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Cigarette Smoking and the Risk of Endometrial Cancer

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Abstract—*The risk of endometrial cancer in relation to cigarette consumption was evaluated in a hospital-based case-control study of breast and genital neoplasms conducted in Milan, northern Italy. For the present analysis, 357 women (cases) with histologically confirmed endometrial cancer were compared to a group of 1122 women (controls) admitted for a large spectrum of acute conditions unrelated to smoking or to any of the known or potential risk factors for endometrial cancer. Compared with never-smokers, the multivariate relative risk estimates were for current 0.45 [95% confidence interval (CI) = 0.30–0.70] and 0.86 (95% CI = 0.50–1.46) for ex-smokers. The negative association of endometrial cancer with current smoking was not influenced by menopausal status as well as by other major identified potential confounding factors, i.e. menstrual and reproductive history, body mass index, oral contraceptive or estrogen replacement therapy use and family gynecologic cancer history. However, there was no evidence of a dose–risk effect, since the relative risks were similar in moderate and heavy smokers. The present study confirms that smoking is less frequent in cases hospitalized for endometrial cancer than in a comparison group of patients with non-smoking-related acute conditions. This negative association is perhaps explained in terms of reduced estrogen levels in smokers, though the influence and the importance of some uncontrolled selection bias (due, for instance, to longer hospital stay of smokers even when admission diagnosis was for non-smoking-related conditions) cannot be ruled out.*

INTRODUCTION

SINCE MacMahon *et al.* [1] demonstrated a reduced excretion of endogenous estrogens in urine samples from women who smoked as compared to non-smokers, several investigations were conducted to study the influence of smoking on the risk of cancer of the breast and the female reproductive organs as well as on other estrogen-dependent phenomena, for example osteoporosis and age at menopause.

Baron [2] recently reviewed and summarized the results from the most relevant studies on this topic. All reports [3–5] related to non-fatal endometrial cancer showed a negative association between smoking and endometrial cancer, though statistical significance was achieved only in one of them [3]. On the contrary, results quoted from two endometrial cancer death studies [6, 7] suggested, if anything, a non-significant increase of risk in smokers.

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At least four additional reports were published subsequently to Baron's review. Smith *et al.*'s data [8] from a population-based case-control study showed a decreased non-significant risk for current smokers (RR = 0.81; 95% CI = 0.44–1.50). The point estimates were lower in post-menopausal women (RR = 0.41; 95% CI = 0.16–1.04). Moreover, Tyler *et al.* [9], analysing a large dataset from the same study, including 437 endometrial cancer cases and 3200 population-based control subjects under age 55, found no overall association between cigarette smoking and the risk of endometrial cancer.

In a hospital-based case-control study of 510 women with endometrial cancer and 727 controls with other neoplasms (coloretal, melanomas, lymphoreticular, thyroid or adrenal gland tumors), Lesko *et al.* [10] found a reduction of about 50% in the risk of endometrial cancer for women who smoked at least 25 cigarettes per day; the association was restricted to post-menopausal women. No reduction of risk appeared either among moderate smokers (< 25 cigarettes/day) or among former

smokers. In the analysis of the last two reports potential confounders were also accounted for by means of multiple logistic regression.

Finally, Baron *et al.* [11] considered the relation between smoking and cancers of the breast and of the female genital tract on the basis of the Rosewell Park Memorial Institute dataset: a consistent and significant decrease in endometrial cancer risk was observed with increasing amount smoked.

The present report provides further data on the relation of cigarette smoking to endometrial cancer risk from an on-going case-control study of breast and female genital tract neoplasms conducted in northern Italy.

SUBJECTS AND METHODS

Since 1983, we have been conducting a case-control study of neoplasms of the female genital tract (ovary, endometrium and cervix). The design of this investigation has already been described [12, 13]. Briefly, trained interviewers identified and questioned women admitted for cancers and for a wide spectrum of their conditions to university and general hospitals of the greater Milan area. On the average, less than 2% of the eligible women (cases or controls) refused to be interviewed.

A standard questionnaire was used to obtain information on personal characteristics and habits, gynecological and obstetrical data, a problem-oriented medical history, history of lifetime use of oral contraceptives and other female hormones.

