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Population Attributable Risk for Endometrial Cancer in Northern Italy

FABIO PARAZZINI,* EVA NEGRI,* CARLO LA VECCHIA,*† PAOLO BRUZZI‡ and ADRIANO DECARLI§

**'Mario Negri' Institute for Pharmacological Research, 20157 Milan, Italy, †Institute of Social and Preventive Medicine, University of Lausanne, 1005 Lausanne, Switzerland, ‡National Cancer Institute, 16132 Genova, Italy and §Institute of Medical Statistics, University of Milan and National Cancer Institute, 20133 Milan, Italy*

Abstract—*The population attributable risk for endometrial cancer has been estimated in relation to its four major risk factors (overweight, estrogen replacement therapy, diabetes and hypertension) using data on 528 cases and 1626 controls collected within the framework of a hospital-based case-control study conducted since 1981 in the greater Milan area, northern Italy. Over 30% of the endometrial cancer cases diagnosed in the study population could be attributed to overweight, 10% to post-menopausal estrogen replacement therapy, and similar proportions (around 10%) to hypertension and diabetes. The overall estimate including the joint effect of the two conceptually preventable factors (overweight and estrogen use) was 40%, while further inclusion of diabetes and hypertension, which are not easily preventable per se but are still closely linked to 'westernization', indicated that over 50% of cases were attributable to the combined effect of these four factors. The validity of these findings, in strict terms, is limited to this area from northern Italy. However, they can be taken as a general indication of the scope for prevention of endometrial cancer in other southern European populations, sharing similarities in lifestyle and pattern of hormonal replacement therapy use.*

INTRODUCTION

SEVERAL epidemiological studies have shown that the risk of endometrial cancer increases markedly with estrogen replacement therapy or increasing body weight [1–7]. These risk factors can be explained in terms of (exogenous or endogenous) 'unopposed estrogens' and are, in principle, preventable. Further, there is clinical as well as epidemiological evidence that diabetes and hypertension (two conditions not directly preventable *per se*, but closely linked to 'westernization') independently increase the risk of endometrial cancer [1, 3, 5].

In terms of relative risk, the estimates obtained are comparable in different populations, but the attributable risk (or etiological fraction) may vary largely in relation to differing distribution of exposure to these factors. It has been estimated, for instance, that in the mid 1970s about 22% of endometrial cancer among women aged 30–69 in the greater Boston area [8], but as much as 50–60% in Los Angeles [9, 10], was due to conjugated estrogen use. In Europe, the proportion was probably smaller on account of the lower frequency (and shorter duration) of estrogen replacement treatment use but, to our knowledge, no quantitative estimates have yet been published.

Thus, in this paper we have quantified the impact of major risk factors for endometrial cancer in a population of northern Italy, using data from a large case-control study of female genital tract neoplasms.

MATERIALS AND METHODS

Since January 1983 we have been conducting a case-control study of endometrial cancer in the greater Milan area. The general design and main results from this investigation have already been described [11]. Briefly, trained personnel identified and interviewed cases and controls using a standard questionnaire. On average, less than 2% of the eligible women refused to be interviewed.

The *cases* were women below the age of 75, residing in the greater Milan area, with histologically confirmed endometrial cancer diagnosed within the year preceding the interview, who had been admitted to the National Cancer Institute and to the Ospedale Maggiore (which includes the four largest teaching and general hospitals in Milan). A total of 528 cases aged 28–74 (median age 61) were interviewed.

Controls: patients residing in the greater Milan area who were admitted for acute conditions to several specialized university clinics or to the Ospedale Maggiore of Milan were eligible as controls.

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Correspondence should be addressed to: Fabio Parazzini, Istituto di Ricerche Farmacologiche, 'Mario Negri', Via Eritrea, 62, 20157 Milan, Italy.

They were admitted for diseases not malignant, hormonal, gynecological or judged to be related to any of the identified or suggested risk factors for endometrial cancer (e.g. explicit exclusion was made of cholelithiasis, which is influenced by weight and parity). Further, control subjects had not undergone hysterectomy and/or bilateral oophorectomy. A total of 1626 controls, aged 25–74 (median age 54), were interviewed; of these, 32% were admitted for traumatic conditions (mostly fractures and sprains), 25% had non-traumatic orthopedic disorders (mostly low back pain and disc disorders), 15% surgical conditions (mostly abdominal, such as acute appendicitis or strangulated hernia) and 28% had other illnesses, such as ear, nose and throat or teeth disorders.

Information was collected on personal characteristics and habits, gynecological and obstetric data, relevant medical history, and history of lifetime use of female hormones.

The distribution of cases and controls according to age and other major covariates of interest (social class and parity) is presented in Table 1. The present report is based on data collected before November 1987.

Table 1. Distribution of 528 cases of endometrial cancer and 1626 controls according to age and selected characteristics. Milan, Italy 1983–1987

	Endometrial cancer		Controls	
	No.	%	No.	%
Age (years)				
<45	30	5.7	459	28.2
45–54	99	18.8	395	24.3
55–64	204	38.6	411	25.3
65–74	195	36.9	361	22.2
*Social class**				
I or II (highest)	33	6.3	135	8.3
III	147	27.8	510	31.4
IV or IV (lowest)	208	39.4	582	35.8
Undefined	140	26.5	399	24.5
Parity				
0	125	23.7	346	21.3
≥1	403	76.3	1280	78.7

*Based on the head of the household's occupation.

