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Anthropometric Indicators of Endometrial Cancer Risk

Carlo La Vecchia, Fabio Parazzini, Eva Negri, Monica Fasoli, Antonella Gentile and Silvia Franceschi

The relation between selected anthropometric indicators and the risk of endometrial cancer was evaluated using data from a case-control study conducted in Northern Italy on 562 cases and 1780 controls in hospital for acute, non-neoplastic or hormone-related disease. There was no appreciable association between height and endometrial cancer: compared with the lowest quintile, the multivariate relative risks (RR) were 0.9, 0.9, 0.7 and 0.8 for each subsequent quintile. Weight was directly associated with risk (RR=2.7 for top vs. bottom quintile), and the positive association was even stronger when indices of body mass which make allowance for height were considered: the relative risks for extreme quintiles were 3.4 for W/H^2 (Quetelet's index, weight and height), 3.8 for $W/H^{1.5}$ and 3.5 for $W^{0.33}/H$. Surface area, which was positively correlated both with height and weight, showed a weaker direct association (RR=2.4 between extreme quintiles). The relations with measures of body weight were apparently stronger in postmenopause, but the point estimates for the upper quintile were also around 2 in premenopausal women. Although the major findings of this study are not new, they provide more detailed information than was hitherto available on the relation between various anthropometric indicators and endometrial cancer risk. In relation to height, with the sample size of this study it was possible to exclude, at the conventional 95% probability, relative risks above 1.0 for the fourth and above 1.1 for the fifth as compared with the lowest quintile. This provides indirect evidence against the hypothesis that nutritional status early in life is related to the subsequent development of endometrial cancer.
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INTRODUCTION

OVERWEIGHT AND obesity are well-defined risk factors for endometrial cancer, most of the published evidence being based on simple measures of weight or relative indices of body mass (chiefly, Quetelet's index) [1–9].

At least two case-control studies of endometrial cancer, however, have found that not only body weight, but also height is directly associated with risk [4,10]. This is consistent with findings for other sex-hormone related neoplasms (breast and prostate [11,12]) and, in aetiological terms, could be related to a potential role of nutritional factors in childhood and adolescence on the subsequent risk of the neoplasms [13].

The issue is of theoretical interest (as well as of practical relevance for prevention) in order to understand the role of nutrition and overweight within the framework of the process of endometrial carcinogenesis, i.e. whether it has essentially a

Table 1. Distribution of 562 cases of endometrial cancer and 1780 controls according to age and menopausal status. Milan, Italy, 1983–1988

	Endometrial cancer no. (%)	Controls no. (%)
Age group (yrs)		
less than 40	11 (2)	301 (17)
40–49	55 (10)	404 (23)
50–59	176 (31)	477 (27)
60–69	189 (34)	411 (23)
70–74	131 (23)	187 (11)
Menopausal status		
Premenopausal	103 (18)	739 (42)
Postmenopausal	459 (82)	1041 (58)

late stage effect (as that of exposure to oestrogens), or a role on earlier stages of the process, too [14,15].

We have therefore systematically considered the influence of various anthropometric indices on the risk of endometrial cancer, using data from a large case-control investigation conducted in Northern Italy.

SUBJECTS AND METHODS

The data were derived from an ongoing case-control study of cancers of the breast and female genital tract conducted in the Greater Milan area since 1983, whose general design has already been described [15]. Briefly, trained interviewers identified and questioned cases and controls using a structured questionnaire, including information on sociodemographic variables, general lifestyle habits (smoking, coffee and alcohol drinking), a few selected indicator foods, a problem-oriented medical history, menstrual and reproductive variables and use of female hormone preparations. Questions on anthropometric variables included height (cm) and weight (kg) before the onset of symptoms of the disease which led to hospital admission. The data considerd in the present analyses were collected before June 1988.

The cases were women with histologically confirmed endometrial cancer, diagnosed within the year before the interview, admitted to the Obstetrics and Gynaecology Clinics of the University, to the National Cancer Institute and the Ospedale Maggiore of Milan, which includes the four major teaching and general hospitals in Milan. A total of 562 women, aged 28–74 (median age 62 years) were interviewed.

Comparison subjects were women admitted during the same time period to the Ospedale Maggiore of Milan and a few specialised university clinics for acute disorders, unrelated to any of the known or potential risk factors for endometrial cancer. Among them, 31% had traumatic conditions, 27% were admitted for non-traumatic orthopaedic diseases (mostly low back pain and disc disorders), 17% for acute surgical diseases, and 25% for other miscellaneous conditions, such as eye, ear, nose and throat or teeth disorders. After exclusion of women who had undergone hysterectomy, a total of 1780 controls (aged 22–74, median age 53) were considered in the present analyses. The catchment areas of cases and controls were well comparable (overall, 83% of the cases and 89% of controls came from the same region, Lombardy), and their distribution according to age and menopausal status is given in Table 1.

