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Appendix
Questions from the baseline and 1982 Cooper Clinic physical activity questionnaire.

"For the last 3 months, which of the following activities have you performed regularly?"	YES	NO	
Walking			How many workouts per week? How many miles per workout? Average duration of workout? Average time per mile?
Jogging or Running			How many workouts per week? How many miles per workout? Average duration of workout? Average time per mile?
Treadmill			How many workouts per week? Average duration of workout? Speed? Grade?
Bicycling (outdoors)			How many workouts per week? How many miles per workout? Average duration of workout? Average time per mile?
Stationary Cycling			How many workouts per week? Average duration of workout? Heart rate during exercise?
Swimming Laps			How many workouts per week? How many miles per workout? Average duration of workout? How many months per year?
Aerobic Dance/Floor Exercises			How many workouts per week? Average duration of workout? Heart rate during exercise?
Vigorous Racquet Sports			How many workouts per week? Average duration of workout?
Other Vigorous Sports/Exercise			How many workouts per week? Average duration of workout?

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対象の内訳	ヒト	動物	地 域	欧米	研究の種類	縦断研究
対象	一般健常者	空白		( )		コホート研究
性別	男性	( )		( )		( )
年齢	20-80歳			( )		前向き研究
対象数	10000以上			( )		( )
調査の方法	実測	( )				

アウトカム						
予 防	なし	なし	ガン予防	なし	死亡	( )
維持・改善	なし	なし	なし	なし	( )	( )

図 表

. Estimates of the association between fitness level* at baseline and prostate cancer, Aerobics Center Longitudinal Study, 1971–1989.

Fitness Level	<13.7 (N = 3225)	13.7–<17.0 (N = 2828)	17.0–<21.0 (N = 3545)	≥21.0 (N = 3575)	
of cases	40	27	21	8	
son-years of follow-up	30,160	26,798	31,114	26,260	
le incidence rate ratio (95% CI)	1.00†	0.76 (0.46–1.23)	0.52 (0.30–0.87)	0.18 (0.08–0.43)	*P* trend = 0.0001
sted incidence rate ratio‡ (95% CI)	1.00†	1.1 (0.63–1.77)	0.73 (0.41–1.29)	0.25 (0.10–0.62)	*P* trend = 0.0026

level expressed in treadmill time (min).
ent category.
ted for age, body mass index, and smoking status.
nfidence interval.

. Estimates of the association between activity level* and prostate cancer, physical activity measured as an average of the baseline and 1982 measures, Aerobics Center dinal Study, 1971–1989.

Activity Level	<1000 (N = 2670)	1000–<2000 (N = 2600)	2000–<3000 (N = 1487)	≥3000 (N = 1493)	
of cases	21	10	8	5	
son-years of follow-up	17,357	22,354	12,418	13,295	
le incidence rate ratio (95% CI)	1.00†	0.36 (0.17–0.76)	0.52 (0.23–1.16)	0.29 (0.11–0.76)	*P* trend = 0.7946
sted incidence rate ratio‡ (95% CI)	1.00†	0.37 (0.17–0.79)	0.62 (0.27–1.41)	0.37 (0.14–0.98)	*P* trend = 0.0263

y level expressed in energy (kcal) expenditure per week.
ent category.
ted for age, body mass index, and smoking status.
nfidence interval.

図表掲載箇所	P101, Table3, Table4
概 要 (800字まで)	本研究は、アメリカのThe Aerobics Center Longitudinal Studyに参加した男性12,975名を対象に18年間の追跡調査を行い、全身持久力と前立腺がんとの関連を検討したものである。全身持久力は、最大トレッドミルテストにより最大酸素摂取量を測定し、測定時間により13.7分未満、13.7-17.0分、17.0-21.0分、21.0分以上の4群に分類した。身体活動量は、過去3ヶ月間において、ウォーキング、ジョギング、ランニング、自転車、水泳、エアロビクス、ラケットスポーツ、その他高強度運動/身体活動を行った週当たりの頻度、時間を尋ね、週当たりの消費エネルギー量を算出し、1000kcal/週未満、1000-2000、2000-3000、3000kcal/週以上の4群に分類した。全身持久力に関して、測定時間が13.7分未満の集団と比較すると21.0分以上行えた集団で前立腺がん発症リスクが0.26(95%信頼区間:0.10-0.63)と有意に減少し、量反応的減少がみられた(Ptrend=0.0036)。身体活動に関しては、1000kcal/週未満の集団と比較すると、1000-2000kcal/週の集団と、3000kcal/週以上の集団で、前立腺がん発症リスクがそれぞれ0.37(0.17-0.79)、0.37(0.14-0.98)と有意に減少した。
結 論 (200字まで)	全身持久力の向上により、前立腺がん発症リスクを減少させることが示唆され、また、高強度身体活動量の増加は、前立腺がんの予防につながる可能性があることが示唆された。
エキスパートによるコメント (200字まで)	我が国の男性における前立腺がんは、年々増加傾向にあり、その予防は重要な課題である。身体活動を高めることや体力を高めることが前立腺がん予防につながることが示されており、身体活動・体力の重要性をより啓蒙していくことが重要である。

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Recreational physical activity and risk of postmenopausal breast cancer in a large cohort of US women

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Abstract

Due to its potential effects on ovarian hormone production, physical activity has been proposed as a modifiable risk factor for breast cancer. The authors analyzed data from the American Cancer Society Cancer Prevention Study II (CPS-II) Nutrition Cohort to examine the association between various measures of physical activity and postmenopausal breast cancer risk. Information on physical activity was obtained in 1992 via a self-administered questionnaire for 72,608 postmenopausal female participants who were cancer-free. During the five year prospective follow-up, 1520 incident breast cancer cases were identified among these women. Cox proportional hazards modeling was used to compute hazard rate ratios (RR) and to adjust for potential confounding factors including mammography. Women who were most physically active (>42.0 MET-h/week) at baseline had 29% lower incidence rates than active women with the least activity (>0–7.0 MET-h/week) (95% CI, 0.49–1.02). The difference in risk was largest for localized breast cancer, and for women who did not use hormone replacement therapy (HRT) at enrollment. Our findings are consistent with other studies that show lower risk of postmenopausal breast cancer associated with regular physical activity.

Abbreviations: CPS-II – Cancer Prevention Study II; CI – confidence interval; ICD – International Classification of Diseases; NDI – National Death Index; RR – rate ratio

Introduction

Cumulative lifetime exposure to estrogen is a key factor in determining a woman's risk of breast cancer [1]. Studies have shown that early age at menarche, late age at menopause, nulliparity, late age at first full-term pregnancy, postmenopausal obesity, adult weight gain, and postmenopausal hormone replacement therapy (HRT) use are associated with increased breast cancer risk [2–8]. Physical activity has been proposed as a potential modifiable risk factor for breast cancer because of its effects on circulating sex hormones and weight gain.

