REPORTS

Effect of Smoking on Breast Cancer in Carriers of Mutant BRCA1 or BRCA2 Genes

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Background: **Smoking has carcinogenic effects, and possibly antiestrogenic effects as well, but it has not been found to be a risk factor for breast cancer in women in the general population. However, hereditary breast cancer is primarily a disease of premenopausal women, and interactions between genes and hormonal and environmental risk factors may be particularly important in this subgroup.** ***Methods:*** **We conducted a matched case–control study of breast cancer among women who have been identified to be carriers of a deleterious mutation in either the BRCA1 or the BRCA2 gene. These women were assessed for genetic risk at one of several genetic counseling programs for cancer in North America. Information about lifetime smoking history was derived from a questionnaire routinely administered to women who were found to carry a mutation in either gene. Smoking histories of case subjects with breast cancer and age-matched healthy control subjects were compared. Odds ratios for developing breast cancer were determined for smokers versus nonsmokers by use of conditional logistic regression for matched sets after adjustment for other known risk factors.** ***Results:*** **Subjects with BRCA1 or BRCA2 gene mutations and breast cancer were significantly more likely to have been nonsmokers than were subjects with mutations and without breast cancer (two-sided *P* = .007). In a multivariate analysis, subjects with BRCA1 or BRCA2 mutations who had smoked cigarettes for more than 4 pack-years (i.e., number of packs per day multiplied by the number of years of smoking) were found to have a lower breast cancer risk (odds ratio = 0.46, 95% confidence interval = 0.27–0.80; two-sided *P* = .006) than subjects with mutations who never smoked.** ***Conclusions:*** **This study raises the possibility that smoking reduces the risk of breast cancer in carriers of BRCA1 or BRCA2 gene mutations. [J Natl Cancer Inst 1998;90:761–6]**

Women who carry mutations in either the BRCA1 or the BRCA2 gene (carriers) have a very high lifetime risk of breast cancer. It has been estimated that the breast cancer risk associated with mutations in either gene exceeds 80% by the time a carrier reaches age 70 *(1,2)*, although some authors estimate the risk to be lower *(3)*. Some carriers will remain unaffected with breast or ovarian cancer throughout their lives. Factors that appear to influence the risk of breast cancer in carriers include parity *(4)* and the position of the mutation in the BRCA2 gene *(5)*. It has also been reported that the risk of cancer has increased in recent generations when compared with preceding generations *(4)*. The age-specific incidence of breast cancer in BRCA1 carriers peaks at about age 45 *(4)* in contrast to noncarriers, for whom the risk continues to rise after menopause. It is possible that this pattern of incidence is explained by an interaction between ovarian hormones and genetic predisposition.

There has been no consistent association observed between smoking and breast cancer risk in the general population *(6)*. However, because hereditary breast cancer has a unique incidence pattern, we speculated that an association between smoking and breast cancer may be found in carriers of BRCA1 and BRCA2 mutations. Cigarette smoke has been found to have antiestrogenic effects *(7)*, and smoking is associated with an early menopause *(7)*, with an increased risk of osteoporosis *(8)*, and with a decreased risk of endometrial cancer *(9)*. To address the possibility that smoking may modify the risk of hereditary breast cancer, we systematically collected information on lifestyle factors and reproductive histories

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See ''Notes'' following ''References.''

of affected and unaffected BRCA1 and BRCA2 carriers who attended our genetics clinics.

Subjects and Methods

Study Population

Eligible study subjects included women who were currently alive and were found to be carriers of BRCA1 and BRCA2 mutations. These women participated in clinical and research protocols at the genetic counseling centers of participating institutions. All study subjects received counseling and provided written informed consent for genetic testing. The study was approved by the institutional review boards of the host institutions. In most cases, testing was offered initially to women who had been affected with breast cancer or ovarian cancer. When a BRCA1 or BRCA2 mutation was identified in a proband or her relative, genetic testing was offered to other at-risk women in her family. Mutation detection was performed with the use of a range of techniques, but all nucleotide sequences were confirmed by direct sequencing of DNA. A subject was deemed eligible for the current study when the molecular analysis established that she was a mutation carrier. The great majority (>95%) of the mutations identified in the study subjects were either nonsense mutations, deletions, insertions, or small frameshifts.

