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PHYSICAL ACTIVITY, ADIPOSITY AND RISK OF ENDOMETRIAL CANCER

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Abstract

OBJECTIVE—We examined the associations of leisure-time physical activity and adiposity with endometrial cancer risk.

METHODS—Eligible subjects were 32,642 healthy U.S. women, ≥45 years, from the Women's Health Study. Women reported on questionnaires their weight, height, and physical activity at baseline (1992–1995), and waist and hip circumference at 72 months. During an average follow-up of 8.8 years, 264 women developed endometrial cancer, confirmed using medical records.

RESULTS—The heaviest women (body mass index, BMI ≥30 kg/m^2) had more than twice the risk of endometrial cancer as those least heavy (BMI <22.5 kg/m^2) (multivariable-adjusted relative risk, RR = 2.49 [95% confidence interval [CI] = 1.73, 3.59]). Neither waist nor waist/hip ratio predicted risk in multivariate analyses. Leisure-time physical activity and walking were also unrelated to risk. Women reporting any vigorous activity had lower risk than those reporting none (multivariable-adjusted RR = 0.74 [0.56, 0.97]) independent of BMI, but there was no trend of declining risk with increasing energy expended in such activities. In examining the joint effects of BMI and physical activity, compared with active (≥15 MET-hours/week), normal weight (BMI <25) women, those who were both inactive (<15 MET-hours/week) and overweight (BMI ≥25) had higher risk (multivariable-adjusted RR = 1.85 [1.26, 2.72]), as did women who were overweight and active (multivariable-adjusted RR = 1.60 [1.01, 2.54]), whereas normal weight, inactive women (multivariable-adjusted RR = 1.17 [0.77, 1.77]) did not.

CONCLUSIONS—This study confirms BMI as a strong predictor of endometrial cancer risk. Central adiposity did not independently predict risk after adjustment for BMI; there also was no clear evidence of an inverse relation with leisure-time physical activity.

Keywords

adiposity; endometrial cancer; exercise; obesity; physical activity

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Introduction

Endometrial cancer is the most common gynecological malignancy in developed countries and accounts for 6% of all new cancer cases among U.S. women[1]. While obesity and use of estrogen therapy unopposed by progesterone are well-established risk factors for endometrial cancer[2], the evidence for physical activity is less consistent. Several cohort studies[3–6] and case-control studies[7–8], but not all[9–12], suggest that higher levels of physical activity decrease the risk of endometrial cancer. Recent reviews[13–14] conclude that physical activity appears to be associated with a reduction in risk; however, they also cite the need for further prospective cohort studies to clarify the magnitude of the risk reduction, and to determine which kinds of physical activity contribute most strongly to reducing risk. Most of the studies relating physical activity to endometrial cancer risk have investigated total activity and provide few data about type or intensity of activity[14]. Moreover, many of these studies did not adjust for post-menopausal hormone use (including type of hormones used) or stratify by hormone use[4,6–11]. Prior to the results from the Women's Health Initiative (WHI) trial[15], post-menopausal hormone use was common among health conscious women, who also tend to be more physically active[16]. Since unopposed estrogen use increases the risk of endometrial cancer, estimates from previous studies that did not adjust for hormone use may have underestimated an association between physical activity and risk.

It is also unclear how obesity might influence the association of physical activity with endometrial cancer risk. Given the fact that physical inactivity and obesity are at epidemic levels both in the U.S. and worldwide[17–18], it is important to better understand the associations among physical activity, obesity and endometrial cancer. While obesity has been conclusively established as a risk factor for endometrial cancer, less is known about how distribution of fat or the joint effects of adiposity and physical activity relate to risk of endometrial cancer.

The purpose of this study is to examine the associations among physical activity, obesity and endometrial cancer in a large prospective cohort. In addition to investigating overall measures of obesity and physical activity, this study also investigates whether: 1) walking (a moderate-intensity physical activity) 2) measures of body fat distribution, and 3) a combined measure of obesity and physical activity, are associated with risk of endometrial cancer.

