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Oestrogen Replacement Treatment and the Risk of Endometrial Cancer: an Assessment of the Role of Covariates

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The relationship between oestrogen replacement treatment and the risk of endometrial cancer was analysed in a case–control study of 158 histologically confirmed incident cases below the age of 75 and 468 controls in hospital for acute, non-neoplastic, non-hormone-related conditions conducted in the Swiss Canton of Vaud in 1988–1992. Overall, 60 (38%) cases vs. 93 (20%) controls had ever used oestrogen replacement treatment: the corresponding mutliple logistic regression relative risk (RR) was 2.7 (95% confidence interval, CI: 1.7–4.1). The risk was directly related to duration of use, and rose to 5.1 (95% CI: 2.7–9.8) for > 5 year-use. The RR was still significantly elevated 10 or more years after stopping use (RR = 2.3, 95% CI: 1.2–4.5). When the role of covariates was considered, a significant interaction was observed with body mass index (RR for long-term oestrogen use = 6.0 for lean or normal weight women vs. 2.4 for overweight women). There was also a hint of a negative interaction with oral contraceptive (OC) use, since the RR for oestrogens was higher (or restricted) to women who had never used OC (RR = 5.4, for long-term oestrogen use), as compared with those who had used OC, who showed no significant evidence of association with oestrogens (RR = 0.9 for long-term use). There was no significant interaction with cigarette smoking. Thus, this study confirms the presence of a strong association between oestrogen replacement treatment and endometrial cancer risk, since in the late 1980s or early 1990s about 25% of cases could be attributed to oestrogen replacement treatment in this Swiss population. Further, it confirms the presence of significant negative interactions of oestrogen use with obesity, and, possibly, with OC as well.
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INTRODUCTION

THE RELATIONSHIP between oestrogen replacement therapy (ERT) and the risk of endometrial cancer was originally suggested on the basis of the observation of a substantial rise in the incidence of this neoplasm in the United States in the early 1970s, following the spread of ERT [1]. In 1975, two case–control studies gave direct and quantitative epidemiological support to the association [2, 3].

Since then, at least 20 studies have been published on the topic. Their overall evidence indicates that the risk is about 3- to 4-fold greater in ever-users than in never users, and rises with the dose and duration of use, being up to 10-fold elevated in women who had used high-dose oestrogen for 10 years or more [4].

If the existence of an association is, therefore, beyond any reasonable discussion, there are still some points open to debate. Firstly, it is useful, on a public health scale, to understand the extent to which, if at all, indications from earlier epidemiological studies modified the subsequent patterns of prescription and risk. Secondly, most studies came from North America, and there were only four published investigations from Europe [5–8], where, at least in terms of attributable risk in the population,

oestrogens are much less important. It has been estimated, for instance, that only 10% of endometrial cancer cases were attributable to menopausal replacement treatment in the 1980s in northern Italy [9], as compared to as much as 50–60% in Los Angeles in 1970s [3]. Further, the interaction between ERT and other established risk factors for endometrial cancer—including overweight and obesity, hypertension, diabetes and oral contraceptives (OC)—needs further clarification [4, 5, 10].

SUBJECTS AND METHODS

Since January 1988, we have been conducting a case–control study of endometrial cancer in the Canton Vaud, Switzerland, whose general design has already been described [11]. Briefly, trained interviewers identified and questioned patients admitted for invasive endometrial cancer and a wide spectrum of other non-neoplastic, non-gynaecological conditions. All interviews were conducted in hospital. Participation rate, for both cases and controls, was over 85%. The present report is based on data collected before July 1992.

A structured questionnaire was used to obtain information on personal characteristics and habits, including smoking, alcohol and a selected list of indicator foods, gynaecological and obstetric data, related medical history, and history of lifetime use of OC, ERT, and other female hormones. The time and duration of each episode of use were recorded as well as the brand name. A list of most common brands was used to assist recall, whenever useful.

Cases

The cases were women with histologically confirmed endometrial cancer below the age of 75, diagnosed within the year before the interview, who had been admitted or referred for follow-up to the University Hospital of Lausanne. Cases identified and interviewed were linked with the incidence data from Vaud Cancer Registry [12] for the corresponding calendar period (i.e. 1987–1992). Over 80% of reported and eligible cases (i.e. below the age of 75) were approached for interview. A total of 158 cases, aged 32–74 (median age, 63 years) was interviewed.

