CIGARETTE SMOKING AND THE RISK OF BREAST AND ENDOMETRIAL CANCER

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AND ENDOMETRIAL CANCER

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AKNOWLEDGMENTS

NOTICE

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Additional material (experimental and design data as well as descriptions of equipment) must be provided in sufficient detail to allow a clear and precise judgment to be made of the importance and originality of the research reported. Abstract, full introduction and conclusion must be included, and where more than one manuscript appears, connecting texts and common abstracts, introduction and conclusions are required. A mere collection of manuscripts is not acceptable; nor can reprints of published papers be accepted."

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SUMMARY

Data from a case-control investigation conducted in Milan, Italy, were analyzed to evaluate the relation between smoking habits and the risk of breast and endometrial cancer. A total of 1,105 breast and 357 endometrial hospital-based cancer cases were compared to 1,279 and 1,122 controls, respectively, admitted for a large spectrum of acute conditions to major University or general hospitals in the greater Milan area. Compared to never smokers, the age-adjusted relative breast cancer risks were 0.99 (95% confidence interval (CI) = 0.71-1.37) for ex smokers, and 0.85 (96% CI = 0.70-1.04) for current smokers. As regards endometrium, the age-adjusted cancer relative risk estimates were for current 0.47 (95% CI = 0.32-0.69) and 0.82 (95% CI = 0.49-1.35) for ex smokers. For both sites, the negative association of cancer with current smoking was not influenced by the major potential identified confounding factors. For breast was there a statistically significant dose-risk effect (multivariate X_1^2 for trend = 9.44; p = 0.002). These negative relationships are perhaps explained in terms of reduced estrogen levels in smokers, though the influence of some uncontrolled selection bias cannot be ruled out.

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RESUME

Dans le cadre d'une étude cas-témoins conduite à Milan, Italie, on a étudié la relation entre la consommation de cigarettes et le risque de cancer du sein et de l'endomètre. Au total, 1,105 cas hospitaliers de cancers mammaires et 357 de l'endomètre ont été comparés, respectivement, à 1,279 et 1,122 témoins admis pour des affections aigües dans les principaux hôpitaux de la ville. Par rapport à celles qui n'avaient jamais fumé, le risque relatif de cancer mammaire ajusté pour l'âge était estimé à 0.99 (intervalle de confiance (IC) à 95% = 0.71-1.34) pour les ex-fumeuses et à 0.85 (IC à 95% = 0.70-1.04) pour les fumeuses actuelles. En ce qui concerne l'endomètre, ces dernières présentaient un risque relatif de 0.47 (IC à 95% = 0.32-0.69), alors que parmi les anciennes consommatrices il était de 0.82 (IC à 95% = 0.49-1.35). Dans le cas du sein autant que dans celui de l'endomètre, l'association négative entre cancer et consommation actuelle de tabac n'était pas influencée par les facteurs de confusion principalement connus. Pour le sein uniquement, on a démontré une relation statistiquement significative entre degré d'exposition et risque de cancer (X^2_1 multivarié pour le trend = 9.44; p= 0.002). Ces relations inverses pourraient s'expliquer par une réduction des niveaux oestrogéniques chez les fumeuses, sans que l'on soit, toutefois, en mesure d'exclure l'influence de facteurs de sélection incontrôlés.

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INTRODUCTION

It has been suggested that cigarette smoking may reduce the incidence of hormone-related cancers by influencing steroid levels. Indeed, a report by Mac Mahon et al (1) of lower urinary estrogen levels during the luteal phase of menstrual cycle in women who smoked than in non smokers has raised widespread interest on the potential influence of smoking on estrogen-related neoplasms, in particular breast and female genital tract cancers. In previous studies (2-3), women smokers had also been reported to have an earlier menopause than non smokers.

In a review on smoking and estrogen-related diseases, Baron (4) found considerable inconsistencies in epidemiologic data.

Regarding *breast cancer* among the 10 case-control studies considered, five showed a reduced risk among smokers, though only in two of them (5-6) did the negative association reach statistical significance. Smith et al (7) compared 420 breast cancer cases to 612 general population controls. After adjustment for age and a wide range of potential confounders, smoking was not significantly related to the development of breast cancer (relative risk = 0.99; 95% CI = 0.97-1.02). Rosenberg et al. (8) compared 2,160 cases to hospital-controls admitted for other cancer sites (ovary, large bowel, melanoma, lympho-reticular neoplasms). No significant association was found either for current smokers of any amount (RR= 1.1; 95% CI = 0.9-1.3) or for smokers of 15 or more cigarettes per day (RR = 1.0; 95% CI =0.8-1.3).

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Moreover, evidence against the hypothesis that smoking may reduce the incidence of breast cancer by as much as 20% (1) persisted even after allowance was made for all identified potential confounders.

Likewise, in the data reported by Le et al. (9) from a case-control study of 500 French women with breast cancer and 945 controls recruited in 66 private surgical clinics and by Porter et al. (10) from two case-control investigations including a total of over 360 breast cancer cases and 430 controls recruited in surgical wards and a prepaid medical plan, respectively, no significant association emerged between smoking and breast cancer.

Data of the Canadian National Breast Screening Study, analyzed using a case-control study design (11), showed among pre-menopausal women (49 cases and controls) a twofold increased risk of breast cancer detection (RR 2.1, CI =1.1-4.0) for ever versus never smokers and a dose-response gradient with increased exposure. No overall association was evident among post-menopausal women (71 cases and 220 controls).

Additional data were also provided by Lund (12) on the dose relationship between smoking and estrogen-related diseases from a prospective study of 13,998 Norwegian women. 259 incident breast cancer cases were registered during a 12-year follow-up. The rate ratio for current smokers vs never smokers was 0.84 but there was a positive linear relation with the amount smoked daily: rate ratios were 0.62 for those smoking 1 to 9 cigarettes/day, 1.24 for smokers of 10 to 19 cigarettes/day. and 1.56 for smokers of >20 cigarettes/day. Thus, these results did not support the hypothesis of a protective effect of smoking on breast cancer risk.

Berkowitz et al. (13) in a large hospital-based case-control study (958 cases and 1,062 controls) conducted in Connecticut, noted for the first time a negative association, adjusted for age and Quetelet index, between current cigarette

smoking and benign breast diseases such as fibrocystic lesions and/or fibroadenomas. A strong negative association was also reported between current cigarette use and the occurrence of two rare lesions which have been found to have an increased malignant potential, i.e. atypical lobular hyperplasia and papillomatosis of the breast (14-15).

Finally, the relationship of smoking to breast cancer risk was recently investigated by Brinton (16) in a case-control study involving 1,547 patients and 1,930 controls recruited through a nationwide breast screening program. The risk was not affected by smoking (RR = 1.2; 95% CI = 1.0-1.4). This study did not support the association of smoking with a reduced risk among naturally menopausal women (RR = 1.06; 95% CI = 0.8-1.3). Also, surprisingly, no general evidence emerged that smokers experience an earlier menopause than non smokers even within the heavy smoking group.

Baron (4) also reviewed and summarized the results from the most relevant studies focusing on the influence of smoking on risk of _endometrial cancer_. All reports related to non fatal cases (17-19) showed a negative association between smoking and endometrial cancer, though statistical significance was achieved in only one of them (17). On the contrary, results quoted from two endometrial cancer death studies (20-21) suggested, if anything, a non significant increase of risk in smokers.

Three additional studies were published subsequently to Baron's review. Smith et al's data (22) 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). Estimates were adjusted for major potential confounders. Tyler et al (23) also investigated 437 endometrial cancer cases and 3,200 general population control

subjects under age 55. No association was shown between cigarette smoking and the risk of endometrial cancer.

Finally in a hospital-based case-control study of 510 women with endometrial cancer and 727 controls with other neoplasms (colorectal, melanomas, lymphoreticular, thyroid or adrenal gland tumours), Lesko et al. (24) 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 per 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

On account of the noticeable inconsistencies in published material and of the large public health relevance of the issue, the present report provides further data on the relation of cigarette smoking to endometrial and breast cancer risk from an on-going case-control study of breast and female genital tract cancers conducted in Northern Italy. For this investigation, detailed informations on smoking and on other endometrial and breast cancer risk factors were available. Thus, the role and influence of confounding and effect modifications could be evaluated.

MATERIALS AND METHODS

Since 1983, a case-control study of breast neoplasms and of the female genital tract (ovary, endometrium and cervix) has been conducted in the greater Milan area, northern Italy.

The design of this investigation has already been described (25-26). Briefly, trained interviewers identified and questioned women admitted for cancers and for a wide spectrum of other 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 (see Appendix D) was used to obtain information on personal characteristics and habits, gynecological and obstretical 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. The smokers and ex smokers (who had last smoked at least one year before) were asked the total duration (in years) of the habit and how many cigarettes par day, on the average, they had smoked. The present study is based on data collected before December, 1985.

CASES - The cases were women with histologically confirmed breast and 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. Women 75 +

years of age were excluded. There were 1,105 and 357 women with, respectively, histologically confirmed breast and endometrial cancer. The median age was 52 for breast and 62 for endometrium.

CONTROLS - Patients below the age of 75 who were admitted to University or general hospitals serving a catchment area comparable to that of the hospitals where cases had been identified, were eligible as controls. About 90% of controls (same figure for cases) were resident within the same region, Lombardy. Potential controls were women admitted for acute diseases other than malignant, hormonal or gynecological disorders or, more generally, judged to be unrelated to smoking or to any of the established or suspected risk factors for breast and endometrial cancer.

A total of 1,279 subjects aged 25 to 74 (median age = 56) were interviewed. Among them, 33% had been admitted because of traumatic conditions, 26% for non traumatic orthopedic disorders (mostly low back pain and disc disorders), 15% for surgical conditions (mostly abdominal, such as appendicitis or strangulated hernia), and 26% for other illnesses such as eye, nose and throat, and teeth disorders.

For estimating endometrial cancer risks, women who had undergone hysterectomy were excluded from the analysis (n= 157).

DATA ANALYSIS AND CONTROL OF CONFOUNDING —For evaluating effects of an exposure factor, the measure of association considered was the relative risk (RR), as estimated by the odds ratios (27), together with its 95% approximate confidence intervals (28). Such estimators were derived from data stratified for age by the usual Mantel-Haenszel procedure (29). For multiple levels of exposure, significance was assessed by a two tailed linear trend test (30).

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 (29).

