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Cigarette Smoking and Risk of Breast Cancer: a Prospective Study of 24 329 Norwegian Women

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The association between cigarette smoking and incidence of breast cancer has been analyzed in 242 cases of breast cancer that developed among 24 329 Norwegian women over 11–14 years of follow-up. At baseline they were aged 35–51. There was no overall association between cigarette smoking and the risk of breast cancer. The age-adjusted incidence rate ratio (IRR) was unity (IRR=1.04, 95% CI 0.76–1.42) for regular smokers (10 or more cigarettes daily) compared with non-smoking women. In women who reported smoking between 1 and 9 cigarettes per day there was an age-adjusted IRR of 1.28 (95% CI 0.95–1.73). The lack of association with cigarette smoking was replicated in subgroup analyses of women diagnosed before age 51 ("premenopausal") and among women diagnosed after this age ("postmenopausal"). However, there was a significant interaction between cigarette smoking, body mass index and age at diagnosis ($P = 0.01$), which might indicate that an interaction between cigarette smoking and body mass exerts differential effects on breast cancer risk in premenopausal and postmenopausal women.
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INTRODUCTION

THE HYPOTHESIS that cigarette smoking may reduce the risk of breast cancer [1–3], possibly due to an anti-oestrogenic effect, has not been confirmed in most epidemiological studies. One cohort study [4] showed a decreased risk in smokers, whereas another [5] yielded opposite results. Some case-control studies have also demonstrated a reduced risk [6, 7] of breast cancer in smokers, but most studies show no effect [8–15].

Although the overall association between smoking cigarettes and breast cancer incidence may approximate unity, characteristics within subgroups may modify the effect. Overweight may be inversely related to breast cancer risk among premenopausal women [16–18], in contrast to the positive association with body mass among postmenopausal women [19]. A relation with oestrogen (and possibly progestagen) metabolism has been suggested [20]. Combined with the evidence that cigarette smoking affects the metabolism of oestradiol [3], an interaction effect on breast cancer risk may exist between cigarette smoking and body mass. Such an interaction should also depend on menopausal status.

In this prospective study we explored the overall relation between cigarette smoking and risk of breast cancer. We then examined whether the effect of smoking might vary between women diagnosed before age 51 ("premenopausal") compared with women diagnosed after this age ("postmenopausal"), before we tested the possible interaction between cigarette smoking, age at diagnosis and body mass index (BMI) in relation to the risk of developing breast cancer.

METHODS

The cohort

Between 1974 and 1978 all men and women aged 35–51 and living in three separate counties in Norway were invited to participate in a health screen organized by the National Health Screening Service. The screen included a questionnaire, and standardized measurements of height, weight and blood pressure [21, 22].

26 252 women were invited; 24 617 (93.8%) attended. To reduce a potential bias due to preclinical changes in smoking habits, all cancer cases (including breast cancer) that had

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occurred before or during the calendar year of examination were excluded. 288 women were thus excluded, giving 24 329 eligible for analysis.

The questionnaire

The questionnaire was primarily designed to obtain information on known and suspected risk factors for cardiovascular disease. For this reason there was a lack of information on factors that are known to predict risk of breast cancer, such as age at menarche, age at first full-term pregnancy, breast cancer in relatives and information on exact age at menopause.

However, the questionnaire did include detailed history of past and current smoking habits and demographic variables. One question asked whether the respondent was a housewife or worked outside the home. Since this factor was associated with cigarette smoking and to some extent might account for differences in reproductive history, it was included as a potentially confounding factor. Ascertainment of cigarette smoking was based on the subjects' answers about the number of cigarettes they presently smoked per day, whether they had previously been daily smokers and the number of years during which they had smoked daily. We report exposure to cigarettes as the number of cigarettes smoked per day at the time of screening. Analysis of the effect of smoking based on duration (in years) of smoking yielded approximately identical results.