Controls

Potential controls were women below the age of 75 years whose primary diagnosis was judged to be unrelated to any of the known or suspected risk factors for endometrial cancer. Women were not eligible if they were admitted for gynaecological, hormonal, metabolic or neoplastic diseases, or had undergone hysterectomy. A total of 468 controls, aged 30–74 (median age, 60 years), was interviewed. Of these, 30% were admitted for traumas, 10% had non-traumatic orthopaedic diseases, 22% surgical conditions, and 38% miscellaneous other disorders, including acute medical, eye, nose and throat, dental diseases, etc. The catchment area of cases and controls was comparable, since 88% of the cases and 93% of the controls resided in the Canton of Vaud.

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Data analysis

We computed the relative risks (RR) of endometrial cancer, according to various indicators of oestrogen replacement treatment, together with their 95% confidence intervals (CI), from data stratified for quinquennia of age using the Mantel–Haenszel procedure [13]. In order to allow simultaneously for the effect of several potential distorting factors, unconditional logistic regression [14], with maximum likelihood fitting [15], was used. Included in the regression equations were terms for age (in decades), area of residence (urban conurbation versus other areas of the Canton), marital status (never married/married), parity (0; 1–2; ≥ 3), body mass index (BMI, weight(kg)/height(m^2)(< 20; 20–24; 25–29; ≥ 30), diabetes (no/yes), hypertension (no/yes), cigarette smoking (never; ex; current smoker < 15 and ≥ 15 cigarettes per day) and OC use (never/ever).

Using the distribution of the risk factors in the cases and the relative risk estimates from the multiple logistic regression models, the population attributable risk for oestrogen replacement treatment was estimated. The method described by Bruzzi *et al.* [16] implies the knowledge of the risk estimates and of the joint distribution of the risk factors in the population of cases only, and thus can be used for data of hospital-based case–control studies.

RESULTS

Table 1 gives the distribution of endometrial cancer cases and the comparison group according to age and selected covariates.

Table 1. Distribution of 158 cases of endometrial cancer and 468 controls according to age and selected variables. Vaud, Switzerland, 1988–1992*

Covariate	Endometrial cancer Number	%	Controls Number	%
Age (years)				
< 45	7	4.4	57	12.2
45–54	20	12.7	84	17.9
55–64	56	35.4	134	28.6
65–74	75	47.5	193	41.2
Education (years)				
< 9	33	20.9	89	19.1
9–13	111	70.3	313	67.2
≥ 14	14	8.9	64	13.7
Body mass index (kg/m^2)				
< 20	13	8.2	51	10.9
20–24	66	41.8	211	45.1
25–29	48	30.4	146	31.2
≥ 30	31	19.6	60	12.8
Diabetes				
No	149	94.3	459	98.1
Yes	9	5.7	9	1.9
Hypertension				
No	114	72.2	369	78.8
Yes	44	27.8	99	21.2
Oral contraceptive use				
Never	138	87.3	364	77.8
Ever	20	12.7	104	22.2
Current cigarette smoking				
Never	105	66.5	293	62.6
Ever	53	33.5	175	37.4

* For some variables, the sum of strata does not add up to the total because of missing values.

Cases were older and somewhat less educated than control subjects. Further, cases were more often obese (age-adjusted RR for BMI ≥ 30 vs. BMI < 25 = 1.6; 95% CI: 1.0–2.7), and reported more frequently diabetes (RR = 2.7; 95% CI: 1.1–6.9) and hypertension (RR = 1.3; 95% CI: 0.9–2.0). Ever cigarette smoking was slightly less frequent among cases (RR = 0.9; CI: 0.6–1.3), whereas the past use of OC was protective on subsequent endometrial cancer risk (RR = 0.7; CI: 0.4–1.2). These factors were therefore considered, on account of their possible confounding or modifying effect, in all analyses on ERT.

Selected measures of ERT are considered in Table 2. A total of 60 (38%) of the cases versus 93 (20%) of the controls had ever used menopausal replacement treatment: the corresponding age-adjusted relative risk was 2.4 (95% CI: 1.6–3.5). There was a significant trend in risk with duration of use: compared with never users, the RR was 1.7 for women who had used oestrogens for 5 years or fewer and 4.2 for longer duration (Table 2). In contrast, there was no clear pattern of risk with time since last use, and the risk estimate was still significantly above unity (RR = 2.0, 95% CI: 1.1–3.8) for women who had stopped use for 10 or more years. Likewise, there was no evidence for the risk to decline with increasing time since first use (RR for ≥ 15 years = 3.5, 95% CI: 1.7–7.5), but time since first use was strongly correlated to duration of ERT. Allowance for several potential confounding variables did not modify substantially any of the reported age-adjusted RR (Table 2).

