Physical Activity and Risk of Endometrial Cancer: A Population-Based Prospective Cohort Study

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Abstract

Physical activity is involved in the regulation of metabolic and hormonal pathways and is one of the factors important for the maintenance of body weight; obesity is a risk factor for endometrial cancer. A connection between physical activity and endometrial cancer risk through hormonal mechanisms, possibly mediated by body weight, is biologically plausible. Only one study has investigated total physical activity, and no previous study has examined leisure time inactivity directly. We investigated the association of total physical activity and different types of physical activity with risk of endometrial cancer in the Swedish Mammography Cohort, a population-based prospective cohort, including 33,723 women and 199 endometrial cancer cases. After adjustments for potential confounders (age, body mass index, parity, history of diabetes, total fruit and vegetable intake, and education), the relative risks for endometrial cancer for the second to fourth quartile of total physical activity compared with the lowest one were 0.80 [95% confidence interval (95% CI), 0.54-1.18], 0.87 (95% CI, 0.59-1.28), and 0.79 (95% CI, 0.53-1.17). High leisure time inactivity (watching TV/sitting ≥5 hours daily) compared with low was associated with increased risk of endometrial cancer (relative risk, 1.66; 95% CI, 1.05-2.61). The associations were not modified by body mass index. Findings from this study suggest that total physical activity is weakly inversely associated with endometrial cancer risk and that leisure time inactivity is statistically significantly associated with increased risk for endometrial cancer. (Cancer Epidemiol Biomarkers Prev 2006;15(11):2136–40)

Introduction

Physical activity is involved in the regulation of metabolic and hormonal pathways and is one of the factors important for the maintenance of body weight (1); obesity is a risk factor for endometrial cancer (2). Therefore, connection between physical activity and endometrial cancer risk indirectly through hormonal mechanisms possibly mediated by body weight and/or through direct effects of physical activity is biologically plausible. Several epidemiologic studies have been reported on associations between selected types of physical activity (but not total) and incidence of endometrial cancer (3-17), but several studies have either not controlled for important covariates (10, 16, 17) or were limited by small sample size (8) or used a very crude assessment (one single question) of physical activity (9, 17). Moreover, only two previous studies used a validated instrument to measure physical activity (3, 6). Total physical activity (covering 24 hours) has been investigated in only one prospective cohort (18), and to our knowledge, no previous study has investigated leisure time inactivity directly.

To address whether physical activity is associated with risk of endometrial cancer, we used data from the Swedish Mammography Cohort, a population-based prospective cohort study of ~40,000 women. We first examined the association between self-reported total physical activity and endometrial cancer risk. In addition, we investigated associations with different specific components of physical activity, such as household work, occupational activity, walking/bicycling, leisure time physical activity, and watching TV/sitting (leisure time physical inactivity). Furthermore, we examined whether body weight modified the observed association after adjusting for other potential risk factors.

Materials and Methods

From 1987 to 1990, all women who lived in the Uppsala County of central Sweden and were born in 1914 to 1948 (n = 48,517) and all women who lived in the adjacent Västmanland County (n = 41,786) and were born in 1917 to 1948 received an invitation by mail to participate in a mammography screening program. A total of 66,651 (74%) women returned a completed questionnaire on diet, weight, height, parity, and education.

In 1997, a second questionnaire was sent to all 56,030 cohort members who were still living in the study area, and the vast majority of the questionnaires came in during late September to early October; the second questionnaire was extended with information on physical activity, medical history, including diabetes and hypertension, age at menarche, history of oral contraceptive use, age at menopause, postmenopausal hormone use, and lifestyle factors, such as cigarette smoking history, and use of dietary supplements; 39,227 (70%) women returned a completed questionnaire.

Information on physical activity was based on six questions about physical activity/inactivity during the previous year. We asked for duration of specific activities and assigned mean metabolic equivalent (MET) values [multiples of MET (kcal kg^{-1} h^{-1})] based on specific activities within corresponding categories in a physical activity compendium (19, 20). For work/occupation, there were six predefined types of work and a question about full-time or part-time employment that allowed us to assign correct work duration. We predefined the following types of occupational activity: mostly sitting (1.3 MET/h), sitting down more than half the time (1.8 MET/h),

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Table 1. Age standardized baseline characteristics of 33,723 women in the Swedish Mammography Cohort according to quartiles of total physical activity