To date, 33 original reports from observational studies have examined the association between physical activity at various points in a woman's lifetime and postmenopausal breast cancer risk [9–18]. Overall, results from previous studies support the hypothesis that regular physical activity may reduce the risk of breast cancer among postmenopausal women. However, it remains unclear whether early or late-life physical activity is important for postmenopausal women. Of the 33 previous studies, 10 specifically examined the association of physical activity during the postmenopausal years and breast cancer risk [10, 13, 15, 18–24], and all but one found that postmenopausal physical activity is associated with lower breast cancer risk [10, 13, 15, 18–21, 23, 24]. It is also unclear whether non-recreational

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physical activity, such as housework, gardening, or shopping contribute an additional benefit to breast cancer risk. The contribution of non-recreational physical activity may be valuable since it is an important component of overall physical activity among older, retired persons [25].

We examined the association of various measures of physical activity with postmenopausal breast cancer risk among women in the American Cancer Society Cancer Prevention Study II (CPS-II) Nutrition Cohort, a large prospective study in the US.

Methods

Study cohort and follow-up

Women in this analysis were drawn from the 97,787 female participants in the CPS-II Nutrition Cohort, which was established in 1992 by the American Cancer Society as a subgroup of the larger 1982 CPS-II cohort [26]. The great majority of participants were 50–74 years of age at enrollment in 1992, and they completed a 10-page self-administered questionnaire that included questions on demographic, medical, reproductive, behavioral, environmental, and dietary factors. A follow-up questionnaire was sent to cohort members between September 1997 and August 1998 to update exposure information and to ascertain newly diagnosed cancers. Cohort members who died during the interval were identified by routine interval linkage of the entire cohort to the National Death Index. The response rate to the 1997/1998 questionnaire among living cohort participants was 91%.

We excluded from this analysis women who were lost to follow-up from 1992 to 1997–1998 (n = 7592), who were missing year of diagnosis of breast cancer (n = 3), who reported prevalent cancer (except non-melanoma skin cancer) at baseline (n = 11,599), or who were not postmenopausal in 1992 (n = 4851). Also excluded were women who left the baseline physical activity question (on all seven activities) blank (n = 1134). After all exclusions, the final analytic cohort consisted of 72,608 women with a mean age at study entry of 62.7 ± 6.1 (Table 1).

A total of 1520 incident breast cancers diagnosed between the date of enrollment and August 31, 1997 were included in this analysis. Of these, 1373 cases were identified by self-report on the 1997–1998 questionnaire and subsequently verified from medical records (n = 1138) or linkage with state cancer registries (n = 235). Verified incident breast cancer cases also included a small number (n = 8) identified during confirmation of another reported cancer diagnosis. Sixty-one incident cases were identified as interval deaths through automated linkage of the cohort with the National Death Index. For these cases, the death certificate listed breast cancer as a primary or contributory cause of death (International Classification of Diseases, Ninth Revision, codes 174.0–174.9) [27] during the interval between the date of enrollment and August 31, 1997. For 39 of the interval deaths, additional information was obtained through linkage with state cancer registries. Previous studies linking cohort participants with state cancer registries have shown that the Nutrition Cohort participants were highly accurate (93% sensitivity) in reporting any past cancer diagnoses [28]; therefore, we also included 78 self-reported breast cancers for which confirmed diagnosis was not obtained.

Table 1. Creation of analytic cohort, CPS-II Nutrition Cohort, 1992–1997

	# of women (%)	# of breast cancer cases (%)
Total	97,787	1763
Exclusions		
Lost to follow-up	7592 (7.8)	0 (0.0)
Missing year of diagnosis	3 (0.01)	3 (0.2)
Prevalent breast cancer	6006 (6.1)	0 (0.0)
Other prevalent cancer	5593 (5.7)	112 (6.4)
Pre-, peri-, or unknown menopausal status	4851 (5.0)	106 (6.0)
Missing exercise data	1134 (1.2)	22 (1.2)
Total exclusions	25,179 (25.7)	243 (13.8)
Total available for analysis	72,608 (74.3)	1520 (86.2)

For those cases with medical or registry records (n = 1420), we then classified by general summary stage (GSS) as recorded on the records. Cases were grouped as *in situ* (stage I, n = 205), localized (stage II, n = 880), regional and distant/systemic disease (stage III and IV, n = 290), or unknown GSS (n = 45).

Assessment of physical activity

Baseline recreational physical activity information was collected using the question 'During the past year, what was the average time per week you spent at the following kinds of activities: walking, jogging/running, lap swimming, tennis or racquetball, bicycling or stationary biking, aerobics/calisthenics, and dancing?' Response to each activity could be 'none', '1–3 h per week', '4–6 h per week', or '7+ h per week'. Summary MET-h/week were calculated for each participant. A MET, or metabolic equivalent is the ratio of metabolic rate during a specific activity to resting metabolic rate [29]. The summary MET score for each participant was

calculated by multiplying the hours spent engaged in each activity (0 for 'none', 1 for '1–3 h per week', 4 for '4–6 h per week', and 7 for '7+ h per week) times the MET score estimated for each activity by Ainsworth *et al.* [29]. Due to the older age of this population, MET-hours per week were calculated using the lowest value of hours spent and moderate intensity MET values for each activity such that summary measures would be estimated conservatively. The following MET scores were used [29]: 3.5 for walking, 7.0 for jogging/running, 7.0 for lap swimming, 6.0 for tennis or racquetball, 4.0 for bicycling/stationary biking, 4.5 for aerobics/calisthenics, and 3.5 for dancing.

In addition to recreational leisure activity at baseline, non-recreational leisure activity was also examined based on information collected from the question 'During the past year, what was the average time per week you spent at the following kinds of activities: gardening/mowing/planting, heavy housework/vacuuming, heavy home repair/painting, and shopping?'. The above algorithm was used to calculate MET-h/week using the following values for each activity [29]: 3.0 for gardening/mowing/planting, 2.5 for heavy housework/vacuuming, 3.0 for heavy home repair/painting, and 2.5 for shopping.

In 1992, we also asked participants to recall physical activity at age 40 based on the question, 'At age 40, what was the average time per week you spent at the following kinds of activities: walking, jogging/running, lap swimming, tennis or racquetball, bicycling or stationary biking, aerobics/calisthenics, and dancing?', which was then summarized using the same method as baseline recreational activity mentioned above. Another measure of past physical activity was available using the original 1982 CPS-II questionnaire data, where participants estimated behavior 10-years prior to baseline. In 1982, participants were asked 'How much exercise do you get (work or play): none, slight, moderate, heavy?' Physical activity as recalled at age 40 and activity in 1982 were combined with baseline 1992 exposure information to assess whether risk of breast cancer was reduced among women who consistently reported being physically active.

