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Selected physical activities and the risk of endometrial cancer

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Summary The relationship between various indicators of physical activity and endometrial cancer risk was analysed using data of a case-control study conducted in 1988–1991 in Switzerland and Italy on 274 histologically confirmed cases and 572 controls admitted to hospital for acute, non neoplastic, non hormone-related diseases. Using a self-rated assessment of total physical activity, there was a systematic tendency for the cases to report more frequently 'low' or 'very low' physical activity. The relative risks were similar for 'very high' or 'moderately high' physical activity, but increased in the two lowest levels, with point estimates, in various decades of age, between 1.3 and 2.3 for 'moderately low' and over 2.5 for 'very low' physical activity. Although the association was apparently stronger at older ages, all the trends in risk were significant. Allowance for major identified potential distorting factors, including body mass index and a measure of total energy intake, could explain only in part the association, and the inverse trends in risk remained statistically significant. When selected types of physical activity were analysed, no association was observed with climbing stairs or walking, but the risk estimates for the lowest level of activity was over 4 for housework, and between 1.5 and 1.9 for sport and leisure and occupational activity. Thus, the present findings suggest that a moderate or high physical activity is an indicator of reduced endometrial cancer risk, although this observation still requires epidemiologic confirmation and clearer definition from a pathogenic point of view.

Endometrial cancer is strongly related to overweight and, possibly, to selected aspects of dietary intake (La Vecchia, 1989; Parazzini *et al.*, 1991). Physical activity is the other main component of energy balance, and appears to exert a favourable effect on a number of chronic conditions, including coronary heart disease, diabetes mellitus, and osteoporosis (Garfinkel & Stellman, 1988; Helmrich *et al.*, 1991). For instance, several studies of coronary heart disease have found protections of the order of 30 to 60% for subjects reporting at least moderate physical activity, and the effect of exercise was apparently independent from that of other recognised risk factors for heart disease (Morris *et al.*, 1973; Paffenbarger & Hale, 1975; Paffenbarger *et al.*, 1978; Garfinkel & Stellman, 1988). An association of inactivity or low physical activity with large bowel cancer has also been reported, and was apparently independent from body mass index, serum cholesterol, alcohol and other identified or potential confounding factors (Ballard-Barbash *et al.*, 1990; Whittemore *et al.*, 1990).

It has been suggested that physical activity may modify serum cholesterol levels (Caspersen *et al.*, 1991), amount and distribution of body fat (Seidell *et al.*, 1991), the ovarian production of female hormones (Frisch *et al.*, 1987) and serum oestrogen levels in postmenopausal women (Cauley *et al.*, 1989). These may influence some of the biologic links between anthropometric and hormonal factors and endometrial cancer risk (La Vecchia, 1989).

With these background considerations, albeit aware of the major difficulties both in the reliable assessment of physical exercise (Washburn & Montoye, 1986) and in sensible allowance for covariates, we considered the relationship between selected measures of physical activity and endometrial cancer risk using data from a case-control study conducted in Switzerland and Italy.

Subjects and methods

Since January 1988, we have been conducting a cooperative case-control study of endometrial cancer in the Swiss Canton of Vaud, and in metropolitan Milan and in Pordenone province, northern Italy. The general design of this investigation has already been described (Levi *et al.*, 1992).

Briefly, in Vaud case recruitment was centered in the main University Hospital of the Canton, and cases were matched with incident cases reported to the local Cancer Registry (Levi, 1987). Overall, over 80% of identified cases were interviewed. In Milan and Pordenone case recruitment was hospital-based, since the areas are not covered by cancer registration schemes. Overall, 274 histologically confirmed incident endometrial cancers were interviewed before June, 1991. The age range was 31–75 (median age 61 years).

The controls were women aged 75 or less, admitted to the same networks of hospitals where cases had been identified, whose primary diagnosis was unrelated to any of the known or potential risk factors for endometrial cancer or to any long-term modification of diet. Specific exclusion was made of women admitted for gynaecologic, hormonal, metabolic or neoplastic diseases or who had undergone hysterectomy. A total of 572 women, aged 30 to 75 (median age 59), were interviewed. Of them, 32% were admitted for traumas, 16% had non-traumatic orthopaedic diseases, 26% surgical conditions and 26% other miscellaneous disorders, including acute medical, eye, nose and throat and dental diseases, etc. Cases and controls were not singularly matched, but, to avoid major imbalances in the age distribution, controls were frequency matched with cases within each centre.

