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RISK FOR ENDOMETRIAL CANCER IN RELATION TO OCCUPATIONAL PHYSICAL ACTIVITY: A NATIONWIDE COHORT STUDY IN SWEDEN

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Notwithstanding its biologic plausibility, the association between physical activity and endometrial cancer has been analyzed in only a few epidemiological studies. Retrospective assessment of exposure and small sample size often hampers interpretation of published data. We studied risk for endometrial cancer in relation to physical activity at work in a large cohort of Swedish women identified in the nationwide censuses in 1960 and 1970, with jobs that could be consistently classified into one of 4 levels of physical demands. Follow-up from 1971 through 1989 was accomplished through record linkages. Multivariate Poisson regression models were used to estimate relative risk. The risk for endometrial cancer increased regularly with decreasing level of occupational physical activity (*p* for trend < 0.001), and was associated more strongly with activity in 1970 than in 1960. In multivariate analyses, adjusted for age at follow-up, place of residence, calendar year of follow-up, and social class, the relative risk among women with the same physical activity level in 1960 and in 1970 was 30% higher for sedentary as compared with high/very high activity level; (*p* for trend = 0.04). The protective effect of physical activity appeared to be confined to women aged 50 to 69, among whom sedentary work was associated with a 60% higher risk than that observed among women estimated to be physically most active. The excess seemed to disappear within 10 years after a change in physical activity level. Although confounding cannot be ruled out in our data, occupational physical activity appears to reduce the risk for endometrial cancer. *Int. J. Cancer* 76:665–670, 1998.
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Although the relationship between physical activity and cancer risk was investigated as early as the 1920s (Sivertsen and Dahlstrom, 1921), until now a protective effect has been well established only for colon cancer. The hypothesis that physical activity reduces risk for endometrial cancer is biologically tenable, but has been incompletely investigated. Lower weight and body fat, late age at menarche, early onset of menopause and anovulation (Frisch *et al.*, 1980; Warren, 1980) might be intermediate steps in a possibly protective chain of events. While most studies show an inverse relationship between physical activity and risk for endometrial cancer (Shu *et al.*, 1993; Zheng *et al.*, 1993; Levi *et al.*, 1993; Sturgeon *et al.*, 1993; Hirose *et al.*, 1996; Olson *et al.*, 1997), data on the relationship by age and according to the interval between onset or change of the estimated physical activity level and diagnosis of this cancer are scarce.

We used the nationwide, population-based Swedish Cancer Environment Registry III (Epidemiologiskt Centrum, 1994) to assess the role of occupational physical activity for the risk of endometrial cancer. This registry was created by linkage of the virtually complete national cancer registry (1971–1989) to the household censuses in 1960 and 1970. The repeated assessment of current job title in 2 censuses allowed us to focus on women estimated to have a stable level of physical activity at work over 10 years or more, and to assess separately the risk in women estimated as having changed their level of physical activity. Moreover, the large number of observed cases permitted us to stratify our data by age at follow-up and thus indirectly estimate risks for endometrial cancer according to menopausal status at follow-up.

SUBJECTS AND METHODS

Swedish census

Since 1960, census information on population and housing has been obtained in Sweden approximately every 5 years, using questionnaires mailed to every Swedish household. The questionnaires cover demographic, occupational (including employment status, job title, industry and work address), and socio-economic factors for each household member during one week in October (Official Statistics of Sweden, 1975). The data are stored together with the national registration number, a unique personal identifier assigned to all Swedish residents (Lunde *et al.*, 1980). Since response to the census questionnaire is obligatory by law, with great efforts devoted to obtaining information from persons who do not initially provide the information requested, censuses are more than 99% complete (Official Statistics of Sweden, 1974).

