Primary research

Smoking and high-risk mammographic parenchymal patterns: a case–control study

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Statement of findings

Current smoking was strongly and inversely associated with high-risk patterns, after adjustment for concomitant risk factors. Relative to never smokers, current smokers were significantly less likely to have a high-risk pattern. Similar results were obtained when the analysis was confined to postmenopausal women. Past smoking was not related to the mammographic parenchymal patterns. The overall effect in postmenopausal women lost its significance when adjusted for other risk factors for P2/DY patterns that were found to be significant in the present study, although the results are still strongly suggestive. The present data indicate that adjustment for current smoking status is important when evaluating the relationship between mammographic parenchymal pattern and breast cancer risk. They also indicate that smoking is a prominent potential confounder when analyzing effects of other risk factors such as obesity-related variables. It appears that parenchymal patterns may act as an informative biomarker of the effect of cigarette smoking on breast cancer risk.

Keywords: mammography, screening, smoking, Wolfe's parenchymal patterns

Abstract

Introduction: Overall, epidemiological studies [1–4] have reported no substantial association between cigarette smoking and the risk of breast cancer. Some studies [5–7] reported a significant increase of breast cancer risk among smokers. In recent studies that addressed the association between breast cancer and cigarette smoking, however, there was some suggestion of a decreased risk [8–10], especially among current smokers, ranging from approximately 10 to 30% [9,10]. Brunet *et al* [11] reported that smoking might reduce the risk of breast cancer by 44% in carriers of *BRCA1* or *BRCA2* gene mutations. Wolfe [12] described four different mammographic patterns created by variations in the relative amounts of fat, epithelial and connective tissue in the breast, designated N1, P1, P2 and DY. Women with either P2 or DY pattern are considered at greater risk for breast cancer than those with N1 or P1 pattern [12–15]. There are no published studies that assessed the relationship between smoking and mammographic parenchymal patterns.

Aims: To evaluate whether mammographic parenchymal patterns as classified by Wolfe, which have been positively associated with breast cancer risk, are affected by smoking. In this case–control study, nested within the European Prospective Investigation on Cancer in Norfolk (EPIC-Norfolk) cohort [16], the association between smoking habits and mammographic parenchymal patterns are examined. The full results will be published elsewhere.

Methods: Study subjects were members of the EPIC cohort in Norwich who also attended the prevalence screening round at the Norwich Breast Screening Centre between November

CI = confidence interval; EPIC = European Prospective Investigation on Cancer; OR = odds ratio.

1989 and December 1997, and were free of breast cancer at that screening. Cases were defined as women with a P2/DY Wolfe's mammographic parenchymal pattern on the prevalence screen mammograms. A total of 203 women with P2/DY patterns were identified as cases and were individually matched by date of birth (within 1 year) and date of prevalence screening (within 3 months) with 203 women with N1/P1 patterns who served as control individuals.

Two views, the mediolateral and craniocaudal mammograms, of both breasts were independently reviewed by two of the authors (ES and RW) to determine the Wolfe mammographic parenchymal pattern.

Considerable information on health and lifestyle factors was available from the EPIC Health and Lifestyle Questionnaire [16]. In the present study we examined the subjects' personal history of benign breast diseases, menstrual and reproductive factors, oral contraception and hormone replacement therapy, smoking, and anthropometric information such as body mass index and waist:hip ratio.

Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated by conditional logistic regression [17], and were adjusted for possible confounding factors.

Results: The characteristics of the cases and controls are presented in Table 1. Cases were leaner than controls. A larger percentage of cases were nulliparous, premenopausal, current hormone replacement therapy users, had a personal history of benign breast diseases, and had had a hysterectomy. A larger proportion of controls had more than three births and were current smokers.

Table 2 shows the unadjusted and adjusted OR estimates for Wolfe's high-risk mammographic parenchymal patterns and smoking in the total study population and in postmenopausal women separately. Current smoking was strongly and inversely associated with high-risk patterns, after adjustment for concomitant risk factors. Relative to never smokers, current smokers were significantly less likely to have a high-risk pattern (OR 0.37, 95% CI 0.14–0.94). Similar results were obtained when the analysis was confined to postmenopausal women. Past smoking was not related to mammographic parenchymal patterns. The overall effect in postmenopausal women lost its significance when adjusted for other risk factors for P2/DY patterns that were found to be significant in the present study, although the results were still strongly suggestive. There was no interaction between cigarette smoking and body mass index.

