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DIABETES AND ENDOMETRIAL CANCER: AN ITALIAN CASE-CONTROL STUDY

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We considered the association between diabetes and risk of endometrial cancer using data from a large case-control study conducted in Italy. Cases were 752 women with incident, histologically confirmed endometrial cancer <75 years of age (median age 60 years, range 28–74) admitted to a network of hospitals in Milan. Controls were 2,606 patients (median age 54 years, range 25–74) aged <75 years, admitted for acute non-neoplastic, non-gynecological, non-hormone-related conditions to the same network of hospitals where cases had been identified. A total of 132 (17.6%) cases and 116 controls (4.5%) reported a history of diabetes. The corresponding multivariate odds ratio (OR) was 2.9 [95% confidence interval (CI) 2.2–3.9]. No association emerged with diabetes diagnosed under age 40 (likely to be insulin-dependent diabetes), whereas the OR of endometrial cancer was 3.1 (95% CI 2.3–4.2) for diabetes diagnosed at age ≥40 years. The OR of endometrial cancer in women with history of diabetes was 3.0 for women with a body mass index (BMI) (QI) kg/m² <25, 3.6 for those with a BMI of 25–29, and 3.3 for those with a BMI ≥30. No consistent interaction or modifying effect was observed for any other covariate. Our results confirm that non-insulin-dependent diabetes is associated with the risk of endometrial cancer. The association may be mediated through elevated oestrogen levels in diabetic women, hyperinsulinemia or insulin-like growth factor-I (IGF-I). ***Int. J Cancer*** **81:539–542, 1999.**
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Several studies have reported an increased risk of cancer of uterine corpus in women with a history of diabetes (Brinton *et al.*, 1992; La Vecchia *et al.*, 1994; Levi *et al.*, 1993; Maatela *et al.*, 1994; O'Mara *et al.*, 1985; Parazzini *et al.*, 1991; Rubin *et al.*, 1990; Weiderpass *et al.*, 1997; Wideroff *et al.*, 1997). The biological explanation of this association, however, remains unclear. The observations that diabetes is more common in overweight women (a well-defined risk factor for endometrial cancer; Parazzini *et al.*, 1991) and that endometrial cancer is a disease of affluent societies, have suggested that a history of diabetes may represent an indicator of nutritional factors related to endometrial cancer risk. Few studies, however, have taken into account the potential confounding role of obesity and other potential confounding factors (O'Mara *et al.*, 1985).

Attention has been paid to the role of hyperinsulinemia, a feature of non-insulin dependent diabetes mellitus (NIDDM), on hormone-related neoplasias (Kazer, 1995). Hyperinsulinemia appears to increase ovarian steroid production (Poretsky and Kalin, 1987), stimulate conversion of testosterone to oestradiol (Garzo and Dorrington, 1984) and suppress circulating concentrations of sex-hormone-binding-globulin (SHBG) (Nestler *et al.*, 1991). Further, hyperinsulinemia is associated with high levels of insulin-like growth factor-I (IGF-I; Kazer, 1995), which may act synergistically with an increased oestrogen activity, and IGF-I has been suggested to have a carcinogenic effect on breast and colon cancer (Aaronson, 1991; Giovannucci, 1995; Kazer, 1995; La Vecchia *et al.*, 1997).

We have therefore considered the association between diabetes and risk of endometrial cancer using data from a case-control study conducted in Italy (Parazzini *et al.*, 1998), based on a large sample size, and with the availability of detailed information on covariates of interest.

SUBJECTS AND METHODS

Between 1983 and 1995, we conducted a case-control study on risk factors for endometrial cancer. The design of this study has been described previously (Parazzini *et al.*, 1998). Cases were 752 women with histologically confirmed endometrial cancer who were <75 years (median age 60 years, range 28–74) whose diagnosis dated back ≤1 year. They were admitted to the Ospedale Maggiore (including the 4 largest teaching and general hospitals in the Greater Milan area), the University Obstetric and Gynecology Clinics, and the National Cancer Institute of Milan. All cases were interviewed in hospital.