Identification of cases

Each participant had an eleven-digit number which facilitated linkage to the Cancer Registry of Norway. This made it possible to identify every incident case of breast cancer that occurred in the cohort from the time of examination till the end of follow-up (1 October 1988). The reporting of malignant diseases to the registry is mandatory, and the registry has a reliable and nearly complete registration of incident cases of breast cancer [23].

242 incident cases occurred in the cohort over 11–14 (mean 12) years of follow-up. Among these, 139 occurred in women younger than 51 and 103 in women aged 51 or older.

The age of 51 may serve as a rough divide between breast cancer occurring among premenopausal and postmenopausal women. This cut-off may reassure that most cases in the younger group (even smokers) were truly premenopausal at diagnosis. A dividing line at a later age would include an increasing number of postmenopausal women, which might have diluted typically premenopausal effects.

Statistical analyses

The number of cigarettes currently smoked per day was divided into three categories: none, 1–9, and 10 or more. Observation-years at risk of developing breast cancer before the age of 51 were computed as the number of years accumulated from the screening examination until withdrawal in the year of diagnosis, at the age of 51, at death from a cause other than breast cancer or at the end of follow-up. Conversely, observation-years at risk of developing breast cancer at the age of 51 or later were computed from the time a person reached the age of 51 until withdrawal. This procedure allowed comparison of incidence rates of breast cancer based on person-time for each category of smoking status, distinguishing diagnoses made before or after the age of 51.

Incidence rate ratios (IRR) were computed as the rate in a specific category of smoking status divided by the estimated rate in the reference group of non-smokers. The precision of the IRR was assessed by 95% confidence intervals by Miettinen's test-based method with Mantel-Haenszel's χ^2 statistics [24]. Adjustments for the effect of 5-year age categories of person-years and for potentially confounding variables in the stratified analyses were done by the Mantel-Haenszel method [25].

Interaction was tested for by fitting the cumulative incidence data of non-smokers and women who smoked 10 or more cigarettes per day to a multiple logistic model [24]. In the model we included the following covariables: age at entry (three categories), age at diagnosis (two categories), occupational status (two categories: housewife vs. not housewife) and body mass index (four categories: population quartiles). In addition we included two-way interaction terms between cigarette smoking and each covariable, and to evaluate interaction between cigarette smoking, age at diagnosis and BMI, we included this three-way product term in the logistic model. We did a backwards stepwise procedure according to a "hierarchy" strategy [24].

To illustrate the effect of interaction between cigarette smoking and BMI within the two surrogate categories of menopausal status, IRRs associated with cigarette smoking were specifically examined in two separate strata of BMI by applying Quetelet's index (weight in kg divided by the squared value of body height in metres) [26]. Thus the relation with smoking was examined in lean (Quetelet index below 24) and more obese women (24 or above) among cases diagnosed before age 51 and among those diagnosed later.

RESULTS

In this cohort there was a greater proportion of daily cigarette smokers among the younger women (Table 1) and after adjustment for age, daily smokers were leaner than non-smoking women, whereas no association was observed between smoking status and body height. For the risk of developing breast cancer there was an overall inverse relation with BMI, which was confined to women diagnosed before the age of 51 [18]. The age-adjusted IRRs ranging from the lowest (mean Quetelet 21) to the highest (mean Quetelet 30) quartile of BMI were 1.0, 0.91, 0.65 and 0.36 respectively (χ^2 trend = 14.22, $P < 0.001$) for cases younger than 51 years. Moreover, there was a positive association between body height and the risk of breast cancer in this population [27]. The overall age-adjusted IRRs of women from the lowest (mean = 155 cm) to the highest (mean = 170 cm) quartile of height were 1.0, 1.46, 1.91 and 2.03, respectively (χ^2 trend = 13.50, $P < 0.001$).