Further, all the identified potential confounding factors were controlled simultaneously by means of multiple logistic regression, fitted by the method of maximum likelihood (27). Included in the regression equations for breast cancer risk estimates, besides the smoking-related factors considered, were terms (selected a priori and in ordinal form) for the 16 following variables . age, marital status, age at menopause, parity, number of livebirths, age at first birth, personal history of benign breast disease and of breast biopsies, family history of breast cancer, body mass index, oral contraceptive and estrogen replacement therapy use. Terms for age at first birth, personal history of benign breast disease and of breast biopsies were excluded from models for endometrial cancer.The logistic equations were fitted using standard statistical packages (31).Pre-menopausal women represented a separate category in the regression model and, for multivariate tests for trend, exposures to smoking were expressed on a continuous scale.

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RESULTS

BREAST CANCER - In table 1 of Appendix A, distributions of various characteristics are presented for cases and controls. Most variables show quite close similarities. Only slight differences are noted for cases who tended to be more educated or in the highest social class, reported older age at first birth and were less frequently multiparous or in post menopause. Personal or family history of either benign or malignant breat diseases was more often evoked by cases.

In table 2 (Appendix A), are compared the smoking habits of breast cancer patients and the control group. A total of 72.4 per cent of the cases and 70.4 per cent of controls reported never having smoked. Among ever smokers, around 7 per cent of cases or controls were ex smokers. Less than 2 per cent of either cases or controls were classified in the heavy current smoker group (=> 25 cigarettes per day). With women who had never smoked as reference category, the age-adjusted relative risk of breast cancer for ex smokers (who had smoked at least one year before) was 0.99 (95 % CI = 0.71-1.39) and the overall relative risk for all current smokers together was 0.85 (95% CI = 0.70-1.04). When simultaneous allowance was made for the 16 major identified potential confounding factors, the overall point estimate for current versus never smokers was 0.74, with 95% confidence interval 0.62-0.92. The lower risk estimates from multiple logistic regression, as compared with age-adjusted ones, was chiefly explainable in terms of social class (as confirmed in table 3-Appendix A) which were positively related both with smoking and breat cancer risk.

In table 3 of Appendix A, separate age-adjusted relative risks are shown for current smoking in various strata of the covariates listed in table 1. For most

covariates, the relative risk estimates were negative accross strata, thus showing no important interactions. The overall Mantel-Haenszel estimates varied between 0.76 for education and 0.92 for age at first birth, and the 95% upper confidence limits were generally close to unity. When attention is focused on menopausal status, there was a stronger significant negative association in the risk related to current smoking among pre or in menopause women (age-adjusted RR = 0.72; 95% CI 0.53-0.97) as compared with post menopause women (RR = 0.93; 95% CI = 0.71-1.13).

Among current smokers of 1 to 14, 15 to 24 and 25 or more cigarettes per day, the overall age-adjusted relative risk estimates were respectively 0.86, 0.82 and 0.58. This negative trend in the relations between smoking and breast cancer risk persisted after simultaneous allowance for the 16 identified potential confounding factors using multiple logistic regression. The multivariate trend of decreasing risk with increasing number of cigarettes smoked was statistically significant (X^2, ex smokers excluded, =9.44; p=0.002).

Breast cancer risk estimates according to smoking habits, adjusted for age and for each individual covariate, are also presented in tables 4 to 17 (Appendix C). The negative trend shown in table 3 (Appendix A) is also confirmed for each covariate, with no substantial difference accross the tables. Although current smokers were lighter than non smokers also in the present study (67 6 per cent of smokers versus 55 9 per cent of non smokers had body mass index < 25), there was no evidence that the effects of smoking were confounded by Quetelet index of body mass. Similar considerations apply to a variety of other breast cancer risk factors, including age at menarche, age at first livebirth, family history of breast cancer, history of benign breast biopsy or disease and exogenous hormone use.

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ENDOMETRIAL CANCER - As compared to controls, women with endometrial cancer were more frequently multiparous, had greater body mass index, were less educated, were less frequently ever users of estrogen replacement therapy or had a later menopause (table 1 of Appendix B).

In table 3 (Appendix B) are examined effect modifications of smoking by 7 covariates. All estimates were significantly below unity, comprised between 0.42 for parity and 0.53 for body mass index. There was no substantial difference in the risk associated with current smoking according either to education, marital status, body mass index or estrogen replacement therapy.

Cases and controls were also compared according to smoking status and level of cigarette exposure (Table 2 - Appendix B). The age-adjusted relative risk of endometrial cancer was 0.82 (95% CI = 0.49-1.35) for ex and 0.45 (95% CI = 0.31-0.67) 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) Similar comparisons were made in tables 18 to 25 (Appendix C) for each single covariate, although, for descriptive purpose, details were given also for subgroup smoking => 25 cigarettes per day. Estimates were in close agreement with those from table 2 in Appendix B. Furthermore, results from the stratified analyses were consistent with those derived from a multivariate approach, which adjusted simultaneously for indicators for age, socio-economic status (social class and education), gynecological and obstetrical history, exposure to exogenous estrogens, familial cancer history and obesity (table 2 of Appendix B) The negative relation between endometrial cancer risk and smoking was not materially modified (multivariate risk for current versus never smokers = 0.46; 95% CI = 0.30-0.70).

GENERAL DISCUSSION AND CONCLUSIONS

This study showed that current smoking is negatively associated with the risk of breast and endometrial cancer. Our findings are consistent with other investigations on breast (5-6) as well as on endometrial cancer risk (17-19, 24). As previously suggested, our multivariate relative breast cancer risk estimates indicated a 26% reduced risk for current smokers, with a 95% confidence interval of 8 to 40% and a statistically significant trend of decreasing risk with increasing cigarette usage. As showed by Vessey (5), ex smokers had a relative risk close to unity, whereas the highest protection (twofold decreased risk) appeared in the heaviest current smoker group (25 or more cigarettes per day). Our results, however, are in contrast with other investigations (7-10,12, 16) that failed to find such an association for breast cancer.

Our investigation suggested an even greater protection by smoking against endometrial cancer, with an overall reduction of about 50 per cent 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, although estimates for former smokers were also close to unity.

The relationship between endometrial as well as breast cancer and smoking could be mediated by estrogen hormone levels which are reduced among smokers as compared with never smokers (1). This hormonal hypothesis is consistent with effect of smoking on other estrogen-related phenomena, i.e. age at menopause and bone density However, the precise role of estrogens in the etiology of breast cancer remains unclear. Some data (11) tend to suggest a non uniform role for smoking with effects that may depend on other factors like menopausal status and parity.

It is unlikely that recall bias considerably influenced the present findings. At the time of data collection, the possible association between cigarette smoking and gynecologic cancers had not yet gained widespread attention in the lay press in Italy and was almost certainly unknown to the large majority of the subjects interviewed as well as to interviewers. Confounding bias is also unlikely since simultaneous adjustments for the major distorting factors and other major risk factors for endometrial and breast cancer did not materially influence risk estimates.

Participation rates in our study were over 98%, controls were admitted for acute diseases requiring hospitalization and judged to be unrelated with smoking and there was no considerable difference in smoking prevalence among various diagnostic subcategories of controls. Nonetheless, it is still possible that the association that emerged in this study is partly or totally due to generalized artifactually raised smoking prevalence among hospital controls 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) (32) do not suggest 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) (33) 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 and breast cancer was partially or totally artefactual.

The larger estimated protection for endometrial cancer, as compared with breast neoplasms, might therefore reflect a stronger estrogen dependency of endometrial epithelium.

Thus, the findings of this study, however clearly unconclusive in terms of precise risk assessment and public health implications, are of interest since they may help clarify hormonal correlates of endometrial and breast cancer and add further data to the current debate of smoking and estrogen-related disease. It is in our opinion impossible to distinguish between two different interpretations: either female hormone correlates of smoking (i.e. the reduced levels of the three major endogenous estrogens) affect breast and endometrial cancer risk (4,4) or a generalized uncontrolled bias is present in various diagnostic subcategories of hospital controls, producing spurious underestimates of the relative risk. Further, our results indicate that the potential modifying or confounding effect of smoking should be considered in further epidemiologic research on estrogen-related neoplasms.

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APPENDIX A

CIGARETTE SMOKING AND THE RISK OF BREAST CANCER IN WOMEN

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SUMMARY

Data from a case-control investigation conducted in Milan, Italy, were analyzed to evaluate the relation between smoking habits and the risk of breast cancer. A total of 1,105 cases of breast cancer was compared to 1,279 controls admitted for a large spectrum of acute conditions to major University or general Hospitals in the greater Milan area. Compared with never smokers, the age-adjusted relative risks were 0.99 (95% confidence interval (CI) = 0.71-1.37) for ex smokers, and 0.85 (95% CI = 0.70-1.04) for current smokers. Among current smokers, the risk estimates were 0.86 for less than 15 cigarettes/day, 0.82 for 15-24 and 0.58 for over 25. Allowance for several identified potential confounding factors including age at menopause, other major risk factors for breast cancer and indicators of socio-economic status failed to explain the negative association between smoking and breast cancer, and the multivariate trend of decreasing risk with increasing number of cigarettes smoked was statistically significant (X_i^2 = 9 44; p= 0.002).

These findings may be explained in one of two ways: either cigarette smoking does affect breast cancer risk, possibly through modifications of estrogen levels, or a generalized uncontrolled bias is present in various diagnostic subcategories of hospital controls, producing spurious underestimates of the relative risk.

INTRODUCTION

A report by Mac Mahon et al. (1) of lower urinary estrogen levels during the luteal phase of menstrual cycle in women who smoke than in non smokers raised widespread interest on the potential influence of smoking on estrogen-related neoplasms, in particular breast and female genital tract cancers In a review on smoking and estrogen-related disease, Baron (2) found considerable inconsistencies in epidemiological data of smoking and breast cancer Among the 10 case-control studies considered, five showed a reduced risk among smokers, though only in two of them (3-4) did the negative association reach statistical significance

Additional studies were subsequently published Smith et al (5) compared 420 breast cases to 612 general population controls After adjustment for age and a wide range of potential confounders, smoking was not significantly related to the development of breast cancer, (relative risk ≈ 0.99; 95% CI $\approx 0.97 \cdot 1.02$) Rosenberg et al (6) compared 2,160 cases to hospital controls admitted for other cancer sites (ovary, large bowel, melanoma, lympho-reticular neoplasms) No significant association was found either for current smokers of any amount (RR=1.1, 95% CI = 0.9-1.3) or for smokers of 15 or more cigarettes per day (RR=1.0, 95% CI= 0.8-1.3) Evidence against the hypothesis that smoking may reduce the incidence of breast cancer by as much as 20% (1) persisted even after allowance was made for all identified potential confounders.