Cancer Register

The national Swedish Cancer Register, founded in 1958, includes more than 98% of all new cancer cases in the country (Mattson, 1977). Malignant diseases are coded according to the International Classification of Disease, seventh revision (ICD-7), during the entire period of study. The proportion of endometrial cancers (ICD-7 code 172) that were histologically verified was 99% in 1978 and 100% in 1993 (Cancer Registry, 1996). The Cancer Register is linked annually to the Swedish Register of Causes of Death, using the national registration numbers as identifiers. The latter register provides information on all deaths, including the underlying and contributing causes derived from the death certificates which physicians are required to complete within a week after death (Statistics Sweden, 1973–1991).

Cancer-Environment Register

The Swedish census data for 1960 and for 1970 were previously linked to the Cancer Register, forming Cancer Environment Registers I and II, respectively. A third version, Cancer-Environment Register III (CERIII) (Epidemiologiskt Centrum, 1994), was established in 1994 by linking the Cancer Register data for 1971–1989 to the national population censuses from 1960 and 1970. The national registration numbers were used to ensure correct matching.

The CERIII proper includes only cancer cases. Those included were cancer patients who had resided in Sweden both in 1960 and in 1970, and thus were recorded in both censuses. A total of 392,941 women with 440,819 tumors are recorded in CERIII. Missing data (individuals found in the cancer register but not in the

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censuses despite verified residence in Sweden both in 1960 and in 1970 according to other independent sources) was estimated to be less than 0.9% (Epidemiologiskt Centrum, 1994).

To allow calculation of person-years at risk and thereby expected numbers of detected cancers, a background register was established, encompassing all individuals who took part in both the 1960 and the 1970 censuses. Except for the tumor data, the information in this background register is virtually the same as in the CERIII proper, including dates (but not causes) of death among the deceased. This background register encompassed 3,347,867 women aged between 11 and 106 years in 1971. After completion of the record linkages, the national registration numbers were removed both from the CERIII proper and from the background register, to ensure confidentiality.

Classification of physical activity and SES

The occupations reported in the census questionnaires were coded, using a 3-digit classification, into 245 categories in the 1960 and 248 in the 1970 census respectively (Official Statistics of Sweden, 1971). This coding scheme, devised by the National Labor Market Board in Sweden (Official Statistics of Sweden, 1975) in collaboration with the National Labor Market Board in Denmark, Norway and Finland (National Labor Market Board, 1965), parallels the classification of the International Labour Office and the United Nations (International Labour Office, 1958). Proceeding from these codes, we classified each occupation according to the estimated physical demands of the job, as very high, high, moderate, light and sedentary activity. Assessments were done independently by 3 Swedish specialists in occupational medicine with long experience in job classification.

To reduce misclassification of the physical-activity level estimated for a job, we considered in the present analysis only occupations consistently classified by the 3 experts: we required absolute agreement between at least 2 of the experts, while the third was allowed to diverge by no more than one category. A total of 202 occupations were thus unequivocally classified. Because few women were classified as having jobs with very high demands, the 2 categories of highest physical activity were subsequently merged to gain statistical power. Table I shows the 4 most prevalent occupations for each estimated level of occupational physical activity.

Socio-economic status was categorized into 4 levels (unskilled blue-collar, skilled blue-collar, unskilled white-collar and skilled white-collar occupations) based on the occupational title, as described in detail elsewhere (Statistics Sweden, 1995). We grouped places of residence into 2 categories: the 3 largest cities (Stockholm, Gothenburg and Malmö), and the rest of Sweden.

Comparison of physical activity classification with self-reported activity levels

The Swedish twin registry (Medlund *et al.,* 1977) provided us with the opportunity to validate our physical-activity matrix with self-reports from a time period close to when the occupational information in our cohort was obtained. Of 18,514 female twins, born in 1926–1958, who in 1973 self-rated their physical activity at work according to a 4-level scale, one member of each pair was randomly selected. Of these, 3,423 (37%) had occupations from our list. Their self-reports were compared with our assessments based on job titles.