Total physical activity (MET/h/d)	Q1, <38.9 (median, 37.1)	Q2, 38.9-42.2 (median, 40.5)	Q3, 42.2-45.9 (median, 44.2)	Q4, ≥45.9 (median, 48.1)
Variables				
Age (y)	62.6	60.4	60.8	61.1
BMI (kg/m^2)	25.4	24.9	24.8	24.8
Age at menarche (y)	13.2	13.2	13.2	13.2
No. children	2.1	2.1	2.2	2.2
Oral contraceptive use (%)	58.0	59.2	56.1	53.2
Age at menopause (y)	49.8	50.0	50.0	50.0
Postmenopausal hormone therapy (%)	51.7	52.1	51.2	48.8
Total energy intake (kcal)	1656	1713	1732	1798
Education ≥12 years (%)	14.9	17.1	16.3	12.3
History of diabetes (%)	4.9	3.3	3.7	3.8
Total fruit and vegetable intake (g/d)	359	387	391	410

NOTE: All values other than for age have been directly standardized according to the age distribution of the cohort.

mostly standing (2.2 MET/h), doing lifts (2.6 MET/h), a lot of lifts (3.0 MET/h), and heavy labor (3.9 MET/h). For household work and walking/bicycling, there were six predefined duration categories for time: home/household work (<1 hour daily to >8 hours daily, 2.5 MET/h) and walking/bicycling (almost never to >1.5 hours daily, 3.6 MET/h). For leisure time activity, there were five predefined duration categories (<1 hour weekly to >5 hours weekly, 5.0 MET/h) and five predefined categories for time spent per day watching TV/sitting (inactive leisure time, <1 hour daily to >6 hours daily, 1.2 MET/h). There was an additional open-ended question about number of hours of sleep per day (0.9 MET/h). We estimated the total activity by adding up the respective products of duration by intensity of specific activities and corrected the self-reported time to 24 hours per day by adding hours (if the total sum was <24 hours) or deleting hours (if the total sum was >24 hours). The correction time was multiplied by the intensity factor 2.0 MET corresponding to the mean intensity of self-care/walking at home and sitting.

The physical activity questions were validated by comparing them with two 1-week-long records of activity done ~6 months apart during two seasons (in late winter-early spring and late summer-early autumn); Spearman correlation coefficient was 0.7 for total physical activity (21), 0.5 for work/occupation, 0.8 for home/household work, 0.4 for walking/bicycling, 0.2 for leisure time activity, and 0.6 for watching TV/reading (22).

Body mass index (BMI) was calculated as weight in kilograms divided with the square of the height in meters (BMI, kg/m^2); the validity for self-reported weight and height compared with measurements in Swedish women has been studied and the correlation coefficient was r = 0.9 and 1.0, respectively (23). Education was assessed with six questions ranging from 6 years of basic education to university studies. Diabetes was self-reported on the questionnaire and assessed with the question ''have you ever been diagnosed with diabetes.'' For women with diabetes who were hospitalized, we also obtained information by linkage of the cohort to the Swedish In-patient Register. Cigarette smoking was measured as pack-years of smoking. Total energy, fruit, and vegetable intake were assessed with the use of a self-administered food frequency questionnaire that included food items (including alcoholic beverages) commonly consumed in Sweden. We used age-specific (<53, 53-65, and >65 years) portion sizes that were based on mean values obtained from 213 randomly chosen women from the study area whose food intake for four 1-week periods was weighed and recorded.[3] Analyses are limited to 1997 data when we included physical activity in the questionnaire.

Follow-up of the Cohort. We did linkage of the cohort with the National Swedish Cancer Register through June 30, 2003 and with the Regional Cancer Register in the study area through June 30, 2005. The Swedish Cancer Register and the Regional Cancer Register have been estimated to be ~100% complete (24).

Furthermore, by linkage with the nationwide Swedish In-patient Register, we identified women who had a hysterectomy for reasons other than endometrial cancer.

Dates of death or migration from the study area were ascertained through the Swedish Death Register and the National Swedish Population Register, respectively.

Of the 39,227 women who responded to the follow-up questionnaire in 1997, we excluded those diagnosed with cancer (other than nonmelanoma skin cancer) and those having had a hysterectomy before returning the follow-up questionnaire. Furthermore, we excluded women with missing information on physical activity. After these exclusions, 33,723 women ages 50 to 83 years at baseline 1997 remained for this analysis, including 199 incident endometrial (adenocarcinoma) cancer cases.

This study was approved by the Ethics Committees at the Uppsala University Hospital (Uppsala, Sweden) and the Karolinska Institutet (Stockholm, Sweden). Completion of the self-administered questionnaire was considered to imply informed consent to participate in this study.