There was no overall relation between smoking 10 or more cigarettes per day and the age-adjusted incidence rate of breast cancer (Table 2) and further adjustment for potentially confounding variables did not alter this result. There was a similar

Table 1. Percentage of women within categories of smoking status, according to age, body mass index (BMI) and body height

		Cigarettes per day	
Age (at entry)	Non-smokers	1–9	≥ 10
35–39 (n = 7660)	47	24	29
40–44 (n = 7702)	50	23	27
45–51 (n = 8967)	54	24	22
BMI < 24*	46	53	57
Height ≥ 163 cm	50	49	52

*Percentages of BMI and body height have been age-adjusted by direct method [23]. BMI = Quetelet's index (weight in kg divided by squared value of height).

lack of association with cigarette smoking both among women diagnosed before age 51 and in cases diagnosed after this age. Moderate smokers diagnosed before age 51 (1–9 cigarettes per day) had an increased risk compared with non-smoking women, but this association disappeared after adjustment for other potentially confounding factors.

To assess possible interaction between cigarette smoking, age at diagnosis and BMI on breast cancer risk, we fitted the cumulative incidence data of non-smokers and women who reported smoking 10 or more cigarettes per day to a multiple logistic model. Table 3 shows the final model: there was a significant three-way interaction between cigarette smoking, age at diagnosis and BMI.

To illustrate the possible effect of this interaction on breast cancer risk we examined the relation with cigarette smoking among lean (Quetelet below 24) and more obese (Quetelet 24 or higher) women separately for cases diagnosed before or at the age of 51 or later (Table 4). Among lean women diagnosed before age 51, smoking 10 or more cigarettes per day was associated with a decreased risk of breast cancer, in contrast to an increased risk among more obese women. For women diagnosed at age 51 or later, the risk pattern was different. In lean women, cigarette smoking was positively associated with breast cancer risk, whereas no association with smoking was observed among more obese women.

*Table 2. Age-adjusted IRR (95% CI) of breast cancer according to levels of daily cigarette smoking**

Age (at entry)	No. of cigarettes: None	1–9	≥ 10
All cases			
35–39			
Cases	31	15	22
Person-years	43 705	22 273	27 026
40–44			
Cases	37	25	16
Person-years	46 620	21 140	23 968
45–51			
Cases	47	28	21
Person-years	56 522	24 804	22 480
Total			
Cases	115	68	59
Person-years	146 847	68 217	73 474‡
Age-adjusted IRR	1.0	1.28 (0.95–1.73)	1.04 (0.76–1.42)
Multivariate IRR†	1.0	1.23 (0.91–1.66)	0.86 (0.62–1.19)
Cases < 51 years			
Cases	62	43	34
Person-years	93 731	44 898	51 018§
Age-adjusted IRR	1.0	1.45 (0.99–2.13)	0.99 (0.65–1.50)
Multivariate IRR	1.0	1.11 (0.73–1.67)	0.79 (0.51–1.23)
Cases ≥ 51 years			
Cases	53	25	25
Person-years	53 091	23 646	22 988 ‖
Age-adjusted IRR	1.0	1.06 (0.66–1.71)	1.09 (0.67–1.76)
Multivariate IRR	1.0	1.02 (0.63–1.66)	0.79 (0.46–1.33)

*Based on 242 incident cases of breast cancer that occurred during 11–14 years of follow-up among 24 329 women aged 35–51 years in year of examination.
†Adjusted for age at entry (3 categories), age at diagnosis (2 categories), occupational status (2 categories) and BMI (4 categories).
Test for trend: ‡$\chi^2 = 0.29$, $P = 0.59$; §$\chi^2 = 0.10$, $P = 0.75$; ‖$\chi^2 = 0.14$, $P = 0.71$.

Table 3. Multiple logistic regression of relation between cigarette smoking (non-smokers vs smokers ≥ 10 cigarettes per day) and cumulative incidence of breast cancer, adjusting for other covariables

Variable	DF	χ^2	P
Smoking	1	0.23	0.63
Age at entry	2	23.36	<0.0001
Age at diagnosis	1	437.77	<0.0001
Occupational status	1	8.49	0.004
BMI	3	6.13	0.11
Smoking × age at diagnosis × BMI*	3	11.23	0.01

*Interaction term.
DF = degrees of freedom.

