7.6)	1.0 (0.5–2.0)[c]		
Morabia, 2000 (69)	Case-control[b]	177/170	Current 20+ cpd *vs.* never exposed			5.3 (1.4–20.5)	1.6 (0.7–6.9)[c]
Millikan, 1998 (66)	Case-control[b]	498/473	>20 years' duration *vs.* never	1.7 (0.7–4.2)	1.3 (0.6–2.8)	1.8 (1.0–3.2)	1.9 (0.7–5.5)
Hunter, 1997 (58)	Cohort[d]	466/466	30+ pack-years *vs.* never			0.8 (0.5–1.5)	1.4 (0.8–2.3)[e]
Ambrosone, 1996 (46)	Case-control[b]	304/327	>18.25 pack-years *vs.* never	2.1 (0.5–7.9)	1.2 (0.4–3.8)	0.9 (0.4–2.1)	2.8 (1.4–5.5)

[a] OR, odds ratio; CI, confidence interval.
[b] A population-based case-control study.
[c] The results shown were based on both premenopausal and postmenopausal women; cpd, cigarettes per day.
[d] A nested case-control study.
[e] The results shown were based on both premenopausal and postmenopausal women. There was no association among premenopausal women of either slow or rapid acetylation genotypes.

it is interesting to note that a recent population-based case-control study from Germany (110) found that long-term active smoking was associated with an increase in breast cancer risk of greater magnitude among *NAT2* slow acetylators than among rapid acetylators, whereas long-term passive smoking was associated with increased risk only among rapid acetylators. Although supporting the observations that nitrosamines are more concentrated in passive smoke than in mainstream smoke (204), the findings of the German study more clearly support those of the Western New York State Study than they do those of the Swiss study in that active smoking appeared to be associated with increased breast cancer risk primarily among *NAT2* slow acetylators. None of the studies that examined the association between cigarette smoking and breast cancer risk by *NAT2* genotype found the *NAT2* genotype itself to be independently associated with breast cancer risk (46, 58, 66, 69, 110).

Two studies have examined the association between cigarette smoking and breast cancer risk according to NAT1 genotypes (76, 77). In the Iowa Women's Health Study cohort of postmenopausal women (76), the *NAT1*11* allele was associated with increased risk of breast cancer, most notably among smokers. Smoking was not associated with breast cancer risk overall, however. Risk was not associated with NAT1 genotypes in the Carolina Breast Cancer Study (77).

PAHs are produced during combustion. The sources of human PAH exposure include tobacco smoke, polluted air, and burnt meat. Unlike aromatic and heterocyclic amines, PAHs are metabolized primarily by enzymes in the CYP family (205, 206) and by GSTs (206, 207). However, few studies have examined the association between cigarette smoking and breast cancer risk according to polymorphisms in these carcinogen-metabolizing genes. The Western New York State Study (72) found weak evidence for a positive association with cigarette

smoking among women with either the DC or CC CYP2E1 genotypes, both of which are possibly involved in the activation of carcinogenic *N*-nitrosamines, another class of potentially carcinogenic substances found in tobacco smoke (22). The positive association in this study was observed to be stronger among premenopausal women. In the Anglian Breast Cancer Study (99), a nested case-control study in England, cigarette smoking was not associated with breast cancer according to CYP1A1 polymorphisms. In contrast, a case-control study nested within the Nurses' Health Study cohort (78) found an increase in breast cancer risk among women who had commenced smoking before the age of 18 years and had the CYP1A1-MspI variant genotype compared with nonsmokers who were homozygous wild type for the polymorphism. However, these results were based on a small number of cases among women who both smoked cigarettes at a young age and had the variant form of the CYP1A1 polymorphism. In addition, two studies have examined smoking over strata of GST genotypes (208, 209). In the Carolina Breast Cancer Study (208), the association between cigarette smoking and breast cancer risk was not modified by GSTM1, GSTT1, or GSTP1 polymorphisms. Similarly, weak to moderate positive associations between pack-years of cigarette consumption and breast cancer risk did not differ according to GSTT1 polymorphisms in the Nurses' Health Study cohort (209).