Statistical Analysis. To estimate the risk of endometrial cancer, we used the Cox proportional hazards method. We calculated person-years of follow-up for each woman from the date of return of the questionnaire in 1997 to the date of an endometrial cancer diagnosis, the date of a hysterectomy, the date of death from any cause, the date of migration out of the study area during June 30, 2003 to June 30, 2005 (because for this time period we only have regional information), or the end of follow-up June 30, 2005, whichever came first. We computed incidence rate ratios by dividing the number of incident cancer cases by the number of person-years of follow-up in each category stratified on age in months. The relative risks (RR) of endometrial cancer [with 95% confidence intervals (95% CI)] were calculated by dividing the incidence rates among women in the three upper quartiles of total physical activity with women in the lowest quartile of total physical activity. We calculated the RR of endometrial cancer (with 95% CI) for different components of physical activity (occupational physical activity, household work, walking/bicycling, and leisure time activity) or inactivity (watching TV/sitting) by dividing the incidence rate among women with a high level of activity or inactivity with women with low level of activity

[3]A. Wolk, unpublished data.

or inactivity. We did age-adjusted (age in months) and multivariable analyses. The main multivariable models simultaneously included such confounders as parity, history of diabetes, education, and total fruit and vegetable intake (as a proxy for healthy behavior), which changed risk estimates of physical activity by 5% to ≥10%. We also did multivariable analysis further adjusted for BMI. In additional multivariable analysis, we further adjusted for other known risk factors as oral contraceptives and postmenopausal hormones, age at menarche and menopause, smoking, and total energy intake. In the analyses on different types of physical activity, the model simultaneously contained all other types of activities. Missing values in a confounder were treated as a separate ''missing category'' in the model. We conducted analyses stratifying on BMI, and the statistical significance of interactions was tested by adding an interaction term to the Cox model, simultaneously containing the main variable, BMI, and age in months. To test for trend, we assigned the mean value to each exposure category and treated this value as a continuous variable in the model. All analyses were done using Statistical Analysis System software version 9.1 (SAS Institute, Cary, NC).

Results

During a mean follow-up time of 7.25 years of 33,723 women in the cohort (244,548 person-years), 199 endometrial cancer cases were diagnosed. The mean age at diagnosis of endometrial cancer was 67.3 (±9.1) years. At baseline, 48.2% of the women were working. Table 1 shows the distribution of known and potential risk factors for endometrial cancer in the cohort by total physical activity in quartiles of MET/h. Women with a low level of total physical activity were older, had higher BMI, larger percentage of them reported history of use of oral contraceptives and postmenopausal hormones, and had lower energy intake and lower consumption of fruit and vegetables and higher frequency of diabetes than women with a higher level of total physical activity. Other characteristics did not vary substantially in respect to total physical activity.

Overall physical activity was inversely, albeit not significantly, associated with endometrial cancer risk in both age-adjusted and multivariate analyses adjusting for several potential confounders, such as parity, education, history of diabetes, and total fruit and vegetable consumption, as well as in multivariate analysis further adjusted for BMI (Table 2). Additional adjustment for use of oral contraceptives and postmenopausal hormones, age at menarche and menopause, smoking, and total energy intake did not change the results [RRs for the second, third, and forth quartile of total physical activity compared with the lowest one were 0.79 (95% CI, 0.53-1.18), 0.86 (95% CI, 0.58-1.26), and 0.75 (95% CI, 0.50-1.11), respectively]. We further investigated the associations between specific types of physical activity and endometrial cancer risk. Table 3 shows that leisure time inactivity (i.e., watching TV/sitting ≥5 hours daily) was associated with a statistically significantly 66% increased risk of endometrial cancer. In contrast, walking/bicycling at least 1 hour daily was associated with a nonsignificantly decreased risk. Occupational activity, household work, and leisure time activity were not associated with endometrial cancer risk.

We also examined whether the observed associations differed according to BMI status by stratifying the cohort into groups with BMI ≤27 kg/m^2 and BMI >27 kg/m^2. We observed no significant differences between the two groups. For total physical activity and walking/bicycling (both weakly inversely associated with endometrial cancer), the interactions with BMI were $P_{interaction}$ = 0.55 and 0.75, respectively. For watching TV/reading (statistically significantly associated with increased risk), $P_{interaction}$ was 0.63. Furthermore, we compared the most inactive women (≥5 hours of inactivity at leisure time daily) who simultaneously had a low level (below the median) of all other activities combined (including 21 cases) with the group of physically active women reporting a short time of leisure time inactivity and simultaneously a high level (above the median) of all other activities (including 79 cases) and observed RR = 1.63 (95% CI, 0.97-2.71). Only three cases had a high level of leisure time inactivity combined with a high level of all other activities; therefore, we could not evaluate if leisure time inactivity may be compensated by other activities.