All interviews were conducted in hospital by trained interviewers (nurses or medical students). Approximate length of the interview was between 40 min and 1 h. Less than 10% of subjects (7% of cases, 8% of controls) approached for interview refused. The main reason for non-response was absence from the ward during the interviewers' visit. The interviewers received the same structured training, to standardise data collection in various centres. Data checking and quality control was centralised.

Information was collected using the same structured questionnaire on socio-demographic factors, personal characteristics and habits (such as smoking, coffee and alcohol drinking), self-reported current and past anthropometric measures (Levi *et al.*, 1992), 40 selected indicator foods, a problem-oriented medical history, menstrual and reproductive factors and use of female hormone preparations. A few indicators of physical activity were also elicited including, for various ages, an overall subjective (self-rated) score for total

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activity arbitrarily subdivided into four levels (high/moderately high/moderately low/very low) and based only on patients' evaluation and report, plus five selected types of activities (housework, climbing stairs, walking, sport and leisure, occupational activity), again assessed in four levels on the basis of quantity (high/moderately high/moderately low/low) and frequency (daily/weekly/occasionally/never).

Data analysis and control of confounding

Relative risks (RR), and the corresponding 95% confidence intervals (CI) (Breslow & Day, 1980) of endometrial cancer according to various indicators of physical activity were first computed from data stratified for study centre and 5-year age group using the Mantel-Haenszel procedure (Mantel & Haenszel, 1959). Further, multiple logistic regression was used, with maximum likelihood fitting (Baker & Nelder, 1976), including terms for study centre, age, education, parity, menopausal status, use of oral contraceptives and oestrogen replacement treatment, body mass index and estimated total calorie intake. This was computed by multiplying the average caloric content of one serving of each of the 40 foods and of beverages (including alcoholic beverages) by its reported frequency of intake, using nutritional values issued by English (Paul & Southgate, 1978) or Italian (Fidanza & Versiglioni, 1988) tables. Estimated average total calorie intake for the overall dataset was 1,980 Kcalories per day.

Results

Table I gives the distribution of endometrial cancer cases and the comparison group according to study centre, age group, menopausal status, and body mass index. Cases were somewhat older than controls, more frequently in post menopause, of similar level of education, but had significantly greater body mass: compared with normal-weight women, the relative risk was 1.4 (95% CI 1.0 to 2.0) for overweight ones, and 2.4 (95% CI 1.3 to 5.1) for the severely obese).

Table II considers an overall subjective score of total physical activity at different ages. In each subsequent age group there was a systematic tendency for the cases to report more frequently 'low' or 'very low' physical activity. The corresponding relative risk estimates are given in Table III. The RRs were similar for 'very high' and 'moderately high' physical activity, but increased in the two lowest levels, with point estimates between 1.3 and 2.3 for 'moderately low' overall physical activity, and over 2.5 for 'very low' physical activity. Although the association was apparently stronger at older ages, all the trends in risk were significant. Allowance for major identified potential distorting factors, including body mass index and a measure of total energy intake, could explain only in part the association with total physical activity, and all the inverse trends in risk remained statistically significant, indicating that physical activity had an independent effect from main recognised risk factors for endometrial cancer.

Selected types of physical activity (housework, climbing stairs, walking, sport and leisure, and occupational activity) during the decade of age before diagnosis or interview are considered in Table IV in terms of frequency distribution of cases and controls and in Table V in terms of relative risk estimates. No association was observed with climbing stairs or walking, but housework, sport and leisure, and occupational activities were inversely and significantly related with endometrial cancer. The risk estimates for the lowest level of activity were over 4 for housework, and between 1.5 and 1.9 for sport and leisure and occupational activity. As for total activity, all trends in risk were not appreciably modified after

Table I Distribution of 274 cases of endometrial cancer and 572 controls according to study centre age, menopausal status, and current body mass index