Two studies have examined the association between cigarette smoking and breast cancer risk according to mutations in genes related to DNA repair. The results of a case-control study conducted in the United States and Canada (50) suggest that smoking might be associated with reduced breast cancer risk among women with inherited *BRCA1* and *BRCA2* mutations. In the Carolina Breast Cancer Study (109), smoking duration was positively associated with breast cancer risk among African-

				ER+ tumors	ER− Tumors
First author, study year	Study design	No. of cases/controls (or no. in cohort)	Comparison	OR (95% CI)[a]	OR (95% CI)
Manjer, 2001 (63)	Cohort	268/10902	20+ cigarettes/day *vs.* never smokers	0.8 (0.5–1.4)	2.6 (1.2–5.9)
Morabia, 1998 (68)	Case-control[b]	242/1059	20+ cigarettes/day *vs.* never	2.4 (1.4–4.5)	4.3 (1.4–13.2)
London, 1989 (192)	Cohort	1788/117557	25+ cigarettes/day *vs.* never smokers	1.4 (1.0–1.8)	1.1 (0.7–1.6)

Table 9   Studies of cigarette smoking and breast cancer risk according to the ER status of the tumor

[a] OR, odds ratio; CI, confidence interval.
[b] A population-based case-control study.

American women with the base excision gene *XRCC1* codon 399 Arg/Arg genotype (but not the Arg/Gln or Gln/Gln genotype), although no association was observed among white women. An updated analysis of the Carolina Breast Cancer Study data (based on a larger number of cases) confirmed the dose-response association between smoking duration and breast cancer risk among women with the *XRCC1* Arg/Arg genotype, but not the Arg/Gln or Gln/Gln genotypes.[3] However, in this more recent analysis, the association was observed both among white and African-American women.

Overall, there are still too few data to evaluate the strength, consistency, and dose-dependent nature of the association between cigarette smoking and breast cancer risk according to polymorphisms in genes related to carcinogen metabolism and DNA repair. Given that many of the findings discussed above have not been replicated by other studies and that the number of cases in many of the analyses stratified by genotype was often small, the lack of clear patterns in the association between cigarette smoking and breast cancer risk according to the genotypes studied is not surprising. Clearly, there is a need for continued evaluation of the association according to polymorphisms in genes that either biologically activate or detoxify the various carcinogens contained in tobacco smoke, but in studies with sample sizes that are sufficiently large.

ER and PR Status. ERs have been shown to mediate estrogenic effects on the growth and recurrence rates of breast tumors, breast tumor responses to hormone therapy, and breast cancer survival (210). ER+ tumors tend to be less aggressive and more responsive to hormone therapy, with consequent better prognosis than ER− breast tumors (210). However, whether ER+ and ER− tumors are etiologically distinct or rather are different stages of the same disease remains unknown. It has been suggested that distinct risk factor profiles for these two types of tumors would suggest the former (155), and such differences have recently been observed (211).

Epidemiological studies that have examined the association between quantitative measures of cigarette smoking and breast cancer risk according to ER status (positive or negative) are shown in Table 9. One of these studies found a statistically significant 160% increased risk of ER− tumors (63) but no clear association with ER+ tumors in women who consumed ≥20 cigarettes/day. The remaining two studies did not show any clear difference in the association with smoking intensity according to ER status (68, 192). The overall findings suggest that smoking may increase risk through pathways other than those mediated by estrogen or perhaps that ER− tumors have evolved from ER+ tumors and therefore have common risk factors (although, as noted earlier, colorectal adenomas and carcinomas have differed in their respective associations with cigarette smoking). One of these studies also examined PR

status in relation to smoking, showing no clear difference in the association with PR− compared to that with PR+ tumors (63).

Passive Smoking

Recent reviews of studies that have examined the association between passive smoking (environmental tobacco smoke) and breast cancer risk suggested the possibility of a weak positive association (212, 213) but noted that causality has not been established. In studies that have examined the association between active smoking and breast cancer risk after the removal of passive smokers from the referent category (60, 84, 214–216), positive associations have sometimes become stronger (60, 214–216), suggesting that the inclusion of passive smokers in the referent group may have biased previous findings toward the null. Furthermore (as mentioned above), nitrosamines and other carcinogens found in tobacco smoke appear to be more concentrated in passive smoke than in mainstream smoke (204). However, it has been argued that the general lack of an association between active smoking and breast cancer risk makes any association with passive smoking implausible [given that women who are active smokers are also exposed to their own passive smoke (212)]. Nevertheless, it is possible that passive smoking of long duration may be associated with increased risk, whereas active smoking of shorter duration may not. Indeed, studies of passive smoking that have attempted to quantify exposure in terms of intensity or duration (57, 60, 61, 69, 73, 84, 88) have tended to show increased risks among women in the highest exposure categories compared with women in the lowest exposure categories (Table 10). However, not all studies that have used quantitative measures of passive smoking have observed an association (84).