The subjects were asked whether they were current smokers, had smoked in the past or were life-long non-smokers. Smokers were women who had smoked at least one cigarette per day for at least one year. Those who had smoked cigarettes within the year before the interview were classified as current smokers, and those who had last smoked at least one year previously as ex-smokers. The smokers and ex-smokers were asked the total duration (in years) of the habit and how many cigarettes per day, on the average, they had smoked. The present study is based on data obtained before December, 1985.

Table 1. Characteristics of women with endometrial cancer and controls. Milan, Italy. 1983–85

Characteristic	Cases % (*n*)*	Controls % (*n*)*
Age (yrs)		
< 40	1.7 (6)	16.4 (184)
40–49	9.5 (34)	19.2 (215)
⩾ 50	88.8 (317)	64.4 (723)
Education (yrs)		
< 7	76.2 (262)	62.6 (681)
⩾ 7	23.8 (82)	37.4 (407)
Marital status		
Never married	17.4 (62)	14.6 (164)
Ever married	82.6 (295)	85.4 (958)
Body mass index (kg/m²)		
< 20	6.6 (23)	14.2 (159)
⩾ 20 < 25	30.2 (105)	46.0 (514)
⩾ 25 < 30	33.0 (115)	29.5 (330)
⩾ 30	30.2 (105)	10.3 (115)
Parity		
0	26.3 (94)	20.7 (232)
1–2	46.5 (166)	53.4 (599)
⩾ 3	27.2 (97)	25.9 (291)
Menopausal status		
Pre + in	21.0 (75)	36.8 (412)
Post	79.0 (282)	63.2 (709)
Age at menopause (yrs)		
< 40	2.4 (7)	3.5 (25)
40–44	6.2 (18)	13.4 (97)
45–49	26.1 (76)	32.4 (234)
⩾ 50	65.3 (190)	50.8 (367)
Use of estrogen replacement therapy		
Never	86.6 (309)	96.3 (1081)
Ever	13.4 (48)	3.7 (41)
Use of oral contraceptives		
Never	97.8 (349)	92.2 (1035)
Ever	2.2 (8)	7.8 (87)

*The number of cases and controls are shown in parentheses. In some items, the sum of the strata does not add up to the total due to a few missing values.

Cases

The cases were women with histologically confirmed endometrial cancer, who were diagnosed within the year prior to interview and who were admitted to the Ospedale Maggiore (including the four largest teaching and general hospitals), to the Obstetrics and Gynecology University Clinics and to the National Cancer Institute of Milan. All cases were interviewed in the hospital during first admission or subsequent follow-up. There were 357 women below the age of 75 with histologically confirmed diagnosis of cancer of the endometrium who met these criteria. The age range was 31–74 (median age 62).

Controls

Patients below the age of 75 who were admitted to university or general hospitals (within the framework of the Ospedale Maggiore, the largest hospital in Milan serving a catchment area comparable to that of the hospitals where cases had been identified) were eligible as controls. About 90% of the cases and of controls were resident of the same region, Lombardy.

Potential controls were women whose primary admission diagnosis was of acute disease other than: (1) malignant, (2) hormonal, (3) gynecological or, more generally, (4) judged to be related to any of

Table 2. Relative risk of endometrial cancer according to smoking status and number of cigarettes smoked per day. Milan, Italy, 1983–85

	Never smoker *n* (%)	Ex smoker *n* (%)	All current *n* (%)	Current smoker (No.cigarettes/day) < 15 *n* (%)	⩾ 15 *n* (%)	$X^2_{1(\text{trend})}$*
Endometrial cancer	301 (84.3)	22 (6.2)	34 (9.5)	21 (5.9)	13 (3.6)	
Controls†	789 (70.3)	75 (6.7)	258 (23.0)	152 (13.5)	106 (9.4)	
M–H‡ Adjusted (95% CI)	1§	0.82 (0.49–1.35)	0.47 (0.32–0.69)	0.44 (0.27–0.71)	0.48 (0.26–0.87)	13.50 ($P < 0.001$)
Multivariate‖ RR (95% CI)	1§	0.86 (0.50–1.46)	0.45 (0.30–0.70)	0.46 (0.28–0.75)	0.44 (0.23–0.86)	12.72 ($P < 0.001$)

*Ex-smokers excluded.
†Hysterectomized controls excluded ($n = 157$).
‡Indicates Mantel–Haenszel procedure; adjusted for age.
§Reference category.
‖Estimates from multiple logistic regression; allowance was made for age, marital status, education, social class, age at menarche, menopausal status, age at menopause, parity, number of live births, family gynecologic cancer history, body mass index, oral contraceptive and estrogen replacement therapy use.

established or suspected risk factors for endometrial neoplasms and to smoking (for instance, specific exclusion was made of subjects admitted for cardio- or cerebro-vascular diseases, gallbladder conditions or diabetes). Women who had undergone hysterectomy were excluded from the analysis ($n = 157$).