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Berkowitz et al. (11) in a large hospital-based case-control study (958 cases and 1,062 controls) conducted in Connecticut, noted for the first time a negative association, adjusted for age and Quetelet's index, between current cigarette smoking and benign breast diseases such as fibrocystic lesions and/or fibroadenomas. A strong negative association was also reported between current cigarette use and the occurrence of two rare lesions which have been found to have an increased malignant potential, i.e. atypical lobular hyperplasia and papillomatosis of the breast (12,13).

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Finally, the relationship of smoking to breast cancer risk was recently investigated by Brinton (14) in a case-control study involving 1,547 patients and 1,930 controls recruited through a nationwide breast screening program. The risk was not affected by smoking (RR = 1.2; 95% CI = 1.0-1.4). This study did not support the association of smoking with a reduced risk among naturally menopausal women (RR =1.06; 95% CI = 0.8-1.3). Also surprisingly, no general evidence emerged that smokers experience an earlier menopause than non smokers even within the heavy smoking group.

On account of the noticeable inconsistencies in published material and of the large public health relevance of the issue, we examined the relation between cigarette smoking and breast cancer risk using data from a large case-control study conducted in Northern Italy

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SUBJECTS AND METHODS

Since January 1983, we have been conducting a case-control study of breast cancer The general basis of this investigation has already been reported (15,16). Briefly, trained interviewers identified and questioned women admitted for breast cancer and for a wide spectrum of other conditions to university and general hospitals of the greater Milan area. 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. The smokers and ex smokers (who had last smoked at least one year before) were asked the total duration of their habit (in years) and how many cigarettes per day, on the average, they had smoked.

The present study is based on data obtained before December, 1985.

CASES- The cases studied were women with histologically confirmed breast cancer, diagnosed within the year prior to interview and who were admitted to the "Ospedale Maggiore" of Milan (including the four largest teaching and general hospitals in Milan) and to the National Cancer Institute of Milan. All cases were interviewed in the hospital during first admission or subsequent follow-up A total 1,105 women below the age of 75 are included in the present analysis The median age was 52 years, and 437 cases (40%) were below 50 years of age.

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 within the same region, Lombardy. Potential controls were women admitted for acute diseases other than malignant, hormonal or gynecological disorders or, more generally, diseases judged to be unrelated to smoking or to any of the established or suspected risk factors for breast cancer. A total of 1,279 subjects aged 25 to 74 (median age = 56 years) were interviewed Among them, 33%·had been admitted because of traumatic conditions, 26% 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 26% for other illnesses such as eye, nose and throat, and teeth disorders

DATA ANALYSIS AND CONTROL OF CONFOUNDING - Odds ratios (as estimators of relative risks) (17), together with their 95% approximate confidence intervals (CI) (18) were computed from data stratified for age by the usual Mantel-Haenszel procedure (19) Tests for linear trend in risk, where appropriate, were done by the method given by Mantel (20)

Other potentially confounding variables, including determinants of smoking and the major risk factors for breast cancer, were examined and controlled for individually using the Mantel Haenszel procedure (19) Further, all the identified potential confounding factors were controlled simultaneously by means of multiple logistic regression, fitted by the method of maximum likelihood (17) Included simultaneously in the regression equations, besides the smoking related, factors considered were terms (selected a priori and in ordinal form) for the 16

following variables, age, marital status, education, social class, age at menarche, menopausal status, age at menopause, parity, number of livebirths, age at first birth, personal history of benign breast disease and of breast biopsies, family history of breast cancer, body mass index, oral contraceptive and estrogen replacement therapy use. The logistic equations were fitted using standard statistical packages (21).

RESULTS

In table 1 characteristics of breast cancer and control subjects are presented. Cases tended to be more educated, in the highest social classes, reported older age at first birth and were less frequently multiparous or in post menopause. Furthermore, cases reported more frequently a personal history of a benign breast disease or of breast biopsies

The smoking habits of patients with breast cancer and of the control group are compared in table 2 With women who had never smoked as the reference category, the age-adjusted relative risk of breast cancer for ex smokers (who had last smoked at least one year before) was 0.99 (95% CI = 0 71-1 39) and the overall relative risk for all current smokers together was 0 85 (95% CI = 0.70-1.04) When simultaneous allowance was made for the 16 major identified potential confounding factors the overall point estimate for current vs never smokers was 0.74, with 95% confidence interval 0.60 -0.92. The lower risk estimates from multiple logistic regression as compared with age-adjusted ones was chiefly explainable in terms of social class indicators, which were positively related both with smoking and breast cancer risk

Among current smokers of 1 to 14, 15 to 24 and 25 or more cigarettes per day the relative risk estimates were respectively 0 86, 0 82 and 0 58.

This negative trend in the relation between smoking and breast cancer risk persisted after simultaneous allowance for the 16 identified potential confounding factors using multiple logistic regression and the multivariate trend of decreasing risk with increasing number of cigarettes smoked was statistically significant (X_1^2 , ex smokers excluded, = 9.44, p = 0.002).

In table 3, separate age-adjusted relative risks are also shown in various strata of the covariates listed in table 1. For most covariates, the association between current smoking and risk of breast cancer was negative accross strata, thus showing no important interactions. The overall Mantel-Haenszel estimates varied between 0.76 for education and 0.92 for age at first birth and the 95% upper confidence limits were generally close to unity.

D I S C U S S I O N

This study showed a negative association between current smoking status and risk of breast cancer. The multivariate relative risk estimates suggest a 26% reduced risk for current smokers, with a 95% confidence interval of 8 to 40% and a statistically significant trend of a decreasing risk with increasing cigarette usage. As shown in a previous study (3), ex smokers had a relative risk close to unity, whereas the highest protection (twofold decreased risk) appeared in the heaviest current smoker group (25 or more cigarettes per day)

It is unlikely that recall bias considerably influenced the present findings At the time of data collection, the possible association between cigarette smoking and breast cancer had not gained widespread attention in the lay press in Italy, and was almost certainly unknown to the large majority of the subjects interviewed as well as to interviewers

Confounding bias is also unlikely, since allowance was made for several covariates, including menopausal status, age at menopause or other major identified risk factors for breast cancer

However, the possibility of selection bias cannot be easily discarded. Although the participation rate was over 98%, controls were admitted for acute diseases requiring hospitalization and judged to be unrelated with smoking, and there was no considerable difference in smoking prevalence among various diagnostic subcategories of controls, it is still possible that an association of the size that emerged in this study is partly or totally due to generalized artifactually raised smoking prevalence among hospital controls. Such a bias might be caused, for instance, by a prolonged hospital stay among smokers, with consequent greater probability of being interviewed. However, data from the 1983 National Health

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Household Survey conducted by the Italian Central Institute of Statistics (ISTAT) (22) do not suggest this view, since the duration of hospital stay was comparable for smokers and non smokers. It is further reassuring that a companion study conducted on the same population with similar methodology and criteria of selection of cases and controls showed elevated risk of cervical cancer in smokers (23).

The less restrictive nature of our control group, which included a broad spectrum of acute conditions, as compared with Rosenberg et al. (6) choice of other cancer patients as controls, may have contributed to reduce the potential bias-toward a negative result evoked by Baron (24). Nevertheless, it is still possible that the moderate negative relation with breast cancer is partly or totally artefactual and that the positive association between cigarette smoking and cervical cancer (23) was indeed underestimated on account of selection bias.

Thus, though the present findings are of clear interest in the current debate of smoking and estrogen-related diseases, it is in our opinion impossible to distinguish between two different interpretations: either female hormone correlates of smoking (i.e., the reduced levels of the three major endogenous estrogens) affect breast cancer risk (1,2) or a generalized uncontrolled bias is present in various diagnostic subcategories of hospital controls, producing spurious underestimates of the relative risk.

TABLE 1

CHARACTERISTICS OF WOMEN WITH BREAST CANCER AND CONTROLS. Milan, Italy, 1983-85.

CHARACTERISTICS	CASES % (N)[+]	CONTROLS % (N)[+]
AGE (yrs)		
< 40	11.5(127)	14.6(187)
40-49	28.1(310)	18.6(238)
→ 50	60.4(668)	66.8(854)
EDUCATION (yrs)		
< 7	55.7(610)	63.6(790)
→ 7	44.3(486)	36.4(453)
SOCIAL CLASS ▪		
I-II (highest)	12.2(135)	8.0(102)
III.	41.2(455)	31.6(404)
IV-V (lowest)	31.9(353)	36.4(466)
UNDEFINED	14.7(162)	24.0(307)
MARITAL STATUS		
Never married	14.6(161)	13.8(176)
Ever married	85.4(944)	86.2(1103)
BODY MASS INDEX (kg/m²)		
< 20	10.8(118)	13.8(176)
→ 20 < 25	48.7(533)	45.5(580)
→ 25 < 30	28.9(316)	30.2(385)
→ 30	11.7(128)	10.5(134)
AGE AT MENARCHE (yrs)		
< 11	16.3(180)	18.7(239)
12-14	67.5(745)	61.4(783)
→ 15	16.1(178)	20.0(254)
PARITY		
0	19.8(219)	20.0(256)
1-2	57.3(633)	53.8(688)
→ 3	22.9(253)	26.2(335)

TABLE 1 (continued)

CHARACTERISTICS	CASES % (N)[+]	CONTROLS % (N)[+]
AGE AT FIRST BIRTH (yrs) [b]		
<=19	4.1(36)	8 4(86)
20-24	35 9(318)	41 1(419)
25-29	39 5(350)	34 6(353)
->30	20 5(182)	15 9(162)
MENOPAUSAL STATUS		
PRE + IN	39 5(436)	32 6(417)
POST	60 5(668)	67 4(861)
AGE AT MENOPAUSE (yrs)		
< 40	7 5(51)	7 1(62)
40-49	43 3(296)	47 1(413)
->50	49 2(336)	45 9(401)
PERSONAL HISTORY OF BREAST BIOPSIES		
NO	92 7(1024)	98 4(1258)
YES	7 3(81)	1.6(21)
PERSONAL HISTORY OF BENIGN BREAST DISEASE		
NO	86 9(960)	93 4(1195)
YES	13 1(145)	6 6(84)
FAMILY HISTORY OF BREAST CANCER		
NO	88 0(972)	94 8(1213)
YES	12 0(133)	5 2(66)
USE OF ORAL CONTRACEPTIVES		
NEVER	90 6(1001)	92.7(1186)
EVER	9 4(104)	7 3(93)
USE OF ESTROGEN REPLACEMENT THERAPY		
NEVER	92.8(1025)	95 8(1225)
EVER	7 2(80)	4.2(54)

[+] 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.