Table 1

Characteristics of the study population

Characteristics	Cases (P2+DY; *n* = 203)	Controls (N1+P1; *n* = 203)
Mean age (years)	59.3	59.3
Mean body mass index	25.2	27.4
Mean waist:hip ratio	2.1	2.4
Menopausal status (*n*)		
Premenopausal	44	24
Postmenopausal	148	165
Unknown	11	14
Mean age at menarche (years)	13.0	12.7
Mean age at menopause (years)	47.7	47.0
Number of children (*n*)		
0	31	16
1	27	26
2	96	82
3	34	47
4+	15	29
Unknown	–	3
History of benign breast diseases (*n*)		
No	188	198
Yes	15	5
Hysterectomy (*n*)		
No	141	152
Yes	60	49
Unknown	2	2
HRT use (*n*)		
Never	106	131
Past	22	25
Current	73	43
Unknown	2	4
Smoking (*n*)		
Never	121	120
Past	62	53
Current	20	30

HRT, hormone replacement therapy.

Discussion: In the present study we found a strong inverse relationship between current smoking and high-risk mammographic parenchymal patterns of breast tissue as classified by Wolfe [12]. These findings are not completely unprecedented; Greendale *et al* [18] found a reduced risk of breast density in association with smoking, although the magnitude of the reduction was unclear. The present findings suggest that this reduction is large.

Recent studies [9,10] have suggested that breast cancer risk may be reduced among current smokers. In a multicentre Italian case–control study, Braga *et al* [10] found that, relative to nonsmokers, current smokers had a reduced risk of breast cancer (OR 0.84, 95% CI 0.7–1.0). These findings were recently supported by Gammon *et al* [9], who reported that breast cancer risk in younger women (younger than 45 years) may be reduced among current smokers who began smoking at an early age (OR 0.59, 95% CI 0.41–0.85 for age 15 years or younger) and among long-term smokers (OR 0.70, 95% CI 0.52–0.94 for those who had smoked for 21 years or more).

The possible protective effect of smoking might be due to its anti-oestrogenic effect [1,2,19]. Recently there has been renewed interest in the potential effect of smoking on breast cancer risk, and whether individuals may respond differently on the basis of differences in metabolism of bioproducts of smoking [20,21]. Different relationships between smoking and breast cancer risk have been suggested that are dependent on the rapid or slow status of acetylators of aromatic amines [20,21]. More recent studies [22,23], however, do not support these findings.

Table 2

Odds ratio estimates for high-risk mammographic patterns according to smoking status

Smoking status	Cases (P2+DY)	Controls (N1+P1)	OR	95% CI	OR*	95% CI*
All women (*n*)						
Never	121	120	1.00	–	1.00	–
Past	62	53	1.18	0.73–1.90	1.02	0.55–1.90
Current	20	30	0.65	0.34–1.24	0.37	0.14–0.94
Postmenopausal women (*n*)						
Never	89	91	1.00	–	1.00	–
Past	45	46	0.99	0.54–1.82	1.27	0.60–2.67
Current	14	28	0.37	0.15–0.90	0.39	0.13–1.11

*Adjusted for menopausal status, parity, hormone replacement therapy, history of benign breast diseases, body mass index and waist:hip ratio in the whole study population; adjusted for parity, hysterectomy, body mass index, and waist:hip ratio in postmenopausal women. OR, odds ratio; CI, confidence interval.

The present study design minimized the opportunity for bias to influence the findings. Because subjects were unaware of their own case–control status, the possibility of recall bias in reporting smoking status was minimized. Systematic error in the assessment of mammograms was avoided because reading was done without knowledge of the risk factor data. Furthermore, the associations observed are unlikely to be explained by the confounding effect of other known breast cancer risk factors, because we adjusted for these in the analysis. We did not have information on passive smoking status, however, which has recently been reported to be a possible confounder [5,6,21,24].

