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Smoking Habits and Risk of Benign Breast Disease

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The relationship between smoking habits and the risk of benign breast disease (BBD) was analyzed using data from a case-control study conducted between 1981 and 1983 in the greater Milan area, Northern Italy. Cases (n = 288) were women with histologically confirmed BBD (203 dysplasia, 85 benign tumours) referred to the National Cancer Institute of Milan for biopsies. Controls were women (n = 291) seen on selected days for a cytological smear for cervical cancer in outpatient clinics of the same Institute. No consistent association emerged between various indicators of smoking habits (smoking status, number of cigarettes smoked per day, duration of smoking) and the risk of BBD. Compared with never smokers the relative risk (RR) of all BBD combined was 0.7 (95% confidence interval, CI: 0.4–1.3) in exsmokers, 1.4 (95% CI: 0.8–2.5) in smokers of less than 10 cigarettes per day, and 1.1 (95% CI: 0.7–1.7) in smokers of 10 or more cigarettes per day. There was some suggestion that the risk may be below unity post-menopause, but the relative risks for smokers were not statistically different in pre- (RR = 1.2; 95% CI: 0.8–1.8) and post-menopausal (RR = 0.6; 95% CI: 0.2–1.7) women. The risk of benign tumours (chiefly fibradenoma) was higher in current smokers, but this finding was not statistically significant (RR = 1.5; 95% CI: 0.9–2.6) and the highest risks were observed in the strata of lighter smokers and those with shorter duration of smoking. Overall these results fail to support a negative association between smoking habits and benign breast disease.

Benign breast disease (BBD) is a heterogeneous group of changes in the female breast that are strongly related to ovarian hormones.[1] For example, BBD is more frequent in nulliparous women,[1–5] and tends to disappear after the menopause.[5–7] Its severity generally increases in the pre-menstrual period.[8] Further, oral contraceptive use has been associated with a short-term decrease in the risk of BBD, particularly that involving less definite histological changes.[9–10] Oestrogen replacement therapy has been reported in several, but not all, studies to increase the risk or exacerbate the symptoms of BBD.[11–14] Similarly, exogenous oestrogen administration has been linked with benign mammary lesions in animal experiments.[15–17]

Cigarette smoking has been shown to reduce oestradiol levels and availability in women taking oral oestradiol,[18] and women who smoke have lower urinary oestrogen levels during the luteal phase of the menstrual cycle compared to non-smokers.[19] More generally, it is thought that women who smoke cigarettes behave as though they are relatively oestrogen-deficient. Thus, smoking women show an increased risk of osteoporosis and early menopause, and a decreased frequency of endometrial cancer,[20,21] and probably of uterine fibroids[22] and pelvic endometriosis.[23]

Although these observations suggest that the risk of BBD might be lower in smokers, the epidemiological evidence is inconsistent.[3,14,21,24–28] For example, Berkowitz *et al.*[25] analysing data from a hospital-based case-control study conducted in the US found that current smokers, particularly post-menopausal women were at decreased risk of fibrocystic and benign breast tumours. The relative risk (RR) for current smokers was 0.7 for fibrocystic breast disease, 0.6 for fibroadenoma, and RRs of similar magnitude were registered for other or combined histological types. A similar association for fibrocystic disease was reported by

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Wyshak *et al.* in a cross-sectional surveillance of more than 5000 former college alumnae,[27] but the association was not significant for former smokers. No association emerged in at least three case-control and cohort studies conducted in the UK,[26] Australia[28] and the US[3] in which the diagnosis of BBD was self-reported[26] or histologically confirmed.[3,28]

The contrasting results have been attributed to differing study design (cohort versus case-control, population-based versus hospital-based), although it is difficult to explain all the apparent contradictions on this basis alone. Other possible reasons for the apparent discrepancies could be due to the age distribution of cases studied, since any effect of smoking could be more evident in post-menopausal women.[14,21,25]

In this paper we report the results of a case-control study conducted in Italy in the early 1980s on the relation between smoking habits and histologically-confirmed BBD. Specific attention was paid to collecting detailed information on the histopathological classification of cases.