Case subjects were selected from among the study subjects if they had a past diagnosis of invasive breast cancer; however, case subjects were excluded if a diagnosis of ovarian cancer preceded the breast cancer diagnosis. There was a total of 300 eligible case subjects in the pool. A single control subject was selected for each case subject, matched according to mutation in the same gene (BRCA1 or BRCA2) and to age within 1 year. Control subjects were women who never had breast cancer and who were known carriers of a mutation in the BRCA1 or BRCA2 gene. A control subject was excluded if she had a diagnosis of ovarian cancer prior to the year of diagnosis of the matched case subject. We were not able to find eligible control subjects for 114 of the case subjects, so those case subjects were excluded.

Case and control subjects were invited to participate in the study and to complete a questionnaire that asked for all relevant information regarding reproductive and medical histories as well as lifestyle factors. Women were asked if they had ever smoked cigarettes regularly, if they currently smoked, at what ages they started and stopped smoking, and the average number of cigarettes they smoked per week during the period of active smoking. To determine lifetime cigarette exposure, we multiplied the duration of smoking (in years) by the average number of cigarettes smoked per day to yield the number of pack-years for the period of active smoking. The estimate of packs smoked per week was based on the period of active smoking for smokers and was entered as zero for nonsmokers. For this study, we were interested in the smoking patterns of case subjects prior to their breast cancer diagnosis. Therefore, we considered only the cigarette smoking exposures (i.e., the number of pack-years of cigarette smoking) of case and control subjects that occurred prior to the year in which cancer was diagnosed in the case subject. Other exposure variables (parity, ages at first and last birth, age at menarche, weight at age 30, and tubal ligation) were censored in the same manner. The mean age at diagnosis of breast cancer for the case subjects was 39.6 years (standard error [SE] = 0.64 years). The mean current age was 49.7 years for both the case subjects and the control subjects.

Data Analysis

Smoking histories were compared between case subjects and control subjects. Because smoking histories were not normally distributed, a nonparametric analysis was chosen for this comparison. For the matched analysis, the Wilcoxon signed-pair test was used. For the comparison of smoking histories among the subgroup of case and control subjects who smoked, the Wilcoxon two-sample test was used. This choice was made because not all subjects smoked and it was, therefore, not possible to retain the matched analysis for the subgroup comparisons. All P values were calculated with the use of two-sided statistical tests.

The odds ratio (OR) for breast cancer associated with smoking was estimated by use of conditional logistic regression for matched sets. ORs were adjusted for reproductive variables (parity, age at first birth, and age at last birth) and geographic residence (Quebec or Canada excluding Quebec or the United States). The ORs for smoking and other risk factors were estimated first by univariate analysis and then by multivariate analysis, adjusting for the reproductive risk factors.

Results

Case and control subjects were similar with regard to age, mutation status, geographic residence, height, weight, and reproductive histories (Table 1).

Case subjects with breast cancer and a BRCA1 or BRCA2 mutation were significantly less likely to have smoked cigarettes at any time in their lives than control subjects (carriers) without breast cancer (Table 2). The mean number of cigarettes smoked per week was significantly greater for women without breast cancer (2.77 packs; SE = 0.29) than for women with breast cancer (1.88 packs; SE = 0.22) (P = .024). However, there was no significant difference in smoking duration between affected and unaffected carriers who smoked.