Materials and Methods

Study Population

We analyzed data from a cohort of women enrolled in the Women's Health Study (WHS), a recently completed randomized trial of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer[19–21]. Female health professionals throughout the United States were recruited between September 1992 and May 1995 and asked to complete a mailed baseline questionnaire on sociodemographic characteristics, health habits, and medical history. Women who continued to be willing and eligible to participate in the trial after a 3-month run-in phase were randomized into the actual trial. A total of 39,876 women free of heart disease, stroke and cancer (other than non-melanoma skin cancer) were randomized to active drug or placebo[22]. Follow-up surveys asking about treatment compliance, risk factors and endpoints of interest were mailed every six months during the first year and annually thereafter. Upon completion of the randomized trial component of the WHS in March 2004, women were invited to continue follow-up in an observational study, and 33,796 did (88.0% of those alive). For the present study, follow-up through February 2007 was included. The study was approved by the Institutional Review Board at Brigham and Women's Hospital.

For the present study, we excluded women who reported having had a hysterectomy at baseline (n = 6,500), who did not report their weight status (n = 717) or physical activity (n = 16) at baseline, or who were subsequently found to have cancer at baseline (n = 1), leaving 32,642 women for the main analyses.

For analyses related to waist and hip circumference that were asked on the 72 month questionnaire, of the 32,642 women, 30,404 returned a questionnaire at 72 months. We excluded 8,778 women with a hysterectomy or cancer between baseline and 72 months, as well as 1,709 women who did not report their waist and/or hip circumference, leaving 19,917 women in these analyses.

Assessment of Adiposity

At baseline, participants reported their weight (in pounds) and height (in feet/inches), allowing the estimation of body mass index (BMI) in kg/m^2. We categorized women into categories of BMI: <22.5, 22.5–24.9, 25–29.9, or ≥30 kg/m^2. In analyzing the joint effects of physical activity and BMI, we classified women as "normal weight" (<25 kg/m^2) or "overweight" (≥25 kg/m^2), based upon current World Health Organization (WHO) criteria[23]. On the 72 month follow-up questionnaire, participants also reported their waist and hip circumferences in inches. From these data, we calculated the waist/hip ratio. We categorized women into categories of approximate fourths for waist measurement, hip measurement and waist/hip ratio (see Table 3 for cut points.).

Assessment of Physical Activity

On the baseline survey, we asked women to estimate the average time (0, 1–19 min/wk, 20–59 min/wk, 1 h/wk, 1.5 h/wk, 2–3 h/wk, 4–6 h/wk, or ≥7 h/wk) spent on eight groups of recreational activities during the past year: walking or hiking; jogging (slower than 10-minute miles); running (10-minute miles or faster); bicycling, including use of stationary machines; aerobic exercise, aerobic dance, use of exercise machines; tennis, squash, or racquetball; lap swimming; and lower-intensity exercise, including yoga, stretching, or toning. We also inquired about the usual pace of walking (do not walk regularly; <3.2 km/h [2.0 mph; easy, casual pace], 3.2–4.7 km/h [2.0–2.9 mph; normal, average pace], 4.8–6.3 km/h [3.0–3.9 mph; brisk pace], or ≥6.4 km/h [4.0 mph; very brisk/striding pace]) and the number of flights of stairs climbed daily (0, 1–2, 3–4, 5–9, 10–14, or 15)[24] on average.

Based on the energy cost of these activities, we assigned a multiple of resting metabolic rate (MET score) to each group of activities and stair climbing. We estimated energy expenditure by multiplying the assigned MET score by hours per week of participation using the midpoint of time categories. We summed MET-hours per week from the eight groups of recreational activities and stair climbing to estimate weekly energy expenditure. We categorized women into approximate fourths of energy expenditure: <2.7, 2.7–8.4, 8.4–20.4, or ≥20.4 MET-hours/week, for analyses of physical activity.

In analyses of the joint effects of physical activity and BMI, we classified women as "inactive" (<15 MET-hours/week) or "active" (≥15 MET-hours/week), based upon a recent expert review on the level of physical activity that is likely to be needed for cancer prevention[25]. We were also interested in whether walking, a moderate-intensity activity and the most common activity carried out by women[26], was associated with risk. We categorized women into groups classified by the time spent walking (no regular walking, 1–59 minutes/week, 1.0–1.5 hours/week, ≥2 hours/week) and usual walking pace (defined above).

Assessment of Other Variables

We gathered information at baseline on factors that could influence the relationship among physical activity, adiposity, and endometrial cancer risk. These included age, smoking, diet (including alcohol use), parity, menopausal status, and use and type of hormone therapy (HT). Participants were asked to report if they currently used HT, had used HT in the past, or had never used HT. HT users were also asked to specify whether they had used estrogen only, estrogen and progesterone, or some other type of HT. Parity was assessed by asking women if they had ever been pregnant. Diet was assessed using a 131-item semi-quantitative food frequency questionnaire[27].