Statistical analysis

We used Cox proportional hazards modeling [30] to calculate hazards rate ratios (RR) and corresponding 95% confidence intervals (CI) to examine the relationship between physical activity measures and breast cancer. For each analysis, we assessed risk in two models, one adjusted only for age and the other adjusting for age and potential confounding factors. Baseline recreational and age 40 physical activity were categorized in MET-h/week as none, >0–7.0, >7.0–17.5, >17.5–31.5, >31.5–42.0, or >42.0. Baseline non-recreational leisure activity was categorized in MET-h/week as none, >0–5.0, >5.0–<10.0, 10.0–<18.5, or ≥18.5. All hazard ratios employ women reporting >0–7.0 MET-h/week as the referent group. Women who reported being inactive were not used as the referent group because of the possibility that their complete inactivity may be due to underlying conditions related in some way to breast cancer risk. If inactive women suffer from other health conditions that are hormone-related and impair their ability to engage in physical activity, the association between inactivity and breast cancer risk may be confounded. Women with missing information for activity at age 40 (1278 women), 1982 exercise (902 women), or baseline non-recreational activity (770 women) were excluded from models that included those variables.

All Cox models were stratified on exact year of age at enrollment. Potential confounders included in the multivariate models were race (white, black, other/missing), education (≤high school graduate, some college, college graduate, missing), family history of breast cancer in mother or sisters (yes, no), history of breast lumps and/or cysts (yes, no), recency of mammography (never had a mammogram, had mammogram within past year, 1–3 years ago, over 3 years ago, missing), smoking (never, current, former, missing), baseline alcohol intake (never, <1 drink/day, 1 drink/day, >1 drink/day, missing), parity (nulliparous, one live birth, 2–3 live births, >3 live births, missing), age at menarche (<12, 12, 13, >13, missing), age at natural or surgical menopause (<45, 45–49, 50–54, ≥55, unknown), oral contraceptive use (never, < 5 years, 5–9 years, ≥10 years, missing), total caloric intake (kcals/day) in quartiles, HRT use (never, current, former, ever user but unknown if a current user, missing), BMI (weight (kg)/height $(m)^2$) (<22.0, 22.0–<25.0, 25.0–<27.0, 27.0–<30.0, ≥30.0, missing), and weight change from age 18 to 1992 (lbs.) (>5 loss, 5 loss–5 gain, >5–15 gain, >15–25 gain, >25–35 gain, >35 gain, missing).

Trend tests for physical activity models using MET-h/week were obtained by assigning the mean MET value to each category, and trend for 1982 exercise used an ordinal value (1–4) for the four reported levels of activity. To test whether any of the potential confounders described above modified the association between baseline recreational physical activity and breast cancer risk, we constructed multiplicative interaction terms between baseline MET-h/week and all other risk factors. Due to small numbers in some strata, categories of potential effect modifiers were sometimes collapsed. We

also assessed whether attained age modified the association using a time-varying covariate for age until the end of follow-up (diagnosis date, death date, or August 31, 1997) for each participant. Statistical interaction was assessed in multivariate models using the likelihood ratio test and a p-value < 0.05 was considered statistically significant [31].

Results

Nine percent (n = 6659) of women in this study population reported no recreational physical activity at baseline, and three percent (n = 1958) reported activity >42.0 MET-h/week. Among women who reported any recreational physical activity at baseline, the median MET expenditure was 9.5 MET-h/week, which is equivalent to approximately three h of moderately paced walking per week. Women who were physically active were more likely to use HRT, drink any alcohol, be nonsmokers, and have had a mammogram within the year prior to baseline. Active women had a lower BMI at enrollment (1992) and were less likely to have gained weight since age 18. There was also a high correlation between baseline recreational physical activity and nonrecreational physical activity, activity recalled at age 40, and activity reported in 1982; active women at all levels were also more likely to engage in low versus moderate or high intensity activities (Table 2).

Women in the highest category of recreational physical activity (>42.0 MET-h/week) had a lower relative risk of postmenopausal breast cancer than women who reported some physical activity not exceeding 7.0 MET-h/week (RR = 0.71; 95% CI, 0.49–1.02), although the result was not statistically significant (Table 3). A test of trend including women who reported no recreational physical activity was of borderline statistical significance (p-trend = 0.08); however, among women who reported any recreational physical activity, there was a significant trend with increasing physical activity (p-trend = 0.03).

We also examined the association of breast cancer risk with both the 1992 report of physical activity at age 40 and with exercise reported prospectively in 1982. Women who reported being the most active at age 40 (>42.0 MET-h/week) had a RR for breast cancer of 0.79 (95% CI, 0.61–1.03), but there was no clear gradient of decreasing risk with greater activity at this age (p-trend = 0.31, p-trend = 0.36 among women reporting any physical activity). A small gradient was observed with exercise reported in 1982, but this was statistically insignificant (p-trend = 0.33, p-trend = 0.16 among exercisers only) (Table 3). Furthermore, the association was not stronger among women who reported being physically active both at baseline and at age 40 or 10-years prior in 1982 compared to women who reported only recreational physical activity in 1992 (data not shown). After adjustment for recreational physical activity, there was no additional change in the relative risk for breast cancer by non-recreational physical activity (RR = 0.95; 95% CI, 0.82–1.10 for ≥18.5 MET-h/week *versus* >0–5.0 MET-h/week non-recreational activity, p-trend = 0.32).

We assessed the association between recreational physical activity at baseline and breast cancer, by stage of disease. The risk of localized breast cancer was most strongly associated with physical activity (RR = 0.55; 95% CI, 0.38–0.80 for >31.5 MET-h/week *versus* >0–7.0 MET-h/week, p-trend = 0.02 among women who reported any recreational physical activity at baseline). No inverse association was seen for *in situ* breast cancer (p-trend = 0.94 among women reported any recreational physical activity) or regional and distant breast cancer (p-trend = 0.62 among women who reported any recreational physical activity) (Table 4).

There were no statistically significant interactions between baseline recreational physical activity levels and attained age or any of the other potential risk factors included in this analysis. The inverse association between recreational physical activity and lower risk of breast cancer was marginally stronger among women who were not currently using HRT at baseline than among those who used HRT (p-interaction = 0.09). There is also a suggestion that physical activity may have a greater impact on women who do not drink alcohol and who are leaner (Table 5).