Studies of Smoking and Breast Cancer in Males

Male carcinoma of the breast is a relatively uncommon disease (217). The extent to which studies of breast cancer in males are relevant to breast cancer in females is unknown, given the differences that may exist in their etiologies and that certainly exist in the "hormonal milieu" in which the respective cancers develop (145, 218). Nevertheless, studies of male breast cancer generally have not shown an association with cigarette smoking (219, 220), although a small case-control study in Greece (221) recently found indications of an inverse association, a finding that was based on only three cases among current smokers. Studies of smoking in relation to testosterone levels generally show no clear association among women (37, 39, 41, 222), but in men there is some evidence for a positive association between cigarette smoking and testosterone levels and also between smoking and levels of estradiol (223). Free, but not bound, serum testosterone levels have been independently positively associated with breast cancer risk in women (224, 225).

[3] R. Millikan, personal communication.

Table 10 Studies of passive smoking and breast cancer risk

First author, study year	Study design	No. of cases/controls (or no. in cohort)	Comparison	OR (95% CI)[a]
Egan, 2002 (84)	Cohort	3140/78206	30+ years lived with regular smoker *vs.* <5	1.0 (0.9–1.2)
Hirose, 1995 (57)	Case-control	1186/23163	Husband smokes 20+ cigarettes/day *vs.* none	1.3 (1.0–1.7)[b]
Smith, 1994 (73)	Case-control	755/755	>20 pack-years lifetime exposure *vs.* none	2.7 (1.1–6.6)[c]
Johnson, 2000 (60)	Case-control	869/909	71+ "smoker-years"[d] *vs.* never exposed	3.0 (1.7–1.8)[e]
Morabia, 1996 (67)	Case-control	244/1032	>50 (hours/day-years) from husband smoking *vs.* none	3.2 (1.5–6.5)
Lash, 1999 (61)	Case-control	266/765	>20 years exposure to passive smoking *vs.* none	2.1 (1.0–4.1)
Wartenburg, 2000 (88)	Cohort	669/146488	Husband smoked 31+ years *vs.* no passive or active	1.1 (0.9–1.4)[f]

[a] OR, odds ratio; CI, confidence interval.

[b] The results shown are for premenopausal women. Among postmenopausal women the OR was also 1.3 (0.9–1.8).

[c] The results for childhood and adulthood exposure to passive smoke shown separately were weaker (but similar) in magnitude from total lifetime exposure.

[d] "Smoker-years" is defined as the number of smokers at the subject's home and office times years in the home and office.

[e] The results shown are for premenopausal women. There were not enough postmenopausal women in this exposure category.

[f] The endpoint examined was breast cancer mortality.

Interpretation

On the basis of the accumulated epidemiological evidence reviewed here, it appears very unlikely that cigarette smoking is associated with reduced risk of breast cancer in women.

Some studies have found smoking cessation to be associated with an increase in risk of breast cancer relative to that in current smokers, (49, 62), which might be expected if, for example, cigarette smoking lowers breast cancer risk through "antiestrogenic" or other effects, and the influence of smoking on such processes is reversible after exposure ends. However, most studies that examined risk in association with time since smoking cessation (47, 56, 63, 84, 186, 189, 192, 195) have not shown an association. Furthermore, the vast majority of at least 20 previous cohort (51, 54, 62, 63, 84, 195) and case-control (47, 49, 53, 56, 64, 66, 67, 129, 175, 185, 187, 188, 193, 226) studies that examined comparable measures of smoking (for example, smoking of 20 years' duration or more) among current and former smokers found no clear pattern indicative of either a decreased risk among current smokers compared with never smokers or a greater risk among former smokers compared with current smokers. Whereas cigarette smoking may have some antiestrogenic effects (and hence, anticarcinogenic effects), these effects may be nullified or exceeded by the deleterious effects of smoking.