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TABLE 2

RELATIVE RISK OF BREAST 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)			$X^2_{1(trend)}$[a]
				<15 N(%)	15-24 N(%)	=> 25 N(%)	
Breast cancer	800(72 4)	75(6 8)	230(20 8)	141(12 8)	77(7 0)	12(1.1)	
Controls	901(70 4)	85(6 6)	293(23 0)	172(13 4)	99(7 7)	22(1.7)	
M-H [b] Adjusted (95% CI)	1[+]	0 99 (0 71-1 37)	0 55 (0 70-1 04)	0 86 (0 65-1 10)	0 82 (0 60-1 13)	0 58 (0 29-1 17)	3 55 (p=0.06)
Multivariate [c] RR (95% CI)	1[+]	0 81 (0 57-1 44)	0 74 (0 50-0 92)	0 82 (0 63-1 06)	0 67 (0 48-0 94)	0 39 (0 18-0 83)	9 44 (p<0.01)

[a] Ex-smokers excluded based on three levels of exposure 0 15 15 cigarettes/day

[b] Indicates Mantel-Haenszel procedure adjusted for age

[c] Estimates from multiple logistic regression allowance was made for 16 identified potential distorting factors

[+] Reference category

T A B L E 3

RELATIVE RISK OF BREAST CANCER (CURRENT VS NEVER SMOKERS) FOR SELECTED COVARIATES. Milan, Italy, 1983-1985.

COVARIATE	CA/CO [+]	RR[§](95% Confidence interval)
AGE (yrs)		
< 40	120/173	0.58(0.36-0.95)
40-49	288/228	0.89(0.61-1.30)
=> 50	622/793	0.94(0.72-1.24)
M-H [*] Adjusted		0.85(0.70-1 04)
EDUCATION (yrs)		
< 7	583/748	0 81(0 61-1.09)
=> 7	438/410	0.72(0.54-0.96)
M-H [*] Adjusted		0.76(0.62-0.94)
SOCIAL CLASS &		
I-II (Highest)	114/88	1.17(0.65-2 10)
III	424/374	0.63(0.46-0.86)
IV-V (Lowest)	337/447	0.69(0.47-1.00)
UNDEFINED	155/285	1.18(0.72-1.96)
M-H [*] Adjusted		0.78(0.63-0 95)
MARITAL STATUS		
EVER MARRIED	880/1033	0.90(0.73-1.13)
NEVER MARRIED	150/161	0.58(0.35-0.96)
M-H [*] Adjusted		0.83(0.68-1.02)
BODY MASS INDEX (kg/m^2)		
< 20	108/161	0.39(0.23-0.67)
=> 20 < 25	494/535	0.84(0.63-1.12)
=> 25 < 30	297/368	1.55(1.04-2.31)
=> 30	121/127	0.56(0.29-1.09)
M-H [*] Adjusted		0.85(0.69-1.04)
AGE AT MENARCHE (yrs)		
< 11	168/219	0.89(0.58-1.37)
12-14	692/731	0.94(0.73-1.22)
=> 15	168/241	0.49(0.29-0.83)
M-H [*] Adjusted		0.84(0.69-1.03)

PARITY

0	203/235	0.63(0.41-0.96)
1-2	588/644	0.71(0.55-0.93)
=> 3	239/315	1.84(1.15-2.92)
M-H *Adjusted		0.83(0.68-1.01)

AGE AT FIRST BIRTH (yrs)

< 20	34/77	0.76(0.29-1.95)
20-24	295/392	0.77(0.53-1.13)
25-29	334/339	1.07(0.72-1.58)
=> 30	164/149	1.05(0.62-1.79)
M-H *Adjusted		0.92(0.73-1.16)

MENOPAUSAL STATUS

PRE - IN	403/396	0.72(0.53-0.97)
POST	626/797	0.93(0.71-1.23)
M-H *Adjusted		0.83(0.68-1.01)

AGE AT MENOPAUSE (yrs)

< 40	47/57	0.31(0.10-0.94)
=> 40	593/755	1.00(0.76-1.32)
M-H *Adjusted		0.93(0.71-1.21)

PERSONAL HISTORY OF BREAST BIOPSIES

NO	955/1174	0.83(0.68-1.02)
YES	75/20	1.14(0.38-3.98)
M-H *Adjusted		0.84(0.69-1.03)

PERSONAL HISTORY OF BENIGN BREAST DISEASE

NO	896/1117	0.80(0.65-0.99)
YES	134/77	0.89(0.48-1.63)
M-H *Adjusted		0.81(0.66-0.99)

FAMILY HISTORY OF BREAST CANCER

NO	914/1136	0.84(0.68-1.03)
YES	116/58	0.59(0.29-1.20)
M-H *Adjusted		0.81(0.66-0.99)

ORAL CONTRACEPTIVE USE

NEVER	937/1107	0.88(0.71-1.10)
EVER	93/87	0.51(0.28-0.92)
M-H Adjusted		0.83(0.68-1.01)

ESTROGEN REPLACEMENT THERAPY

NEVER	954/1146	0.81(0.66-0.99)
EVER	76/48	1.14(0.48-2.71)
M-H Adjusted		0.82(0.67-1.01)

+   Number of Cases/Number of controls, in some items, differences between totals are due to a few missing values

▮   Relative risk estimate adjusted for age (only in each stratum of various covariates considered)

▪   Indicates Mantel-Haenszel overall estimates adjusted for age and for each single covariate

&   Based on the head of the household's occupation

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APPENDIX B

CIGARETTE SMOKING AND THE RISK OF ENDOMETRIAL CANCER

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SUMMARY

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 1,122 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 age-adjusted relative risk estimates were for current 0 47.(95% confidence interval (CI) = 0 32-0 69) and 0.82 (95% CI = 0 49-1 35) 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 Consequently, simultaneous allowance for the major identified potential confounding factors did not materially influence the risk estimates (multiple logistic relative risk = 0 46; 95% CI = 0 30-0 70) 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. It was not possible to show that this finding was incidental and was due to confounding or other obvious bias Therefore, 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

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even when admission diagnosis was for non smoking-related conditions) cannot be ruled out.

INTRODUCTION

Since Mac Mahon et al. (1) demonstrated a reduced excretion of endogenous estrogens in urine sampled from women who smoked as compared to non smokers, several investigations were conducted to study the influence of smoking on 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

Three additional studies 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) Estimates were adjusted for major potential confounders Tyler et al (9) also investigated 437 endometrial cancer cases and 3,200 population-based control subjects under age 55 No association was shown between cigarette smoking and the risk of endometrial cancer

Finally, in a hospital-based case-control study of 510 women with endometrial cancer and 727 controls with other neoplasms (colorectal, melanomas, lymphoreticular, thyroid or adrenal gland tumours), Lesko et al (10) found a reduction of about 50 per cent 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

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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.

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 (11,12). Briefly, trained interviewers identified and questioned women admitted for cancers and for a wide spectrum of other 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. The smokers and ex-smokers (who had last smoked at least one year before) 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.

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 median age was 62 years

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 admitted for acute diseases other than.

1)malignant, 2)hormonal or 3)gynecological or, more generally, 4)judged to be unrelated to any of the established or suspected risk factors for endometrial neoplasms and to smoking Women who had undergone hysterectomy were excluded from the analysis (n= 157)

Of this final control series (1,122 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 median age was 54 years.

DATA ANALYSIS AND CONTROL OF CONFOUNDING - Odds ratios (as

estimators of relative risks, RRs) (13), together with their 95% approximate
confidence intervals (CI) (14) were derived from data stratified for age by the
usual Mantel-Haenszel procedure (15). Tests for linear trend in risk, where
appropriate, were done by the method given by Mantel (16).   —

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 (13) Included in the regression equations, besides the
smoking-related variables considered, were terms (in ordinal form)for age,
marital status, education, social class, age at menarche, menopausal status, age at
menopause, parity, number of livebirths, family gynaecologic cancer history, body
mass index, oral contraceptive and estrogen-replacement therapy use. The logistic
equations were fitted using standard statistical packages (17).

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 reference category, the

age-adjusted relative risk of endometrial cancer was 0.82 (95% CI = 0.49-1.35) for ex-, and 0.45 (95% CI = 0.31-0.67) 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).

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 demonstrated accross most of the strata considered.

Consequently, when indicators for age, socio-economic status (social class and education), gynecological 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 versus never smokers = 0.46 ; 95% CI = 0.30-0 70)

DISCUSSION

Our analyses showed a negative association between smoking and risk of endometrial cancer, with an overall reduction of about 50 per cent 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) (18) 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) (19). 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

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based on a series of over 1,000 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, as compared with breast neoplasms, might therefore reflect a stronger estrogen dependency of endometrial epithelium.

Thus, the findings of this study, however clearly unconclusive 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 considered in further epidemiological research on endometrial cancer

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)
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)

+ 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

T A B L E   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(%)	CURRENT smoker (No. cigarettes/day) <15 N (%)	=> 15 N(%)	$X^2_{1(trend)}$[a]
Endometrial cancer	301(84 3)	22(6.2)	21(5 9)	13(3 6)	
Controls *	789(70 3)	75(6 7)	152(13 6)	106(9 4)	
M-H [b] Adjusted (95% CI)	1*	0 82 (0 49-1 35)	0 44 (0 27-0 71)	0 48 (0 26-0-87)	13.50 (p < 0.001)
Multivariate [c] RR (95% CI)	1*	0.86 (0 50-1 46)	0 46 (0 28-0 75)	0 44 (0 23-0 86)	12 72 (p < 0.0001)

* Hysterectomized controls excluded (n=157)

a Ex-smokers excluded

b Indicates Mantel-Haenszel procedure adjusted for age

c Estimates from multiple logistic regression, allowance was made for all potential distorting factors

* Reference category

T A B L E 3

RELATIVE RISK OF ENDOMETRIAL CANCER (CURRENT VS NEVER SMOKERS) FOR 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		
EVER MARRIED	56/149	0.42(0.18-0.97)
NEVER MARRIED	279/898	0.45(0.29-0.69)
M-H *Adjusted		0.44(0.30-0.65)
BODY MASS INDEX (kg/m²)		
< 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)

TABLE 3 (continued)

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)

+ 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

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APPENDIX C

ADDITIONAL TABLES (table 4 to table 25)

T A B L E   4

RELATIVE RISK OF BREAST CANCER ACCORDING TO SMOKING HABITS AND ADJUSTED FOR EDUCATION   Milan, Italy, 1983-85.