The present data indicate that adjustment for current smoking status is important when evaluating the relationship between mammographic parenchymal pattern and breast cancer risk. They also indicate smoking as a prominent potential confounder when analyzing effects of other risk factors such as obesity-related variables. It seems that parenchymal patterns may act as an informative biomarker of the effect of cigarette smoking on breast cancer risk.

Full article

Introduction

Overall, epidemiological studies [1–4] have reported no substantial association between cigarette smoking and the risk of breast cancer. Some studies [5–7] reported a significant increase of breast cancer risk among smokers. It has been suggested [5,6,21,24] that passive exposure to cigarette smoking may alter prior associations seen when only active smoking was assessed, with increased risk being observed for passive smoking exposure. Furthermore, there is a possibility of heterogeneity in the response to the carcinogenic effect of smoking, which might explain inconsistent findings for cigarette smoking as a risk factor for breast cancer [20].

In recent studies that addressed the association between breast cancer and cigarette smoking, however, there was some suggestion of a decreased risk [8–10], especially among current smokers, ranging from approximately 10 to 30% [9,10]. Brunet *et al* [11] reported that smoking might reduce the risk of breast cancer by 44% in carriers of *BRCA1* or *BRCA2* gene mutations.

Wolfe [21] described four different mammographic patterns that are created by variations in the relative amounts of fat, epithelial and connective tissue in the breast, designated N1, P1, P2 and DY. Women with either P2 or DY patterns are considered to be at greater risk for breast cancer than those with N1 or P1 pattern [12–15].

There are no published studies that assessed the relationship between smoking and mammographic parenchymal patterns.

The aim of the present study was to evaluate whether mammographic parenchymal patterns as classified by Wolfe [12], which have been positively associated with breast cancer risk, are affected by smoking. In the present case–control study, nested within the European Prospective Investigation on Cancer in Norfolk (EPIC-Norfolk) cohort [16], the association between smoking habits and mammographic parenchymal patterns are examined. The full results will be published elsewhere.

Materials and methods

Study subjects were members of the EPIC cohort in Norwich [16], who also attended the prevalence screening round at the Norwich Breast Screening Centre between November 1989 and December 1997 and were free of breast cancer at that screening. A case–control study was designed within this cohort.

Cases were defined as women with a P2/DY Wolfe's mammographic parenchymal pattern on the prevalence

screen mammogram. Assuming a 2.5-fold increase in risk of P2/DY mammographic patterns from the lowest quintile of a quantitative factor to the highest, 200 cases and 200 controls will yield a power of approximately 90%. A total of 203 women with P2/DY patterns were identified as cases and were individually matched by date of birth (within 1 year) and date of prevalence screening (within 3 months) to 203 women with N1/P1 patterns who served as controls. Additional information regarding case selection is presented elsewhere [25].

We examined the screening records of each woman. Mammograms of both breasts were collected. Two views, the mediolateral and craniocaudal mammograms, of both breasts were independently reviewed by two of the authors (ES and RW) to determine the Wolfe mammographic parenchymal pattern. The inter-reader agreement in the classification of mammographic parenchymal patterns was 95% on the four pattern categories, and 99% when the P2 and DY categories were combined, but for the purposes of the present study we used only the films in which we agreed on the patterns.

Considerable information on health and lifestyle factors was available from the EPIC Health and Lifestyle Questionnaire [16]. In the present study we examined the subjects' personal and family history of benign breast diseases and cancer, menstrual and reproductive factors, oral contraception and hormone replacement therapy, physical activity, smoking, and anthropometric information such as body mass index and waist:hip ratio.

Statistical methods

Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated by conditional logistic regression, which takes into account the matching of controls to cases [17]. Adjustment was performed for those variables that were previously found to be associated with high-risk mammographic parenchymal patterns [25].

Results

The characteristics of the cases and controls are presented in Table 1. The mean age of cases and controls was similar (because they were matched on date of birth). Cases were leaner than controls. A larger percentage of cases were nulliparous, similar proportions of cases and controls had between one and three births, and a larger proportion of controls had more than three births. A larger proportion of cases were premenopausal, current hormone replacement therapy users, had a personal history of benign breast diseases, and had had a hysterectomy, whereas a larger proportion of controls were current smokers. The cases and controls were similar with respect to age at menarche and age at menopause.