Finally, to eliminate potential effects of early undiagnosed endometrial cancer, we repeated our analysis after excluding endometrial cancer cases diagnosed during the 1st year of follow-up. Results from this analysis did not differ substantially from those for the whole cohort [e.g., multivariable RRs for the second, third, and forth quartile of total physical activity compared with the lowest one were 0.76 (95% CI, 0.50-1.17), 0.77 (95% CI, 0.51-1.19), and 0.80 (95% CI, 0.52-1.21), respectively].

Discussion

In this prospective cohort study, we found that leisure time inactivity (watching TV/sitting ≥5 hours daily) was statistically significantly associated with an increased risk of endometrial cancer incidence. Total physical activity and walking/bicycling were associated with a nonsignificant decreased risk. We have not observed associations with occupational, household work, or leisure time activity. The associations were not modified by BMI.

To our knowledge, leisure time inactivity has not been directly investigated previously. However, the observed increased risk of endometrial cancer among women being inactive during leisure time is in an indirect agreement with previous studies showing a statistically significant inverse association with high levels of leisure time physical activities (which might also reflect a low level of inactivity; refs. 3, 4, 6, 7, 9, 13, 15, 17). Our results agree with the only other prospective

Table 2. Rate ratios and 95% CIs of endometrial cancer according to quartiles of total physical activity among 33,723 women in the Swedish Mammography Cohort

Total physical activity (MET/h/d)	Q1, <38.9	Q2, 38.9-42.2	Q3, 42.2-45.9	Q4, ≥45.9	P_{trend}
No. cases	75	39	43	42	
Person-years	75,638	54,804	55,958	58,149	
Age-adjusted RR (95% CI)*	1.00 (reference)	0.77 (0.52-1.14)	0.81 (0.55-1.18)	0.74 (0.50-1.09)	0.14
Multivariate RR (95% CI)†	1.00 (reference)	0.78 (0.53-1.16)	0.83 (0.56-1.21)	0.73 (0.49-1.08)	0.13
Multivariate RR (95% CI)‡	1.00 (reference)	0.80 (0.54-1.18)	0.87 (0.59-1.28)	0.79 (0.53-1.17)	0.27

*Rate ratios from Cox proportional hazards models adjusted for age in months.
†Rate ratios from Cox proportional hazards models adjusted for age in months, parity (0, 1-2, 3+), history of diabetes (yes/no), total fruit and vegetable (intake in quartiles <239 g, 239-344 g, 345-482 g, 483+ g), and education.
‡Additionally adjusted for BMI [<20, 20-25, 26-30, 30+ (kg/m)].

Table 3. Associations of physical activity with rate ratios and 95% CIs of endometrial cancer for 33,723 women in the Swedish Mammography Cohort

Variable	Physical activity	No. cases	Person-years	RR (95% CI)*	RR (95% CI)†	RR (95% CI)‡
Work/occupation§	Low	109	127,891	1.00	1.00	1.00
	High	90	116,657	0.91 (0.68-1.21)	0.97 (0.72-1.31)	1.01 (0.75-1.37)
Household work‖	Low, <5 h/d	139	180,841	1.00	1.00	1.00
	High, ≥5 h/d	60	63,707	1.03 (0.75-1.41)	1.05 (0.76-1.46)	0.99 (0.71-1.38)
Walking/bicycling (mainly for transportation)¶	Low, <1 h/d	175	203,090	1.00	1.00	1.00
	High, ≥1 h/d	24	41,458	0.66 (0.43-1.02)	0.67 (0.43-1.04)	0.71 (0.45-1.10)
Leisure time activity (including exercise)¶	Low, <20 min/d	99	191,191	1.00	1.00	1.00
	High, ≥20 min/d	100	53,357	0.85 (0.60-1.22)	0.90 (0.67-1.21)	0.99 (0.73-1.32)
Leisure time inactivity (watching TV/sitting)¶	Low, <5 h/d	175	229,558	1.00	1.00	1.00
	High, ≥5 h/d	24	14,990	1.92 (1.23-3.00)	1.80 (1.14-2.83)	1.66 (1.05-2.61)

*Rate ratios from Cox proportional hazards models adjusted for age in months.
†Rate ratios from Cox proportional hazards models adjusted for age in months, parity (0, 1-2, 3+), history of diabetes (yes/no), total fruit and vegetable (intake in quartiles <239 g, 239-344 g, 345-482 g, 483+ g), education, and work/occupation, walking/bicycling, household work, leisure time activity, and leisure time inactivity (watching TV/sitting) simultaneously.
‡Additionally adjusted for BMI [<20, 20-25, 26-30, 30+ (kg/m)].
§High: mostly standing up, doing lifts, a lot of lifts, and heavy labor; low: mostly sitting down and sitting down more than half of the time.
‖High level is >50th percentile in the cohort.
¶High level is >75th percentile in the cohort.