Controls were patients <75 years of age admitted for acute, non-gynecological non-hormone-related, non-neoplastic conditions to the same network of hospitals where cases had been identified. Women who had undergone hysterectomy were not eligible as controls. A total of 2,606 controls (median age 54 years, range 25–74) were included in the present analysis. Of these, 34% were admitted for traumatic conditions (mostly fractures and sprains), 30% for non-traumatic orthopaedic disorders (mostly low back pain and disk disorders), 15% for surgical conditions (mostly abdominal, such as acute appendicitis or strangulated hernia) and 21% for other miscellaneous illnesses, such as eye, ear, nose and throat, or dental disorders. Fewer than 4% of cases and controls approached for interview refused to participate.

Trained interviewers used a standard questionnaire to identify and question cases and controls. Information was collected on general characteristics and habits, gynecological and obstetric data, and history of use of oral contraceptives and female hormones for other indications. Height and weight were self-reported by women. The questionnaire also ascertained information on diabetes and other selected diseases or medical procedures. By definition, these had to precede by at least 1 year the onset of the disease that led to admission. Age at onset/first diagnosis was recorded. Information regarding diabetes and other diseases was checked with medical records whenever useful by the interviewer, thus minimizing the risk of diagnostic errors.

Women were defined as pre-menopausal (with regular menstruation), in peri-menopause (women whose menstrual bleedings had naturally ceased for less than 12 months) or post-menopausal (menses had naturally ceased for 12 or more months). Age at menopause was considered the age at last menstruation. Ovariectomized women were included in the post-menopausal group consid-

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ering the date of surgery as the date of menopause. Women using hormonal replacement therapy were considered post-menopausal if reported a period lasting 12 or more months without spontaneous menstrual cycles.

Data analysis

We estimated the odds ratios (OR) of endometrial cancer, together with their 95% confidence intervals (CI), according to history of diabetes. Unconditional multiple logistic regression, with maximum-likelihood fitting, was used (Breslow and Day, 1980). Included in the regression equations were terms for age (as continuous variable), calendar year at interview, education, body mass index (BMI) (as categorized variable, <25, 25–30, >30), parity, oral contraceptive and hormonal replacement therapy use, age at menopause, hypertension and smoking.

TABLE I – DISTRIBUTION OF 752 CASES OF ENDOMETRIAL CANCER AND 2,606 CONTROLS ACCORDING TO AGE AND SELECTED COVARIATES (MILAN, ITALY, 1983–1995)

	Endometrial cancer		Controls	
	Number	(%)	Number	(%)
Age (years)				
<45	38	(5.1)	640	(24.6)
45–54	147	(19.3)	692	(26.6)
55–64	307	(40.8)	735	(28.2)
≥65	260	(34.6)	539	(20.7)
Education (years)				
<7	523	(69.5)	1536	(58.9)
7–11	147	(19.5)	634	(24.3)
≥12	82	(10.9)	436	(16.7)
Body mass index (kg/m^2)				
<25	298	(39.6)	1580	(60.6)
25–30	255	(33.9)	776	(29.8)
>30	199	(26.5)	250	(9.6)
Oral contraceptive (years of use)				
Never	726	(96.5)	2366	(90.8)
≤2	12	(1.6)	119	(4.6)
>2	14	(1.9)	121	(4.6)
Hormone replacement therapy (years of use)				
Never used	663	(88.2)	2512	(96.4)
≤2	65	(8.6)	79	(3.0)
>2	24	(3.2)	15	(0.6)
Age at menopause (years)				
Premenopause	141	(18.8)	1208	(39.4)
<50	219	(29.1)	712	(27.3)
≥50	392	(52.1)	866	(33.2)
Parity				
0	162	(21.7)	512	(19.7)
1	175	(23.5)	624	(24.0)
2	209	(28.0)	804	(30.9)
≥3	200	(26.8)	662	(25.4)
Hypertension				
No	506	(67.3)	2154	(82.7)
Yes	246	(32.7)	452	(17.3)
Smoking				
Never	608	(80.9)	1783	(68.4)
Ever	144	(19.1)	823	(31.6)

In some cases the sum of strata does not add up to total because of missing values.