Data analysis

Odds ratios (as estimators of relative risks, RR), together with their 95% approximate confidence intervals (CI) [12] were first computed from data stratified in five-year intervals of age by the Mantel–Haenszel procedure [13]. When a factor could be classified in more than two levels, the significance of the linear trend was assessed by the test described by Mantel [14].

Relative risks were then obtained after simultaneous allowance for potential confounding effects of age (as a cardinal term), social class, parity and the four risk factors considered (body mass index, estrogen replacement therapy, hypertension and diabetes) through unconditional multiple logistic regression equations, fitted by the method of maximum likelihood [15].

The population attributable risk percentage (etiologic fraction, attributable fraction), representing the fraction of total disease experienced in a population that would not have occurred if the effect(s) associated with the risk factor(s) of interest were absent, is a useful measure of public health and prevention relevance. Under a multiplicative model of disease etiology, attributable risk for any given set of risk factors can be computed using the multivariate relative risk estimates and the distribution of this factors among cases only. Thus, using the multivariate relative risks, population attributable risks were computed for each separate factor, for obesity and estrogen replacement therapy together, and the four factors combined, using the method described by Bruzzi *et al.* [16], which provides a summary attributable risk (AR) for multiple factors, after allowance for confounding. The method requires information only on the joint distribution of the risk factors among cases and on the adjusted relative risk associated with each risk factor. Provided that unbiased relative risk estimates are obtained and that the cases can be assumed to be representative of all cases in the population in terms of exposure distribution, this method can be applied to data from hospital-based case-control studies. It has to be underlined that, whenever risk factors are not mutually exclusive, their combined attributable risk will differ from the simple sum of the attributable risk of each factor [16].

RESULTS

The relative risk of endometrial cancer according to the major identified risk factors are given in Table 2.

As expected, the risk of endometrial cancer increased with increasing body weight: compared to women whose Quetelet's (kg/m^2) index was less than 25, the relative risk estimates for the groups with indices of 25–29.9 and ≥30 were respectively 1.5 and 3.8. Likewise, use of estrogen replacement therapy was more common among cases than controls. The relative risk estimates increased with duration of use, being 3.3 among users for ≤2 and 4.8 in >2 years. A previous history of diabetes (treated with diet or drugs) and drug treated hypertension was associated with an increased risk of endometrial cancer, the age-adjusted point estimates being 2.0 and 3.5 respectively.

Table 2. Relative risk of endometrial cancer according to major identified risk factors. Milan, Italy 1983–1987

	Endometrial cancer	Controls	Relative risk estimates (95% CI)	
			M–H*	Multivariate†
Body mass index (kg/m²)				
<25	195	994	1‡	1‡
25–29.9	176	473	1.52 (1.19–1.93)	1.49 (1.16–1.92)
⩾30	148	154	3.79 (2.88–5.00)	3.78 (2.80–5.11)
Undefined	9	5	—	—
χ^2_1 (trend)			80.42 ($P < 0.001$)	69.80 ($P < 0.001$)
Estrogen replacement treatment				
Never used	457	1573	1‡	1‡
Used ⩽2 years	51	42	3.33 (2.21–5.04)	3.98 (2.54–6.23)
Used >2 years	20	11	4.84 (2.41–9.70)	5.77 (2.62–12.72)
χ^2_1 (trend)			47.74 ($P < 0.001$)	50.64 ($P < 0.001$)
Hypertension				
No	342	1346	1‡	1‡
Yes	186	280	1.95 (1.55–2.45)	1.49 (1.16–1.92)
Diabetes				
No	421	1544	1‡	1‡
Yes	107	82	3.46 (2.56–4.67)	2.68 (1.92–3.76)

*Mantel–Haenszel estimates adjusted for age.
†Estimates from multiple logistic regression equations, including terms for age, social class, parity plus the four variables listed above.
‡Reference category.

The relative risks for overweight and estrogen use did not materially change after allowance for the major potential confounding factors as well as the simultaneous inclusion of terms for these risk factors in multiple logistic equations. The multivariate relative risks for hypertension and diabetes were somewhat lower than the Mantel–Haenszel estimates adjusted for age only, but remained appreciably (and significantly) above unity (RR = 1.5 for hypertension and 2.7 for diabetes, Table 2). No interaction term among these four risk factors achieved statistical significance.

The proportion of cases of endometrial cancer in the population under surveillance attributable to these risk factors is given in Table 3. Since interaction terms were not significant, their coefficient were not included in the attributable risk presented.

Over 30% of the endometrial cancers could be attributed to overweight and obesity (body mass index ⩾25), 10% to post-menopausal estrogen replacement therapy, and a similar proportion (around 10%) to hypertension and diabetes.

