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The Joint Effect of Risk Factors on Endometrial Cancer

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Abstract—*The joint effect of risk factors on endometrial cancer was examined by applying general statistical models to the data of a hospital-based case-control study conducted in Copenhagen, Denmark. The analysis included 149 cases of histologically confirmed adenocarcinoma of the endometrium and 154 age-matched controls with cervical cancer. Information on risk factors derived from the medical records. Estrogen use and body mass were found to be the main predictors of endometrial cancer risk. In the model proposed, women who ever used non-contraceptive estrogens had a 10-fold increased risk irrespective of their weight and height. Among non-users of estrogen, the risk of endometrial cancer rose with increasing body mass, the largest showing a five-fold increased risk. These data provide further evidence of the significant role that excess estrogens play, whether exogenous from replacement therapy or endogenous from enhanced androgen conversion, in the etiology of endometrial cancer.*

INTRODUCTION

DETERMINANTS of endometrial cancer risk can be divided into endogenous and exogenous factors. Among the former, obesity is probably the most important since many of the other endogenous risk factors are related to obesity. Several studies [1–4] have found that early age at menarche and late age at menopause increase the risk of endometrial cancer, and there is evidence that age at menarche and at natural menopause at least partly depend on body weight [5–7]. One possible mechanism by which obesity could act is by increasing the level of circulating estrogens through the conversion of plasma androstenedione in adipose tissue [8]. Weaker risk factors, such as hypertension and diabetes mellitus, are also highly correlated with obesity. Furthermore, even family clusters of endometrial cancer have been associated with the tendency of obesity to aggregate in families [9]. Obesity has been established as a risk factor regardless of age and menopausal status, whereas the effect of other factors, especially those related to reproduction, may vary at different ages [4, 10, 11].

Since 1975 numerous studies have demonstrated an increased endometrial cancer risk in women using estrogens for menopausal symptoms. Most studies find that the risk associated with estrogen use is lower in obese than in non-obese women [12–16]. Furthermore, the results of McDonald *et al.* [17], La Vecchia *et al.* [3] and Kelsey *et al.* [4], reanalyzed by Walker and Rothman [18], indicate that the effects of obesity and exogenous estrogens may be additive. In order to examine more closely the joint effect of risk factors on endometrial cancer, we analyzed data from a Danish case-control study by modelling through multivariate logistic regression.

MATERIALS AND METHODS

Study subjects

Study subjects were women referred for radiotherapy at the Oncology Department II, the Finsen Institute, Copenhagen, indentified from diagnostic indices. Eligibility criteria included a histological diagnosis of invasive adenocarcinoma of the endometrium and measurements of body weight and height on admission. Excluded from both the case and control groups were women referred with recurrent disease, women who had a previous diagnosis of cancer in the breast or ovaries and women suffering from psychiatric or other diseases which precluded reliable information in the medical records. Between October 1977 and the end of December 1978, 209 potentially eligible cases were

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identified. Seven were excluded according to the criteria stated above and two hospital records could not be located. The ages at diagnosis of the remaining 200 women with endometrial cancer ranged from 44 to 89 years with a mean of 66 years.

The control group consisted of 200 women with cervical cancer who were admitted to the same hospital as the cases. They were frequency matched to the cases on age at diagnosis within 5-year intervals and adhered to the same eligibility criteria as described above. A histologically confirmed diagnosis of invasive squamous cell carcinoma of the cervix uteri was also required to rule out the possibility of misclassification or metastatic spread from an adenocarcinoma arising in the corpus uteri. While cervical cancer patients might not represent an ideal control group, they possess intact uteri at risk up until the time of diagnosis. In addition, they derived from the same population (catchment area) as the cases and were subject to the same quality and intensity of medical care.

Data collection

All data were abstracted from the hospital records of the cases and controls by one of the authors (ME). Information on marital and socio-economic status, age at menarche, type and age of menopause, parity and use of estrogen was ascertained from patient medical histories. Estrogen use was defined as any use of non-contraceptive estrogen prior to the cancer diagnoses. No reliable information on estrogen dose and duration of use was available. Body mass was evaluated by Quetelet's index (weight/height squared) from the measurements of height and weight on admission. Persons who received antihypertensive medication were considered hypertensive irrespective of their blood pressure. Otherwise, hypertension was defined as blood pressure readings exceeding the mean plus two standard deviations for the particular age group [19]. All pathology reports were reviewed to verify the histological diagnoses.