SUBJECTS AND METHODS

Between November 1981 and March 1983 we conducted a hospital-based case-control study of BBD. The design of the investigation has already been described.[5] Briefly, trained interviewers identified and questioned cases and controls using a structured questionnaire including information on sociodemographic factors and personal characteristics and habits, gynaecological and obstetric data, related medical history and use of selected medication. Questions on smoking included smoking status (ever-smokers being defined as subjects who had smoked at least one cigarette per day for at least one year; exsmokers those who had stopped at least one year previously). The smokers and exsmokers were asked the total duration (in years) of the habit and the average number of cigarettes smoked per day.

Cases were women with histologically confirmed BBD admitted for the first time to the Division of Medical Oncology of the Milan Cancer Institute to undergo breast biopsy. A total of 288 women aged 17–64 years (median age 41) met these criteria. Among them, 85 (30%) had benign tumours (77 fibroadenomas and 8 papillomas) and 203 (70%) had dysplastic lesions (21 ductal hyperplasias, 49 other dysplasias such as fibrosclerosis or adenosis, and 133 mixed lesions). Only clinically important breast lumps, often suspected of malignancy, are referred for biopsy at the National Cancer Institute in Milan. It represents a 'second level' referral centre from a network of outpatient clinics covering the Great Milan area, for surveillance and diagnosis of breast diseases.

Eligible controls were women seen on selected days for a cytological smear for cervical cancer in outpatient clinics of the National Cancer Institute of Milan. These women should constitute a representative sample of the population in the area attending routine cervical screening centres. A total of 291 women aged 18 to 68 (median age 40) were identified. None of the eligible cases or controls refused to be interviewed. Although cases and controls were not strictly matched, their age distribution was comparable (Table 1).

Data Analysis

We estimated the odds ratios of BBD, as estimators of (RRs), together with their 95% confidence intervals (CI), according to smoking habits, from data stratified for quinquennia of age by the Mantel-Haenszel procedure.[29] In order to allow for the effects of several potential confounding factors simultaneously, unconditional multiple logistic regression, with maximum likelihood fitting,[30] was used. Included in the regression equations were terms for age, education, menopausal status, Quetelet's index, parity, age at menarche, oral contraceptive use and, in turn, various indicators of smoking habits.

RESULTS

The distribution of cases and controls according to histopathological classification, age and selected characteristics is shown in Table 1. As expected, women with benign tumours were younger than those with dysplasias (42% and 22% respectively were less than 35 years old). No significant difference emerged in relation to menopausal status or Quetelet's index.

The smoking habits of cases and controls and the smoking-associated risks are considered in Table 2 and Table 3. No consistent association emerged between

TABLE 1 *Distribution of 288 cases of benign breast disease and 291 controls according to selected characteristics Milan, Italy, 1981–83*

	Cases					
	Benign tumours		Dysplasias		Controls	
	No.	%	No.	%	No.	%
Age (years)						
≤25	13	15	8	4	21	7
26–35	23	27	37	18	62	21
36–45	33	39	88	43	130	45
46–55	15	18	51	25	59	20
≥56	1	1	19	9	19	7
Menopausal status						
Pre	78	92	163	80	249	86
Post	7	8	40	20	42	14
Quetelet's index (kg/m²)						
≤20	32	38	64	32	88	30
20–22	25	29	57	28	80	27
≥23	28	33	82	40	123	42

various indicators of smoking habits (smoking status, number of cigarettes smoked per day, or duration of smoking) and risk of BBD. Compared with never smokers, the overall RR for all BBD was 0.7 (95% CI: 0.4–1.3) for exsmokers, and 1.1 (95% CI: 0.8–1.6) for current smokers. Among current smokers the RR was 1.4 for fewer than 10 and 1.0 for 10 or more cigarettes smoked per day. Likewise, there was no relationship with duration of smoking, with RRs of 1.1 for <20 and 1.2 for ≥20 cigarettes per day. The risk of benign tumours (chiefly fibroadenoma[1]) was higher in current smokers, but this finding was not statistically significant (RR = 1.5; 95% CI: 0.9–2.5), and the highest risks were observed in strata of lighter smokers and shorter duration of smoking. All the multivariate RRs were largely comparable to the age-adjusted ones.