Identification of Endometrial Cancer

Every 6 months during the first year and then annually, women completed brief mailed surveys that inquired about endpoints of interest to the trial. Women reported a diagnosis of endometrial cancer on these questionnaires, or wrote or telephoned the study staff. Deaths were reported by family members or postal authorities and by searching the National Death Index. We sought medical records, pathology reports and other relevant information, including death certificates and autopsy reports, for women reporting endometrial cancer, and for decedents. Reported diagnoses of endometrial cancer were considered confirmed only after examination of all available information by an endpoints committee of physicians. Only confirmed cases were included in analyses.

Statistical Analysis

We first examined the baseline characteristics of women, according to approximate fourths of leisure-time energy expenditure. We tested for differences across physical activity categories using analysis of variance comparing the mean values of continuous variables and chi-squared tests comparing the frequency of occurrence of categorical variables. We used proportional hazards regression to estimate hazard ratios (relative risks [RRs]) of endometrial cancer as a function of the different measures of physical activity and adiposity. For women who underwent a hysterectomy after baseline, follow-up time was censored at the date of self-reported hysterectomy. Thus, follow-up time was calculated from study entry to the earliest of the following: date of hysterectomy, diagnosis of endometrial cancer, death, end of follow-up in February 2007, or loss to follow-up (<3% of women)[21]. Analyses that considered waist and hip measurements started follow-up only after 72 months, since these measurements were obtained on the 72 month questionnaire. In addition to total energy expenditure, walking time, and walking pace, we also estimated hazard ratios as a function of vigorous physical activity, which was defined as any activity requiring ≥6 METs[28]. We then created a combined measure of physical activity and BMI in order to analyze these jointly. For the combined measure, we created a total of 4 categories: normal weight (i.e., BMI <25 kg/m^2), active (i.e., ≥15 MET-hours/week of physical activity) women (referent); normal weight, inactive (i.e., <15 MET-hours/week of physical activity); overweight (i.e., BMI ≥25 kg/m^2), active women; and overweight, inactive women. We carried out both age-adjusted and multivariable-adjusted proportional hazards regression for all analyses. In multivariable-analyses, we adjusted for the following: age, smoking status (never, past, current), alcohol use (never, any), saturated fat intake (gm/day), fiber intake (gm/day), fruit/vegetable intake (servings/day), parity (never, any), use of hormone therapy (never, past, current), type of hormone therapy (estrogen alone, progesterone and estrogen, other), and menopausal status (pre- or postmenopausal, or uncertain status). We also adjusted for BMI in analyses of physical activity to account for higher energy expenditures among heavier women.

Results

Table 1 shows the baseline characteristics of the study population by approximate fourths of leisure-time energy expenditure. More active women had lower BMI, smaller waist and hip circumferences and higher current use of hormone therapy when compared to less active women. They also had higher alcohol, fiber and fruit/vegetable consumption but lower saturated fat intake, were less likely to be current smokers, and more likely to be pre-menopausal than less active women. There were no significant differences in parity by energy expenditure.

During follow-up, 9,853 women reported having a hysterectomy and their follow-up was censored at the time of hysterectomy. The mean follow-up in this group was 2.5 years, while in the remaining 22,789 women who did not have a hysterectomy, the mean follow up was 11.5 years. Among all women in the study, the mean follow-up was 8.8 years, during which 264 women were diagnosed with endometrial cancer. The associations between various measures of obesity and endometrial cancer risk are provided in Table 2. The heaviest women (BMI ≥30 kg/m^2) were more than twice as likely to develop endometrial cancer than the least heavy women (BMI <22.5 kg/m^2) (multivariable-adjusted RR = 2.49; 95% confidence interval [CI] = 1.73, 3.59), but risk among overweight women (25< BMI ≤30 kg/m^2) was not increased compared to the least heavy women (multivariable-adjusted RR = 1.09; 95% CI = 0.75, 1.58). Central adiposity (as measured by waist circumference and waist/hip ratio) was not an independent predictor of endometrial cancer risk in multivariate analyses that adjusted for potential confounding variables, and results were further attenuated after adjusting for BMI (Table 2). Large-waisted women (≥39 inches) had no greater risk than small-waisted women (<31 inches) (multivariable-adjusted RR=1.42; 95% CI = 0.61, 3.32). Hip circumference was also not significantly associated with risk of endometrial cancer in multivariate analysis that adjusted for BMI.