Discussion

We observed lower incidence of postmenopausal breast cancer in women who reported higher levels of recreational physical activity at the time of enrollment into our study. These findings are similar to the results of six [10, 13, 15, 19–21] of the seven [10, 13, 15, 19–22] previous prospective cohort studies and three population-based case–control studies [18, 23, 24] that examined physical activity during the postmenopausal years and breast cancer risk. Breast cancer incidence was approximately 29% lower among active women in the highest category compared to active women in the lowest category of physical activity.

Compared to slightly active women, we observed a small reduction in risk of breast cancer among completely inactive women. Conditions such as osteoporosis are associated with lower levels of circulating estrogens and lower breast cancer risk; additionally, women with

Table 2. Age-adjusted percentages of various factors at baseline by recreational physical activity MET expenditure, CPS-II Nutrition Cohort, 1992–1997

Variable	Recreational leisure-time activity MET expenditure (total n = 72,608)						
	n	None (n = 6659)	>0–7.0 (n = 24,739)	>7.0–17.5 (n = 23,478)	>17.5–31.5 (n = 13,436)	>31.5–42.0 (n = 2338)	>42.0 (n = 1958)
Median MET-h/week	–	0	3.5	13.5	24.5	35.5	52.5
Intensity of activities[a]							
Low	–	0.0	97.6	92.2	89.2	77.5	60.9
Moderate	–	0.0	2.4	7.8	10.8	22.5	39.1
Age at baseline							
< 50	568	10.9	31.7	31.5	20.6	2.8	2.5
50–59	22,889	9.4	35.1	31.8	17.5	3.4	2.7
60–69	37,700	8.8	33.3	32.9	19.2	3.2	2.7
70+	11,451	9.8	34.7	31.7	18.3	2.9	2.6
Race							
White	70,701	9.1	34.0	32.4	18.5	3.2	2.7
Black	1053	11.0	36.8	29.4	16.4	3.6	2.8
Other/missing	854	10.4	32.9	31.8	19.4	2.8	2.7
Education							
≤HS grad	26,996	11.7	36.3	30.4	17.2	2.5	1.9
Some college	22,778	8.5	34.2	32.5	18.6	3.4	2.7
≥College grad	22,338	6.8	31.2	34.5	20.0	3.9	3.7
Missing	496	9.8	34.6	33.2	17.9	1.8	2.7
HRT use							
Never	35,013	10.0	34.4	31.4	18.4	3.1	2.7
Current	24,929	7.9	33.3	33.8	18.8	3.5	2.8
Former	10,318	9.1	34.6	32.4	18.1	3.2	2.6
Ever use, Unknown status	1388	9.2	32.9	31.6	19.7	3.1	3.6
Missing	960	12.7	35.7	29.5	17.1	2.4	2.6
BMI							
< 22.0	16,627	7.6	30.5	32.4	21.0	4.4	4.2
22.0–< 25.0	21,168	7.0	32.2	33.8	20.4	3.6	3.0
25.0–< 27.0	11,481	8.3	34.6	33.2	18.7	3.0	2.2
27.0–< 30.0	11,219	10.6	36.8	31.9	16.4	2.6	1.7
≥30.0	11,048	15.1	39.1	29.2	13.6	1.6	1.4
Missing	1065	11.8	38.2	30.5	14.9	2.3	2.4
Weight change (age 18 to 1992) (lbs.)							
>5 loss	3838	9.0	28.3	31.4	22.1	4.4	4.8
≤5 loss–≤5 gain	7479	6.2	29.3	32.7	22.4	4.7	4.6
>5–15 gain	11,789	6.7	30.3	33.8	21.1	4.6	3.5
>15–25 gain	12,733	7.3	33.1	33.8	19.8	3.3	2.7
>25–35 gain	11,369	8.5	35.1	32.7	18.4	3.0	2.2
>35 gain	23,995	12.5	38.2	30.7	14.9	2.0	1.6
Missing	1405	11.4	36.0	31.9	15.8	2.3	2.6
Family history of breast cancer							
No	62,549	9.2	34.0	32.4	18.5	3.2	2.7
Yes	10,059	9.0	34.3	32.1	18.5	3.3	2.8
Smoking							
Never	39,851	8.4	35.6	32.7	18.1	2.9	2.3
Current	5984	15.4	35.4	26.7	16.9	2.8	2.8
Former	25,776	8.9	31.4	33.2	19.5	3.8	3.2
Missing	997	10.2	35.4	29.0	18.5	2.6	4.2
Alcohol intake							
Non-drinker	33,262	10.9	36.4	31.1	17.1	2.5	2.1
< 1/day	20,207	7.6	32.6	34.1	19.4	3.5	2.8

Table 2. (Continued)

Variable	Recreational leisure-time activity MET expenditure (total n = 72,608)						
	n	None (n = 6659)	>0-7.0 (n = 24,739)	>7.0–17.5 (n = 23,478)	>17.5–31.5 (n = 13,436)	>31.5–42.0 (n = 2338)	>42.0 (n = 1958)
1/day	10,437	6.8	30.8	34.1	20.4	4.3	3.6
>1/day	5770	8.3	30.7	31.7	20.6	4.6	4.1
Missing	2932	10.2	36.5	28.9	18.0	3.1	3.4
Caloric intake (kcals)							
≤1000	15,721	9.2	34.9	32.4	18.1	3.1	2.3
>1000–1300	17,783	8.6	33.3	33.8	18.5	3.3	2.5
>1300–1600	15,294	8.8	34.5	32.2	18.7	3.1	2.7
>1600	17,522	9.4	33.2	31.6	19.2	3.5	3.1
Missing	6288	10.6	35.3	30.6	17.4	2.9	3.2
Last mammogram							
Never	5325	13.7	34.8	27.2	19.2	2.7	2.2
<1 year	47,891	7.9	33.6	33.2	18.9	3.4	2.9
1–3 years	14,816	10.1	34.7	32.7	17.2	3.0	2.1
>3 years	4280	13.4	36.1	27.8	17.7	2.5	2.5
Missing	296	16.6	33.2	31.8	14.5	1.6	2.4
Leisure-time MET-h/week at age 40							
None	10,492	30.0	32.4	25.6	10.2	1.1	0.7
>0–7.0	20,971	8.0	50.2	28.9	10.8	1.4	0.8
>7–17.5	19,522	5.3	33.2	41.7	15.9	2.5	1.5
>17.5–31.5	12,828	3.8	22.1	32.9	34.3	4.1	2.9
>31.5–42.0	3632	2.5	16.0	30.2	33.5	11.6	6.2
>42.0	3885	2.7	9.3	23.0	31.7	12.4	21.0
Missing	1278	9.8	45.1	29.9	13.1	1.2	0.9
Exercise in 1982							
None	1073	28.6	40.4	22.7	7.1	0.4	0.8
Slight	18,013	13.7	41.7	30.2	12.1	1.5	0.8
Moderate	48,740	7.3	32.1	33.7	20.5	3.6	2.8
Heavy	3880	6.6	21.6	27.4	26.4	7.8	10.2
Missing	902	8.5	32.8	35.5	17.1	4.1	2.0
Baseline non-recreational MET-h/week							
None	1135	35.4	32.3	21.4	8.3	1.9	0.7
>0–5	17,822	10.9	39.4	32.3	13.6	2.1	1.7
>5–<10	16,841	6.9	35.8	35.6	16.9	2.9	1.9
10–<18.5	17,560	8.2	33.2	33.1	19.5	3.6	2.6
≥18.5	18,480	8.7	28.2	29.5	24.6	4.3	4.7
Missing	770	11.2	38.4	30.0	15.0	3.4	2.0