The relationship between ERT use and endometrial cancer risk is further considered in Table 3 in separate strata of major covariates. A significantly negative interaction was observed with body mass index. The RR for oestrogen use were significantly higher among women whose BMI was below 25 (RR = 6.0 for > 5 year-use) than in overweight women (RR = 2.4) (Table 3). The risk estimates for oestrogen users were also somewhat higher among women without diabetes (RR = 4.1 for long-term use) and without hypertension (RR = 4.9), as compared with those with these covariates. A hint of a negative, although not significant, interaction was also observed with history of OC use, since the RR for oestrogen use was higher (or restricted) to women who had never used contraceptives (RR = 5.4 for long-term oestrogen use). Women who reported OC use showed no significant trend of increasing risk of endometrial cancer with increasing duration of ERT. No interaction emerged between the effect of oestrogen replacement treatment and cigarette smoking (Table 3).

DISCUSSION

The present study confirms the presence of a strong association between oestrogen replacement treatment and endometrial cancer risk on a population level in Switzerland. Despite the fact that an elevated risk of endometrial cancer among oestrogen users has been reported for more than 15 years [2, 3], it appears that this amount of epidemiological evidence has not led to the elimination or attenuation of the oestrogen-related risk of endometrial cancer and, in fact, the relative risks for long-term oestrogen use in this study were still above a factor of 5. In the late 1980s or early 1990s about 25% of all endometrial cancer cases in this Swiss population could be attributed to oestrogen replacement treatment.

This is almost certainly due to the fact that oestrogen replacement treatment has favourable effects not only on the clinical symptoms of menopause, but also on the cardiovascular system and the bone [17, 18]. Thus, the ultimate impact of oestrogen replacement treatment at an individual and public health level is still open to debate, but likely to be favourable [18]. For such a risk-benefit evaluation, however, the indication emerging from this study that the oestrogen-related risk remains elevated several years after stopping use is clearly of substantial relevance.

Table 2. Distribution of 158 cases of endometrial cancer and 468 controls according to various measures of oestrogen replacement treatment. Vaud, Switzerland, 1988–1992

Covariate	Endometrial cancer	Controls	Relative risk estimates (95% C.I.) M-H*	MLR†
Oestrogen replacement treatment use				
Never	98	375	1‡	1
Ever	60	93	2.4 (1.6–3.5)	2.7 (1.7–4.1)
Duration of use (years)				
≤ 5	32	69	1.7 (1.1–2.8)	1.9 (1.1–3.2)
> 5	28	24	4.2 (2.4–7.6)	5.1 (2.7–9.8)
χ^2_1 (trend)				25.89; $P < 0.001$
Time since last use (years)§				
< 2	16	29	2.5 (1.3–4.7)	2.5 (1.3–5.1)
2–9	25	31	2.9 (1.7–5.1)	3.4 (1.8–6.5)
≥ 10	19	31	2.0 (1.1–3.8)	2.3 (1.2–4.5)
Time since first use (years)				
< 15	29	62	1.9 (1.2–3.1)	1.8 (1.0–3.2)
≥ 15	31	31	3.5 (1.7–7.5)	4.1 (2.3–7.5)

* Mantel–Haenszel estimates adjusted for age.

† Estimates from multiple logistic regression models including terms for age, area of residence, marital status, parity, body mass index, history of diabetes and hypertension, smoking habits and oral contraceptive use.

‡ Reference category.

§ Two missing values among controls.

Table 3. Relationship between oestrogen replacement treatment and endometrial cancer risk in separate strata of various covariates. Vaud, Switzerland, 1988–1992