Because it is possible that the observed effect of smoking on breast cancer risk could be attributed to the effect of other covariates, a multivariate matched analysis was performed. Conditional logistic regression was performed, adjusting for reproductive variables. The effect of smoking was equally great in the adjusted analysis—the risk of breast cancer in smokers remained roughly one-half that of nonsmokers (Table 3). No other variable was as important as smoking in predicting breast cancer risk. The reduction in breast cancer incidence with smoking was significant for carriers of BRCA1 mutations who had smoked the equivalent of 4 or more pack-years (OR = 0.47; 95% confidence interval [CI] = 0.26–0.86). For BRCA2 carriers, the magnitude of the reduction was greater, but it was not significant, possibly because of the small sample size (OR = 0.39; 95% CI = 0.10–1.49).

The breast cancer protection associated with smoking increased with the number of pack-years. Based on multivariate analysis, the OR associated with up to 4 pack-years of smoking for carriers of mu-

Table 1. Comparison of case and control subjects

Variable	Case subjects (n = 186)	Control subjects (n = 186)
Mean age, y	49.73	49.71
Mutation		
BRCA1	76.9%	76.9%
BRCA2	23.1%	23.1%
Residence*		
United States	69.4%	63.4%
Quebec	10.2%	16.7%
Canada minus Quebec	20.4%	19.9%
Mean height, cm	163.5	163.6
Mean weight at age 30, kg	58.63	58.51
Mean age at menarche, y	12.70	12.80
Parity	2.16	2.10
Mean age at first birth, y	24.63	23.84
Mean age at last birth, y†	29.02	28.53

*Residence at the time of testing.

†Parity and age at last birth refer to the period prior to the age at which breast cancer was diagnosed in the case subjects and to the equivalent time period in the matched control subjects.

Table 2. Comparison of smoking histories in carriers of BRCA1 or BRCA2 gene mutations by history of breast cancer*

Variable	Case subjects (n = 186)	Control subjects (n = 186)	*P*
Ever smoked	38.7%	52.2%	.012†
Mean pack-years			
All subjects	4.51	6.14	.043‡
Smokers	11.64	11.78	.836§
Mean packs per week			
All subjects	1.88	2.77	.024‡
Smokers	4.87	5.31	.768§
Mean age started smoking, y	17.74	18.70	.723§
Mean age last smoked, y	33.00	33.57	.731§

*All information regarding the subjects' smoking histories refers to the period prior to the age at which breast cancer was diagnosed in the case subjects and to the equivalent time period in the matched control subjects.

†Two-sided *P* value was calculated with the use of Fisher's exact test.

‡Two-sided *P* values were calculated with the use of the Wilcoxon signed-pair test.

§Two-sided *P* values were calculated with the use of the Wilcoxon two-sample test.

tant BRCA1 or BRCA2 genes was 0.65 (95% CI = 0.36–1.17); for greater than 4 pack-years of smoking, the OR was 0.46 (95% CI = 0.27–0.80) (*P* for trend = .005) (Table 3).

The magnitude of this estimate and the significance of this result did not depend on the cutoff point used for pack-years of cigarette exposure. The result remained significant at the 5% level when smoking was categorized with the use of any cutoff point up to 10 pack-years. For example, the OR associated with more than 3 pack-years (versus nonsmoking) was 0.50 (95% CI = 0.30–0.84; *P* for trend = .009), and the OR for a cutoff point of more than 5 pack-years was 0.49 (95% CI = 0.28–0.85; *P* for trend = .011).

The smoking habits of the women varied according to birth year. Among smokers, cigarette consumption was maximal for women born between 1925 and 1944 (an average 12.83 pack-years before age 40). Women born before 1925 smoked an average 6.98 pack-years before age 40, and women born during the period of 1945 through 1954 smoked an average 11.51 pack-years before age 40. The mean number of pack-years was greater for control subjects than for case subjects among women born in all decades, with the exception of the 43 subjects born during the period of 1925 through 1934 (Fig. 1).