[a] Low intensity activities are defined as those with MET scores of 3.5–4.5 (walking, biking, aerobics/calisthenics, or dancing), and moderate intensity activities are defined as those with MET scores of 6.0–7.0 (jogging/running, swimming, or tennis/racquetball).

osteoporosis are also less likely to engage in regular physical activity. Information on osteoporosis and fractures was not available at baseline in 1992. However, using data from the 1997 questionnaire, we found that inactive women in this population were more likely to suffer from hip fractures, a consequence of osteoporosis. Since we were unable to adequately control for conditions such as osteoporosis or fractures at baseline, we did not use inactive women as the referent group. Our choice of referent group is supported by the findings of Cerhan *et al.* [10] who controlled for physical function in their analysis of physical activity and postmenopausal breast cancer and observed a lower risk among women who reported inactivity due to physical disability.

Engaging in non-recreational physical activity, such as shopping, gardening, and housework, was not associated with lower risk of breast cancer in this population. Although these activities comprise a large part of total activity among older women, they may not be vigorous enough to infer any physiologic response (such as influencing hormone levels or promoting weight loss) necessary to lower breast cancer risk. We also did not

Table 3. RRs for recreational leisure-time physical activity at various times during a woman's lifetime and breast cancer, CPS-II Nutrition Cohort, 1992–1997

	# cases/person-years	RR[b] (95% CI)	RR[c] (95% CI)
MET-h/week in 1992[a]			
None	126/28,698	0.86 (0.71–1.04)	0.86 (0.70–1.04)
>0–7.0	554/107,746	1.00 (Ref.)	1.00 (Ref.)
>7.0–17.5	488/102,711	0.92 (0.82–1.04)	0.92 (0.81–1.04)
>17.5–31.5	281/58,834	0.92 (0.80–1.07)	0.94 (0.81–1.09)
>31.5–42.0	40/10,237	0.76 (0.55–1.05)	0.77 (0.56–1.06)
>42.0	31/8570	0.70 (0.49–1.01)	0.71 (0.49–1.02)
	p-trend[d] = 0.08 (among active women, p-trend = 0.03)		
MET-h/week at age 40[e]			
None	224/46,009	1.04 (0.88–1.22)	1.03 (0.88–1.21)
>0–7.0	431/91,528	1.00 (Ref.)	1.00 (Ref.)
>7.0–17.5	428/85,495	1.06 (0.93–1.22)	1.05 (0.92–1.20)
>17.5–31.5	269/55,711	1.02 (0.88–1.19)	1.01 (0.87–1.18)
>31.5–42.0	87/15,744	1.18 (0.94–1.48)	1.16 (0.92–1.46)
>42.0	64/16,829	0.81 (0.62–1.05)	0.79 (0.61–1.03)
	p-trend[d] = 0.31 (among active women, p-trend = 0.36)		
Exercise in 1982[f]			
None	20/4632	0.81 (0.52–1.28)	0.80 (0.51–1.25)
Slight	414/78,717	1.00 (Ref.)	1.00 (Ref.)
Moderate	1000/212,636	0.88 (0.78–0.98)	0.93 (0.83–1.04)
Heavy	72/16,847	0.80 (0.62–1.03)	0.87 (0.68–1.13)
	p-trend[d] = 0.32 (among active women, p-trend = 0.16)		

[a] MET-h/week based on the following activities reported at baseline in 1992: walking, jogging/running, bicycling, swimming, aerobics/calisthenics, tennis/racquetball, and dancing.

[b] Age-adjusted RR and corresponding 95% CI.

[c] Multivariate-adjusted RR and 95% CI adjusted for: age, race, BMI, weight change from age 18 to 1992, family history of breast cancer, personal history of breast cysts, duration of OC use, HRT use, parity, age at menarche, age at menopause, smoking, alcohol intake, caloric intake, education, and mammography history.

[d] Trend tests conducted in multivariate models.

[e] MET-h/week calculated same as above based on recall on 1992 survey of activity at age 40 (1278 women (17 cases) excluded for missing information).

[f] Physical activity reported on 1982 CPS-II survey as 'how much exercise do you get?': none, slight, moderate, or heavy (902 women (14 cases) excluded for missing information).

observe a stronger association with prolonged physical activity in this population, although misclassification of recalled exposure information may increase the likelihood of bias towards the null.

When examining risk by stage of disease, we found the greatest reduction in risk for localized breast cancer. This finding suggests that the impact of physical activity is greater among women with a more favorable prognosis; however, we did not observe a reduction in risk for *in situ* breast cancer. The lack of association in *in situ* disease may be real or may be due to residual confounding from screening. Women who are physically active are more likely to be screened [32]. Since *in situ* breast cancer is virtually always detected with mammography, there may be an overrepresentation of active women among *in situ* cases resulting in a bias towards the null. When examining risk of *in situ* breast cancer among only women screened within the year prior to baseline, we found a lower risk with increasing physical activity compared to analyses including all women (data not shown). For localized and regional/distant cancer, no differences were seen when the analysis was limited to only women who were screened. One other study examined risk of postmenopausal breast cancer by stage of disease and found a significant inverse trend with physical activity and localized breast cancer. The inverse association was not significant for distant cases; however, the study was limited in their number of distant cases (n = 12), and *in situ* cases were not included in the analysis [10].

