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),...
Variables compared with measurements in Swedish women has been. Analyses are chosen women from the study area whose food intake for four
used age-specific (<53, 53-65, and >65 years) portion sizes that
alcoholic beverages) commonly consumed in Sweden. We
frequency questionnaire that included food items (including
intake were assessed with the use of a self-administered food
Swedish In-patient Register. Cigarette smoking was measured
we also obtained information by linkage of the cohort to the
diabetes.'' For women with diabetes who were hospitalized,
ranging from 6 years of basic education to university studies.
respectively (23). Education was assessed with six questions
(kilograms divided with the square of the height in meters
2.0 MET corresponding to the mean
corrected the self-reported time to 24 hours per day by adding
products of duration by intensity of specific activities and
estimated the total activity by adding up the respective
1.2MET/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
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 compar-
ing 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 coeffi-
cient 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/m²); 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. 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 hyster-
ectomy 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

<table>
<thead>
<tr>
<th>Total physical activity (MET/h/d)</th>
<th>Q1, &lt;38.9 (median, 37.1)</th>
<th>Q2, 38.9-42.2 (median, 40.5)</th>
<th>Q3, 42.2-45.9 (median, 44.2)</th>
<th>Q4, ≥45.9 (median, 48.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>62.6</td>
<td>60.4</td>
<td>60.8</td>
<td>61.1</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.4</td>
<td>24.9</td>
<td>24.8</td>
<td>24.8</td>
</tr>
<tr>
<td>Age at menarche (y)</td>
<td>13.2</td>
<td>13.2</td>
<td>13.2</td>
<td>13.2</td>
</tr>
<tr>
<td>No. children</td>
<td>2.1</td>
<td>2.1</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>Oral contraceptive use (%)</td>
<td>58.0</td>
<td>59.2</td>
<td>56.1</td>
<td>53.2</td>
</tr>
<tr>
<td>Age at menopause (y)</td>
<td>49.8</td>
<td>50.0</td>
<td>50.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Postmenopausal hormone therapy (%)</td>
<td>51.7</td>
<td>52.1</td>
<td>52.1</td>
<td>48.8</td>
</tr>
<tr>
<td>Total energy intake (kcal)</td>
<td>1656</td>
<td>1713</td>
<td>1732</td>
<td>1798</td>
</tr>
<tr>
<td>Education ≥12 years (%)</td>
<td>14.9</td>
<td>17.1</td>
<td>16.3</td>
<td>12.3</td>
</tr>
<tr>
<td>History of diabetes (%)</td>
<td>4.9</td>
<td>3.3</td>
<td>3.7</td>
<td>3.8</td>
</tr>
<tr>
<td>Total fruit and vegetable intake (g/d)</td>
<td>359</td>
<td>387</td>
<td>391</td>
<td>410</td>
</tr>
</tbody>
</table>

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

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

7A. 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 fourth 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/m² and BMI >27 kg/m². 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 fourth 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

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

*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 <229 g, 229-334 g, 343-482 g, ≥483 g), smoking, and education.
‡Additionally adjusted for BMI (≤20, 20-25, 25-30, 30+ [kg/m²]).
Table 3. Associations of physical activity with rate ratios and 95% CIs of endometrial cancer for 33,723 women in the Swedish Mammography Cohort

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

*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 servings (0, 1-2, 3+), history of hypertension (yes/no), and 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/m²)).

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 androgen. Estrogens have been shown to increase androgenic endometrial cancer risk by stimulating an increased production of sex hormone-binding globulin (25, 26). Estrogens are shown to induce 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 (27-29) 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 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 (30, 31). Decreased circulating insulin-like growth factor-binding protein-3 levels also have a direct regulatory role in cell growth control and cancer (20, 32). Finally, it has recently been reported that hyperinsulinemia is closely associated with lower circulating levels of an endogenous insulin sensitizer, adiponectin (33). It has been shown that low adiponectin levels are associated with low levels of physical activity (34, 35), higher levels of body fat and visceral tissue (36), higher concentrations of circulating estradiol (37, 38), and increased endometrial cancer risk (39, 40). Importantly, we have recently shown that physical activity increases adiponectin levels independently of body weight changes (35).

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.
We thank Professor Donna Spiegelman and her group at Harvard School of Public Health (Boston, MA) for contributing statistical programs used in the data analyses.

Acknowledgments

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

Emilie Friberg, Christos S. Mantzoros and Alicja Wolk

Cancer Epidemiol Biomarkers Prev 2006;15:2136-2140.

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