Of this final control series (1122 patients), 32% had been admitted because of traumatic conditions, 25% for non-traumatic orthopedic disorders (mostly low back pain and disc disorders), 15% for surgical conditions (mostly abdominal, such as acute appendicitis or strangulated hernia) and 28% for other illnesses such as eye, nose and throat and teeth disorders. The age range was 25–74 (median age 54).

Data analysis and control of confounding

Odds ratios (as estimators of relative risks, RRs) [14], together with their 95% approximate confidence intervals (CI) [15] were derived from data stratified for age by the usual Mantel–Haenszel procedure [16]. Tests for linear trend in risk, where appropriate, were done by the method given by Mantel [17]. Other potentially confounding variables, including determinants of smoking habits in this population and the major risk factors for the disease studied, were examined and controlled for individually using the Mantel–Haenszel procedure [15].

Further, all the identified potential confounding factors were controlled simultaneously by means of multiple logistic regression, fitted by the method of maximum likelihood [18]. Included in the regression equations, besides the smoking-related variables considered, were terms for age (in cardinal form), marital status, education, social class, age at menarche, menopausal status, age at menopause, parity, number of live births, family gynecologic cancer history, body mass index, oral contraceptive and estrogen replacement therapy use.

RESULTS

As compared to controls, women with endometrial cancer were more frequently nulliparous, had greater body mass index, were less educated, were less frequently ever users of estrogen replacement therapy or had a later menopause (Table 1).

In Table 2, cases and controls are compared according to smoking status and level of cigarette exposure. When considering never-smokers as a reference category, the age-adjusted relative risk of endometrial cancer was 0.82 for ex- and 0.47 for current smokers. However, among current smokers there was no evidence of a dose–risk relationship (point estimate = 0.44 for < 15 cigarettes per day and 0.48 for ⩾ 15). There were insufficient numbers for heavier smokers to permit meaningful analysis (i.e. only four cases smoked 25 cigarettes per day or over). Relative risks of endometrial cancer were individually adjusted for age and for several relevant covariates (Table 3). All estimates were also significantly below unity, comprised between 0.42 for parity and 0.53 for body mass index. Likewise, negative associations between current smoking and cancer risk were evident across various strata and, on account of the obvious effect of large random variation of the estimates due to small numbers in single strata, no important interaction

Table 3. Relative risk of endometrial cancer (current vs. never-smokers) in separate strata of selected covariates. Milan, Italy, 1983–1985

Covariate	CA/CO*	RR† (95% confidence interval)
Age (yrs)		
< 40	5/170	0.84 (0.14–5.20)
40–49	28/206	0.37 (0.13–1.07)
⩾ 50	302/671	0.47 (0.31–0.73)
M–H‡ adjusted		0.47 (0.32–0.69)
Education (yrs)		
< 7	251/644	0.51 (0.31–0.83)
⩾ 7	72/369	0.44 (0.23–0.84)
M–H‡ adjusted		0.48 (0.32–0.71)
Marital status		
Never married	56/149	0.42 (0.18–0.97)
Ever married	279/898	0.45 (0.29–0.69)
M–H‡ adjusted		0.44 (0.30–0.65)
Body mass index (kg/m^2)		
< 20	21/146	0.28 (0.08–0.96)
⩾ 20 < 25	94/474	0.77 (0.43–1.37)
⩾ 25 < 30	112/315	0.74 (0.36–1.51)
⩾ 30	99/109	0.13 (0.04–0.40)
M–H‡ adjusted		0.53 (0.35–0.78)
Parity		
0	85/212	0.48 (0.25–0.91)
1–2	159/561	0.35 (0.20–0.63)
⩾ 3	91/274	0.53 (0.20–1.43)
M–H‡ adjusted		0.42 (0.28–0.62)
Menopausal status		
Pre + in	69/391	0.46 (0.23–0.93)
Post	266/655	0.44 (0.28–0.70)
M–H‡ adjusted		0.44 (0.30–0.66)
Age at menopause (yrs)		
⩽ 49	97/328	0.40 (0.20–0.83)
⩾ 50	179/340	0.49 (0.27–0.89)
M–H‡ adjusted		0.43 (0.27–0.69)
Estrogen replacement therapy		
Never	289/1009	0.49 (0.33–0.74)
Ever	46/38	0.18 (0.05–0.65)
M–H‡ adjusted		0.44 (0.30–0.66)
Use of oral contraceptives		
Never	328/966	0.46 (0.31–0.69)
Ever	7/81	0.39 (0.07–2.18)
M–H‡ adjusted		0.46 (0.31–0.67)