Although we did not find any significant effect modification by other risk factors, we did observe a stronger association between recreational physical activity and breast cancer risk among women who did not report current HRT use in 1992. One may speculate that the influence of moderate levels of physical activity on

Table 4. RRs for recreational leisure-time physical activity at baseline and breast cancer risk, by stage[a], CPS-II Nutrition Cohort, 1992–1997

	MET-h/week[b]				
	None	>0–7.0	>7.0–17.5	>17.5–31.5	>31.5
In situ breast cancer					
# cases/person-years	25/28,464	68/106,611	66/101,713	33/58,254	13/18,679
RR[c] (95% CI)	1.39 (0.88–2.19)	1.00 (Ref.)	1.01 (0.72–1.42)	0.89 (0.59–1.35)	1.09 (0.60–1.97)
RR[d] (95% CI)	1.47 (0.93–2.34)	1.00 (Ref.)	0.99 (0.71–1.40)	0.90 (0.59–1.36)	1.04 (0.57–1.90)
	p-trend[e] = 0.38 (among active women, p-trend = 0.94)				
Localized breast cancer					
# cases/person-years	64/28,553	331/107,256	281/102,232	172/58,559	32/18,714
RR[c] (95% CI)	0.73 (0.56–0.96)	1.00 (Ref.)	0.89 (0.76–1.04)	0.95 (0.79–1.14)	0.55 (0.39–0.80)
RR[d] (95% CI)	0.74 (0.56–0.96)	1.00 (Ref.)	0.88 (0.75–1.03)	0.95 (0.79–1.15)	0.55 (0.38–0.80)
	p-trend[e] = 0.10 (among active women, p-trend = 0.02)				
Regional and distant breast cancer					
# cases/person-years	29/28,465	98/106,687	99/101,787	50/58,274	14/18,672
RR[c] (95% CI)	1.11 (0.73–1.68)	1.00 (Ref.)	1.05 (0.80–1.39)	0.93 (0.66–1.31)	0.81 (0.46–1.42)
RR[d] (95% CI)	1.08 (0.71–1.63)	1.00 (Ref.)	1.08 (0.81–1.43)	0.97 (0.69–1.37)	0.85 (0.49–1.50)
	p-trend[e] = 0.56 (among active women, p-trend = 0.62)				

[a] 45 cases with missing stage data excluded from stage analyses.

[b] MET-h/week based on the following activities: walking, jogging/running, bicycling, swimming, aerobics/calisthenics, tennis/racquetball, and dancing.

[c] Age-adjusted RR and corresponding 95% CI.

[d] Multivariate-adjusted RR and 95% CI adjusted for: age, race, BMI, weight change from age 18 to 1992, family history of breast cancer, personal history of breast cysts, duration of OC use, HRT use, parity, age at menarche, age at menopause, smoking, alcohol intake, caloric intake, education, and mammography history.

[e] Trend tests conducted in multivariate models.

hormone levels in women with a favorable estrogen profile (*i.e.* lower baseline levels of hormones) may be sufficient to reduce risk, whereas women with higher levels of baseline circulating estrogens, such as current HRT users or obese women, may not experience a reduction in risk with moderate physical activity. Women with higher baseline estrogen levels may require more vigorous and frequent activity to substantiate a reduction in risk. Only three previous studies have examined potential effect modification by HRT, but none found a significant interaction [22, 24, 33]. Two [19, 23] of 17 studies [11, 14, 15, 17, 19–24, 33–39] that examined possible effect modification by body mass found that leaner women had a significantly greater reduction in risk compared to overweight women. The study publications reporting no effect modification have not provided details of analyses; therefore, it is difficult to assess whether or not this is due to a lack of statistical power.

A limitation of our study was the lack of information on physical activity in adolescence and young adulthood, which may be critical to the multistage induction of invasive breast cancer. The only measures of past physical activity available are based on recalled information at age 40 and information reported prospectively in 1982. Furthermore, the 1982 question is very crude in its physical activity assessment; thus, we may have substantial misclassification of past exposure. We also lack updated information during follow-up; however, we expect this to have minimal effect due to the short (five-year) follow-up period. Other limitations of our study are that we have a limited range in the type of activities commonly done by our participants and no individual information on intensity. Most highly active women in the study engaged in walking with the addition of modest amounts of the other six reportable activities. The lack of information on the intensity of individual behavior increases the misclassification of true energy expenditure.

Another limitation of this study is that a subset of participants originally recruited in 1982 for the CPS-II follow-up study subsequently volunteered to participate in this Nutrition Cohort in 1992. These participants who volunteered to participate in 1992 are healthier than non-respondents or the general population, and represent a select population. Although study participants are on average more affluent, educated, and health conscious than the average US population, these differences are unlikely to compromise internal validity. While the relatively homogenous nature of the women in this study reduces the likelihood of residual confounding, it also reduces the range of the physical activity exposure variable.

Table 5. RRs for 1992 reported baseline recreational physical activity and postmenopausal breast cancer risk stratified by various factors, CPS-II Nutrition Cohort, 1992–1997

	# of cases and RR[a] (95% CI) for 1992 baseline exercise				
	None	>0–7.0 MET-h /week	>7.0–17.5 MET-h /week	>17.5–31.5 MET-h /week	>31.5 MET-h/week
Attained age					
<60	26	84	93	37	12
	1.16 (0.74–1.80)	1.00 (Ref.)	1.21 (0.90–1.63)	0.87 (0.59–1.28)	0.79 (0.43–1.45)
60–64	27	165	120	77	23
	0.62 (0.41–0.93)	1.00 (Ref.)	0.79 (0.62–1.00)	0.92 (0.70–1.20)	0.85 (0.55–1.32)
65–69	35	156	149	87	18
	0.88 (0.61–1.27)	1.00 (Ref.)	0.92 (0.74–1.16)	0.93 (0.71–1.21)	0.62 (0.38–1.02)
≥70	38	149	126	80	18
	0.92 (0.64–1.31)	1.00 (Ref.)	0.90 (0.71–1.15)	1.01 (0.77–1.32)	0.73 (0.45–1.20)
HRT use					
Current	44	210	182	113	38
	0.87 (0.63–1.21)	1.00 (Ref.)	0.85 (0.70–1.04)	0.97 (0.77–1.21)	0.98 (0.70–1.39)
Former	12	77	65	24	6
	0.58 (0.32–1.07)	1.00 (Ref.)	0.89 (0.64–1.23)	0.60 (0.38–0.95)	0.48 (0.21–1.09)
Never	68	244	228	139	26
	0.98 (0.75–1.29)	1.00 (Ref.)	1.02 (0.85–1.23)	1.08 (0.88–1.33)	0.64 (0.43–0.97)
			p-interaction = 0.09		
Alcohol intake					
Non-drinker	62	257	208	112	19
	0.81 (0.62–1.08)	1.00 (Ref.)	0.94 (0.78–1.13)	0.95 (0.76–1.18)	0.60 (0.38–0.96)
Drinker	57	275	264	160	51
	0.88 (0.66–1.17)	1.00 (Ref.)	0.90 (0.76–1.07)	0.94 (0.77–1.14)	0.84 (0.62–1.14)
			p-interaction = 0.74		
Caloric intake					
≤1300 kcals	54	252	236	127	32
	0.83 (0.61–1.11)	1.00 (Ref.)	0.95 (0.79–1.13)	0.93 (0.75–1.16)	0.77 (0.53–1.11)
>1300 kcals	63	251	218	132	36
	0.94 (0.72–1.25)	1.00 (Ref.)	0.92 (0.77–1.10)	0.96 (0.77–1.18)	0.79 (0.56–1.12)
			p-interaction = 0.96		
Weight change from age 18 to 1992					
≤15 gain	29	136	148	98	27
	0.95 (0.64–1.42)	1.00 (Ref.)	0.95 (0.75–1.20)	0.96 (0.74–1.25)	0.66 (0.43–0.99)
>15 lbs. gain	93	403	336	181	43
	0.83 (0.66–1.04)	1.00 (Ref.)	0.93 (0.80–1.08)	0.95 (0.80–1.13)	0.81 (0.59–1.12)
			p-interaction = 0.87		
BMI					
<25	53	258	271	152	46
	0.94 (0.70–1.26)	1.00 (Ref.)	0.99 (0.83–1.17)	0.89 (0.73–1.09)	0.75 (0.55–1.03)
25–<30	34	180	133	84	22
	0.73 (0.51–1.05)	1.00 (Ref.)	0.79 (0.63–0.99)	0.95 (0.73–1.23)	0.90 (0.57–1.40)
≥30[b]	35	103	82	46	
	0.89 (0.61–1.31)	1.00 (Ref.)	1.05 (0.78–1.40)	1.06 (0.75–1.50)	
			p-interaction = 0.81		