Table 3 shows the associations between various physical activity measures and endometrial cancer risk. Women in the least active quartile of energy expenditure (<2.7 MET-hours/week) did not have a higher risk of endometrial cancer than those in the most active quartile (≥20.4 MET-hours/week) (multivariable-adjusted RR = 1.15; 95% CI = 0.79, 1.67). Women who reported no regular walking did not have an increased risk compared with those who walked ≥2 hours/week (multivariable-adjusted RR = 0.88; 95% CI = 0.61, 1.27) and a slower walking pace similarly did not confer higher risk of endometrial cancer. Women who reported any vigorous activity had a lower risk of endometrial cancer compared with those reporting no vigorous activities (multivariable-adjusted RR = 0.74; 95% CI = 0.56, 0.97). However, there was no clear trend of lower risks with incrementally higher levels of energy expended in vigorous activities.

When we examined the joint effects of BMI and physical activity, women who were both inactive (<15 MET-hours/week) and overweight (BMI ≥25 kg/m^2) were at higher risk of endometrial cancer than their active (≥15 MET-hours/week, normal weight counterparts (BMI <25 kg/m^2) (multivariable-adjusted RR = 1.85; 95% CI = 1.26, 2.72) (Table 4). Using the same referent group, active, overweight (multivariable-adjusted RR = 1.60; 95% CI = 1.01, 2.54) women were also at higher risk, whereas inactive, normal weight women (multivariable-adjusted RR = 1.17; 95% CI = 0.77, 1.77) were not at higher risk.

We repeated analyses among women who reported never having used post-menopausal hormones at baseline to avoid the influence of exogenous hormones on the results (16,539 women, 142 cases). The effect of BMI on endometrial cancer risk was now stronger, with multivariate relative risks of 1.00 (referent), 1.34, 1.97, and 4.39, respectively, for categories of increasing BMI; p, trend < 0.0001. For the total energy expended on leisure-time physical

activity, the results were little changed, with multivariate relative risks of 0.96, 0.98, 1.10, and 1.00 (referent), respectively, for categories of increasing physical activity; p, trend = 0.74.

Discussion

In the present study, we confirmed body mass index as a strong predictor of endometrial cancer risk, with the heaviest women (BMI ≥30 kg/m^2) being more than twice as likely to develop endometrial cancer than the least heavy women (BMI <22.5 kg/m^2). Central adiposity was not related to risk. Overall, leisure-time physical activity was not related to risk of endometrial cancer, and neither were walking time or pace. While vigorous physical activity was associated with lower risk, there was no trend of decreasing risk with greater participation in these actitivities; however, because few women participated in vigorous activities, statistical power may have been limited to detect such a trend. Jointly classifying women according to their BMI and physical activity did not augment the increased risk seen with higher BMI alone.

Several plausible biologic pathways support potential associations between BMI or physical activity and risk of endometrial cancer[25]. Obese postmenopausal women have higher levels of estrogen than their lean counterparts because of the conversion of androstenedione to estrogen in adipose tissue. Changes in body composition, which may be induced by physical activity, can result in changes to circulating levels of adipokines, cytokines, insulin, and sex hormones. Physical activity mediated effects on insulin resistance, inflammatory factors, and immune function also may occur, influencing endometrial cancer risk.

Higher BMI has been consistently linked to increased risk of endometrial cancer, and the current study results agree with such findings[29]. However, fewer studies have looked beyond weight or BMI to other measures of adiposity, and those that did present mixed findings.[30–37]. The current study results agree with studies showing no relationship between central adiposity and risk of endometrial cancer, after taking into account overall adiposity by controlling for BMI[29–34].