cohort study that investigated total physical activity (covering 24 hours) and risk of endometrial cancer and reported very similar results (RR, 0.8; 95% CI, 0.6-1.0; ref. 18). The observation for walking/bicycling (mainly for transportation) agrees with three previous studies showing a statistically significant decreased risk of endometrial cancer in women with more walking and bicycling (3, 4, 15). Occupational activity was investigated in 10 studies (3, 5, 7, 11-16). Five of them have shown a statistically significantly reduced risk of endometrial cancer with increasing occupational activity (5, 7, 10, 13, 15), whereas our results for occupational activity agree with five other studies showing no association (3, 11, 12, 14, 16). However, we have to note that <50% of women in our cohort were working at baseline due to old age, and thus, we had small numbers of women in the high occupational activity categories. The apparent lack of an inverse association between leisure time activities in our study may be due to a lower validity of this question than our other physical activity questions and possibly a low validity in previous studies not showing an association (5, 11, 14).

There are several mechanisms that could be potentially involved in the development of endometrial cancer in inactive women. It has been shown that physically active women have lower levels of endogenous estrogen (25, 26). Estrogens have been shown to increase endometrial cancer risk by stimulating proliferation of the endometrial tissue (27) when unopposed by progesterone (28, 29). Physical inactivity is a major determinant of body weight and may shift the body composition toward more body fat and visceral tissue. Obesity induces an excess of circulating bioactive endogenous estrogens in perimenopausal and postmenopausal women due to an increased estrogen production from aromatization of androgen in peripheral fat tissue (30-32) and/or through a decreased production of sex hormone-binding globulin (33). Obesity is also associated with insulin resistance and hyperinsulinemia (34-36). Importantly, physical inactivity has been shown to affect insulin resistance and hyperinsulinemia (37, 38) not only through obesity but also directly, and physical activity has been shown to promote insulin sensitivity (39, 40). Hyperinsulinemia may increase levels of free estrogen through decreasing concentrations of circulating sex hormone-binding globulin (41, 42), and several epidemiologic studies have observed an increased risk of endometrial cancer in relation to high prediagnostic C-peptide indicating hyperinsulinemia (43). It has also been suggested that hyperinsulinemia and insulin resistance are associated with a more aggressive course of endometrial cancer (44). Furthermore, hyperinsulinemia through decreasing levels of insulin-like growth factor-binding protein-3 increases circulating free insulin-like growth factor-I, which, by binding and activating insulin-like growth factor-I receptors in the endometrium, stimulates cell proliferation (45-49). Decreased circulating insulin-like growth factor-binding protein-3 levels may also have a direct regulatory role in cell growth control and cancer (50, 51). Finally, it has recently been reported that hyperinsulinemia is closely associated with lower circulating levels of an endogenous insulin sensitizer, adiponectin (52). It has been shown that low adiponectin levels are associated with low levels of physical activity (53, 54), higher levels of body fat and visceral tissue (36), higher concentrations of circulating estradiol (55), and increased endometrial cancer risk (56). Importantly, we have recently shown that physical activity increases adiponectin levels independently of body weight changes (57).

Major strengths of our study include its population-based design and the completeness of identification of endometrial cancer cases through the Swedish cancer registries. The prospective nature of the study makes it highly unlikely that the associations we observe were due to recall or selection biases, which might lead to spurious associations in case-control studies. We have used validated questions about physical activity and validity of estimates of total physical activity and specific types of activities, except leisure time activity, were relatively high. Furthermore, we had information on all major potential confounders and were able to take into account the amount of all major types of activities using mutually adjusted models. Although the possibility of uncontrolled or residual confounding cannot be entirely eliminated, we have adjusted for multiple potential confounders and we observed little difference between the age-adjusted and multivariate models. A potential limitation of the study is that we have a relatively narrow range of total physical activity and of the duration of the specific types of activities because we have a relatively active population. Due to low number of women in the lowest activity categories of the specific activities, we were unable to use these categories as reference groups.

In conclusion, our results support the importance of physical activity in the etiology of endometrial cancer, and if confirmed by other studies and in other populations, these data may prove to be of major public health significance given the increasing prevalence of physical inactivity and obesity in Western societies. Interventions to minimize inactivity and increase physical activity may have important implications in terms of prevention of endometrial cancer.

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