[a] Multivariate-adjusted RR and 95% CI adjusted for: age, race, BMI, weight change from age 18 to 1992, family history of breast cancer, personal history of breast cysts, duration of OC use, HRT use, parity, age at menarche, age at menopause, smoking, alcohol intake, caloric intake, education, and mammography history.

[b] For BMI ≥ 30, highest category of physical activity had only two cases; therefore, categories collapsed as activity >17.5 mets/week.

There are many strengths of this study that should be mentioned. The prospective design reduces the likelihood of differential reporting of recalled exposure information, and eliminates the possibility of recall bias for baseline activity measures. We have a large sample size as well as the ability to test for potential confounding by most important breast cancer risk factors. Occupational physical activity could confound the association between recreational leisure-time activity and breast cancer risk if women who reported little recreational physical activity were very active in the workplace. However, there is likely to be little, if any, confounding by occupational physical activity in this population because most women reported being housewives for their 'main lifetime' occupation, and of those who did work outside of the home, the majority of women were in clerical occupations where physical activity in the workplace would be minimal [40]. Finally, any protection observed with light or moderate activity during the postmenopausal years may be of public health importance.

Baseline reported physical activity in this study likely reflects those women who have been consistent exercisers over their lifetime as well as women who have initiated exercising recently; therefore, it is difficult to ascertain whether our findings reflect benefit of late-life physical activity or being a long-term exerciser. We assessed risk combining physical activity measures at age 40 and in 1982 with baseline physical activity, but found no differences in risk in women who reported activity in the past and at baseline compared to women who reported only baseline physical activity. Furthermore, it is biologically plausible that the initiation of late-life physical activity may be beneficial in reducing breast cancer risk.

Physical activity has been consistently associated with lower weight, lower BMI, and weight loss [9]. It is, however, likely that mechanistic pathways other than the effects of physical activity on body weight explain, at least in part, the relationship between physical activity and postmenopausal breast cancer. Studies have shown that after adjustment for body mass, physical activity during postmenopausal years is still associated with lower levels of serum estrone, estradiol, and androgens, and higher levels of SHBG [9]. Furthermore, independent of its effects on body mass, studies have shown that postmenopausal women with low to moderate levels of physical activity have increased insulin sensitivity and decreased plasma insulin levels [9]. Insulin sensitivity may impact breast cancer risk because higher levels of insulin are associated with decreased levels of SHBG, and consequently a higher level of free-estradiol [41]. Current evidence does not allow clear conclusions to be drawn regarding the possible association between physical activity and IGF levels [9]. Thus, physical activity after menopause may directly suppress sex hormones or increase insulin sensitivity. The lack of understanding of the minimal dose of physical activity necessary to cause any hormonal change is a major limitation of the existing literature; however, regular moderate intensity exercise, such as that in our highest physical activity category, is thought to be sufficient to induce some physiologic responses [9].

In summary, postmenopausal women who engaged in high amounts of recreational physical activity at baseline were at a lower risk of breast cancer than those engaged in low levels of physical activity. There is sufficient biologic plausibility for this association to warrant further research on late-life activity and primary prevention of breast cancer in postmenopausal women.

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対象の内訳		ヒト	動物	地 域	欧米	研究の種類	縦断研究
	対象	一般健常者	空白		( )		コホート研究
	性別	女性	( )		( )		( )
	年齢	50－74歳	[redacted]		( )		前向き研究
	対象数	10000以上	空白		( )		( )
調査の方法		質問紙	( )				
アウトカム	予 防	な し	な し	ガン予防	な し	( )	( )
	維持・改善	な し	な し	な し	な し	( )	( )

図 表

Table 3. RRs for recreational leisure-time physical activity at various times during a woman's lifetime and breast cancer, CPS-II Nutrition Cohort, 1992–1997

	# cases/person-years	RR[b] (95% CI)	RR[c] (95% CI)
MET-h/week in 1992[a]			
None	126/28,698	0.86 (0.71–1.04)	0.86 (0.70–1.04)
>0–7.0	554/107,746	1.00 (Ref.)	1.00 (Ref.)
>7.0–17.5	488/102,711	0.92 (0.82–1.04)	0.92 (0.81–1.04)
>17.5–31.5	281/58,834	0.92 (0.80–1.07)	0.94 (0.81–1.09)
>31.5–42.0	40/10,237	0.76 (0.55–1.05)	0.77 (0.56–1.06)
>42.0	31/8570	0.70 (0.49–1.01)	0.71 (0.49–1.02)
	p-trend[d] = 0.08 (among active women, p-trend = 0.03)		
MET-h/week at age 40[e]			
None	224/46,009	1.04 (0.88–1.22)	1.03 (0.88–1.21)
>0–7.0	431/91,528	1.00 (Ref.)	1.00 (Ref.)
>7.0–17.5	428/85,495	1.06 (0.93–1.22)	1.05 (0.92–1.20)
>17.5–31.5	269/55,711	1.02 (0.88–1.19)	1.01 (0.87–1.18)
>31.5–42.0	87/15,744	1.18 (0.94–1.48)	1.16 (0.92–1.46)
>42.0	64/16,829	0.81 (0.62–1.05)	0.79 (0.61–1.03)
	p-trend[d] = 0.31 (among active women, p-trend = 0.36)		
Exercise in 1982[f]			
None	20/4632	0.81 (0.52–1.28)	0.80 (0.51–1.25)
Slight	414/78,717	1.00 (Ref.)	1.00 (Ref.)
Moderate	1000/212,636	0.88 (0.78–0.98)	0.93 (0.83–1.04)
Heavy	72/16,847	0.80 (0.62–1.03)	0.87 (0.68–1.13)
	p-trend[d] = 0.32 (among active women, p-trend = 0.16)		