Covariate	Oestrogen replacement treatment use* Never‡	≤ 5 years	> 5 years	χ^2_1 (trend)
Body mass index (kg/m²)†				
	[37:206]§	[18:35]	[24:21]	
< 25	1‡	2.5(1.3–4.8)**	6.0(2.8–12.8)	23.8¶
	[61:169]	[12:24]	[6:13]	
≥ 25	1	1.1(0.5–2.3)	2.4(0.7–7.7)	1.4
Diabetes				
	[90:367]	[30:58]	[29:34]	
No	1	1.8(1.1–2.9)	4.1(2.2–7.7)	21.4¶
		[1:1]		
	[8:8]	1.0(0.04–24.6)		
Yes	1			
Hypertension				
	[71:305]	[19:40]	[24:24]	
No	1	1.7(1.0–3.1)	4.9(2.4–9.9)	19.8¶
	[27:70]	[11:19]	[6:10]	
Yes	1	1.3(0.5–3.0)	2.1(0.6–7.4)	1.4
Oral contraceptive use				
	[85:290]	[25:52]	[28:22]	
Never	1	1.6(0.9–2.7)	5.4(2.7–10.7)	23.2¶
	[13:85]	[5:7]	[2:12]	
Ever	1	1.8(0.5–6.4)	0.9(0.1–5.2)	0.04
Cigarette smoking				
	[67:240]	[16:30]	[22:23]	
Never	1	1.7(0.9–3.2)	3.9(1.9–8.0)	14.0¶
	[31:135]	[14:29]	[8:11]	
Ever	1	1.8(0.8–4.1)	3.8(1.2–11.8)	6.0‖

* Relative risk estimates from multiple logistic regression models including terms for age, area of residence, marital status, parity, body mass index, history of diabetes and hypertension, smoking habits and oral contraceptive use.
† χ^2_1 for heterogeneity of slope: 4.45; $P < 0.05$.
‡ Reference category.
** 95% confidence interval of the RR is given within parentheses.
§ Number of cases and controls is given in brackets.
‖ $P < 0.05$; ¶ $P < 0.01$.

From the viewpoint of our understanding the mechanisms of endometrial carcinogenesis, the major interest of this study was the analysis of subgroups and interactions. This was particularly relevant for obesity, which was the other major risk factor for endometrial cancer, and may act on similar biological mechanisms. This study, in fact, confirmed that the oestrogen-related endometrial cancer risks were greater in lean than in overweight women, thus supporting the indication that exogenous oestrogens and obesity have an additive (rather than a multiplicative) effect on endometrial carcinogenesis, and hence that both factors probably act by increasing levels of available oestrogens [4–6, 19]. This leads to a significant negative interaction on a multiplicative scale that suggests either an upper risk threshold and/or the existence of some limiting factor (e.g. sex hormone receptors) which impedes the oestrogen-raising effect of obesity and exogenous hormone use to accumulate beyond a certain level [5]. Similar, although non-significant, interactions were observed with diabetes and hypertension even if, for these factors, the underlying biological mechanism is more difficult to understand and may still be partly attributable to excess of overweight subjects with chronic diseases [4].

The present study further suggests that the oestrogen-related risk of endometrial cancer is reduced among women who had used oral contraceptives. A similar observation was made in the Cancer and Steroid Hormone Study (CASH) [10], a population-based case–control investigation of women below the age of 55. The finding of such a long-term protective effect of oral contraceptive use on the oestrogen-related risk, if confirmed, would be of major interest, both on an aetiopathological viewpoint (since it would indicate that oral contraceptive use may render the endometrium persistently less susceptible to hormonal carcinogenesis), and on a public health level, since the incidence of endometrial cancer substantially increases after the menopause [19]. It may also help formulate new types of menopausal replacement therapy with a lower unfavourable impact on the endometrium.

Although these indications are interesting and potentially important, any inference on subgroups and interactions in this study should be made with due caution, on account of the small numbers of oestrogen and oral contraceptive users and, hence, of the limited statistical power. Other potential limitations of this study are its hospital-based design (although case identifi-

cation was based on a cancer registration scheme), with all the consequent weaknesses and strengths. In particular, we excluded hormone-related conditions from the comparison group, participation rate was almost complete, and the catchment areas of cases and controls were well comparable. Some traumatic conditions may be inversely related to oestrogen replacement treatment [20]. However, the results were consistent across separate comparisons of cases with major diagnostic categories of the controls. Further, the similar setting of the interviews, which were all performed in hospital wards, may help obtain comparable history of drug use in cases and controls [13].

In conclusion, therefore, this study—one of the few based on European women—confirms that even in the late 1980s or early 1990s there was a strong association—as reflected by relative and population attributable risk—between oestrogen use and endometrial cancer, and confirms that there is a negative interaction on the relative risk between oestrogens and obesity. Further, it suggests that the oestrogen-related risk may be attenuated in former users of oral contraceptives.

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