	Endometrial cancer		*Controls*	
	Number	*%*	*Number*	*%*
Study centre				
Vaud	138	50.4	406	71.0
Milan	112	40.9	122	21.3
Pordenone	24	8.8	44	7.7
Age group (years)				
<45	16	5.8	65	11.4
45–54	51	18.6	128	22.4
55–64	112	40.9	187	32.7
65–75	95	34.7	192	33.6
Menopausal status				
Pre- in menopause	56	20.4	156	27.3
Post-menopause	218	79.6	416	72.7
Current body mass index ($kg\ m^{-2}$)				
<20	17	6.2	60	10.5
20–24	112	40.9	253	44.2
25–29	93	33.9	190	33.2
⩾30	52	19.0	69	12.1

Table II Distribution of 274 cases of endometrial cancer and 572 controls according to reported measures of total physical activity at different ages

	Age (years)									
	25		*35*		*45*		*55*		*65*	
	Cases	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*
Measure of physical activity										
1 (highest)	111	247	105	246	88	206	53	121	17	45
2	99	258	101	261	112	261	121	247	66	147
3	50	57	53	53	50	61	46	70	47	77
4 (lowest)	14	10	14	11	17	12	23	9	23	8

Table III Relative risk estimates (and 95% confidence intervals) of endometrial cancer according to reported measures of physical activity at different ages

	Age (years)									
	25		*35*		*45*		*55*		*65*	
	M–H[a]	*MLR*[b]	*M–H*[a]	*MLR*[b]	*M–H*[a]	*MLR*[b]	*M–H*[a]	*MLR*[b]	*M–H*[a]	*MLR*[b]
Measure of physical activity										
1 (highest)	1[c]	1[c]	1[c]	1[c]	1[c]	1[c]	1[c]	1[c]	1[c]	1[c]
2	0.8	0.8	0.9	0.9	1.0	1.0	1.2	1.1	1.1	1.0
	(0.6–1.1)	(0.5–1.1)	(0.6–1.2)	(0.6–1.2)	(0.7–1.4)	(0.7–1.4)	(0.8–1.9)	(0.7–1.8)	(0.5–2.5)	(0.4–2.5)
3	1.8	1.6	2.3	2.1	1.7	1.5	1.4	1.2	1.3	1.0
	(1.2–2.9)	(1.0–2.6)	(1.4–3.6)	(1.3–3.6)	(1.0–2.7)	(0.9–2.5)	(0.8–2.4)	(0.7–2.2)	(0.5–3.0)	(0.9–2.7)
4 (lowest)	2.6	2.5	2.7	2.4	3.6	2.9	11.9	8.6	8.5	6.3
	(1.1–6.2)	(1.0–6.2)	(1.1–6.2)	(1.0–5.8)	(1.6–8.4)	(1.3–6.9)	(4.2–33.8)	(3.0–25.3)	(2.4–29.8)	(1.7–23.8)
χ^2_1 (trend)	6.04[d]	4.10[d]	10.18[e]	7.81[e]	8.97[e]	5.72[d]	16.04[e]	10.27[e]	9.45[e]	5.48[d]

[a]Mantel-Haenszel estimates adjusted for study centre and age. [b]Estimates from multiple logistic regression equations adjusted for study centre, age, education, parity, menopausal status, oral contraceptive and oestrogen replacement treatment use, body mass index and estimated calorie intake. [c]Reference category. [d]$P<0.05$. [e]$P<0.01$.

Table IV Distribution of cases of endometrial cancer and controls according to selected types of physical activity

	Type of physical activity									
	Housework		*Climbing stairs*		*Walking*		*Sport & leisure*		*Occupational activity*	
	Cases	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*	*Cases*	*Controls*
Measure of physical activity										
1 (highest)	54	117	112	260	114	219	12	34	62	189
2	96	236	22	43	65	186	39	128	14	33
3	59	145	46	144	59	91	45	149	18	44
4 (lowest)	65	74	94	124	36	76	176	261	178	305

Table V Relative risk estimates (and 95% confidence intervals) of endometrial cancer according to selected types of physical activity