Data analysis and controls of confounding

Besides height (H) and weight (W), four indices were considered: W/H^2 (Quetelet's index), $W/H^{1.5}$ (the National Health and Nutrition Examination Survey anthropometric index for women [11]), $W^{0.33}/H$ (Ponderal index) and surface area, computed as surface area $= 0.0235 \times (H \text{ in cm}^{0.422}) \times (W \text{ in kg}^{0.515})$.

Table 2 gives the correlation matrix between various indices. As expected, the three body mass indices were highly correlated with weight, but $W/H^{1.5}$ was the least correlated with height.

Relative risks (RR) of endometrial cancer according to quintiles of the overall distribution of cases and controls for various anthropometric variables were computed, together with their 95% approximate confidence intervals [16]. Initially, the data were examined through simple stratification by quinquiennia of age and the Mantel–Haenszel procedure [17]. Further, since cases were more frequently nulliparous, had later menopause, were less frequently smokers and users of oral contraceptives, but more frequently users of oestrogen replacement treatments, unconditional multiple logistic regression was used [18], including all the above listed variables plus quinquennia of age. Relative risks adjusted for age only were not appreciably different from multivariate ones; therefore, only the latter are presented.

RESULTS

Table 3 gives the relative risk of endometrial cancer according to the various anthropometric variables considered. There was no appreciable association with height, but compared with the lowest quintile, all the point estimates for subsequent quintiles were below unity. Consequently, on account of the large dataset, an inverse relation emerged of borderline statistical significance.

In contrast, weight was directly related with endometrial cancer risk, and the relation was even stronger when indices of body mass (which provide allowance for height) were considered: the point estimates for top vs. bottom quintile ranged between

Table 2. Mean values and correlation matrix between age and various anthropometric indicators among 562 cases of endometrial cancer and 1780 controls. Milan, Italy, 1983–1988

	Age (yr)	H	W	W/H^2	$W/H^{1.5}$	$W^{0.33}/H$	Surface area
Mean values	54.7	1.60	64.5	25.1	31.8	2.46	1.70
Correlation coefficients							
Age (yr)	1						
H	−0.12	1					
W	0.21	0.24	1				
W/H^2	0.27	−0.16	0.91	1			
$W/H^{1.5}$	0.26	−0.06	0.95	0.99	1		
$W^{0.33}/H$	0.28	−0.36	0.81	0.98	0.95	1	
Surface area	0.19	0.40	0.98	0.86	0.89	0.71	1

H = height (m), W = weight (kg).

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Table 3. Relation between endometrial cancer risk and various anthropometric variables in the overall dataset (562 cases, 1780 controls). Milan, Italy, 1983–1988

	Relative risk estimates*					
Quintile	Height (H,cm)	Weight (W,kg)	W/H^2	$W/H^{1.5}$	$W^{0.33}/H$	Surface area
1	1† (155.1)	1† (54.2)	1† (21.1)	1† (26.7)	1† (2.33)	1† (1.56)
2	0.9 (159.6)	0.9 (60.1)	1.1 (23.6)	1.2 (29.5)	1.0 (2.41)	0.9 (1.65)
3	0.9 (161.2)	1.2 (65.6)	1.1 (25.6)	1.2 (32.3)	1.2 (2.48)	1.1 (1.74)
4	0.7 (165.4)	1.3 (73.9)	1.6 (28.6)	1.6 (35.9)	1.5 (2.58)	1.5 (1.84)
5	0.8	2.7	3.4	3.8	3.5	2.4
χ^2_1(trend)	4.3	47.9	65.0	66.9	64.5	38.2
P	= 0.04	< 0.001	< 0.001	< 0.001	<0.001	< 0.001

The upper limit of the quintile is given in parentheses.
*Estimates from multiple logistic regression equations including terms for age, social class, smoking, parity, age at menarche and at menopause, oral contraceptive and oestrogen replacement treatment use.
†Reference category.

3.4 for Quetelet's index and 3.8 for $W/H^{1.5}$. Surface area, which is correlated both with height and weight, was directly, but less strongly, associated with endometrial cancer risk.

Table 4 gives the corresponding relative risks for premenopausal women only. Although all the estimates were considerably less stable, since only 103 cases were in premenopause, the inverse relation with height was apparently stronger, and the trend statistically significant. The associations with measures of body mass were still evident but weaker, with relative risks of about two (of borderline statistical significance) for top vs. lower quintile.