Previous cohort studies have reported mixed results as to the relationship between physical activity and endometrial cancer. One Swedish[3] and one Dutch study[5], which assessed physical activity differently from the present study, observed significant associations between increased physical activity and decreased risk of endometrial cancer, even after accounting for BMI. Similarly, another Swedish study[4] as well as a Chinese study evaluating occupational physical activity[6] found women with low physical activity occupations had an increased incidence of endometrial cancer. Our results are more similar to those of Colbert et al.[9], who reported that total physical activity, as well as moderate and vigorous activity, was unrelated to risk during eight years of follow-up. They suggested that prolonged exposure and more follow-up beyond eight years might be necessary to observe a relationship between physical activity and endometrial cancer[29]. Consistent with their hypothesis, neither of two recent European cohort studies[10,12], both involving <10 years of follow up, found any consistent association between physical activity and endometrial cancer risk. However, a recent American cohort study with 11 years of follow-up also mainly found no associations between physical activity and endometrial cancer risk in analyses adjusting for BMI[38]. This study did observe a significant inverse relation among overweight/obese women only; this may have reflected residual confounding by adiposity because weight was not adjusted for in these analyses. In our study, we found no evidence for an association between physical activity and risk of endometrial cancer among either normal weight or overweight/obese women. Compared with active, normal weight women, the elevated risk among inactive, overweight women (RR = 1.85) did not differ significantly from that among active, overweight women (RR = 1.60) (P = 0.47) indicating that physical inactivity did not augment the increased risk seen with higher BMI

alone. Our results agree with those from two other studies in the United States and Sweden[9–10].

Further evidence regarding the link between endometrial cancer and physical activity has come from case-control studies, several of which have found a significantly reduced risk of endometrial cancer associated with physical activity[4,7–8]. In one such recent study, Matthews et al. reported associations between higher levels of both adolescent and adult physical activity, and more time spent walking for transportation, and reduced risk of endometrial cancer[8]. A potential concern with the case-control studies is the potential for recall bias, since physical activity was assessed after the onset of cancer in cases.

Strengths of our study include a large cohort, detailed information about leisure-time physical activity collected using a validated instrument and information about anthropometric measures beyond BMI[24]. We also had good measures of HT use (including type of HT) and controlled for this possible confounder, which few cohort studies have done[5,12]. In a secondary analysis, we were able to assess the association among never users of HT and found stronger associations for BMI and endometrial cancer risk, as expected, once the influence of exogenous hormones was removed. Our study was limited, however, by the use of self-reported adiposity measures. This was unlikely to have caused a major bias since self-reported weight, height, waist and hip measures have been shown to be reasonably valid among nurses[39]. Furthermore, because weight was reported prospectively, any bias is likely to be nondifferential, causing results to be diluted; thus, the association of BMI with risk that we observed is likely to be stronger. Additionally, waist and hip measurements were not asked until the 72 month follow-up survey, which reduced the number of cases of endometrial cancer for analyses. We assessed physical activity and body mass index at baseline (note: the other anthropometric measures were assessed at 72 months, rather than baseline) only and did not update these over the course of follow-up. We also did not have these measures from earlier in life, and early exposures may be important[33,36]. Our measurement of physical activity was limited to primarily leisure-time activities; we did not have any information on other kinds of activities, such as household or occupational activity. Finally, the WHS comprises well-educated, predominantly white U.S. female health professionals, which may limit the generalizability of the current findings to other populations.

The current study adds to the literature on the relationships of obesity and physical activity with risk of endometrial cancer and also highlights the need for more research in this area. Future studies should examine how variability in physical activity over adulthood relates to risk, and further investigate the relationship between intensity of activity and endometrial cancer risk. More precise measurements of central adiposity (e.g., using Dual Energy X-ray Absorptiometry (DEXA) or computed tomography (CT)) may also help to further elucidate whether fat distribution contributes to endometrial cancer risk.

Given the results of the current study and others, women should aim to maintain a healthy body weight to reduce risk of endometrial cancer. While the present study did not clearly show physical activity to decrease endometrial cancer risk, health care providers should still encourage women to be physically active for weight maintenance and many other documented health benefits, such as reduction in risk of coronary heart disease[25] and colon and breast cancers[29].

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TABLE 1

Baseline characteristics of participants (N=32,642), according to physical activity