We found good agreement [Spearman rank correlation coefficient (Rosner, 1990), 0.62, $p < 0.0001$, and weighted Cohen's kappa (Cohen, 1968), 0.56] between the twins' self-scoring and the experts' scoring.

Study cohorts

In 1960, a total of 704,904 women in the background register reported employment in a job that had been unequivocally classified with regard to physical activity. They constituted our sub-cohort A. Sub-cohort B was formed by the 982,270 women whose occupation as reported in the 1970 census was also unequivocally classified according to physical-activity level. Altogether 253,336 women, contributing 4,421,602 person-years of observation, had

TABLE I – CLASSIFICATION OF SWEDISH WOMEN BY OCCUPATIONAL PHYSICAL ACTIVITY BASED ON OCCUPATIONAL CODES IN CENSUS DATA FROM 1960 AND 1970[1]

Level of physical activity	1960 census		1970 census	
	Occupation	Number (%)	Occupation	Number (%)
Very high/High	Charworkers, cleaners and related workers	41,947 (35.7)	Nursing personnel not elsewhere classified	95,811 (40.9)
	Nursing personnel not elsewhere classified	40,702 (34.6)	Cleaners and related workers	81,544 (34.8)
	General farm workers; field-crop and vegetable-farm workers; farm machinery operators; livestock workers	18,152 (15.5)	General farm workers; field crop and vegetable farm workers; farm machinery operators; livestock workers	38,638 (16.6)
	Dockers and freight workers	6,622 (5.6)	Dockers and freight workers	9,171 (3.9)
	All with very high/high-level activity	117,479 (100)	All with very high/high-level activity	234,465 (100)
Medium	Maids and related housekeeping service workers not elsewhere classified	93,695 (44.3)	Maids and related housekeeping service workers not elsewhere classified	128,044 (43.4)
	Waiters, bartenders and related workers	25,582 (12.1)	Professional nurses	29,699 (10.1)
	Professional nurses	19,876 (9.4)	Waiters, bartenders and related workers	28,938 (9.8)
	Cooks	11,920 (5.6)	Cooks	12,840 (4.3)
	All with medium-level activity	211,325 (100)	All with medium-level activity	294,799 (100)
Light	Sewing-machine operators	36,289 (16.6)	Elementary-school teachers	32,274 (11.9)
	Elementary-school teachers	25,264 (11.5)	Sewing-machine operators	23,121 (8.5)
	Hairdressers, barbers, beauticians and related workers	16,443 (7.5)	Hairdressers, barbers, beauticians and related workers	17,752 (6.5)
	Wholesalers	13,328 (6.1)	Cashiers	17,047 (6.3)
	All with light activity	218,970 (100)	All with light activity	272,794 (100)
Sedentary	Bookkeepers	61,589 (39.2)	Secretaries	68,676 (36.7)
	Secretaries	49,371 (31.5)	Bookkeepers	44,109 (23.6)
	Telephone operators	13,806 (8.8)	Workers in telephone-answering services	14,916 (8.0)
	Workers in telephone-answering services	9,021 (5.7)	Tellers	10,722 (5.7)
	All with sedentary work	157,130 (100)	All with sedentary work	187,212 (100)

[1]The 4 most frequent occupations are shown for each physical-activity class together with number of individuals and percentage in each category.

jobs classified as having the same physical activity level in both the 1960 and the 1970 censuses (Table II); this group of women constituted sub-cohort C. Sub-cohort D was made up of the 99,884 women who had unequivocally classified jobs based on their reported occupation in both 1960 and 1970 censuses, but who had changed physical-activity level between the two census reports (data not shown in Table II).

To ascertain cancer outcomes in these cohorts and their dates of diagnosis, we linked the background register with the CERIII proper, matching on all census variables and dates of death. We analyzed only first cancers. Cancers diagnosed incidentally first at autopsy were not counted. Person-years were calculated from 1 January, 1971, until the diagnosis of any malignant tumor, death, or end of follow-up (31 December, 1989), whichever occurred first.