	NEVER smoker N (%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N (%)	15-24 N (%)	=> 25 N(%)
EDUCATION < 7 YEARS					
Breast cancer	490(80.3)	27(4.4)	64(10.5)	25(4.1)	4(0.7)
Controls	613(77.6)	42(5 3)	92(11 6)	35(4.4)	8(1 0)
EDUCATION -> 7 YEARS					
Breast Cancer	302(62.1)	48(4.9)	77(15.8)	51(10.5)	8(1.6)
Controls	253(55.8)	43(9.5)	79(17.4)	64(14.1)	14(3.1)
M-H a RR	1 +	0.89	0.81	0.73	0.54
(95% CI)		(0.64-1.24)	(0 63-1 03)	(0 53-1 00)	(0 28-1.06)

a Indicates Mantel-Haenszel procedure, adjusted for age and education

+   Reference category

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TABLE 5
RELATIVE RISK OF BREAST CANCER ACCORDING TO SMOKING HABITS AND ADJUSTED FOR SOCIAL CLASS Milan, Italy, 1983-85.

	NEVER smoker N(%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N(%)	15-24 N(%)	-> 25 N(%)
CLASS I-II (Highest)					
Breast cancer	68(50 4)	21(15.6)	25(18 5)	17(12 6)	4(3 0)
Controls	57(55 9)	14(13 7)	13(12 7)	13(12 7)	5(4 9)
CLASS III					
Breast Cancer	326(71 6)	31(6.8)	58(12 7)	35(7 7)	5(1.1)
Controls	253(62 6)	30(7 4)	69(17 1)	42(10 4)	10(2.5)
CLASS IV-V (Lowest)					
Breast Cancer	284(80 5)	16(4 5)	38(10 8)	14(4 0)	1(0 3)
Controls	355(76 2)	19(4 1)	54(11 6)	34(7 3)	4(0 9)
CLASS UNDEFINED					
Breast Cancer	122(75 3)	7(4 3)	20(12 3)	11(6 8)	2(1 2)
Controls	236(78 7)	22(7 3)	36(12 0)	10(3 3)	3(1 0)
M-H [a] RR	1[+]	0 90	0 86	0.76	0.53
(95% CI)		(0.64-1 26)	(0 68-1 10)	(0 55-1 04)	(0 26-1.06)

[a] Indicates Mantel-Haenszel procedure, adjusted for age and social class

[+] Reference category

TABLE 6

RELATIVE RISK OF BREAST CANCER ACCORDING TO SMOKING HABITS AND ADJUSTED FOR MARITAL STATUS Milan, Italy, 1983-85.

	NEVER smoker N (%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N (%)	15-24 N (%)	=> 25 N(%)
NEVER MARRIED					
Breast cancer	116(72 0)	11(6 8)	18(11 2)	15(9 3)	1(0.6)
Controls	107(60.8)	15(8 5)	33(18 8)	17(9 7)	4(2 3)
EVER MARRIED					
Breast Cancer	684(72 5)	64(6.8)	123(13 0)	62(6 6)	11(1.2)
Controls	794(72.0)	70(6.3)	139(12 6)	82(7.4)	18(1.6)
M-H [a] RR	1[+]	0 98	0.86	0 82	0.59
(95% CI)		(0.71-1 36)	(0 67-1 10)	(0 60-1 12)	(0 30-1 17)

[a] Indicates Mantel-Haenszel procedure, adjusted for age and marital status

[+] Reference category

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T A B L E 7

RELATIVE RISK OF BREAST CANCER ACCORDING TO SMOKING HABITS AND ADJUSTED FOR BODY MASS INDEX Milan, Italy, 1983-85.

	NEVER smoker N (%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N (%)	15-24 N (%)	=> 25 N (%)
BODY MASS INDEX < 20					
Breast cancer	83(70 3)	10(8.5)	17(14 4)	7(5.9)	1(0.8)
Controls	92(52 3)	15(8.5)	40(22 7)	26(14 8)	3(1 7)
INDEX 20 < 25					
Breast Cancer	376(70 5)	39(7 3)	77(14 4)	35(6 6)	6(1 1)
Controls	396(68.3)	45(7.8)	81(14.0)	45(7.8)	13(2 2)
INDEX 25 <30					
Breast Cancer	230(72 8)	19(6 0)	34(10 8)	28(8 9)	5(1 6)
Controls	312(81 0)	17(4 4)	32(8 3)	18(4 7)	6(1 6)
INDEX -> 30					
Breast Cancer	104(81.3)	7(5.5)	12(9.4)	5(3.9)	-
Controls	99(73 9)	7(5.2)	18(13 4)	10(7.5)	-
M-H a RR	1[+]	1.00	0 87	0.82	0.59
(95% CI)		(0.72-1.39)	(0 68-1.12)	(0 60-1 12)	(0.30-1 17)

a Indicates Mantel-Haenszel procedure; adjusted for age and body mass index

[+] Reference category

TABLE 8

RELATIVE RISK OF BREAST CANCER ACCORDING TO SMOKING HABITS AND ADJUSTED FOR AGE AT MENARCHE Milan, Italy, 1983-85.

	NEVER smoker N (%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N (%)	15-24 N (%)	=> 25 N(%)
AGE AT MENARCHE < 11					
Breast cancer	116(64 4)	13(7 2)	28(15.6)	20(11 1)	4(2.2)
Controls	147(61 5)	20(8.4)	41(17.2)	24(10.0)	7(2.9)
AGE 12-14					
Breast Cancer	539(72.3)	53(7.1)	94(12 6)	52(7 0)	7(0.9)
Controls	569(72.7)	52(6 6)	89(11 4)	63(8 0)	10(1 3)
AGE -> 15					
Breast Cancer	144(80 9)	10(5.6)	18(10 1)	5(2.8)	1(0.6)
Controls	182(71.7)	13(5.1)	42(16 5)	12(4.7)	5(2.0)
M-H [a] RR	1[+]	1.01	0 88	0 83	0.62
(95% CI)		(0 73-1.40)	(0.69-1 13)	(0.60-1 13)	(0.31-1.24)

[a] Indicates Mantel-Haenszel procedure, adjusted for age and age at menarche

[+] Reference category

T A B L E   9

RELATIVE RISK OF BREAST CANCER ACCORDING TO SMOKING HABITS AND ADJUSTED FOR PARITY Milan, Italy, 1983-85.

	NEVER smoker N (%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N (%)	15-24 N (%)	=> 25 N(%)
PARITY 0					
Breast cancer	151(68 9)	16(7 3)	29(13 2)	20(9 1)	3(1 4)
Controls	154(60.2)	21(8.2)	51(19.9)	24(9.4)	6(2.3)
PARITY 1-2					
Breast Cancer	460(72.7)	45(7 1)	83(13 1)	38(6 0)	7(1 1)
Controls	470(68.3)	44(6.4)	99(14 4)	63(9.2)	12(1 7)
PARITY => 3					
Breast Cancer	189(74.7)	14(5 5)	29(11 5)	19(7 5)	2(0.8)
Controls	277(82.7)	20(6 0)	22(6.6)	12(3.6)	4(1.2)
M-H * RR	1[+]	0 97	0 85	0 81	0.57
(95% CI)		(0 70-1 35)	(0 67-1 09)	(0 59-1 10)	(0 29-1 13)

* Indicates Mantel-Haenszel procedure, adjusted for age and parity

+ Reference category

T A B L E   10

RELATIVE RISK OF BREAST CANCER ACCORDING TO SMOKING HABITS
AND ADJUSTED FOR AGE AT FIRST BIRTH Milan, Italy, 1983-85.

	NEVER smoker N(%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N(%)	15-24 N(%)	=> 25 N(%)
AGE 1ST BIRTH < 19					
Breast cancer	26(72 2)	2(5 6)	2(5.6)	6(16 7)	-
Controls	54(62.8)	9(10.5)	8(9.3)	12(14.0)	3(3.5)
AGE 1ST BIRTH 20-24					
Breast Cancer	235(73.9)	23(7 2)	37(11 6)	21(6 6)	2(0.6)
Controls	300(71 6)	27(6 4)	49(11.7)	35(8.4)	8(1.9)
AGE 1ST BIRTH 25-29					
Breast Cancer	264(75.4)	16(4.6)	50(14.3)	16(4.6)	4(1 1)
Controls	277(78 5)	14(4.0)	37(10.5)	20(5 7)	5(1.4)
AGE 1ST BIRTH => 30					
Breast Cancer	124(68.1)	18(9 9)	23(12 6)	14(7 7)	3(1.6)
Controls	115(71 0)	13(8 0)	26(16 0)	8(4 9)	-
M-H [a] RR	1[+]	1.08	0.98	0 86	0 63
(95% CI)		(0.74-1.59)	(0 73-1.30)	(0.60-1 24)	(0 27-1 44)

[a] Indicates Mantel-Haenszel procedure, adjusted for age and age at first birth

[+] Reference category

T A B L E   11

RELATIVE RISK OF BREAST CANCER ACCORDING TO SMOKING HABITS AND ADJUSTED FOR MENOPAUSAL STATUS   Milan, Italy, 1983-85.

	NEVER smoker N(%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N(%)	15-24 N(%)	=> 25 N(%)
PRE- + IN-MENOPAUSE					
Breast cancer	287(65.8)	33(7.6)	72(16.5)	39(8 9)	5(1.1)
Controls	253(60 7)	21(5 0)	74(17.7)	57(13.7)	12(2.9)
POST-MENOPAUSE					
Breast Cancer	512(76.6)	42(6.3)	69(10.3)	38(5 7)	7(1.0)
Controls	647(75.1)	64(7 4)	98(11.4)	42(4 9)	10(1.2)
M-H [a] RR	1[+]	0.99	0.85	0 82	0.58
(95% CI)		(0.71-1 37)	(0 67-1 09)	(0 60-1.12)	(0 29-1.16)

[a] Indicates Mantel-Haenszel procedure, adjusted for age and menopausal status

[+] Reference category

T A B L E   12

RELATIVE RISK OF BREAST CANCER ACCORDING TO SMOKING HABITS
AND ADJUSTED FOR AGE AT MENOPAUSE Milan, Italy, 1983-85.

| | NEVER smoker N(%) | EX smoker N(%) | CURRENT smoker (No. cigarettes/day) | | |
			<15 N(%)	15-24 N(%)	=> 25 N(%)
AGE AT MENOPAUSE < 40					
Breast cancer	42(82 4)	4(7 8)	5(9.8)	-	-
Controls	42(67.7)	5(8 1)	12(19.4)	3(4.8)	-
AGE AT MENOPAUSE 40-49					
Breast Cancer	212(71 6)	16(5 4)	42(14 2)	22(7 4)	4(1.4)
Controls	299(72 4)	31(7.5)	51(12 3)	27(6 5)	5(1.2)
AGE AT MENOPAUSE => 50					
Breast Cancer	269(80 1)	23(6.8)	25(7.4)	16(4.8)	3(0.9)
Controls	315(78.6)	30(7.5)	38(9.5)	13(3.2)	5(1.2)
M-H [a] RR	1[+]	0.82	0 87	1.13	0 89
(95% CI)		(0.55-1 23)	(0.62-1 20)	(0.72-1.78)	(0.34-2.32)

[a] Indicates Mantel-Haenszel procedure, adjusted for age and age at menopause

[+] Reference category

T A B L E   13

RELATIVE RISK OF BREAST CANCER ACCORDING TO SMOKING HABITS AND ADJUSTED FOR HISTORY OF BREAST BIOPSY. Milan, Italy, 1983-85.