Characteristics at baseline	Baseline Physical Activity, MET-hours/week				*p*-value[a]
	<2.7 n=8124	2.7–8.4 n=8128	8.4–20.4 n=8221	≥20.4 n=8169	
Mean age, years	54.3	54.2	54.4	54.5	0.09
Mean body mass index, kg/m^2	27.6	26.2	25.5	24.6	<0.0001
Mean waist circumference, inches[b]	36.7	35.0	34.0	32.9	<0.0001
Mean hip circumference, inches[b]	43.2	42.0	41.2	40.4	<0.0001
Mean waist/hip ratio[b]	0.85	0.83	0.82	0.81	<0.0001
Smoking status, %					
Never	48.9	52.2	53.3	50.1	<0.0001
Past	31.7	34.2	37.0	41.0	
Current, <15 cigarettes/d	5.9	5.1	4.0	4.4	
Current, ≥15 cigarettes/d	13.5	8.6	5.7	4.6	
Alcohol use, %					<0.0001
Rare	53.4	45.0	41.5	37.7	
1–3 drinks/mo	12.5	13.8	13.4	12.9	
1–6 drinks/wk	25.3	31.2	34.3	37.5	
≥1 drinks/d	8.9	10.0	10.8	11.9	
Mean saturated fat intake, gm/d	21.2	20.1	19.2	18.3	<0.0001
Mean fiber intake, gm/d	17.0	18.4	19.4	20.9	<0.0001
Mean fruit and vegetable consumption, servings/d	5.1	5.9	6.3	7.2	<0.0001
Hormone therapy, %					
Never	51.9	51.7	49.7	49.8	<0.0001
Past	11.1	9.6	9.9	9.1	
Current	37.0	38.7	40.4	41.1	
Type of hormone therapy (past users), %					
Estrogen	50.9	39.5	44.5	40.3	0.0002
Estrogen & Progesterone	34.3	41.1	38.6	42.2	
Other	14.8	19.4	16.9	17.5	
Type of hormone therapy (current users), %					

Characteristics at baseline	Baseline Physical Activity, MET-hours/week				*p*-value[a]
	<2.7 n=8124	2.7–8.4 n=8128	8.4–20.4 n=8221	≥20.4 n=8169	
Estrogen	44.6	42.3	40.3	39.0	<0.0001
Estrogen & Progesterone	50.1	53.0	54.4	56.9	
Other	5.3	4.8	5.4	4.1	
Menopausal status, %					
Premenopausal	31.3	33.7	33.2	33.0	0.04
Postmenopausal	60.1	58.1	58.5	59.0	
Uncertain	8.6	8.3	8.3	7.9	
Ever pregnant, %	89.1	89.2	89.6	89.3	0.72

[a] Using ANOVA to test for trend across physical activity categories for continuous variables, and chi-square test for categorical variables.

[b] Waist and hip measurements were reported by 19,917women at the time of the 72-month follow-up questionnaire, and are classified according to 72 month physical activity categories.

TABLE 2

Relative risks (RR) of endometrial cancer according to body mass index (BMI) at baseline, waist circumference, hip circumference, and waist/hip ratio[a]

	No. of women	No. of cases	Age-adjusted RR (95% confidence interval)	Multivariable-adjusted RR1[b] (95% confidence interval)	Multivariable-adjusted RR2[c] (95% confidence interval)
Baseline BMI, kg/m^2:					
<22.5	8495	57	1.00 (referent)	1.00 (referent)	
22.5–24.9	8352	50	0.91 (0.62–1.33)	0.97 (0.65–1.44)	
25.0–29.9	9896	68	1.06 (0.75–1.51)	1.09 (0.75–1.58)	
≥30.0	5899	89	2.53 (1.81–3.53)	2.49(1.73–3.59)	
			p,trend < 0.0001	p.trend < 0.0001	
Waist circumference, inches:					
<31.0	4954	23	1.00 (referent)	1.00 (referent)	1.00 (referent)
31.0–34.4	5247	26	1.04 (0.59–1.82)	0.99 (0.55–1.79)	0.95 (0.50–1.82)
34.5–38.9	5033	25	1.02 (0.58–1.80)	0.94 (0.51–1.73)	0.90 (0.43–1.90)
≥39	4683	42	1.87 (1.12–3.10)	1.61 (0.91–2.83)	1.42 (0.61–3.32)
			p.trend = 0.01	p.trend = 0.11	p.trend = 0.46
Hip circumference, inches:					
<39.0	5221	22	1.00 (referent)	1.00 (referent)	1.00 (referent)
39.0–41.4	5117	32	1.50 (0.87–2.58)	1.55 (0.89–2.71)	1.47 (0.78–2.76)
41.5–44.5	4585	18	0.94 (0.50–1.75)	0.71 (0.35–1.42)	0.65 (0.28–1.50)
≥44.5	4994	44	2.18 (1.31–3.64)	1.84 (1.05–3.22)	1.52 (0.63–3.66)
			p.trend = 0.01	p.trend = 0.16	p.trend = 0.70
Waist/hip ratio:					
<0.78	5284	24	1.00 (referent)	1.00 (referent)	1.00 (referent)
0.78–0.82	4940	32	1.39 (0.82–2.35)	1.54 (0.87–2.73)	1.47 (0.82–2.62)
0.83–0.86	3689	21	1.20 (0.67–2.17)	1.25 (0.65–2.37)	1.15 (0.59–2.23)
≥0.87	6004	39	1.32 (0.79–2.20)	1.34 (0.75–2.37)	1.18 (0.64–2.17)
			p.trend = 0.43	p.trend = 0.53	p.trend = 0.89