Analyses

Data in grouped form was used in the analyses to estimate the risk for endometrial cancer in the study cohort. Attained age (age at follow-up) was divided into 11 categories of 5 years each (<40, 40–44, . . . , 80–84, 85+years). The 19 calendar years of follow-up were divided into 9 2-year intervals and 1 1-year interval (1 January 1971–31 December 1972, ′73–′74, . . . , 1 January 1989–31 December 1989).

First we made external comparisons with the source population. The expected number of cancers was calculated by multiplying the number of person-years observed by 5-year age- and calendar-year-specific cancer-incidence rates, derived from the entire Swedish female population. The standardized incidence ratio (SIR), defined as the ratio of observed number of cancers to number of those expected, was then computed. The 95% confidence intervals (CI) were calculated on the assumption that the observed number of cancers follows a Poisson distribution.

To allow more complete adjustment for potential confounding factors, we then made an internal comparison between exposure groups within the cohort, using multivariate Poisson models estimated by the maximum-likelihood method. In the baseline model, attained age (age at follow-up) was the only explanatory variable. The effects of socio-economic status, place of residence and calendar year of follow-up on the risk estimates were then analyzed and adjusted in expanded multivariate models. The deviance was of the same order as the degrees of freedom, thus no correction for over-dispersion was necessary.

RESULTS

We observed 4,462 and 5,287 and 1,949 and 634 cases of primary endometrial cancer during 19 years of follow-up in sub-cohorts A, B, C and D respectively. At start of follow-up, age ranged from 16 to 95 years (mean 45 years) in the combined sub-cohorts, while age at cancer diagnosis ranged from 22 to 95 years (mean 61 years). Table I shows the 4 most prevalent occupations for each estimated level of occupational physical activity.

Table II shows the distribution of person-years by category of estimated physical activity in sub-cohorts A to C. The table also shows the number of observed cases, and SIRs with 95% CI. Overall, the incidence of endometrial cancer was significantly (5 to 14%) higher in the study cohort of working women than in the entire Swedish female population. There was a monotonic increase in risk for endometrial cancer with decreasing physical-activity level. This trend was strongest in women estimated as having the same level of occupational physical activity in 1960 and 1970, with a more than 32% gradient between the lowest and highest SIRs.

Our multivariate analyses, based on internal comparisons within the cohort, are shown in Table III. In simple age-adjusted models we found the same monotonic increase in risk for endometrial cancer with decreasing physical-activity level. The trend was stronger using estimated physical activity level assessed for jobs held in 1970, *i.e.*, closer to the period of follow-up, than for those held in 1960. The relative risk was 1.31 (95% CI 1.12 to 1.54) among women classified as holding sedentary jobs both in 1960 and in 1970, relative to those estimated as having the physically most demanding jobs. Further adjustment for socio-economic status, place of residence and calendar year of follow-up changed the risk estimates only marginally (Table III). There was no effect modification by calendar year, a proxy measure for duration of follow-up after the last census in 1970 (data not shown).

Table IV shows the relative risks by age at follow-up in sub-cohort C. The inverse monotonic relationship of the risk of endometrial cancer and physical activity seemed to be confined to women who were aged 50 to 69 years at follow-up. At those ages, risk for endometrial cancer was about 60% higher in sedentary than in the most physically active women.