RESULTS

Table I presents the distribution of cases and controls according to age, education and selected risk factors for endometrial cancer. Cases were less educated, less frequently smokers and pre-menopausal, and more frequently nulliparous and overweight, and more frequently reported a history of hypertension and estrogen replacement therapy use. These factors, therefore, were adjusted for in subsequent analyses.

Table II presents the distribution of cases and controls according to history of diabetes. A total of 132 (17.6%) cases and 116 controls (4.5%) reported a history of diabetes. The corresponding multivariate OR was 2.9 (95% CI 2.2–3.9). No association emerged with diabetes diagnosed under age 40 (which is likely to be insulin-dependent diabetes), whereas the OR of endometrial cancer was 3.1 (95% CI 2.3–4.2) for the disease diagnosed at age ≥40 years. Considering only women with a diagnosis of diabetes at 40 years of age or older, the OR of endometrial cancer was 3.8 for women reporting a diagnosis of diabetes less than 5 years before diagnosis of endometrial cancer and 3.3 for those reporting diagnosis of diabetes ≥5 years before.

Table III illustrates the relationship between diabetes mellitus and the risk of endometrial cancer in strata of age and other selected covariates. No significant interaction was observed, and in all the strata considered the OR of endometrial cancer for a history of diabetes was over 2. In particular, the OR was 2.6 at age 40–59 years and 3.4 at age 60–74 years; OR was 3.0 for women with BMI <25 kg/m^2, 3.6 for those with BMI 25–29 and 2.9 for those with a BMI ≥30. Likewise, the ORs were similar across strata of age at menopause, smoking and hypertension.

DISCUSSION

Potential limitations of the study must be considered. First of all, information bias should be taken into account, because endometrial cancer cases can be more sensitized than controls in reporting history of diabetes. However, it is difficult that a major long-term condition like diabetes is appreciably and systematically misreported.

Further, the hospital-based design represents an optimal framework for analysing medical histories (Breslow and Day, 1980; Kelly *et al.*, 1990). Cases and controls, in fact, were similarly investigated and should be similarly sensitized towards recalling

TABLE II – DISTRIBUTION OF 752 CASES OF ENDOMETRIAL CANCER AND 2,606 CONTROLS ACCORDING TO HISTORY OF DIABETES, AND CORRESPONDING ODDS RATIOS (OR)[1] (MILAN, ITALY, 1983–1995)

	Cases	Controls	OR (95% CI)	
	Number (%)	Number (%)	MH[2]	MLV[3]
History of diabetes				
Never	620 (82.4)	2490 (95.5)	1[4]	1[4]
Ever	132 (17.6)	116 (4.5)	3.6 (2.7–4.8)	2.9 (2.2–3.9)
at age <40	4 (0.5)	15 (0.6)	1.0 (0.3–3.4)	1.0 (0.3–3.6)
at age ≥40	128 (17.0)	101 (3.9)	3.8 (2.9–5.1)	3.1 (2.3–4.2)
Years since diagnosis of diabetes[1]				
<5	64 (8.7)	42 (1.9)	5.1 (3.3–7.6)	3.8 (2.5–5.9)
≥5	64 (8.7)	59 (2.7)	3.0 (2.1–4.5)	2.6 (1.8–3.9)

CI = confidence interval.–[1]Subjects aged 40 years or more only.–[2]Mantel Haenszel (MH) estimates adjusted for age.–[3]Derived from multiple logistic regression equations including term for age, calendar year at interview, education, Quetelet's index, parity, oral contraceptive and hormone replacement therapy use, age at menopause, hypertension, and smoking.–[4]Reference category.

TABLE III – ODDS RATIO (OR)[1] OF ENDOMETRIAL CANCER ACCORDING TO HISTORY OF DIABETES DIAGNOSED AT AGE ≥40 IN STRATA OF COVARIATES (MILAN, ITALY, 1983–1995)[2]