[a] Waist and hip measures were reported at the 72 month follow-up. Cases occurring in the first 72 months were deleted from analyses of waist and hip measurements.

[b] Adjusted for age, physical activity, smoking status, alcohol use, saturated fat intake, fiber intake, fruit/vegetable intake, parity, use and type of hormone therapy, and menopausal status.

[c] Additionally adjusted for BMI.

TABLE 3

Relative risks (RR) of endometrial cancer according to different measures of physical activity at baseline

	No. of women	No. of cases	Age-adjusted RR (95% confidence interval)	Multivariable-adjusted RR[a] (95% confidence interval)
Total energy expenditure, MET-hours/week:				
<2.7	8124	80	1.42 (1.01–1.98)	1.15 (0.79–1.67)
2.7–8.4	8128	66	1.14 (0.81–1.62)	0.99 (0.68–1.44)
8.4–20.4	8221	58	1.97 (0.68–1.40)	0.93 (0.64–1.35)
≥20.4	8169	60	1.00 (referent)	1.00 (referent)
			p,trend = 0.02	p.trend = 0.39
Time spent walking per week:				
No regular walking	6727	55	1.07 (0.76–1.50)	0.88 (0.61–1.27)
1–59 minutes	8682	65	0.99 (0.71–1.37)	0.90 (0.64–1.27)
1.0–1.5 hours	6960	61	1.13 (0.81–1.57)	1.07 (0.76–1.51)
≥ 2 hours	10273	83	1.00 (referent)	1.00 (referent)
			p.trend = 0.87	p.trend = 0.37
Usual walking pace, km/hr:				
No regular walking	5825	48	1.12 (0.78–1.61)	0.82 (0.55–1.22)
<3.2	3815	44	1.55 (1.07–2.24)	1.08 (0.72–1.62)
3.2–4.7	12459	94	1.00 (0.74–1.35)	0.85 (0.62–1.16)
≥ 4.8	10543	78	1.00 (referent)	1.00 (referent)
			p.trend = 0.19	p.trend = 0.54
Vigorous energy expenditure, MET-hours/ week:				
None (0)	18875	177	1.00 (0.69–1.47)	0.87 (0.58–1.31)
1–3.3	3455	26	0.84 (0.50–1.42)	0.71 (0.41–1.23)
3.3–7.5	3448	14	0.46 (0.24–0.86)	0.38 (0.20–0.76)
7.5–15.0	3531	16	0.49 (0.27–0.90)	0.51 (0.27–0.93)
<15.0	3333	31	1.00 (referent)	1.00 (referent)
			p.trend = 0.04	p.trend = 0.23

[a] Adjusted for age, BMI, smoking status, alcohol use, saturated fat intake, fiber intake, fruit/vegetable intake, parity, use and type of hormone therapy, and menopausal status.

TABLE 4

Relative risks (RR) of endometrial cancer according to physical activity and BMI at baseline

	Overweight, Inactive [a]	Overweight, Active	Normal. Weight, Inactive	Normal. Weight, Active
No. of women	11450	4345	9945	6902
No. of cases	119	38	67	40
Age-adjusted RR (95% confidence interval)	1.94 (1.36–2.78)	1.56 (1.00–2.44)	1.19 (0.80–1.76)	1.00 (referent)
Multivariable-adjusted RR (95% confidence interval) [b]	1.85 (1.26–2.72)	1.60 (1.01–2.54)	1.17 (0.77–1.77)	1.00 (referent)

[a] Overweight defined as BMI≥25; Inactive defined as total weekly energy expenditure due to physical activity <15 MET-hours/wk.

[b] Adjusted for age, BMI, smoking status, alcohol use, saturated fat intake, fiber intake, fruit/vegetable intake, parity, use and type of hormone therapy, and menopausal status.