*Number of cases/number of controls (ex-smokers excluded). In some items, differences between totals are due to a few missing values.

†Relative risk estimates adjusted for age only (in each stratum of various covariates considered).

‡Indicates Mantel–Haenszel overall estimates adjusted for age and for each single covariate.

emerged with age, menopausal status or any of the covariates considered.

Consequently, when indicators for age, socio-economic status (social class and education), gyn-ecological and obstetrical history, exposure to exogenous estrogens, familial cancer history and obesity on the smoking–endometrial cancer risk relationship were simultaneously considered in multiple logistic regression equations, the negative relation between endometrial cancer risk and smoking was not materially modified (multivariate RR for current vs. never smokers = 0.45; 95% CI = 0.30–0.70).

DISCUSSION

The findings of this study showed a negative association between smoking and risk of endometrial cancer, with an overall reduction of about 50% in risk for women who currently smoke. However, there was no evidence of a trend of decreasing risk with increasing number of cigarettes among smokers, and the risk estimates for former smokers were close to unity.

The relationship between endometrial cancer and smoking could be mediated by estrogen hormone levels which are reduced among smokers as compared with never-smokers [1, 2]. This hormonal hypothesis is consistent with effect of smoking on other estrogen-related phenomena, i.e. age at menopause and bone density.

It is unlikely that information bias largely accounted for the present results since, at the time of data collection, this hypothesis was unknown to the interviewers and, probably, to the majority of the patients. Confounding bias is also unlikely since simultaneous adjustment for the major potential distorting factors, including menopausal status, age at menopause, estrogen use and other major risk factors for endometrial cancer did not materially influence the risk estimates. However, the possibility of selection bias cannot be easily ruled out. Although participation rate was practically 100%, controls were admitted for acute conditions unrelated to smoking, and the distribution of smoking prevalence among diagnostic subcategories of controls were similar, our estimates may have been biased if the prevalence of smoking in the hospital control series was excessive. This bias might be created, for instance, by a prolonged hospital stay among smokers, even when admitted for acute non-smoking-related conditions, with a consequent greater probability of being interviewed. However, data from the 1983 National Health Household Survey conducted by the Italian Central Institute of Statistics (ISTAT) [19] do not support this view, since the duration of hospital stay was comparable for smokers and non-smokers. It is further reassuring that, from a companion study conducted with similar methodology and criteria of selection of cases and controls, emerged an elevated risk of cervical cancer in smokers (multivariate risk for current vs. never-smokers = 1.80) [20]. It is still possible that the positive association between cigarette smoking

and cervical cancer was indeed underestimated within the framework of this case-control surveillance conducted in northern Italy, and that the negative relation with endometrial cancer was partly or totally artefactual. Finally, similar analyses based on a series of over 1000 breast cancer cases gave an overall multivariate relative risk of 0.74 (95% CI = 0.60–0.92) for current smokers (Levi *et al.*, unpublished manuscript). The larger estimated protection for endometrial cancer cancer, as compared with breast neoplasms, might therefore reflect a stronger estrogen dependency of endometrial epithelium.

Thus, the findings of this study, however, clearly inconclusive in terms of precise risk assessment and public health implications, are of interest since they may help clarify hormonal correlates of endometrial cancer and add further data to the current debate of smoking and estrogen-related diseases. Further, they indicate that the potential modifying or confounding effect of smoking should be considerd in further epidemiological research on endometrial cancer.

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