Discussion

Our data provide strong evidence of a protective effect of smoking against breast cancer in BRCA1 and BRCA2 mutation carriers. In light of the known antiestrogenic effects of smoking, this association is plausible *(7)*. The magnitude of the risk reduction was large, and the possibility that this finding was due to chance is remote. The risk reduction was greater for women with more than 4 pack-years of smoking than for women with less than or equal to 4 pack-years of smoking. In the majority of women, smoking patterns had been established by age 25, before the risk of breast cancer was appreciable. Smoking was the strongest predictor variable in the dataset, and adjusting for other covariates had a negligible effect on the magnitude of this association.

For practical reasons, we restricted our study to living carriers because of the difficulty in establishing mutation-carrier status for deceased individuals and we wanted to ensure that accurate smoking histories were obtained. Because we studied prevalent cases of breast cancer, it is possible that the observed effect of smoking relates to a decreased incidence of breast cancer among carriers, to a de-

Table 3. Odds ratios for breast cancer associated with selected factors in carriers of mutant BRCA1 or BRCA2 genes*

		Univariate analysis			Multivariate analysis		
Variable	Definition	OR (95% CI)	*P*	*P* for trend	OR (95% CI)	*P*	*P* for trend
Age at menarche, y	<12	1.0 (referent)	—		—	—	
	⩾12	0.79 (0.47–1.32)	.363		—	—	
Parity	Continuous	1.04 (0.89–1.20)	.651		0.92 (0.77–1.11)	.385	
Age at first birth, y	Continuous	1.05 (0.99–1.10)	.102		1.03 (1.00–1.06)	.053	
Age at last birth, y	Continuous	1.02 (0.98–1.07)	.338		—	—	
Height, cm	<168	1.0 (referent)	—		—	—	
	⩾168	1.17 (0.71–1.92)	.529		—	—	
Weight at age 30, kg	<60	1.0 (referent)	—		—	—	
	⩾60	0.95 (0.51–1.78)	.873		—	—	
Ever smoked	Never	1.0 (referent)	—		1.0 (referent)	—	
	Ever	0.57 (0.37–0.87)	.010		0.54 (0.34–0.84)	.007	
Packs per week	0	1.0 (referent)	—	.009	1.0 (referent)	—	.005
	>0; <5	0.63 (0.38–1.06)	.081		0.61 (0.36–1.06)	.079	
	⩾5	0.51 (0.30–0.87)	.013		0.46 (0.26–0.81)	.008	
Pack-years	0	1.0 (referent)	—	.007	1.0 (referent)	—	.005
	>0; ⩽4	0.67 (0.38–1.20)	.177		0.65 (0.36–1.17)	.152	
	>4	0.51 (0.31–0.85)	.009		0.46 (0.27–0.80)	.006	

*OR = odds ratio; CI = confidence interval. In multivariate model, we also adjusted for residence. Only one smoking variable at a time was introduced in the multivariate model. The *P* values for trend are defined as a discrete scaling of the categorical definition. All *P* values are two-sided and were calculated with the use of the conditional logistic regression model.