Analysis

The data were analyzed by logistic regression techniques [20] using the computer program GENSTAT [21]. Accordingly, the effect of all potential risk factors could be estimated simultaneously, adjusting for the concomitant influence of the other variables included in the regression. Factors evaluated and their univariate relative risk estimates are shown in Table 1. Interactive effects arising from combinations of variables were also investigated. Although a frequency matching was adopted in the study design, an unconditional rather than a conditional analysis was carried out due to the numerically large strata. Accordingly, age at diagnosis was included as a variable in the analysis.

Since complete information on all variables included in the analysis was required, 51 cases and 46 controls had to be excluded in the final model primarily because of missing information on estrogen use.

A combination of backward and forward elimination procedures was adopted to identify variables of statistical significance. First, all variables were included then the model reduced as much as possible, cf. Fig. 1. Secondly, all variables were tested, one at a time, against the final model to ensure that no important effects were overlooked in the backward elimination procedure.

Several models were tried to achieve the most accurate description of a possible interaction between Quetelet's index and estrogen usage. Due to the apparent lack of a linear trend in the observed relative risk associated with estrogen usage, an alternative to the multiplicative and additive models was sought. In this alternative model, the risk increases to reach a plateau where no further increase is seen (Fig. 2). Maximum likelihood test statistics were used to test the statistical significance of these models. The test statistics for difference between the saturated and the fitted models were assumed to be chi-square distributed.

RESULTS

Table 1 shows the distribution of cases and controls and estimates of relative risk (RR) based on a simple univariate analysis. It is seen that significant associations were found between endometrial cancer and Quetelet's index and estrogen use. None of the factors, including place of residence and socio-economic status, showed RRs significantly different from unity.

Since the usage of a body mass indicator might conceal an association with height, separate and combined effects of body weight and height were tested. The strongest association with endometrial cancer was found to be a combination of height and weight such as Quetelet's index, while height was not an independent risk factor.

Figure 1 presents the steps of the multivariate analysis where the variables were categorized as indicated in Table 1. Age at menarche was not included in this analysis due to the scarcity of information. Its effect was tested in relation to the other risk factors and found non-significant in a reduced dataset, where persons with missing age at menarche were excluded.

Of the variables included, neither marital status nor parity made significant contributions to the description of endometrial cancer risk, and adjustment for marital status and age at diagnosis did not alter the effect of parity. Childbirths in excess of one did not offer further protection. A slight increase in risk was observed for increasing age at natural

Table 1. Relative risk of endometrial cancer associated with various personal characteristics and medical conditions based on a univariate analysis

Characteristic	Categories	Number of cases $n = 149$	Number of controls $n = 154$	RR (95% CI)*
Marital status	Ever	138	144	1.0 (R)†
	Never	11	10	1.1 (0.5–2.8)
Parity	1+	123	129	1.0 (R)
	0	26	25	1.1 (0.6–2.0)
Age at menarche	<12	3	3	1.0 (R)
	12–15	53	56	1.0 (0.2–4.9)
	16+	11	22	0.5 (0.1–2.9)
	Unknown	82	73	—
Age at natural menopause	Pre/perimenopausal	19	16	1.0 (R)
	<50	57	71	0.7 (0.3–1.4)
	50	36	43	0.7 (0.3–1.6)
	51–54	26	19	1.2 (0.5–2.8)
	55+	11	5	1.9 (0.5–6.5)
Quetelet's index (W/H^2)	<22	28	48	1.0 (R)
	22–	41	48	1.5 (0.8–2.7)
	25–	37	28	2.3 (1.2–4.4)
	28+	43	30	2.6 (1.3–4.7)
Estrogen use	Never	65	121	1.0 (R)
	Ever	84	33	4.7 (2.9–7.7)
Hypertension	No	127	134	1.0 (R)
	Yes	22	20	1.2 (0.6–2.2)

*Relative risk with 95% confidence interval.
†R denotes reference category.

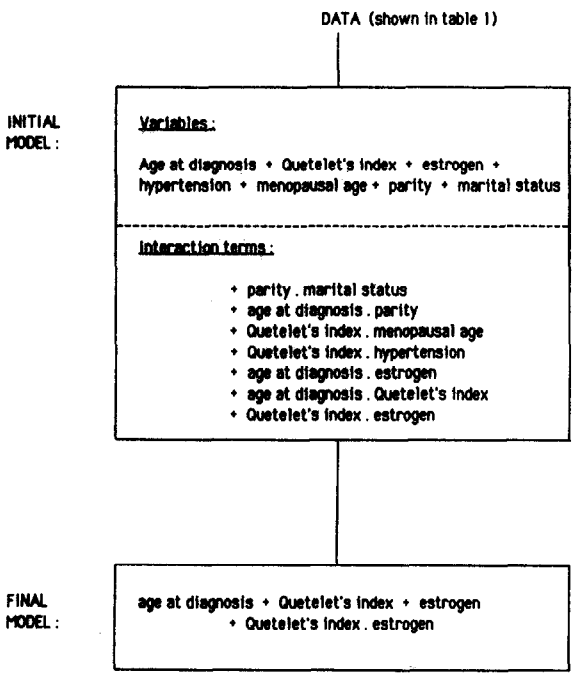

Fig. 1. Variables and interaction terms used in the multivariate analysis (for further explanation, see text).