The women in sub-cohort D (n = 99,884) were evaluated, with the main focus on those classified as having sedentary jobs in 1960 but then changing to jobs characterized by having high/very high activity levels in 1970, and vice-versa. While these analyses were hampered by small numbers of outcomes, the most recent exposure level appeared decisive in predicting risk for endometrial cancer, in agreement with our previous analyses (Table III). Compared with those who maintained a high/very high physical-activity level, women who switched from sedentary in 1960 to high/very high in 1970 had similar risk. Conversely, women with a sedentary job in

TABLE II – CHARACTERISTICS OF THE COHORT, BY OCCUPATIONAL PHYSICAL ACTIVITY LEVEL IN 1960 AND IN 1970

Census	Occupational physical activity	Number of women at risk[1]	Number of person-years at risk	Number of observed primary endometrial cancer[2]	SIR[4]	95% CI
1960	Very high/High	117,479	1,908,558	736	1.01	0.94–1.09
	Medium	211,325	3,484,538	1,294	1.06	1.00–1.12
	Light	218,970	3,659,085	1,442	1.11	1.06–1.17
	Sedentary	157,130	2,733,432	990	1.19	1.12–1.26
	All	704,904	11,785,614	4,462	1.09	1.06–1.13
1970	Very high/High	234,465	4,148,366	1,319	0.96	0.91–1.02
	Medium	294,799	5,226,171	1,644	0.98	0.94–1.03
	Light	272,794	4,889,584	1,417	1.12	1.06–1.18
	Sedentary	187,212	3,392,443	907	1.22	1.14–1.30
	All	989,270	17,656,563	5,287	1.05	1.02–1.07
1960 and 1970[3]	Very high/High	39,990	690,545	283	0.99	0.88–1.11
	Medium	66,456	1,149,743	501	1.06	0.97–1.16
	Light	87,960	1,535,617	692	1.17	1.09–1.27
	Sedentary	58,930	1,045,697	473	1.32	1.20–1.44
	All	253,336	4,421,602	1,949	1.14	1.09–1.20

[1]At start of follow-up in 1971.–[2]During follow-up through 1989.–[3]Women classified to same level of occupational physical activity in 1960 and 1970.–[4]Standardized Incidence Ratio.

TABLE III – RELATIVE RISK (RR) WITH 95% CI FOR ENDOMETRIAL CANCER BY ESTIMATED OCCUPATIONAL PHYSICAL ACTIVITY IN 1960 AND 1970[1]

Census	Occupational physical activity	RR[2]	95% CI	RR[3]	95% CI
1960	Very high/High	1.00	Reference	1.00	Reference
	Medium	1.05	0.96–1.15	1.03	0.94–1.13
	Light	1.10	1.01–1.20	1.05	0.94–1.16
	Sedentary	1.18	1.06–1.29	1.13	0.99–1.29
	p value for trend	<0.001		0.11	
1970	Very high/High	1.00	Reference	1.00	Reference
	Medium	1.02	0.95–1.10	1.02	0.95–1.10
	Light	1.15	1.07–1.24	1.16	1.05–1.27
	Sedentary	1.26	1.15–1.37	1.32	1.17–1.50
	p value for trend	<0.001		<0.001	
1960 and 1970	Very high/High	1.00	Reference	1.00	Reference
	Medium	1.08	0.93–1.24	1.04	0.89–1.22
	Light	1.18	1.03–1.36	1.11	0.94–1.31
	Sedentary	1.33	1.15–1.54	1.30	1.03–1.65
	p value for trend	<0.001		0.04	

[1]Results obtained by Poisson regression.–[2]Relative risk adjusted for age in 5-year intervals.–[3]Relative risk adjusted for age in 5-year intervals, place of residence, calender year of follow-up, and socio-economic status.

TABLE IV – RELATIVE RISK (RR) WITH 95% CI FOR ENDOMETRIAL CANCER AMONG WOMEN WITH THE SAME ESTIMATED OCCUPATIONAL PHYSICAL ACTIVITY IN 1960 AND 1970, BY AGE AT FOLLOW-UP