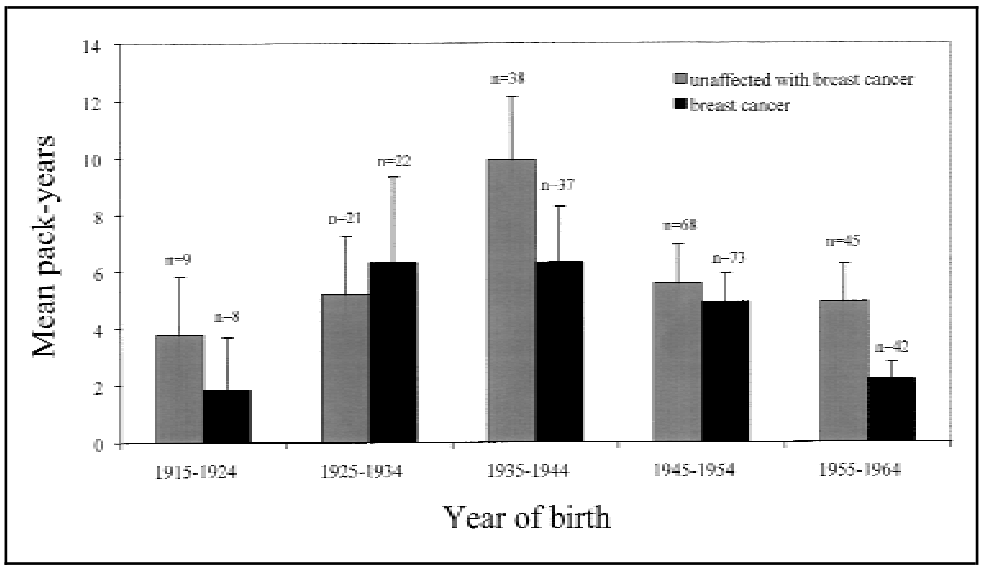

Fig. 1. Pack-years of smoking by decade of birth of the study subjects; this information refers to the period prior to the age at which breast cancer was diagnosed in the case subjects and to the equivalent time period in the matched control subjects. Error bars represent the standard error of the mean.

creased survival of women with breast cancer associated with smoking, or to a combination of both. Calle et al. *(10)* found an excess of breast cancer mortality among case subjects who currently smoked compared with nonsmoking case subjects. For smokers of greater than 40 cigarettes per day, the increase in mortality was statistically significant (relative risk = 1.74, 95% CI = 1.15–2.62). However, the majority of carriers in our study smoked much less than this, and most did not smoke after the breast cancer was diagnosed; of the 186 case subjects with breast cancer, 114 never smoked, 48 stopped smoking before their diagnosis, four quit within 2 years of diagnosis, and 20 continued to smoke thereafter. The diagnosis of breast cancer may have prompted women to quit smoking. This would lead to a shorter duration of smoking on average for breast cancer case subjects than for control subjects. However, we considered only the cigarette exposure (for both case and control subjects) prior to the age when breast cancer was diagnosed in the case subjects. Furthermore, there was no difference in the average age at smoking cessation between case and control subjects. Of the women with cancer who smoked, all had begun smoking more than 5 years before their breast cancer was diagnosed. Smokers may also be less likely to go for regular mammograms than nonsmokers *(11)*, but this has not been studied in younger women who are carriers of BRCA1 or BRCA2 mutations.

Ideally, we would like to have studied a sample of carriers, independent of both disease status or vital status. This was not feasible because we excluded deceased carriers and we included only women who wished to have their mutation status determined. Once a BRCA1 or BRCA2 mutation was found in a family, female relatives unaffected by breast cancer were offered testing. If unaffected women who smoke are more likely to accept genetic testing than nonsmokers, then a spurious protective association between smoking and breast cancer may be generated. It is unlikely that women who smoke would be overrepresented among the control subjects because, in a previous study *(12)*, the willingness of women to undergo genetic testing was positively associated with socioeconomic factors, including education beyond high school, current employment and access to health insurance. These factors tend to be inversely related to cigarette use. If, in fact, women who smoke are less likely to request genetic testing than nonsmokers, then we will have underestimated the protective effect of smoking on breast cancer incidence.

Smoking has not been found to be a consistent risk factor for breast cancer in the general population. For example, in a recent study of 6888 breast cancer case subjects and 9529 population-based control subjects *(6)*, current smoking was the same for both case and control subjects (relative risk = 1.00; 95% CI = 0.92–1.09). The authors of that study proposed that there may be opposing carcinogenic and antiestrogenic effects associated with smoking. In support of this hypothesis, Ambrosone et al. *(13)* found that smoking was a risk factor for postmenopausal breast cancer among those with the slow-acetylator phenotype of the *N*-acetyltransferase 2 polymorphism and was protective for rapid acetylators; they suggested that tobacco carcinogens may be a risk factor among the subgroup of slow acetylators.