	Cases: controls with diabetes	OR (95% CI)	χ^2 interaction
Age (years)			
40–59	32:36	2.6 (1.5–4.5)	
≥60	99:65	3.4 (2.3–5.0)	1.26 (1 df) (p = NS)
Education (years)			
<7	100:84	2.8 (2.0–3.9)	
≥7	28:17	5.7 (2.8–11.5)	2.37 (1 df) (p = NS)
Body mass index (kg/m^2)			
<25	29:41	3.0 (1.8–5.2)	
25–29	44:35	3.6 (2.1–6.0)	0.60 (2 df)
≥30	55:25	3.3 (1.9–5.8)	(p = NS)
Hormone replacement therapy			
Never users	117:96	3.3 (2.4–4.5)	
Ever users	11:5	2.1 (0.6–7.1)	0.07 (1 df) (p = NS)
Age at menopause (years)			
Premenopause	9:8	5.5 (1.8–16.8)	
<50	47:46	3.0 (1.8–4.9)	
≥50	72:47	3.1 (2.0–4.7)	0.47 (2 df) (p = NS)
Smoking habits			
Never smokers	104:85	2.8 (2.0–3.9)	
Ever smokers	24:16	4.8 (1.8–12.6)	1.71 (1 df) (p = NS)
Hypertension			
No	63:62	3.2 (2.2–4.8)	
Yes	65:39	3.0 (1.9–4.8)	0.01 (1 df) (p = NS)

CI = confidence interval; df = degrees of freedom; NS = not significant.–[1]Derived for multiple logistic regression equation including terms for age, calendar year at interview, education, Quetelet's index, parity oral contraceptive and hormone replacement therapy use, age at menopause, hypertension, and smoking.–[2]Reference category: no diabetes.

diseases in the past. A multicentre, case-control study from the United States, Canada and Israel found a correlation coefficient more than 0.9 for history of diabetes in repeated interviews (Kelly *et al.*, 1990). Furthermore, the 4.5% disease prevalence in the comparison group is consistent with estimates from Italian national population-based surveys (Negri *et al.*, 1988). Cases and controls were identified in hospitals with comparable catchment area, and participation was almost complete.

With regard to confounding, the results were consistent in strata of selected covariates, the ORs did not change markedly after taking into account several covariates, including the main recognised risk factors for endometrial cancer, and in particular obesity, which, in principle, could be a relevant confounding factor. Indeed, the multivariate OR of endometrial cancer for diabetic women computed without allowance for BMI was 3.3 (95% CI 2.5–4.5). It has been suggested, moreover, that the association between obesity and endometrial cancer is unlikely to be mediated through elevated insulin levels (Troisi *et al.*, 1997), pointing to an independent mechanisms of the 2 risk factors. The possibility of a residual confounding factor (due to an incomplete adjustment for overweight and/or dietary habits) cannot, however, be excluded. Recent loss of weight due to the tumor may represent a potential bias. We had not collected information on stage of the disease, as a proxy for duration of the condition; however, in the participating centre about 90% of endometrial cancer cases are diagnosed at stage I (La Vecchia *et al.*, 1983).

Our results indicate that the association between endometrial cancer risk and diabetes mellitus is limited to NIDDM. Indeed, even in the absence of direct information on type of diabetes, only diabetes mellitus diagnosed after 40 years of age was associated with the risk of endometrial cancer. This finding suggests that hyperinsulinemia and hence, possibly, IGF-I is a correlate of endometrial cancer risk. However, Troisi *et al.* (1997) did not found any association between C-peptide, a proxy for insulin production, and endometrial cancer.

The present results are consistent with most previous epidemiological findings. The OR for a history of diabetes mellitus was between 2 and 3 in most case-control studies of endometrial cancer (Parazzini *et al.*, 1991) and the standardized incidence ratio of endometrial cancer was 1.7 (95% CI 1.5–1.9) in a Swedish cohort study of 80,000 diabetic women, after exclusion from the analysis of women with a diagnosis of obesity (Weiderpass *et al.*, 1997). The latter findings are unlikely to be affected by information or recall bias.

In conclusion, our results confirm, providing more accurate quantification than previously available, that NIDDM is associated with the risk of endometrial cancer, that this association persists after taking into account the potential confounding effect of recognised risk factors for endometrial cancer, particularly overweight, and is consistent across strata of major identified covariates. This association may be related to elevated estrogen levels in diabetic women (Deutsch and Benjamin, 1978), hyperinsulinemia or IGF-I, which is a promotor of carcinogenesis *in vitro* (Preston-Martin *et al.*, 1990), as also suggested to explain the association between diabetes and colon and breast cancer.

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