The effect of smoking was also calculated by menopausal status. Post-menopausal women were defined as women whose last menstrual cycles occurred at least one year before interview. Among pre-menopausal and post-menopausal women the RR of benign breast disease for current smokers was respectively 1.2 (95% CI: 0.8–1.8) and 0.6 (95% CI: 0.2–1.7), and 0.7 (95% CI: 0.3–1.3) and 0.8 (95% CI: 0.2–3.1) for exsmokers. The post-menopausal risks were, however, based on seven current and five exsmoker cases versus 14 current and three exsmoker controls only.

DISCUSSION

The results of this analysis do not show any consistent association between smoking habits and risk of histologically confirmed breast dysplasia or benign tumours. The overall absence of an association was confirmed in separate strata of histopathological diagnosis of BBD.

It should be stressed that the subjects included in the present study are not representative of all cases of clinical BBD. They were chosen because they had pathologically confirmed benign breast lesions often suspected of being malignant and were referred for biopsy to the Cancer Institute in Milan. Selection is probably the major source of potential bias in studies of BBD and of benign conditions in general.[5] For example, benign breast lumps may be more frequently detected in women more conscious of health issues (including for example the health consequences of smoking). In this regard women referred for cervical screening seemed an appropriate choice as controls because of their likely comparable attitudes to health. Further, this control group, although identified and interviewed in hospital, does not share the limitation of hospital controls, particularly the potential over-representation of smokers.[20] Further, these women were not specifically referred for cervical abnormalities or genital infections, and should therefore be a representative sample of women attending a routine screening procedure. Among the determinants of cervical screening in this population are higher education and social class (which, if anything, tend to be higher in BBD cases too), but not smoking.[31]

TABLE 2 *Distribution of 288 cases of benign breast disease and 291 controls according to smoking habits. Milan, Italy, 1981–83*

	Cases					
	Benign tumours		Dysplasias		Controls	
	No.	%	No.	%	No.	%
Smoking habits						
Never	47	55	132	65	182	63
Ex	5	6	14	7	28	10
Current (cigarettes/day)						
<10	18	21	21	10	29	10
≥10	15	18	36	18	52	19
Duration of smoking (years)						
<20	34	89	46*	68	83*	78
≥20	4	11	22	32	23	22

*The sum does not add to the total due to some missing values.

It is unlikely that case-control status influenced the reporting of smoking habits, since at the time of data collection the potential association between smoking and BBD had not received widespread attention in Italy. With regard to confounding, allowing for major potential distorting factors (including socioeconomic status or potential risk factors for BBD) did not appreciably change the estimated RR.

Clinical and experimental observations have suggested that oestrogens may play a role in the development of BBD. However, available epidemiological evidence regarding a possible association with smoking appears inconsistent (see Table 4 for a review). Among seven studies considered[3,14,24–28] an inverse association was found between smoking habits and fibrocystic disease in two case-control[14,25] and one cross-sectional study.[27] Fibroadenoma was inversely associated with smoking status in a case-control study[25] and a weak inverse association was observed in the Walnut Creek cohort investigation.[24] Other studies, however found risks of BBD in smokers around unity.[26,28] A direct relationship between smoking and cystic disease (but not fibroadenoma) was reported in a population-based case-control study from Washington county,[3] perhaps reflecting incomplete adjustment for socioeconomic correlates.

These apparent discrepancies are only partly explained in terms of potential bias, different study designs or diagnostic criteria. For example no association with smoking was observed in studies considering either clinical[26] or histologically confirmed[28] diagnosis

TABLE 3 *Relative risk (and 95% confidence interval) of benign breast disease according to histopathological classification and selected indicators of smoking habits. Milan, Italy, 1981–83*

	Benign tumours		Dysplasias		Total	
	MH†	MLV‡	MH†	MLV‡	MH†	MLV‡
Smoking habits						
Never	1*	1*	1*	1*	1*	1*
Ex	0.7	0.6	0.7	0.7	0.7	0.7
	(0.3–1.9)	(0 2–1.8)	(0.4–1.4)	(0.3–1.4)	(0 4–1.3)	(0.4–1.3)
Current (all)	1.5	1.5	1.0	1.1	1.1	1.2
	(0.9–2.5)	(0 9–2.6)	(0.7–1.5)	(0.7–1.6)	(0.8–1.6)	(0.8–1.8)
Current (no. of cigarettes/day)						
<10	2.3	2.3	1.0	1 1	1.4	1.4
	(1.1–4.4)	(1.1–4.8)	(0.6–1.6)	(0.6–2.1)	(0.8–2.3)	(0.8–2.5)
≥10	1.0	1.0	1.0	1 0	1.0	1.1
	(0.5–2.0)	(0.5–2.1)	(0.6–1.6)	(0 6–1.7)	(0.6–1.6)	(0.7–1.7)
Duration of smoking (years)						
<20	1.6	1.6	0.9	0.9	1.1	1.2
	(0.9–2.8)	(0.9–3.0)	(0.5–1.4)	(0.6–1.6)	(0.7–1.6)	(0.8–1.8)
≥20	0.9	1.1	1.3	1 4	1.2	1.3
	(0.3–3.0)	(0.3–3.5)	(0.7–2.6)	(0.7–2.8)	(0.6–2.4)	(0.7–2.6)