Cigarette smoking of very long duration might be associated with increased risk of breast cancer. However, smokers of long duration tend to have commenced smoking at an early age and have long smoking latency (time since smoking commencement), and separating the independent effects of these variables is difficult in practice. The observed association with breast cancer risk was somewhat stronger for smoking duration than for latency in a recent cohort study in Canada (195), although two other studies that examined these measures did not show results for latency that were appreciably different from those for smoking duration (49, 56). As mentioned above, these two smoking measures tend to be highly correlated, and positive associations with breast cancer risk would be consistent with an initiating role of smoking in breast cancer in either case (while not excluding a role in promotion). Approximately half of the case-control studies with more recent data collection (1990 to present) have shown positive associations between cigarette smoking of long duration and breast cancer risk (48, 49, 53, 56, 64, 66, 67), as have two of the three cohort studies that examined smoking duration (51, 84, 195). This tendency may be due to chance or possibly to the fact that women did not smoke in substantial numbers before the late 1940s and 1950s (159), thereby limiting the number of smokers of very long duration in studies conducted before the 1980s or 1990s. Another explanation for this trend in study results is the fact that epidemiological studies of cigarette smoking and breast cancer risk have variably adjusted their relative risk estimates for certain potentially confounding variables, with generally greater attention to covariates in recent years. However, studies that controlled for a wide range of potentially confounding variables, such as age, relative body weight, education, physical activity, parity, age at menarche and menopause, exogenous hormone use, alcohol consumption, and family history of breast cancer, have shown positive (51, 195), inverse (56), and null (58, 84, 183) associations with various measures of cigarette smoking. Furthermore, adjustment for these variables has usually not led to important changes compared with the crude relative risk estimates within these studies, although residual confounding by the variables included in multivariate models could still have occurred if, for example, those variables were measured with error. Whereas publication bias, which refers to the underrepresentation in the literature of studies that found no association, may have occurred to some extent, it is unclear to what extent or indeed whether such bias has been more or less common in recent years.

Studies of the timing of cigarette smoking relative to a first full-term pregnancy might provide further insight into the nature of the association between cigarette smoking and breast cancer. A positive association with smoking before a first full-term pregnancy is compatible with the notions that breast epithelium undergoes differentiation after a first full-term pregnancy (227) and that differentiation reduces the likelihood of breast cancer initiation (228). Studies of cigarette smoking in relation to a first full-term pregnancy have been scarce, although the largest and most recent study to date (84) found a positive association with smoking before a first full-term pregnancy. However, the results of studies that examined smoking among very young women in general, without consideration of the timing of exposure relative to a first pregnancy, suggest that the adolescent breast is not particularly sensitive to the cancer-promoting chemicals in tobacco smoke.

A number of mechanisms have been proposed, both for possible protective effects of cigarette smoking on breast cancer risk and for carcinogenic effects. Cigarette smoking has been hypothesized to lower the risk of breast cancer through antiestrogenic mechanisms, such as the enhanced metabolism of estradiol to inactive catechol estrogens, and several other mechanisms, including increased binding of estrogens by serum sex hormone-binding globulin and lowered levels of estrogen derived from adipose tissue (31). Because circulating levels of

estrogen among current smokers often do not differ clearly from those among former smokers or nonsmokers (37–44), it may be the type rather than the absolute levels of circulating estrogens that is important. Estrogen can be metabolized along two major pathways, to 16α-OHE1 or to 2-OHE1. 16α-OHE1 is considered to be the more biologically active of the two estrogen metabolites, and it has been observed to increase mammary epithelial cell proliferation rates in experimental studies (229). In contrast, 2-OHE1 might decrease epithelial cell proliferation rates (229, 230). If cigarette smoking increases estradiol 2-hydroxylation, as has been suggested (231), thereby increasing the ratio of 2-OHE1:16α-OHE1, an inverse association between smoking and breast cancer risk might be observed. However, only one study (231) has directly examined 2-hydroxylation in relation to cigarette smoking. Using injected radiolabeled estradiol, that study found a 50% increased estradiol 2-hydroxylation in premenopausal women who smoked at least 15 cigarettes/day compared with nonsmokers. Two studies of urinary estrogens found increased excretion of 2-OHE1 and decreased excretion of estriol among smokers (232, 233), which may also support the hypothesis that smoking decreases the formation of active estrogen metabolites along the 16-α-hydroxylation pathway. However, the ratio of urinary 2-OHE1: 16α-OHE1 was not related to breast cancer risk in the one case-control study that examined the association (234).

Cigarette smoking has also been associated with an earlier age at natural menopause in several studies (31, 129, 184, 188, 193), and a relatively early age at menopause has been associated with reduced risk of breast cancer, especially those breast cancers that are ER+ (210). However, few studies in general have found decreased breast cancer risk with any measure of smoking, including those in which an earlier age at natural menopause was observed among smokers (184, 188, 193). Again, this does not necessarily rule out potential antiestrogenic effects due to smoking, although it would appear that such effects do not result in a decreased risk of breast cancer compared with that in women who never smoked.