	NEVER smoker N (%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N (%)	15-24 N (%)	=> 25 N(%)
BREAST BIOPSY NO					
Breast cancer	742(72 5)	69(6 7)	128(12 5)	74(7 2)	11(1 1)
Controls	885(70 3)	84(6 7)	168(13 4)	99(7.9)	22(1.7)
BREAST BIOPSY YES					
Breast Cancer	58(71 6)	6(7.4)	13(16.0)	3(3.7)	1(1.2)
Controls	16(76 2)	1(4 8)	1(4.8)	-	3(14.3)
M-H [a] RR. (95% CI)	1[+]	0.99 (0 71-1 37)	0.88 (0.69-1 13)	0.82 (0.60-1 12)	0.51 (0 25-1 00)

[a] Indicates Mantel-Haenszel procedure; adjusted for age and history of breast biopsy

[+] Reference category

T A B L E   14

RELATIVE RISK OF BREAST CANCER ACCORDING TO SMOKING HABITS AND ADJUSTED FOR HISTORY OF BENIGN BREAST DISEASE Milan, Italy, 1983-85.

	NEVER smoker N (%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N (%)	15-24 N (%)	=> 25 N(%)
BENIGN BREAT DISEASE NO					
Breast cancer	708(73 8)	64(6.7)	113(11.8)	65(6.8)	10(1.0)
Controls	850(71 1)	78(6 5)	160(13 4)	86(7 2)	21(1.8)
BENIGN BREAST DISEASE YES					
Breast Cancer	92(63 4)	11(7 6)	28(19.3)	12(8.3)	2(1.4)
Controls	51(60 7)	7(8 3)	12(14.3)	13(15.5)	1(1.2)
M-H a RR	1+	0 97	0 83	0.80	0.59
(95% CI)		(0 70-1 35)	(0 65-1.07)	(0 59-1 10)	(0.30-1.16)

a Indicates Mantel-Haenszel procedure; adjusted for age and history of benign breast disease

+ Reference category

T A B L E   15

RELATIVE RISK OF BREAST CANCER ACCORDING TO SMOKING HABITS AND ADJUSTED FOR FAMILY BREAST CANCER HISTORY Milan, Italy, 1983-85.

	NEVER smoker N (%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N (%)	15-24 N (%)	=> 25 N(%)
FAMILY BREAST CANCER HISTORY NO					
Breast cancer	714(73 5)	58(6 0)	129(13.3)	65(6.7)	6(0.6)
Controls	863(71 1)	77(6 3)	160(13 2)	94(7.7)	19(1 6)
FAMILY BREAST CANCER HISTORY YES					
Breast Cancer	86(64 7)	17(12 8)	12(9 0)	12(9.0)	6(4.5)
Controls	38(57 6)	8(12 1)	12(18 2)	5(7 6)	3(4.5)
M-H [a] RR	1[+]	0.91	0 86	0 80	0.45 [a]
(95% CI)		(0 71-1 37)	(0 67-1 09)	(0.58-1 09)	(0 22-0.93)

[a] Indicates Mantel-Haenszel procedure, adjusted for age and family breast cancer history

[+] Reference category

T A B L E   16

RELATIVE RISK OF BREAST CANCER ACCORDING TO SMOKING HABITS AND ADJUSTED FOR ORAL CONTRACEPTIVE USE Milan, Italy, 1983-85.

	NEVER smoker N (%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N (%)	15-24 N (%)	=> 25 N(%)
ORAL CONTRACEPTIVE USE NO					
Breast cancer	744(74 3)	64(6.4)	117(11 7)	65(6,5)	11(1.1)
Controls	863(72 8)	79(6.7)	153(12 9)	73(6.2)	18(1 5)
ORAL CONTRACEPTIVE USE YES					
Breast Cancer	56(53 8)	11(10.6)	24(23.1)	12(11 5)	1(1.0)
Controls	38(40.9)	6(6.5)	19(20.4)	26(28.0)	4(4.3)
M-H ^{a} RR	1[+]	0.97	0.85	0 81	0.57
(95% CI)		(0.70-1 35)	(0 66-1 09)	(0 60-1 12)	(0 28-1.15)

[a] Indicates Mantel-Haenszel procedure; adjusted for age and oral contraceptive use

[+] Reference category

T A B L E   17

RELATIVE RISK OF BREAST CANCER ACCORDING TO SMOKING HABITS AND ADJUSTED FOR ESTROGEN REPLACEMENT THERAPY   Milan, Italy, 1983-85.

	NEVER smoker N (%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N (%)	15-24 N (%)	=> 25 N(%)
ESTROGEN REPLACEMENT THERAPY NEVER					
Breast cancer	743(72 5)	71(6 9)	129(12 6)	72(7.0)	10(1.0)
Controls	864(70.5)	79(6 4)	164(13 4)	98(8 0)	20(1.6)
ESTROGEN REPLACEMENT THERAPY EVER					
Breast Cancer	57(71 3)	4(5.0)	12(15.0)	5(6.3)	2(2.5)
Controls	37(68 5)	6(11.1)	8(14 8)	1(1.9)	2(3.7)
M-H [a] RR	1[+]	0.98	0.85	0 82	0.54
(95% CI)		(0 71-1 36)	(0 67-1 09)	(0 60-1 13)	(0 27-1 10)

[a] Indicates Mantel-Haenszel procedure, adjusted for age and estrogen replacement therapy

[+] Reference category

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T A B L E   18

RELATIVE RISK OF ENDOMETRIAL CANCER ACCORDING TO SMOKING HABITS AND ADJUSTED FOR EDUCATION Milan, Italy, 1983-85.

	NEVER smoker N (%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N(%)	15-24 N(%)	=> 25 N(%)
EDUCATION < 7 YEARS					
Endom. cancer	230(87.8)	11(4.2)	10(3.8)	10(3 8)	1(0 4)
Controls*	533(78 3)	37(5 4)	78(11 5)	27(4.0)	6(0.9)
EDUCATION => 7 YEARS					
Endom. cancer	59(72.0)	10(12.2)	12(14.6)	1(1.2)	-
Controls*	223(54 8)	38(9.3)	73(17.9)	59(14 5)	14(3.4)
M-H[a] RR	1[+]	0.82	0.47	0.54	0.20
(95% CI)		(0.50-1.35)	(0.29-0.76)	(0 28-1.06)	(0.03-1.44)

[a] Indicates Mantel-Haenszel procedure; adjusted for age and education.

[+] Reference category   * Hysterectomized controls excluded (n=157)

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T A B L E 19
RELATIVE RISK OF ENDOMETRIAL CANCER ACCORDING TO SMOKING HABITS
AND ADJUSTED FOR SOCIAL CLASS Milan, Italy, 1983-85.

	NEVER smoker N(%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N(%)	15-24 N(%)	=> 25 N(%)
CLASS I-II (Highest)					
Endom. cancer	17(77.3)	1(4.5)	2(9.1)	2(9.1)	-
Controls*	52(55.9)	12(12.9)	13(14.0)	12(12.9)	4(4.3)
CLASS III					
Endom. cancer	72(78.3)	6(6.5)	8(8.7)	6(6.5)	-
Controls*	213(61.4)	26(7.5)	61(17.6)	37(10.7)	10(2.9)
CLASS IV-V (Lowest)					
Endom cancer	111(84.1)	9(6.8)	9(6.8)	2(1.5)	1(0.8)
Controls*	305(76.1)	18(4.5)	47(11.7)	27(6.7)	4(1.0)
CLASS UNDEFINED					
Endom cancer	101(91.0)	6(5.4)	3(2.7)	1(0.9)	-
Controls*	219(77.9)	19(6.8)	31(11.0)	10(3.6)	2(0.7)
M-H[a] RR	1[+]	0.85	0.47	0.47	0.15
(95% CI)		(0.52-1.38)	(0.29-0.75)	(0.24-0.91)	(0.02-0.94)

[a] Indicates Mantel-Haenszel procedure; adjusted for age and social class

[+] Reference category   * Hysterectomized controls excluded (n=157)

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T A B L E   20

RELATIVE RISK OF ENDOMETRIAL CANCER ACCORDING TO SMOKING HABITS AND ADJUSTED FOR MARITAL STATUS Milan, Italy, 1983-85.

	NEVER smoker N(%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N(%)	15-24 N(%)	=> 25 N(%)
NEVER MARRIED					
Endom. cancer	48(77 4)	6(9 7)	8(12 9)	-	-
Controls*	97(59 1)	15(9 1)	32(19 5)	16(9 8)	4(2 4)
EVER MARRIED					
Endom. cancer	253(85.8)	16(5.4)	14(4.7)	11(3 7)	1(0 3)
Controls*	692(72.2)	60(6.3)	120(12.5)	70(7.3)	16(1.7)
M-H a RR	1+	0.79	0 44	0 49	0.16
(95% CI)		(0.48-1.31)	(0.28-0.71)	(0.25-0 93)	(0 03-0 95)

a Indicates Mantel-Haenszel procedure, adjusted for age and marital status

+ Reference category   * Hysterectomized controls excluded (n=157)

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T A B L E 21

RELATIVE RISK OF ENDOMETRIAL CANCER ACCORDING TO SMOKING HABITS AND ADJUSTED FOR BODY MASS INDEX (Kg/m²) Milan, Italy, 1983-85.

	NEVER smoker N (%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N (%)	15-24 N (%)	=> 25 N(%)
BODY MASS INDEX < 20					
Endom. cancer	18(78.3)	2(8.7)	3(13 0)	-	-
Controls*	85(53 5)	13(8 2)	36(22 6)	22(13 8)	3(1 9)
INDEX 20 < 25					
Endom. cancer	77(73 3)	11(10 5)	10(9 5)	6(5.7)	1(1 0)
Controls*	350(68 1)	40(7 8)	75(14 6)	38(7 4)	11(2.1)
INDEX 25<30					
Endom. cancer	101(87.8)	3(2 6)	6(5.2)	5(4.3)	-
Controls*	267(80.9)	15(4 5)	25(7 6)	17(5 2)	6(1.8)
INDEX => 30					
Endom. cancer	96(91 4)	6(5.7)	3(2 9)	-	-
Controls*	85(73 9)	6(5 2)	15(13 0)	9(7 8)	-
M-H ª RR	1+	0 94	0.54	0 57	0.20
(95% CI)		(0.57-1.56)	(0 34-0 87)	(0.30-1.07)	(0.04-1 19)

ª Indicates Mantel-Haenszel procedure, adjusted for age and body mass index

+ Reference category   * Hysterectomized controls excluded (n=157)

T A B L E 22

RELATIVE RISK OF ENDOMETRIAL CANCER ACCORDING TO SMOKING HABITS AND ADJUSTED FOR PARITY Milan, Italy, 1983-85.