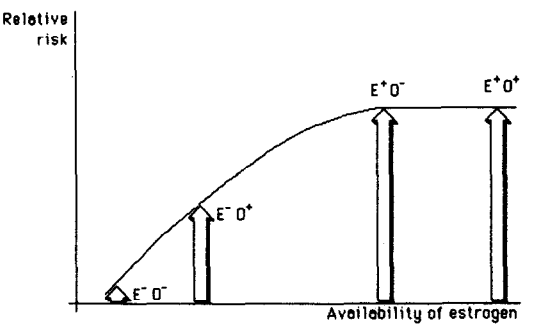

Fig. 2. An alternative model of association between estrogen usage (E, + = exposed, − = non-exposed), obesity (O, + = obese, − = non-obese) and endometrial cancer risk.

menopause, but this was not significant, and there was no interaction between the effects of body mass and menopausal age. No significant association was found between hypertension and endometrial cancer.

Left in the statistical model were two variables of significance, Quetelet's index and estrogen, and their joint effect. The risk associated with body mass and estrogen remained the same in all age groups; consequently age at diagnosis was present only as a non-interactive variable in the final model (see Fig. 1). Table 2 shows the test statistics of the fitted models (multiplicative, additive and alternative) as departures from the 'saturated' model, which is equivalent to a simple, stratified analysis where no

Table 2. Test statistics of various models of association between endometrial cancer, estrogen usage and body mass index, adjusted for age

Model	Number of parameters	Maximum likelihood	Chi-square (departure from saturated model)	Degrees of freedom	*P* value
Saturated	7	−359.5	—	—	—
Multiplicative	4	−366.1	6.6	3	0.09
Additive	4	−363.3	3.8	3	0.28
Alternative	4	−362.8	3.3	3	0.35
Estrogen, fitted singly	1	−379.9	20.4	6	0.002
Quetelets's index, fitted singly	3	−410.6	51.1	4	<0.001

Table 3. Relative risk (RR) of endometrial cancer by estrogen usage and body mass index (Quetelet's) under various statistical models

Quetelet's index		Estrogen usage Numbers		Observed RR (saturated model)		RR in a multiplicative model		RR in an additive model		RR in an alternative model	
		No	Yes	No	Yes	No	Yes	No	Yes	No	Yes
<22	Cases	10	18	1.0 (R)	9.0	1.0 (R)	5.5	1.0 (R)	8.3	1.0 (R)	10.3
	Controls	40	8								
22–	Cases	13	28	1.5	8.0	1.2	6.8	1.5	9.8	1.5	10.3
	Controls	34	14								
25–	Cases	11	26	1.9	20.8	2.0	11.2	2.1	10.5	1.9	10.3
	Controls	23	5								
28+	Cases	31	12	5.2	8.0	3.3	18.5	4.9	13.3	5.0	10.3
	Controls	24	6								

constraints are applied to the data. It is seen that the alternative model provided the best fit ($P = 0.35$) and that neither Quetelet's index nor estrogen, fitted singly, adequately predicted outcome.

The risk estimates obtained in the various models appear in Table 3. In all models, the risk of endometrial cancer increased with increasing body mass in women who had no history of estrogen usage. In the alternative model, the risk increase was most pronounced for women with a Quetelet's index of 28 or more who, compared to women with an index of less than 22, had a RR of 5.0 (95% CI 2.1–12.2). The same trend was not seen among estrogen users, the observed RRs varying in no systematic way between 8.0 and 20.8. The hypothesis that this reflected an underlying constant risk associated with estrogen usage was tested in the alternative model which resulted in a RR of 10.3 (95% CI 4.6–23.1) regardless of body mass.