Obesity is an established risk factor for postmenopausal breast cancer, and it might be associated with a lower risk among premenopausal women (235–237). Although adipose tissue is the main determinant of estrogen levels among postmenopausal women (238), and relative body weight is inversely associated with cigarette smoking (44, 239, 240), statistical adjustment for the effects of relative body weight (*e.g.,* body mass index) and other covariates generally has not altered appreciably the crude or age-adjusted results of studies of cigarette smoking and breast cancer risk in premenopausal women (175, 181, 183, 185, 192) or postmenopausal women (175, 181, 185, 192).

In several animal experiments, mammary tumors were induced by compounds found in cigarette smoke via administration by gavage, i.v. injection, and direct application (22, 206), especially *PAHs*, a class of carcinogens that has several sources in the environment, including diet, air pollution, and tobacco smoke. Specific PAHs (and other compounds) that have shown tumor-inducing effects in rodents include BP, 2-toluidine, 4-aminobiphenyl, 1,3-butadiene, isoprene, nitromethane, ethylene oxide, and benzene (17, 21). When rodents were exposed to these compounds via inhalation, however, the effects on mammary tumorigenesis were less clear. The results of two early studies suggested that inhalation of tobacco smoke might reduce the risk of mammary tumors in rats (241, 242), although results were statistically significant only in one of those studies (242). A more recent study of longer-term exposure to tobacco smoke showed no important

difference in the development of mammary tumors between exposed and unexposed rats (243). Nonetheless, it is important to view all of these findings in light of the uncertain relationship between mammary tumors in rodents and breast cancer in humans.

In human studies, as well as in animal experiments, investigators increasingly have been concerned with the identification of biological markers of cancer risk that can be linked to specific exposures. Several studies have compared urinary levels of tobacco-related carcinogens or their metabolites in smokers and nonsmokers (reviewed in Ref. 17). These studies have generally found that smokers have higher urinary levels than nonsmokers of 1-hydroxypyrene, a carcinogenic metabolite of PAH pyrene. Urinary levels of aromatic amines (2-toluidine and 4-aminobiphenyl) were also observed to be higher among smokers than nonsmokers, but the differences were not statistically significant. Findings from a small number of studies suggest that urinary levels of heterocyclic amine PhIP and certain metabolites of 1,3-butadiene do not vary clearly with smoking status.

Carcinogen-DNA adducts, formed through the covalent binding of carcinogens (usually after metabolic activation to reactive electrophiles) to nucleic acids, are potential biological markers of exposure, internal and/or biologically effective dose, and cancer risk. Adduct levels are likely an integrated function of carcinogen exposure and polymorphisms in genes involved in carcinogen metabolism and DNA repair. DNA adduct formation, which may represent the initial stage of tumor induction, can lead to alterations in oncogenes and tumor suppressor genes and malignant cell transformation (17, 244–246). Numerous DNA adducts have been identified to date, several of which have been linked to compounds found in tobacco smoke, including, for example, BP (247), crotonaldehyde [a metabolite of *N*-nytrosopyrolidine (248)], acetaldehyde (248), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (249), *N'*-nitrosonornicotine (249), 1,3-butadiene, (250), 7-methylguanine (251), 4-aminobiphenyl (252), and several methylated anilines (253, 254). Nonetheless, it is important to note that the presence of DNA adducts is not sufficient for tumorigenesis (244, 255).

With regard to breast cancer, the formation of adducts from PAHs has been observed in human breast epithelial cells *in vitro* (256–259), and PAH-DNA adducts have been found in exfoliated ductal epithelial cells in human breast milk (260, 261). However, relatively few epidemiological studies have examined the association between smoking-specific DNA adducts and risk of the disease. Two case-control studies used the ^{32}P-postlabeling assay to compare levels of aromatic-DNA adducts in breast tumor tissue and adjacent nontumor tissue (cases) with levels in normal breast tissue from women seeking breast reduction surgery [controls (24, 262)]. The presence of the diagonal radioactive zone adduct pattern, which often has been linked to smoking (203, 263), was associated with cigarette smoking in both studies. A BP-like adduct spot also was identified in one study, but its presence was not associated with smoking (262). In both of these studies, greater levels of DNA adducts were detected in tissue samples from cases than in those from controls. Several methodological issues with these studies should be noted, however, including small sample sizes, the lack of adjustment for potentially confounding variables, the cross-sectional study design, and the fact that women seeking breast reduction surgery were not representative of the population that gave rise to the cases (28). Several other issues also can be raised, including the fact that the link between smoking and diagonal radioactive zone adduct patterns has not

been clearly established and that the method used to detect adducts (^{32}P postlabeling) is not specific to PAHs (255, 264).