	NEVER smoker N(%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N(%)	15-24 N(%)	-> 25 N(%)
PARITY 0					
Endom cancer	70(74 5)	9(9 6)	13(13 8)	2(2 1)	-
Controls*	136(58 6)	20(8 6)	48(20 7)	22(9 5)	6(2.6)
PARITY 1-2					
Endom cancer	145(87 3)	7(4 2)	6(3.6)	7(4.2)	1(0 6)
Controls*	411(68.6)	38(6.3)	85(14.2)	54(9.0)	11(1.8)
PARITY => 3					
Endom. cancer	86(88 7)	6(6.2)	3(3.1)	2(2.1)	-
Controls*	242(83.2)	17(5 8)	19(6.5)	10(3.4)	3(1.0)
M-H ª RR	1+	0 77	0 42	0 47	0.18
(95% CI)		(0.47-1.28)	(0.26-0 67)	(0 24-0.91)	(0.03-1 17)

ª Indicates Mantel-Haenszel procedure, adjusted for age and parity

+ Reference category   * Hysterectomized controls excluded (n=157)

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T A B L E 23

RELATIVE RISK OF ENDOMETRIAL CANCER ACCORDING TO SMOKING HABITS
AND ADJUSTED FOR MENOPAUSAL STATUS. Milan, Italy, 1983-85.

	NEVER smoker N (%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N (%)	15-24 N (%)	=> 25 N(%)
PRE- + IN-MENOPAUSE					
Endom. cancer	58(77 3)	6(8 0)	7(9 3)	4(5 3)	-
Controls*	252(61 2)	21(5.1)	72(17.5)	55(13 3)	12(2.9)
POST-MENOPAUSE					
Endom. cancer	243(86 2)	16(5.7)	14(5 0)	8(2 8)	1(0.4)
Controls*	536(75 6)	54(7 6)	80(11.3)	31(4 4)	8(1.1)
M-H ª RR	1⁺	0.77	0 43	0 51	0.15
(95% CI)		(0.47-1.26)	(0 27-0 70)	(0 27-0 98)	(0 02-0 95)

ª Indicates Mantel-Haenszel procedure, adjusted for age and menopausal status

⁺ Reference category   * Hysterectomized controls excluded (n=157)

T A B L E 24

RELATIVE RISK OF ENDOMETRIAL CANCER ACCORDING TO SMOKING HABITS AND ADJUSTED FOR AGE AT MENOPAUSE Milan, Italy, 1983-85.

	NEVER smoker N (%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N (%)	15-24 N (%)	=> 25 N(%)
AGE AT MENOPAUSE < 40 YEARS					
Endom. cancer	7(100 0)	-	-	-	-
Controls*	17(68 0)	2(8.0)	5(20 0)	1(4.0)	-
AGE AT MENOPAUSE 40-44 YEARS					
Endom cancer	16(88 9)	-	2(11.1)	-	-
Controls*	69(71 1)	10(10 3)	11(11.3)	6(6.2)	1(1.0)
AGE AT MENOPAUSE 45-49 YEARS					
Endom cancer	65(85.5)	4(5 3)	4(5 3)	3(3.9)	-
Controls*	174(74 4)	16(6 8)	30(12 8)	12(5.1)	2(0 9)
AGE AT MENOPAUSE => 50 YEARS					
Endom. cancer	164(86 3)	11(5.8)	10(5.3)	4(2 1)	1(0 5)
Controls*	287(78 4)	26(7.1)	36(9.8)	12(3 3)	5(1.4)
M-H a RR	1[+]	0 61	0 45	0 52	0 25
(95% CI)		(0.34-1 12)	(0 26-0.77)	(0 23-1 21)	(0 03-1.80)

a Indicates Mantel-Haenszel procedure, adjusted for age and age at menopause

[+] Reference category   *   Hysterectomized controls excluded (n=157)

T A B L E   25

RELATIVE RISK OF ENDOMETRIAL CANCER ACCORDING TO SMOKING HABITS
AND ADJUSTED FOR ESTROGEN REPLACEMENT THERAPY - Milan, Italy, 1983-85.

	NEVER smoker N (%)	EX smoker N(%)	CURRENT smoker (No. cigarettes/day)		
			<15 N(%)	15-24 N(%)	=> 25 N(%)

ESTROGEN REPLACEMENT THERAPY NEVER

Endom cancer	258(83 5)	20(6 5)	20(6.5)	11(3.6)	-
Controls[*]	762(70 5)	72(6 7)	144(13 3)	85(7 9)	18(1.7)

ESTROGEN REPLACEMENT THERAPY EVER

Endom cancer	43(89.6)	2(4 2)	2(4 2)	-	1(2 1)
Controls[*]	27(65 9)	3(7.3)	8(19.5)	1(2.4)	2(4.9)

M-H[a] RR	1[+]	0 83	0 45	0 53	0 25
(95% CI)		(0 50-1 38)	(0 28-0 72)	(0 27-1.02)	(0 04-1 65)

[a] Indicates Mantel-Haenszel procedure, adjusted for age and estrogen replacement therapy

[+] Reference category   [*] Hysterectomized controls excluded (n=157)

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APPENDIX D

QUESTIONNAIRE (Italian)

MAMMELLA/OVAIO/ENDOMETRIO

CARD. 1

Studio n°	/ / /	1-2
Paziente n°	/ / / / /	3-7
Caso =1 Controllo =2	/ /	8
Card n°	/1/	9

Intervistatore: .... / / / 10-11

Nome del paziente _____

Indirizzo _____

Tel.   /

Sesso: Maschile=1   Femminile=2 /2/ 12

Ospedale: _____ / / / 13-14

Reparto: medicina =1   chirurgia=2   ostet.ginecol.=3
           ortopedia=4   ORL   =5   altro   =6   / / 15

Data di ammissione   / / / / / /

Data intervista   g   m   a   / / / / / / / 16-19

Cartella n°   / / / / / / /

Data di nascita   g   m   a   / / / / / / 20-25

Età / / / 26-27

Peso (in Kg) / / / / 28-30

Altezza (in cm) / / / / 31-33

Stato civile: mai sposato/a   =1   coniugato/a =2
                separato/a, divorziato/a =3   vedovo/a   =4   / / 34

Età al primo matrimonio / / / 35-36

Anni di istruzione   paziente   / / / 37-38
                                                  coniuge   / / / 39-40

Professione paziente _____ / / 41

Professione coniuge _____ / / 42

Diagnosi principale _____ (I.C.D.) / / / / / 43-46

Area di Residenza: Lombardia=4; Nord/Centro=5; Sud=6   / /0/ 47-48

Data di diagnosi   m   a   / / / / 49-52

Diagnosi secondaria _____ (I.C.D.) / / / / / 53-56

N° preparati istologici / / / / / / / / /   / / / / / / / /

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FUMO

Mai fumatore/trice=1;   fumatore/trice=2;   ex-fumatore/trice=3   /_/ 57

se ex-fumatore/trice, da quanti anni ha smesso di fumare?   /_/_/ 58-59

se fumatore/ex-fumatore/trice: sigarette, n°/die   /_/_/ 60-61

sigari, n°/die   /_/_/ 62-63

pipa, grammi tabacco/die   /_/_/ 64-65

durata (anni)   /_/_/ 66-67

Tipo di sigarette principalmente fumate,
nome commerciale: _____   /_/ 68

ASSUNZIONE DI METILXANTINE

Beve :	n° tazze/die	Durata (anni)	
Caffè	/_/	/_/_/	69-71
Caffè decaffeinato	/_/	/_/_/	72-74
Tè	/_/	/_/_/	75-77
Bevande contenenti cola	/_/	/_/_/	78-80

CARD 2

Paziente n°   /_/_/_/_/_/ 1-5

Caso=1   Controllo=2   /_/ 6

Card n°   /2/ 7

BEVANDE ALCOOLICHE

Beve?	n° giorni/settimana	n° bicchieri/die	Durata (anni)	
Vino	/_/	/_/	/_/_/	8-11
Birra	/_/	/_/	/_/_/	12-15
Liquori	/_/	/_/	/_/_/	16-19

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ABITUDINI DIETETICHE

Consuma abitualmente ?

Latte (n° bicchieri/settimana) .... (assunzione occasionale = 98) / / / 20-21

Carne (n° porzioni/settimana) .... " ...... " ..... " / / / 22-23

Fegato (n° porzioni/settimana) .... " ...... " ..... " / / / 24-25

Carote (n° porzioni/settimana) .... " ...... " ..... " / / / 26-27

Vegetali verdi (n° porzioni/settimana) ...... " ...... " ..... " / / / 28-29

Frutta fresca (n° porzioni/settimana) .... " ...... " ..... " / / / 30-31

Uova (n°/settimana) .... " ...... " ..... " / / / 32-33

Prosciutto ed insaccati (n° porzioni/settimana)" ...... " ..... " / / / 34-35

Pesce (n° porzioni/settimana) .... " ...... " ..... " / / / 36-37

Formaggio (n° porzioni/settimana)............ " ...... " ..... " / / / 38-39

Pane integrale, o altri alimenti integrali:

                                    mai =1
  saltuariamente (> 1 giorno/settimana)=2
  abitualmente (> 4 giorni/settimana)   =3   / / 40

Come descrive (*) il suo consumo di:

  burro... / / 41

  margarina .... / / 42

  olio .... / / 43

(*) scarso =1   normale =2   elevato =3

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ANAMNESI PATOLOGICA

Ha mai avuto le seguenti patologie (od effettuato i seguenti trattamenti) ?