In postmenopausal women (Table 5) there was no significant association with height, and the relation with indices of body mass was apparently stronger, with point estimates between 4.0 for W/H^2 and 4.3 for $W/H^{1.5}$. The interaction between anthropometric variables and menopausal status, however, was not statistically significant and the figures were comparable when age was used as stratification variable in lieu of menopausal status.

DISCUSSION

The findings of this study are not new and, essentially, they confirm that there is a strong positive association between overweight and endometrial cancer risk [1–9]. Their interest lies in the large dataset and in the simultaneous examination of various indices, thus providing more detailed information than previously available on the relation between various anthropometric indicators and endometrial cancer.

It is of interest that different indices of body mass produced comparable results, and that not only was there no positive association with height, but even a small inverse one. Two studies [4,10], in fact, have suggested an independent association between height and endometrial cancer, thus indirectly indicating that nutritional status early in life might be related to the subsequent development of endometrial cancer [10, 13]. With the sample size of this study, it was possible to exclude, at the conventional 95% probability, relative risks above 1.0 for the fourth and above 1.1 for the fifth as compared with the lowest quintile of height.

Table 4. Relation between endometrial cancer risk and various anthropometric variables in premenopausal women (103 cases, 739 controls). Milan, Italy, 1983–1988

	Relative risk estimates for					
Quintile	Height	Weight	W/H^2	$W/H^{1.5}$	$W^{0.33}/H$	Surface area
1	1†	1†	1†	1†	1†	1†
2	1.3	0.8	1.0	1.1	1.0	0.7
3	0.6	0.7	0.8	0.8	1.0	0.6
4	0.4	1.1	1.2	1.3	1.1	1.0
5	0.5	1.2	1.9	2.1	2.0	1.0
χ^2_1(trend)	7.6	0.7	2.7	2.9	2.4	0.1
P	< 0.01	NS	0.10	0.09	0.12	NS

†Reference category.
NS = not significant.

Table 5. Relation between endometrial cancer risk and various anthropometric variables in postmenopausal women (459 cases, 1041 controls). Milan, Italy, 1983–1988

	Relative risk estimates for					
Quintile	Height	Weight	W/H^2	$W/H^{1.5}$	$W^{0.33}/H$	Surface area
1	1†	1†	1†	1†	1†	1†
2	0.8	0.9	1.0	1.1	1.0	1.0
3	0.9	1.5	1.3	1.3	1.4	1.2
4	0.8	1.4	1.8	1.7	1.7	1.7
5	0.8	3.3	4.0	4.3	4.2	3.0
χ^2_1(trend)	1.3	52.4	67.3	68.7	67.6	43.3
P	NS	< 0.001	<0.001	< 0.001	< 0.001	< 0.001

†Reference category.
NS = not significant.

The differences observed in various studies might be attributed to the different nutritional status of different populations in subsequent time periods, which are reflected in the corresponding sequences of increase in height over the last decades. However, in the generation of middle-aged and older Italian women who constituted the majority of endometrial cancer cases in this study, height was still increasing [19] and hence was probably influenced by nutrition in childhood and adolescence, besides of course by the genetic component. This is reflected in the negative correlation between height and age in this study.

The present study is a typical hospital based case-control investigation and, as such, has all the relative strengths and weaknesses. Self-reported measures of weight and height are known to be, respectively, somewhat under and overestimated [20, 21]; if specifically reducing the precision of the measures for cases and controls (since it is unlikely that the case/control status influenced reporting of height and weight), this should lead to an underestimate of the true associations [16].

The choice of hospital controls for studying measures of body weight may also lead to underestimation of the associations, since overweight is related to several diseases [21]. However, in this study the relative risks were similar when comparison was made with various categories of controls. In relation to other possible sources of bias, cases and controls were drawn from institutions covering comparable catchment areas, participation rate was almost complete, and allowance for major risk factors for endometrial cancer did not materially influence the relative risks.

In postmenopausal women the association between overweight and endometrial cancer is attributed to increased peripheral conversion of plasma androstenedione to estrone, and to lower levels of sex hormone binding globulin [22–24]. It is difficult to explain, on the same grounds, the elevated risk in obese premenopausal women observed in this study as well as in a case-control study of endometrial cancer in young women conducted in California [7]. In the premenopausal period a plausible aetiological interpretation should be considered in terms of relative progesterone deficiency, since obesity is associated with irregular menstrual periods, amenorrhea and luteal phase progesterone deficiency [25].

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