†Mantel Haenszel estimates adjusted for age only.
‡Estimates from multiple logistic regression equations including terms for age, education, menopausal status, Quetelet's index, parity, age at menarche, oral contraceptive use and, in turn, the above variables.
*Reference category.

of breast disease. In most studies, however, the case series consisted of women seen for biopsy or surgery of a breast lump and a potential protective effect could be stronger on less definite (functional) lesions, as suggested for oral contraceptives.[10] Similarly scanty data are available on post-menopausal women, where the anti-oestrogenic effect of smoking could be more relevant.[21] Two American case-control studies showing a

TABLE 4 *Main results from selected epidemiological studies on the relationship between smoking habits and risk of benign breast disease*

Authors, country, year	Study design (number of considered patients)	Main results
Nomura *et al*, US 1977[3]	Case (n = 320)—control (n = 320) study. Histologically confirmed diagnosis.	RR* ever versus never smokers = 1.8 for cystic disease and 0.8 for fibroadenoma.
Walnut Creek study, US 1981[24]	Cohort study. Hospital discharge diagnoses	Heavy smokers appeared to be at slightly decreased risk of fibroadenoma.
Berkowitz *et al.*, US 1985[25]	Case (n = 959)—control (n = 1062) study. Histologically confirmed diagnosis.	RR (adjusted for age and Queletet's index) current smokers versus never = 0.6 (95% CI: 0.5–0.8) for fibrocystic disease, 0.7 (95% CI: 0.5–0.9) for fibroadenoma and 0.6 (95% CI: 0.3–1.0) for mixed lesion. No association in exsmokers. Stronger association in post-menopause.
Mant *et al.*, UK 1986[26]	Cohort study (Oxford-Family Planning Association Contraceptive study). Mainly pre-menopausal women.	The first hospital visit rates for BBD were 5.7, 5.9 and 6.4/1000 woman-years respectively in never smokers and in current smokers of 1, 14 and 15 or more cigarettes/day.
Pastides, US 1987[14]	Case (n = 255)—control (n = 787) study. Post-menopausal women only. Histologically confirmed diagnosis.	RR (age-adjusted) ever versus never smokers = 0.5 (95% CI: 0.2–0.8) for fibrocystic disease.
Wyshak *et al.*, US 1988[27]	Cross-sectional analysis of 5398 college alumnae (aged 21–80 years). Diagnosis self-reported.	RR of current versus never smokers = 0.5 (95% CI: 0.3–0.8) for breast biopsy or fibrocystic disease.
Rohan *et al.*, Australia 1989[28]	Case (n = 383)—control study; two control groups: community controls (n = 383) and biopsy controls (n = 192). Histologically confirmed diagnoses.	RR current smokers versus never = 0.9 (95% CI: 0.7–1.3) versus community controls and 1.1 (95% CI: 0.7–1.6) versus biopsy controls. No association both in pre- and post-menopause.

*RR = relative risk; CI = confidence interval.

protective effect of smoking on BBD found a stronger relationship in post-menopausal women,[14,25] but an Australian study of proliferative lesions did not observe any relationship in either pre- or post-menopausal women.[28] In our series the risk of BBD was about 40% lower in post-menopausal current smokers; this finding was based on seven current smokers cases only and was not statistically significant. The present study, therefore, provides only limited information on the relationship between smoking and BBD after menopause.

In conclusion, despite a plausible biological rationale,[21] and some suggestive previous findings, the present data (as well as several other studies) fail to support the presence of a consistent negative association between smoking and BBD.

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