Table 2 shows the unadjusted and adjusted OR estimates for Wolfe's high-risk mammographic parenchymal patterns and smoking in the total study population and in postmenopausal women separately. Current smoking was strongly and inversely associated with high-risk patterns, after adjustment for concomitant risk factors. Relative to never smokers, current smokers were significantly less likely to have a high-risk pattern (OR 0.37, 95% CI 0.14–0.94). Similar results were obtained when the analysis was confined to postmenopausal women. Past smoking was not related to the mammographic parenchymal patterns. The overall effect in postmenopausal women lost its statistical significance when adjusted for other risk factors for P2/DY patterns that were found to be significant in this study, although the results are still strongly suggestive. There was no interaction between cigarette smoking and body mass index ($P=0.73$ and 0.72 in the whole study population and in postmenopausal women, respectively).

Discussion

In the present study, we found a strong inverse relationship between current smoking and mammographic parenchymal patterns of breast tissue as classified by Wolfe [12]. These findings are not completely unprecedented; Greendale *et al* [18] found a reduced risk of breast density in association with smoking, although the magnitude of the reduction was unclear. Our findings suggest that this reduction is large.

Recent studies [9,10] suggest that breast cancer risk may be reduced among current smokers. In a multicentre Italian case–control study, Braga *et al* [10] found that, relative to nonsmokers, current smokers had a reduced risk of breast cancer (OR 0.84, 95% CI 0.7–1.0). These findings were recently supported by Gammon *et al* [9], who reported that breast cancer risk in younger women (younger than 45 years) may be reduced among current smokers who began smoking at an early age (OR 0.59, 95% CI 0.41–0.85 for age 15 years or younger) and among long-term smokers (OR 0.70, 95% CI 0.52–0.94 for those who had smoked for 21 years or longer).

The possible protective effect might be due to the antioestrogenic effect of smoking [1,2,19]. Exposure to cigarette smoking causes an earlier menopause [1,26]. Smoking appears to alter the metabolism of oestradiol leading to enhanced formation of the inactive catechol estrogens [1]. Furthermore, smoking increases circulating androgens through adrenal cortical stimulation [2], but the conversion rates of androgens to oestrogens are lower in those who smoke [27]. There has been a recent resurgence of interest in the potential effect of smoking on breast cancer risk, and whether individuals may respond differently on the basis of differences in metabolism of bioproducts of smoking [20,21]. Different relationships between smoking and breast cancer risk have been suggested that are dependent on the rapid or slow status of acetylators of aromatic amines [20,21], rapid acetylators

being better able to inactivate the potential carcinogenic tobacco compounds. More recent studies [22,23] do not support these findings, however.

The present study design minimized the opportunity for bias to influence the findings. Systematic error in the assessment of mammograms was avoided because reading was done without knowledge of the risk factor data. Because subjects were unaware of their own case–control status, the possibility of recall bias in reporting smoking status was minimized. Furthermore, the associations observed are unlikely to be explained by the confounding effect of other known breast cancer risk factors, because we adjusted for these in the analysis. We did not have information on passive smoking status, however, which has recently been reported as a possible confounder [5,6,21,24].

Although, ideally we would have liked to evaluate the relationship between intensity and duration of smoking and mammographic parenchymal patterns among current smokers, the numbers were too small to perform the analysis. Trends for intensity and duration of smoking were not monotonic, and *P* values were inconclusive (between 0.05 and 0.1). Age at menopause and time since menopause were not related to mammographic patterns in the present study (data not shown). Although current smokers were likely to have an early menopause (70% of current smokers were postmenopausal before age 50 years), there was no difference among mean age at menopause in the three smoking categories ($P=0.15$). There was no difference in time since menopause among current smokers.

These data indicate that adjustment for current smoking status is important when evaluating the relationship between mammographic parenchymal patterns and breast cancer risk. They also indicate smoking to be a prominent potential confounder when analyzing effects of other risk factors, such as obesity-related variables. It appears that parenchymal patterns may act as an informative biomarker of the effect of cigarette smoking on breast cancer risk.

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