Three subsequent studies used immunohistochemical analysis (265) to detect PAH-DNA adducts in breast tumor and nontumor tissue (26, 27, 264). A case-control study in Poland (264) found no clear evidence for increased PAH-DNA adduct levels among smokers or breast cancer patients compared with women with benign breast disease. A study in New Jersey that analyzed tissue samples from cases only (26) found statistically nonsignificant positive associations between PAH-DNA adducts and cigarette smoking duration, intensity, and pack-years and a nonsignificant inverse association with age at smoking commencement. The largest of these studies (27), a case-control study in New York City, found significantly elevated PAH-DNA adducts in tumor tissue from women with breast cancer compared with levels in tissue from women with benign breast disease, but adduct levels were not associated with smoking. Based on the finding that adduct levels were associated with the expression of ERs, the authors noted the possibility that variability in adduct levels caused by intra- and interindividual differences in hormone levels may have obscured associations with smoking and other exposure variables. Furthermore, when nontumor tissue from breast cancer patients was used instead of tumor tissue, the association with adduct levels (although still positive) was statistically nonsignificant. Regarding this, the authors noted the possibility that tumor and nontumor tissue may have important differences with respect to carcinogen metabolism; thus, to some extent, adducts may have formed after the initiation of tumorigenesis. In addition, the composition of the control group might have had an impact on the study results. Specifically, although controls with benign breast disease come to the clinic through the same referral system as the cases, this group is at higher risk of breast cancer than a control group of healthy women drawn from the source population, which could have led to the attenuation of observed associations (27). It also has been noted that immunohistochemical analysis does not quantify specific PAH-DNA adducts but rather measures them as a group (265, 266). Most recently, a large-scale population-based, case-control study from Long Island (111) used a competitive ELISA to detect PAH-DNA adducts in blood mononuclear cells taken from women with *in situ* and invasive breast cancer and from controls. In this study, the risk of breast cancer was increased approximately 50% among women with PAH-DNA adduct levels above that of women in the lowest quintile, but with no suggestion of a monotonic trend. Furthermore, mean adduct levels did not vary among controls according to qualitative smoking status (*e.g.,* current, former, passive, and never active or passive), which led the investigators to suggest that adduct levels may be better indicators of the body's response to the carcinogenic insult than indicators of exposure level (111). The ELISA assay, with a polyclonal antiserum recognizing BP and structurally related diolepoxide-DNA adducts (267), is more specific to PAH adducts than ^{32}P-postlabeling, but in this study adducts were measured in blood mononuclear cells and not in breast tissue (111). In general, DNA adduct levels may reflect relatively recent, but not long-term, exposure to environmental carcinogens; as noted above, long-term exposure to cigarette smoke may be more important with respect to breast cancer risk. Overall, the findings of studies to date do not show a consistent pattern of increased breast cancer risk with increased levels of PAH-DNA adducts, and the association of adducts with smoking has not been substantiated.

Mutations in the *p53* tumor suppressor gene, which are found in 15–30% of breast cancers (268), may be another biological marker of cancer risk that can be linked to smoking-specific carcinogens. More specifically, distinct patterns of p53 "mutation spectra" (transversions, transitions, deletions, and insertions) may be linked to certain carcinogen exposures. In the Carolina Breast Cancer Study (25), an increased prevalence and altered spectrum of *p53* mutations in breast tumors were observed among current smokers compared with never smokers; thus, smoking may be associated with genetic damage in breast epithelium. It is noteworthy that the breast tumors with the most pronounced smoking-related mutational pattern (for example, a greater number of G:C→T:A transversions) were from women who had smoked for more than 20 years, although total *p53* mutations were not associated with smoking duration. In another United States population-based case-control study (55), current cigarette smoking was associated with a statistically nonsignificant increased risk of breast cancers that were positive for p53 protein expression by immunohistochemistry, but not with cancers that were negative for p53 protein expression.

In summary, the association between cigarette smoking and breast cancer risk remains unclear. The results of epidemiological studies to date suggest that smoking does not decrease the risk in the majority of women. Recent findings of an increased risk with smoking of long duration, smoking before a first full-term pregnancy, and passive smoking require confirmation in future epidemiological studies, as do suggestions of increased risk among women with certain genotypes. In addition to epidemiological studies, investigations are needed to unravel the molecular mechanisms underlying any effect of cigarette smoking on breast cancer risk.

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