Age at follow-up	Occupational physical activity	Number of observed cases	Number of person-years	RR[1]	95% CI
<50	Very high/High	38	185, 393	1.00	Reference
	Medium	44	316, 312	0.72	0.44–1.18
	Light	64	519, 885	0.61	0.36–1.05
	Sedentary	67	458, 961	0.74	0.36–1.50
	p value for trend			0.21	
50–59	Very high/High	81	179, 754	1.00	Reference
	Medium	180	302, 514	1.38	1.04–1.83
	Light	238	432, 867	1.30	0.96–1.75
	Sedentary	209	309, 770	1.62	1.09–2.40
	p value for trend			0.06	
60–69	Very high/High	105	209, 923	1.00	Reference
	Medium	187	344, 922	1.00	0.77–1.29
	Light	267	381, 575	1.21	0.92–1.60
	Sedentary	170	204, 890	1.60	1.10–2.33
	p value for trend			0.02	
70+	Very high/High	59	115, 476	1.00	Reference
	Medium	90	186, 096	0.87	0.62–1.24
	Light	123	201, 290	1.01	0.69–1.49
	Sedentary	27	72, 076	0.62	0.32–1.20
	p value for trend			>0.5	

[1]Relative risk adjusted for age in 5-year intervals, place of residence, calender year of follow-up, and socio-economic status.

1970 had between 30 and 90% higher risk than those in the highest categories of physical activity, regardless of their occupational activity in 1960 (data not shown).

DISCUSSION

We found a clear dose-dependent inverse association between estimated level of work-place physical activity and risk for endometrial cancer. This inverse relationship appeared to be restricted to post-menopausal women aged 50 to 69 years and to wear off within 10 years after a change in physical-activity level.

The long and virtually complete follow-up of endometrial-cancer occurrence, the size of the cohort, and the exposure assessment on 2 occasions 10 years apart, are unique characteristics of this study. The large number of endometrial cancers allowed us to separately evaluate cancer risk among women who changed physical-activity level compared with women who had the same level of physical activity both in 1960 and in 1970. The prospective study design, with reporting of occupations before the occurrence of any outcome, insures that misclassification of exposure is non-differential. The exposure assessment of physical-activity level through the job title is quite crude. Misclassification is therefore likely to be substantial, and we expect under-estimation rather than exaggeration of any association between physical activity and endometrial cancer.

Information about potentially confounding risk factors for endometrial cancer, such as parity, age at menarche, age at menopause, obesity, diabetes, and use of oral contraceptives or hormone replacement, was not available in our database. To the extent that physical characteristics may govern the choice of occupation, obesity, an established risk factor for endometrial cancer (Parazzini *et al.,* 1991), may act as a confounder. But body-mass index may also be in the causal chain between physical activity and protection against endometrial cancer, since high energy expenditure may prevent obesity.

Considering the diverse mix of occupations forming each physical-activity exposure level, strong confounding effects from life-style factors seem unlikely. The most serious potential for confounding would arise if use of oral contraceptives or hormone replacement were related to occupational physical activity. However, the public medical services in Sweden are readily available at low cost for everybody, thus ensuring equal access to treatment with exogenous hormones for most women. Moreover, any gradient in the use of estrogenic hormones is more likely to be linked to socio-economic status than to occupational physical activity. We therefore found it reassuring that adjustment for socio-economic status did not attenuate the risk estimates. Our risk estimates would be biased if the prevalence of hysterectomy is related to estimated physical exercise at work; the observed trend would become exaggerated if women with strenuous work undergo hysterectomy more often than those with sedentary work. However, hysterectomy rates in Sweden (Adami *et al.,* 1989) are much lower than, for example, in the US (Walker and Jick, 1979). Hence any major bias due to differences in hysterectomy appears unlikely.

The external validity of our data should be satisfactory, given the population-based design which entailed inclusion of all Swedish women with the studied occupations. However, compared with the entire source population, including women with no or unclassifiable occupation, we found a slightly increased overall risk in our cohort (Table II). This finding may be consistent with an effect by physical activity, since non-employed women in 1960 or earlier were often housewives or farmer's wives, who at that time often involved heavy work. Therefore it is conceivable that non-employed women, in general, had a higher level of physical activity than those who were gainfully employed.