The overall estimate including the joint effect of the two conceptually preventable factors (overweight and estrogen treatment) was 40%, while further inclusion of the two less obviously avoidable ones (diabetes and hypertension) indicated that over 50% of endometrial cancers are attributable to the combined effect of these four factors.

Since overweight was the major determinant of endometrial cancer in the study population, we further calculated the impact of various degrees of overweight and strategies to intervention. Thus, 11% of endometrial cancer was attributable to overweight (body mass index 25–29.9) and 22% to gross obesity. About 17% of cases could be avoided by an intervention on gross obesity only (i.e. reducing Quetelet's Index from ⩾30 to 25–29.9) whereas 28% of endometrial cancers could be avoided by shifting the body mass index of all obese and overweight women downwards (i.e. from ⩾30 to 25–29.9 and from 25–29.9 to below 25).

DISCUSSION

The analyses presented indicate that obesity, estrogen replacement treatment, history of diabetes and hypertension explain about 50% of cases of endometrial cancer in this population from northern

Table 3. Attributable risk percentage of endometrial cancer in relation to selected risk factors and their combination. Milan, Italy, 1983–1987

Risk factor	Attributable risk percentage		
Overweight	32.2		
		40.0	
Estrogen replacement treatment	10.4		
			51.4
Hypertension	11.9		
		22.2	
Diabetes	12.6		

Italy. In strict terms, the validity of this estimate is obviously limited only to the area under surveillance, although this population shares large similarities in nutrition and patterns of hormonal replacement therapy use with other southern European ones.

In the overall computation of the proportion of cases attributable to 'westernization', we also considered diabetes and hypertension. Although there is a variety of evidence of their independent effects on the risk of endometrial cancer [1, 3, 5], the etiopathogenic mechanism is still unclear and any specific preventive effect of treatment of hyperglycemia and high blood pressure on endometrial cancer risk is obviously merely speculative.

Further limitations should be discussed in terms of potential biases in the computation of relative risks and assumptions required for estimating population attributable risks. Cases and controls were collected in the main general and teaching hospitals in the greater Milan area. Although the study protocol indicated that all new consecutive cases should be interviewed, the design was not strictly population-based and hence it is likely that some cases did not enter the study (for instance simply because they were not present in the ward at the time of the interviewers' visit). Further, women admitted to general and teaching hospitals could differ, for example, from those treated in private ones in relation to socio-demographic characteristics (although these factors were allowed for in the estimation of multivariate relative risks). However, endometrial cancer cases treated out of the surveyed hospitals represent a small percentage of incident cases.

In the North of Italy the use of estrogen replacement therapy has never been common. In the present sudy only about 13% of the cases and 3% of control subjects were 'ever users'. Consequently, only about 10% of cases of endometrial cancer were attributable to hormonal replacement therapy, a much smaller proportion than in North America for the mid 1970s (20–60%) [8–10]. Although, to our knowledge, no more recent figure has been published, it is likely that the estrogen-related attributable risk is now lower in North America, too, on account of the decreased prevalence of use of hormonal replacement therapies in more recent years [17].

In this population, obesity was the major determinant of endometrial cancer with an attributable fraction of 32%, which is higher than the 25% estimated on a series covering a 30-year period in Minnesota [18]. If the body mass index of all overweight women decreased about 5 units, a reduction of about 30% in endometrial cancer incidence would be observed. Since there are about 2000 deaths per year for cancer of the corpus uteri in the whole of Italy [19], this would imply the prevention of about 600 deaths (1.2% of all cancer deaths in women) per year.

However, this is likely to be the upper limit of possible estimates; it appears in fact that endometrial cancer cases who are obese or have a history of exogenous estrogens have more favorable prognostic features and experience a significantly better survival than cases without these two factors [20–24]. The lower limit of the excess mortality linked to these factors may well be much less if it is accepted that the hazard rate for endometrial cancer death among obese women and estrogen users is between 1/2 and 1/4 that among women without such characteristics [24]. However, those survival estimates [24] were based on very limited numbers of patients and are hence largely unstable. Moreover, on a public health scale, the impact of intervention on weight would certainly be much greater, since other neoplasms (i.e. gall bladder and chiefly breast in post-menopause [25–27]) are also related to obesity in women.

In general, the 40–50% population attributable risk of well-identified and (theoretically) avoidable risk factors underlines the scope for prevention of this neoplasm through the application of existing epidemiologic knowledge. This is, nonetheless, certainly an underestimate of the theoretical possibili-

ties for prevention related to the indications derived from international comparisons. The cumulative incidence rate of endometrial cancer in the study catchment area is not known, but is probably close to the 1.9% below age 75 which is observed in the nearby province of Varese [28]. This incidence is about 20 times higher than that observed in low-risk areas of the world [25, 28], while the four risk factors considered in our analysis account, at best, for a two-fold variation (under the assumption that all women in the low-risk areas belong to the lowest risk class in each of these factors). This indicates that other factors are probably responsible for the substantial incidence and mortality variability (i.e. an incidence ratio of 30 between California and Japan [25, 28]). It is possible that diet has a role [29–31], but evidence is still scant and preliminary.

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