	Type of physical activity[a]											
	Housework		*Climbing stairs*		*Walking*		*Sports & leisure*		*Occupational activity*	
	M–H[b]	*MLR*[c]	*M–H*[b]	*MLR*[c]	*M–H*[b]	*MLR*[c]	*M–H*[b]	*MLR*[c]	*M–H*[b]	*MLR*[c]
Measure of physical activity										
1 (highest)	1[d]	1[d]	1[d]	1[d]	1[d]	1[d]	1[d]	1[d]	1[d]	1[d]
2	1.6	1.7	1.1	1.2	0.9	0.8	1.0	1.0	1.2	1.1
	(1.0–2.6)	(1.0–2.7)	(0.6–2.0)	(0.7–2.2)	(0.6–1.3)	(0.6–1.2)	(0.5–2.2)	(0.5–2.4)	(0.6–2.4)	(0.5–2.3)
3	1.9	2.0	0.7	0.7	1.5	1.4	1.0	1.0	1.1	1.0
	(1.2–3.3)	(1.1–3.3)	(0.5–1.1)	(0.4–1.0)	(1.0–2.3)	(0.9–2.2)	(0.5–2.0)	(0.5–2.3)	(0.6–2.1)	(0.5–2.2)
4 (lowest)	4.4	4.2	1.3	1.2	0.9	0.8	1.8	1.9	1.7	1.5
	(2.5–7.6)	(2.4–7.5)	(0.9–1.9)	(0.8–1.8)	(0.5–1.6)	(0.5–1.3)	(0.9–3.7)	(0.9–4.0)	(1.2–2.4)	(1.0–2.2)
χ^2_1 (trend)	27.67[e]	24.16[f]	0.34	0.09	0.54	0.01	10.01[f]	9.18[f]	8.81[f]	5.17[e]

[a]In the decade of age before diagnosis/interview. [b]Mantel-Haenszel estimates adjusted for study centre and age. [c]Estimates from multiple logistic regression equations adjusted for study centre, age, education, parity, menopausal status, oral contraceptive and oestrogen replacement treatment use, body mass index and estimated calorie intake. [d]Reference category. [e]$P<0.05$. [f]$P<0.01$.

allowance for major identified potential confounding factors.

Similar results were obtained when the same indicators of physical activity were considered across subsequent age groups. Likewise, similar analyses conducted in the two study areas separately (Switzerland/Northern Italy) yielded comparable results (data not shown).

Table VI considers the interaction between estimated total physical activity, body mass index and total calorie intake. There was a suggestion for the association to be stronger in heavier women and in those who reported higher calorie intake, although the point estimates for the lowest level of physical activity tended to be above unity in most strata considered. The interaction term was significant only for body mass index ($\chi^2_1 = 12.33$, $P<0.01$).

Discussion

The present study suggests that physical activity is an indicator of reduced endometrial cancer risk. The association was evident and consistent with an overall self-rated assessment of total physical activity across various periods of life, and with a few selected types of physical activities (housework, sport and leisure, occupational activity), which probably represent the indicators of physical activity with the best discriminating ability. The observed association was not explained by major established risk factors for endometrial cancer and other main correlates of energy balance, including calorie intake and body mass index.

If the strength and the consistency of the results allow to exclude confidently chance or obvious bias as an explanation of the associations observed, it is nonetheless difficult to formulate and discuss any inference on a causal role of exercise on endometrial carcinogenesis. Epidemiologically, there are major difficulties in studying exercise (Washburn & Montoye, 1986). Occupational exercise, in fact, is strongly correlated to social class and hence to a wide range of other environmental and lifestyle exposures. Leisure time exercise is also confounded, though to a lesser extent, by social class indicators, and can be a consequence, as well as a cause, of general health conditions.

To further complicate the issues, physical activity is difficult to quantify, and the related methods of validation and analysis are still open to discussion (Washburn & Montoye, 1986). Although the assessment of physical activity through questionnaires is still open to debate, it has been suggested that even simple questions provide useful information on the issue (Schechtman *et al.*, 1991). We used therefore a simplified overall subjective score for physical activity, plus a few specific questions on a number of selected types of activities which are commonest in the study population. Although each one of these measures may be open to criticism, the consistency of the findings with reference to several different types of physical activity lends support to the validity of the results.

Further difficulties are posed by the lack of a simple biologic interpretation of the observed association. It has been suggested that physical activity decreases body fat (independently from potential modifications of body mass index (Frisch *et al.*, 1987)) and influence body fat distribution (Seidell *et al.*, 1991) and serum lipoprotein levels (Caspersen *et al.*, 1991). Another plausible biologic link would be through serum oestrogen levels, since more active women had been found to have lower levels of oestrone (Cauley *et al.*, 1989) or increased metabolism of oestrogens to less potent forms (Frisch *et al.*, 1985), and this observation is consistent with the especially stronger association observed in this study in obese women and in those reporting higher calorie intake.