We lacked information on leisure physical activity. It is reasonable to assume that such exercise has effects in the same direction as exercise at work. Our inability to take leisure physical activity into account may bias our risk estimates in an unpredictable direction. The true association would be attenuated if women with sedentary jobs were more physically active and over-estimated if they were less physically active after work than women with more strenuous occupations. The former of these alternatives may be more likely, but reliable population-based data on leisure activity in different occupational groups is lacking. In any case, it is highly unlikely that work-leisure differences in physical activity could create a spurious association between physical activity and cancer risk.

The overall decreasing risk for endometrial cancer with increasing physical activity found in our study is consistent with most studies that have examined the relationship between physical activity and cancer of the endometrium (Shu *et al.,* 1993; Zheng *et al.,* 1993; Levi *et al.,* 1993; Sturgeon *et al.,* 1993; Hirose *et al.,* 1996; Olson *et al.,* 1997). A hospital-based case-control study (Levi *et al.,* 1993) showed a protective effect of high physical activity, notably if this activity was recent. A record-linkage study from Shanghai (Zheng *et al.,* 1993) revealed an approximately 30% gradient in risk for endometrial cancer across job categories associated with decreasing energy expenditure. In a Chinese case-control study (Shu *et al.,* 1993), there was a 60% risk gradient with decreasing occupational energy expenditure. The association remained unchanged after adjustment for caloric intake, body-mass index, and number of pregnancies. Similarly, high occupational physical activity was inversely associated with risk for endometrial cancer in women above the age of 50 in a case-control study in the US (Sturgeon *et al.,* 1993); adjustment for body-mass index and non-recreational physical activity attenuated the protection conferred by recreational physical activity, whereas adjustment for body mass and recreational physical activity did not alter the protection conferred by occupational physical activity. A hospital-based case-control study in Japan (Hirose *et al.,* 1996) showed 40% reduction in risk for endometrial cancer among physically active women when compared with women with no physical activity. In a case-control study, Olson *et al.* (1997) showed no relation between occupational physical activity and the risk for endometrial cancer; the interpretation was hampered, however, by the low level and minimal variation in occupational physical activity, although vigorous exercise during adolescence and 20 years before the interview was associated with a 50% risk reduction. In contrast to the majority of studies, a case-control study from Turkey (Dosemeci *et al.,* 1993) found a positive association between physical activity and risk of cancer of the uterus, but the majority of cases were under 50 years of age.

Novel findings in our study include the apparent lack of effect in women under the age of 50, and the indication that the effects are reversible within a decade or two. Also, the greater strength of the relationship among women with the same physical-activity level determined 10 years apart than among those whose physical-activity levels differed between the 2 observation points adds to the credibility of our conclusion that physical activity, in fact, is the critical factor.

The concentration of circulating estrogen is lower in physically active than in sedentary women. Physical activity also reduces body fat (Sturgeon *et al.,* 1993) and consequently decreases the aromatization in adipose tissue of androstenedione to estrone, the major source of estrogens in post-menopausal women (Enriori and Reforzo-Membrives, 1984). Reduced absorption of sterol excreted from the bile duct, because of the decreased fecal transit time due to increased bowel motility in physically active women, (Holdstock *et al.,* 1970) is also possible. Hence, the inverse association with physical activity is consistent with the prevailing concept of estrogen dependence in endometrial carcinogenesis (Grady and Ernster, 1996) and therefore a biological possibility. In particular, the relatively short-lived protection supports the hypothesis of hormone-mediated effects during late stages of the carcinogenic process.

We conclude that our findings provide clues in the search for the etiology of endometrial cancer. Further studies of physical exercise in relation to endometrial cancer are clearly important, because of the implications for primary prevention. Such studies should include data collection of additional, potentially confounding variables. Even more important, particularly if exact quantification of the effect is the goal, is a detailed assessment of type, intensity and timing of physical exercise during both work and leisure.

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