DISCUSSION

Previous studies have focused on identifying risk factors for endometrial cancer, and a fairly clear pattern has emerged [8]. In the present analysis, we incorporated known risk factors into a general statistical model to predict major effects of single factors and to examine more closely joint effects of several factors simultaneously. The results confirmed that obesity and estrogen use were the main determinants of endometrial cancer risk. The observed trend of increasing risk with increasing body mass among non-users of estrogen is in accordance with the studies of La Vecchia *et al.* [3] and Kelsey *et al.* [4]. Noting lower RRs for obesity among estrogen users and a lower estrogen-related risk in larger compared with smaller women, these reports suggested that the effects of obesity and estrogen usage were additive. Using the present data, an additive model was clearly better than a multiplicative. On the other hand, since the data showed no evidence of a trend in risk by body mass in estrogen users, it could be assumed that the risk associated with estrogen use was constant and independent of body mass. Statistically, this alternative model gave the best fit, slightly better than the additive.

In biological terms, obesity and exogenous estrogens are presumed to affect the same step in the carcinogenic process, i.e. they increase the availability of estrogen to the endometrial tissue [22].

Compared to normal subjects, obese women may have a 4–5-fold increased rate of conversion of androgen to estrogen [23], which agrees well with the risk elevation seen in non-users of estrogen. Depending on the type of estrogen administered, the daily dosage for relief of menopausal symptoms is 10–100 times higher than the normal production and 2–20 times higher than an obese woman's production. According to our model, as illustrated in Fig. 2, an increased availability of estrogen, say 10 times higher than normal, would be sufficient to result in a risk elevation. At this level, the contribution from endogenous sources could be considered negligible. It would be interesting to incorporate the actual dosage and duration of estrogen use into this model. Unfortunately, such information was not available.

Several sources of bias might influence the association between estrogens and endometrial cancer [24]. In Denmark, little publicity was given to estrogen as a possible causative factor at the time when the medical histories were obtained, and contrary to the experience in the United States, the national consumption figures continued to rise after 1975 [25]. Cases and controls were interviewed by the same doctors who, despite their prior knowledge of the diagnosis, did not give any information on estrogen use in about 20% of both cases and controls. Thus, the possibility of information bias seems small but cannot be excluded.

Horwitz and Feinstein [26] have claimed that the magnitude of the association between estrogens and endometrial cancer has been overestimated because of detection bias, introduced by estrogen-induced bleeding leading to the diagnosis of an asymptomatic cancer. Others [27] have argued that an invasive endometrial cancer will ultimately be diagnosed. The present series included invasive cancers only. Compared to the stage distribution of all endometrial cancers diagnosed in Denmark from 1973 to 1977, more advanced stages of disease were found in the case group. This suggests that detection bias either was not present or was minimal in our series. Furthermore, it confirms the results reported by Shapiro *et al.* [28].

A control group of cervical cancer patients would not be optimal if there was a correlation—positive or negative—between risk factors for endometrial and cervical cancer. Socio-economic status has been identified as a risk factor for both cancers, women of high socio-economic status being at high risk for endometrial cancer and those of low socio-economic status at high risk for cervical cancer, although the importance of the latter appears to have diminished over the years [8]. In the present study, socio-economic status was assessed from information in the medical records on occupation of the patient and her husband. We found no difference in socio-economic status between cases and controls, which may reflect that they derived from a homogeneous population with easy access to free medical care. Interestingly, the exposure frequency to estrogens among the cervical cancer patients was approx. 20% over all weight categories and did not differ from other control groups recently studied. In Connecticut, for example, the exposure frequency was 21.9% [18]. This suggests that at least with regard to estrogen usage, the cervical cancer patients did not differ appreciably from other women with intact uteri.

Multiparity has been associated with cervical cancer as a correlate of other risk factors related to sexual practises [8, 29]. In studies of endometrial cancer, married nulliparous women have been at higher risk than unmarried and parous women in whom the risk declined with increasing number of childbirths [2, 4, 10]. It was therefore surprising that this study showed no significant association between endometrial cancer and parity whichever classification was used, and adjustment for marital status and age did not change the risk estimates. The results of Henderson *et al.* [10] and La Vecchia *et al.* [11] suggest that the effect of parity is seen mainly in premenopausal women. It is possible that the apparent lack of association in the present material may be partly due to the relatively few premenopausal women (about 7%).

Among other reproductive variables, this study does not support a role of late age at natural menopause as an independent risk factor. We have no obvious explanation for the discrepancy with two other studies which seem to have controlled for a potential confounding effect of obesity [4, 11]. Although the present data weakly indicate that early age at menarche may increase the endometrial cancer risk, no overall effect could be confirmed. However, information on this variable was particularly scarce.

In conclusion, this study confirms that body mass and estrogen use are the main determinants of endometrial cancer risk. The identification of such predictors of risk are important to clinicians as well as epidemiologists who are engaged in prevention of disease.

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