The reduction in breast cancer risk in carriers of BRCA1 and BRCA2 mutations may be associated with reduced levels of circulating estrogens. Smoking has been associated with an earlier menopause *(7)* and an increased risk of osteoporosis *(8)*. Postmenopausal women with decreased bone density are at decreased risk of breast cancer *(14)*. Smokers are also at a decreased risk of endometrial cancer, another hormone-dependent cancer *(9)*. MacMahon et al. *(15)* found a decreased level of urinary estrogens among smokers, but this finding has not been confirmed in other studies *(16,17)*. Berta et al. *(17)* found no differences in the levels of serum or urinary estrogens in smokers and nonsmokers in a large cross-sectional study. It has been hypothesized *(18)* that the antiestrogenic effect of smoking is related to the increased hepatic metabolism of estrogens by levels of estradiol 2–hydroxylation. Michnovicz et al. *(18)* found that the level of estradiol 2-hydroxylation was increased by approximately 50% in premenopausal women who smoked 15 or more cigarettes per day. Increased activity of this enzyme results in a greater conversion of estrogens to 2-hydroxyestrogens, which are less potent and which are rapidly cleared *(18)*. Michnovicz et al. *(18)* also found a significantly lower ratio of estradiol to estrone in the urine of smokers. In two small case–control studies *(19,20)*, the ratio of 2-hydroxyestrone to 16α-hydroxyestrone was found to be lower in postmenopausal women with breast cancer than in age-matched control subjects. Because decreased estrogen levels have been measured in postmenopausal smokers receiving estrogen replacement therapy, compared with nonsmokers receiving estrogen replacement therapy

(21), it is likely that the effect is due to the increased metabolism of estrogens in smokers, rather than to their reduced production. It is likely that this increased metabolism is related to hepatic induction of the cytochrome P450 enzymes by some component of cigarette smoke.

Other mechanisms, however, are possible. Birth weight has been found to be a predictor of breast cancer *(22),* and this association has been proposed to be related to insulin and insulin-like growth factor-1 (IGF-1) levels *(23).* In our study, height was a risk factor in the univariate analysis, and the average height of the members of the cohort is increasing with year of birth. The mean height of women born before 1945 was 161.5 cm compared with a mean height of 163.9 cm for women born during the period of 1945 through 1955 and 166.2 cm for women born after 1955 ($P = .0001$). A correlation was observed between height and serum IGF-1 levels in 1030 healthy subjects *(24).* IGF-1 levels are potent breast mitogens and appear to be lower in smokers than in nonsmokers *(25).* IGF-1 levels have been reported to be higher in women with breast cancer than in healthy control subjects *(26)* and recently, in a large prospective study, serum IGF-1 levels were positively and significantly correlated with breast cancer risk *(27).*

We have found statistically significant reductions in risk associated with smoking in both BRCA1 and BRCA2 carriers. The lifetime risk of breast cancer is similar in carriers of mutations of either type. Our data do not permit us to distinguish between the size of the effect in the two subgroups. Further data clarifying the magnitude of the risk ratios in the two groups and their interactions are needed. If the relationship between smoking and breast cancer risk is modulated by estrogen levels, then exogenous estrogen in the form of hormone replacement therapy might be a risk factor for breast cancer in BRCA1 and BRCA2 carriers. We believe that the risk of hormone replacement therapy in BRCA1 and BRCA2 carriers might be different from the risk in noncarriers, and these women therefore deserve specific studies. Studies of the risk of breast cancer following prophylactic oophorectomy, with and without hormone replacement therapy, are now under way. Identification of the exact agents and pathways involved in this relationship could allow us to develop novel strategies for reducing the risk of breast cancers associated with BRCA1 and BRCA2.

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