A few studies have suggested an inverse relationship between physical activity and colorectal (Whittemore *et al.*, 1990), breast and female genital tract cancer risk (Frisch *et al.*, 1987). However, the favourable breast cancer risk pattern among ballet dancers (as indicated by delayed menarche and amenorrhea (Frisch *et al.*, 1980, 1981)) and other groups of women with high physical activity in adolescence has been

Table VI Relative risk estimates (and 95% confidence intervals)[a] of endometrial cancer according to reported measures of total physical activity in selected strata of body mass index and total calorie intake

	Total physical activity[b]				
Variable	*1*[c] *(highest)*	*2*	*3*	*4 (lowest)*	χ^2_1 *(trend)*
Body mass index kg m^{-2}					
<25	1	0.7 (0.4–1.2)	0.6 (0.3–1.1)	1.8 (0.6–5.2)	0.08
⩾25	1	1.0 (0.6–1.8)	1.8 (0.9–3.4)	4.7 (1.9–11.3)	14.38[d]
Total calorie intake, tertile[e]					
1 (lowest)	1	0.9 (0.4–2.1)	0.6 (0.2–1.7)	1.0 (0.2–3.7)	0.26
2	1	0.7 (0.3–1.4)	1.0 (0.5–2.2)	2.3 (0.5–9.8)	0.85
3 (highest)	1	0.7 (0.4–1.5)	0.9 (0.4–2.0)	3.7 (1.2–11.3)	3.71

[a]Mantel-Haenszel estimates adjusted for study centre and age. [b]In the decade of age before diagnosis/incidence.[c]Reference category.[d]$P < 0.01$.[e]Cut off points, 1,782, 2,188 Kcalories/day.

generally interpreted in terms of the effect of thinness (and related hormonal factors), rather than of a direct influence of physical activity (Frisch *et al.*, 1987; La Vecchia, 1989).

To further complicate any inference, some other epidemiologic observations are inconsistent with the hypothesis that physical exercise reduces overall cancer incidence. The American Cancer Society One Million Cohort Study (Garfinkel & Stellman, 1988), for instance, found reduced standardised mortality ratios (SMR) for all causes and ischaemic heart disease in subjects reporting heavy exercise, but elevated rates in women (SMR = 120) for all cancers. Likewise, in a cohort study of over 50,000 alumni, physical activity (⩾5 h per week) was associated with reduced rectal cancer risk (RR = 0.6, 95% CI 0.2–1.0), but no consistent protection for other cancer sites (Albanes *et al.*, 1989). Again, confounding cannot be excluded, but these data do not support the view that physical exercise *per se* reduces cancer risk. The NHANES I cohort study (Albanes *et al.*, 1989) showed that the risks of all cancers, colorectal and lung cancers were elevated among inactive males, when non-recreational activity was considered, but the pattern was less consistent for females, with an increased risk of cervical cancer among inactive women and a non-significant association between inactivity and postmenopausal breast cancer.

Other limitations and strengths of this study are common to most hospital-based case-control investigations (Mantel & Haenszel, 1959; Breslow & Day, 1980). Although hospital controls can in principle be criticized for the investigation of lifestyle habits, it is unlikely that patients admitted to hospital for a wide spectrum of acute diseases reported systematically more physical activity than the general population. Separate comparison with various diagnostic categories of the controls, moreover, did not find any appreciable difference in any of the risk estimates. Selection, information, or confounding bias are unlikely to play a major role, since participation rate was almost complete, the catchment areas of cases and controls were comparable, and there is no reason for suggesting differential recall of physical exercise by cases and controls. In addition, allowance for a number of major covariates in multivariate analyses did not appreciably modify any of the risk estimates.

In conclusion, therefore, the present study suggests that a moderate or high physical activity is an indicator of protection against endometrial cancer risk, although the observation still requires epidemiologic confirmation and also pathogenetic interpretation to be integrated within our knowledge of endometrial carcinogenesis.

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