	Età di prima diagnosi
Diabete mellito	/. / / 44-45
Patologie della tiroide (specificare _____)	/ / / 46-47
Obesità (> 20% del peso ideale)	/ / / 48-49
Ipertensione (trattata,con farmaci)	/ / / 50-51
Iperlipidemie	/ / / 52-53
Colelitiasi	/ / / 54-55
Cisti/tumori ovarici	/ / / 56-57
Fibromiomi uterini	/ / / 58-59
Problemi di sterilità.	/ / / 60-61
Patologia mammaria benigna	/ / / 62-63
Biopsie mammarie	/ / / 64-65
Tumori maligni _____ (I.C.D.) / / / / /	/ / / 66-71
(specificare)	
Isterectomia	/ / / 72-73
Ovariectomia monolaterale	/ / / 74-75
Ovariectomia bilaterale	/ / / 76-77
Infezioni pelviche (salpingiti, etc.)	/ / / 78-79

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CARD 3

Paziente n°   /_/_/_/_/_/ 1-5

Caso=1   Controllo=2   /_/ 6

Card n°   /3/ 7

STORIA OSTETRICA E GINECOLOGICA

Età al menarca   /_/_/ 8-9

Cicli mestruali:

    regolari=1   irregolari=2   /_/ 10

Stato menopausale

pre- =1   in- =2   post-menopausa=3   /_/ 11

Se in post-menopausa: età alla menopausa   /_/_/ 12-13

Tipo di menopausa:

    naturale=1   chirurgica =2
    atcinica=3   farmacologica=4   /_/ 14

Numero totale di:

Nati   /_/ 15

Aborti spontanei   /_/ 16

I.V.G.   /_/ 17

Età alla prima gravidanza   /_/_/ 18-19

Età al primo parto   /_/_/ 20-21

Età all'ultimo parto   /_/_/ 22-23

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HA MAI USATO I SEGUENTI CONTRACCETTIVI O FARMACI?

Contraccettivi orali=1; farmaci per minaccia d'aborto=2; per irregolarità mestruali=3; terapia della sterilità=4; altri ormoni femminili (per acne, ipertricosi,...) =5; IUD=6; diaframma od altri contraccettivi di barriera (preservativo) con regolarità=7; vitamina A=8; terapie sostitutive in menopausa=9.

Età inizio	Durata mesi	Indicazione	Farmaco, nome commerciale:	Codifica
/_/_/	/_/_/	/_/	_____	/_/_/ 24-30
/_/_/	/_/_/	/_/	_____	/_/_/ 31-37
/_/_/	/_/_/	/_/	_____	/_/_/ 38-44
/_/_/	/_/_/	/_/	_____	/_/_/ 45-51
/_/_/	/_/_/	/_/	_____	/_/_/ 52-58
/_/_/	/_/_/	/_/	_____	/_/_/ 59-65
/_/_/	/_/_/	/_/	_____	/_/_/ 66-72

ANAMNESI FAMILIARE

n° sorelle (vive o decedute)   /_/ 73

Sua madre o le sue sorelle hanno mai avuto:

	Madre/si=1	Sorelle: segnare n° con tumore
Tumori maligni della mammella	/_/	/_/ 74-75
Tumori maligni del corpo dell'utero (endometrio)	/_/	/_/ 76-77
Tumori maligni dell'ovaio	/_/	/_/ 78-79

ADDENDUM

Durata media cicli mestruali: <21 giorni =1; 21-25 =2; 26-30 =3;

31-35 =4; >35 giorni =6;

Totalmente irregolari =8;   /_/ 80

Non so =9

Paziente n°   / / / / / /   1-5

Caso=1   Controllo=2   / /   6

Card n°   /4/   7

DIAGNOSI PRECOCE DEL CARCINOMA DELLA MAMMELLA

Esegue solitamente autopalpazione mammella

   (almeno 1 volta al mese)?   NO=1   SI=2   / /   8

   Se SI, da quale età?   / . / /   9-10

Quante mammografie ha eseguito

   (prima della diagnosi o sospetto dell'attuale patologia)?   / /   11

A quale età ha eseguito la prima?   / / /   12-13

A quale età l'ultima?   / / /   14-15

Quante termografie ha eseguito

   (prima della diagnosi o sospetto dell'attuale patologia)?   / /   16

A quale età ha eseguito la prima?   / / /   17-18

A quale età l'ultima?   / / /   19-20

RECETTORI (carcinomi mammella/ovaio)

Estrogenici :   Negativi=1   Incerti=2   Positivi=3

           Non dosati/Non so =9   / /   21

   Livello (Fmol/mg)   / / /   22-23

Progestinici: Negativi=1   Incerti=2   Positivi=3   / /   24

   Livello (Fmol/mg)   / / /   25-26

APPENDIX E

QUESTIONNAIRE (English)

CARD 1

Study No	1-2
Patient No	3-7
Case = 1 Control = 2	8
Card No	9

Interviewer :.. 10-11

Name of the patient _____

Address _____

                                    Tel. ____/_____

Sex : Male = 1 Female = 2	12
Hospital : _____	13-14
Ward : medicine = 1 surgery = 2 obstet-gynecol. = 3	
orthopedy= 4 ORL = 5 other = 6	15
Date of admission _____	
Date of interview _____	16-19
File No _____	
Date of birth	20-25
Age	26-27
Weight (in Kgs)	28-30
Height (in cm)	31-33
Civil status : never married = 1 married = 2	
separate, divorced = 3 widow = 4	34
Age at first marriage	35-36
Years of education patient	37-38
husband	39-40
Profession of patient _____	41
Profession of husband _____	42

Main diagnosis _____. (I.C.D.)	43-46
Residential Area : Lombardy = 4; North/Center = 5; South = 6	47-48
Date of diagnosis	49-52
Secondary diagnosis _____ (I.C.D.)	53-56

No histological exams _____   _____

SMOKING

Never smoker = 1;   smoker = 2;   ex-smoker = 3   57

if ex-smoker,sinns how many years have you stopped ?   58-59

if smoker / ex-smoker :   cigarettes No/day   60-61

                                       cigars   No/day   62-63

                                       pipe, grams tobacco/day   64-65

                                       duration (years)   66-67

Type of cigarette principally smoked,
commercial name : _____   68

ABSORPTION OF METHYLXANTHINES

Do you drink ?	No cups/day	Duration (years)	
Coffee	_____	_____	69-71
Decaffeinated coffee	_____	_____	72-74
Tea	_____	_____	75-77
Drinks containing Kola	_____	_____	78-80

CARD 2

Patient No   1-5

Case = 1   Control = 2   6

Card No   7

ALCOHOLIC BEVERAGES

Do you drink ?	No days/week	No glasses/day	Duration (years)	
Wine	_____	_____	_____	8-11
Beer	_____	_____	_____	12-15
Liquors	_____	_____	_____	16-19

DIETARY HABITS

Usual consumption ?

Milk (No glasses/week)	(occasionally = 98)		20-21
Meat (No portions/week)	"	"	22-23
Liver (No portions/week)	"	"	24-25
Carots (No portions/week)	"	"	26-27
Green vegetables (No portions/week)	"	"	28-29
Fresh fruits (No portions/week)	"	"	30-31
Eggs (No/week)	"	"	32-33
Jam and sausages (No portions/week)	"	"	34-35
Fish (No portions/week)	"	"	36-37
Cheese (No portions/week)	"	"	38-39

Wholemealbread :

$$\begin{array}{ll} \text{never} & = 1 \\ \text{intermittently} \ (> \ 1 \ \text{day/week}) & = 2 \\ \text{usually} \qquad (> \ 4 \ \text{days/week}) & = 3 \end{array}$$

40

How do you describe (*) your consumption of :

butter	41
margarine	42
oil	43

(*) scarce = 1   normal = 2   high = 3

PATHOLOGICAL ANAMNESIS

Have you ever had the following diseases or/therapies ?

	Age of first diagnosis
Diabetes mellitus	44-45
Diseases of thyroid (specify_____)	46-47
Obesity (> 20 %/o of ideal weight)	48-49
Hypertension (medically treated)	50-51
Hyperlipidemias	52-53
Cholelithiasis	54-55
Ovarian cysts/tumours	56-57
Uterine fibromyomas	58-59
Sterility problems	60-61
Benign disease of breast	62-63
Breast biopsies	64-65
Malignant tumours_____ (I.C.D.)_____ (specify)	66-67
Hysterectomy	72-73
Monolateral ovariectomy	74-75
Bilateral ovariectomy	76-77
Pelvic infections (salpingitis, etc.)	78-79

Patient No   1-5

Case = 1   Control = 2   6

Card No   7

OBSTETRICAL AND GYNECOLOGICAL HISTORY

Age at menarche   8-9

Menstrual cycles :

                 regular = 1   irregular = 2   10

Menopausal status

pre = 1   in- = 2   post-menopausal = 3   11

If in post-menopause : age at menopause   12-13

Type of menopause :

                 natural = 1   surgical   = 2

                 actinic = 3   pharmacological = 4   14

Total number of :

Births   15

Spontaneous abortions   16

Induced abortions   17

Age at first pregnancy   18-19

Age at first birth   20-21

Age at last birth   22-23

HAVE YOU EVER USED THE FOLLOWING OC OR DRUGS :

Oral contraceptives = 1;   drugs for miscarriages = 2;   menstrual irregularities = 3;
sterility = 4;   other femals hormones (for acne, hypertrichosis)= 5 ;   IUD = 6;
diaphragm or other contraceptives (preservatives) regularly = 7;   vitamine = 8 ;
estrogen replacement therapy for menopause = 9.

Age start	Duration months	Indication	Drug, commercial name	
___	___	___	___	24-30
___	___	___	___	31-37
___	___	___	___	38-44
___	___	___	___	45-51
___	___	___	___	52-58
___	___	___	___	59-65
___	___	___	___	66-72

FAMILIAL ANAMNESIS

No sisters (alive, or dead)   73

Have your mother or your sister ever had :

	Mother/yes = 1	Sister : note No with tumour	
Malignant breast tumours	_____	_____	74-75
Malignant tumours of uterine corpus (endometrium)	_____	_____	76-77
Malignant tumours of ovary	_____	_____	78-79

ADDENDUM

Duration of menstrual cycles : < 21 days = 1;   21-25 =.2;   26-30 = 3;
                               31-35 = 4 ; > 35 days = 6 ;
                               Totally irregular = 8
                               Don't know = 9   80

Patient No.   1-5

Case = 1   Control = 2   6

Card No.   7

EARLY DIAGNOSIS OF BREAST CANCER

Do you usually practice breast self-examination ?

   (at least once a month)   NO = 1   YES = 2   8

   If YES, since what age ?   9-10

How many mammographies did you have ?

   (before the diagnosis or suspect of actual disease ?)   11

At what age did you have the first one ?   12-13

At what age the last one ?   14-15

How many thermographies did you have ?

   (before the diagnosis or suspect of actual disease ?)   16

At what age did you have the first one ?   17-18

At what age the last one ?   19-20

RECEPTORS (breast/ovarian cancer)

Estrogenic :   Negative = 1   Uncertain = 2   Positive = 3

              Not assessed/Don't know = 9   21

Level (Fmol/mg)   22-23

Progestinic :   Negative = 1   Uncertain = 2   Positive = 3   24

Level (Fmol/mg)   25-26