DISCUSSION

In this study there was no overall association between cigarette smoking and risk of breast cancer, and this also applied to breast cancer diagnosed both before and at the age of 51 or later. Further adjustment for potentially confounding factors (occupation, BMI) did not alter the results, which accord with most prospective studies, although some reports about this relation have yielded opposite results [1]. However, the association with smoking has typically been weak, and only occasionally has the proposed hypothesis of a reduction in breast cancer risk due to smoking been confirmed in a statistically significant manner [6]. Despite the lack of any direct association with

Table 4. Age-adjusted IRR (95% CI) of breast cancer in non-smoking and regularly smoking cases of breast cancer

	No. of cigarettes: None	≥ 10
Cases < 51 years		
BMI < 24 (mean = 22)		
Age-adjusted IRR	1.0	0.7 (0.4–1.3)
BMI ≥ 24 (mean = 28)		
Age-adjusted IRR	1.0	1.6 (0.9–3.0)
Cases ≥ 51 years		
BMI < 24 (mean = 22)		
Age-adjusted IRR	1.0	1.6 (0.9–3.0)
BMI ≥ 24 (mean = 28)		
Age-adjusted IRR	1.0	0.9 (0.4–1.8)

Interaction between cigarette smoking (non-smokers vs. smokers), age at diagnosis (< 51 and ≥ 51) and BMI (population quartiles): $\chi^2 = 11.23$, DF, $P = 0.01$.

cigarette smoking in our study, there was a significant interaction between cigarette smoking, age at diagnosis and BMI.

Because of the prospective nature of our study we would not expect any major bias from selection of subjects or misclassification of information. About 94% of the total eligible women living in the three counties at the time of examination were included, and both completeness and the large number of participants, matched with standardized measurements by trained personnel from the National Health Screening Service, are reassuring factors.

A limitation of our study is the lack of information on factors that are known to affect the risk of breast cancer. Apart from being independent risk factors for the disease in the absence of the exposure under study, potentially confounding variables should be associated with the exposure [25]. Consequently cigarette smoking should be associated with variables, such as age at menarche, age at first full-term pregnancy [28] and age at menopause, for confounding from these factors to be anticipated in the data [29, 30]. Occupation (housewife vs. not housewife) was associated with cigarette smoking and might to some degree account for differences in parity. However, adjusting for this factor had only minor influence on the estimates of effect. A lower fecundity in regularly smoking women may implicate both a later age at first full-term pregnancy and a lower total parity than in non-smokers. In addition, smoking may be the most important cause for natural menopause to occur on average 1–2 years earlier in smoking than in non-smoking women [30]. The net effect of such contradictory relations with smoking on known risk factors for breast cancer cannot be easily predicted, but a potentially confounding effect on the results of this study should not be excluded.

Furthermore, a greater proportion of regularly smoking breast cancer cases diagnosed before age 51 will be postmenopausal at the time of diagnosis, and analogously, a greater proportion of non-smoking cases diagnosed at the age of 51 or later will be premenopausal at this time. For both strata, however, one would expect that the smoking effect on menopausal timing in lean (Quetelet below 24) and more obese (Quetelet 24 or higher) women would be approximately similar; and thus, the interaction between cigarette smoking, age at diagnosis and BMI may not be seriously complicated by this effect.

Evaluating a possible interaction between cigarette smoking and body mass should distinguish between premenopausal and postmenopausal breast cancer, since body mass appears to have opposite effects on the risk depending on menopausal status [16–19]. There was strong evidence for an interaction in our study, and its possible effects (Table 4) show a need to resolve the underlying biological mechanisms.

Thus we have confirmed the lack of any overall association (positive or negative) between cigarette smoking and breast cancer risk that has been reported in most studies. In our study, however, we did find an interaction between cigarette smoking, age at diagnosis and BMI, which indicates that body size may modify the relation between cigarette smoking and risk of breast cancer.

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