図表掲載箇所	P525, Table3
概 要 (800字まで)	The American Cancer Society Cancer Prevention Study II (CPS-II) Nutrition Cohortに参加している72608名の閉経後女性を対象に、5年間の追跡調査を行い、身体活動と乳がん発症との関係を調べた論文である。身体活動量は、ウォーキング(3.5)、ジョギングやランニング(7)、水泳(7)、テニスやラケットボール(6)、自転車やエアロバイク(4)、エアロビクス(4.5)、ダンス(3.5)を週何時間実施しますか？(各()の数字でMETs換算した。)という質問に回答してもらいメッツ・時/週により評価した。ベースラインにおいて、身体活動を0.－7.0メッツ時/週行っているものと比較して、まったくしていない者、7.0-17.5, 17.5-31.5, 31.5-42.0, 52.0以上の者では、乳がんになるリスクが、0.86(0.70-1.04), 0.92(0.81-1.04), 0.94(0.81-1.09), 0.77(0.56-1.06), 0.71(0.49-1.02)であった。これらを乳がんの種別でみると、局所性乳がんにおいて身体活動の予防効果が認められた。またアルコールの摂取がない群や、ホルモン治療を行っていない群においては、身体活動の予防的効果が明らかとなった。
結 論 (200字まで)	閉経後女性において、身体活動と乳がん発症との関係について、乳がんの種類やアルコール摂取の有無、ホルモン補充療法の有無により、身体活動の乳がん発症の予防的効果があることが明らかとなった。
エキスパートによるコメント (200字まで)	乳がん発症に対する身体活動の予防的効果は、多くの研究により支持されているところである。この関係は、様々な因子により影響を受けることが本研究により示されており、身体活動のみでなく、他の因子も同時に考慮して、乳がん予防に取り組むことが重要である。

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The role of body weight in the relationship between physical activity and endometrial cancer: Results from a large cohort of US women

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Factors influencing circulating estrogen levels, insulin-mediated pathways or energy balance through obesity-related mechanisms, such as physical activity, have been proposed as potential risk factors for endometrial cancer. We examined measures of physical activity in relation to endometrial cancer risk in the American Cancer Society Cancer Prevention Study II Nutrition Cohort, a prospective study of cancer incidence and mortality, using information obtained at baseline in 1992. From 1992 to 2003, 466 incident endometrial cancers were identified among 42,672 postmenopausal women with intact uteri who were cancer-free at enrollment. Cox proportional hazards modeling was used to compute hazard rate ratios (RR) while adjusting for potential confounders. To assess the role of body mass index (BMI) in this relationship, we computed multivariate RR with and without adjustment for BMI and stratifying by BMI. All measures of physical activity and the avoidance of sedentary behavior were associated with lower endometrial cancer risk. Baseline recreational physical activity was associated with 33% lower risk (RR = 0.67, 95% CI 0.44–1.03 for 31.5+ *vs.* <7 MET-hr/week, trend $p = 0.007$) in the multivariate model without BMI. However, the trend was attenuated after further adjustment for BMI (trend $p = 0.18$). BMI significantly modified the association between physical activity and endometrial cancer risk (heterogeneity of trends $p = 0.01$). The inverse relationship was seen only among overweight or obese women (trend $p = 0.003$) and not in normal weight women (trend $p = 0.51$). In summary, light and moderate physical activity including daily life activities were associated with lower endometrial cancer risk in our study, especially among women who are overweight or obese.

Key words: physical activity; exercise; sedentary behavior; endometrial cancer; prospective cohort

Endometrial cancer is the fourth most common incident cancer among US women.[1] Important risk factors for endometrial cancer include obesity, postmenopausal unopposed estrogen use and nulliparity.[2] Type II diabetes has also been associated with increased risk.[3] Few other risk factors for endometrial cancer have been well-established. Physical activity has been proposed to protect against endometrial cancer. Physical activity influences circulating estrogen levels and insulin-mediated pathways both through its effects on energy balance and adiposity and directly through independent pathways.[4–6]

To date, 17 observational studies have examined the relationship between recreational (leisure-time) physical activity and endometrial cancer risk (reviewed in Refs. 7–10). Although only half of these studies reached statistical significance in their findings,[9–16] the majority suggest a benefit with regular physical activity in lowering endometrial cancer risk. A recent meta-analysis[8] provided summary risk estimates of a 27% decreased risk of endometrial cancer from case-control studies (95% CI, 0.62–0.86) and a 23% decreased risk from cohort studies (95% CI, 0.70–0.85) when comparing the most active women with the least active women.

Researchers have also examined the association between endometrial cancer and nonrecreational activities in daily life, such as household chores, shopping and gardening. These activities are usually less intense than the recreational activities generally recommended for chronic disease prevention, but are as or more commonly done. Whether these activities have any potential health benefits is unknown. Five previous studies (reviewed in Ref. 7) have examined the role of these household activities; 4 of these reported a significant inverse relationship between the highest levels of household activity and risk of endometrial cancer.[9,11,17,18] Two other studies reported an increased risk of endometrial cancer in sedentary women.[11,19]

Another important unresolved question is whether body weight confounds, modifies or is an intermediary in the relationship between physical activity and endometrial cancer risk. Most previous studies have adjusted for measures of body mass in multivariate models (reviewed in Ref. 8). Body mass index (BMI) attenuates the relationship between physical activity and risk when added to multivariate models. Eleven previous studies also examined whether body weight is an effect modifier of the relationship between physical activity and endometrial cancer.[9,11,12,15,17–23] Most of these studies found no statistical interaction between BMI and physical activity on the multiplicative scale; however, 3 studies reported significantly lower relative risk estimates associated with regular physical activity among overweight or obese women than normal weight women.[17,18,21]

To further clarify the relationship between physical activity and risk of endometrial cancer, we examined whether recreational physical activity, nonrecreational household activities or sedentary behavior was associated with endometrial cancer risk, and whether these associations differed by body weight among postmenopausal women in the American Cancer Society Cancer Prevention Study II (CPS-II) Nutrition Cohort, a large prospective study in the US.

Material and methods

Study population

Women in this analysis were drawn from the 97,786 female participants in the CPS-II Nutrition Cohort, a prospective study of cancer incidence and mortality established by the American Cancer Society in 1992 as a subgroup of the larger 1982 CPS-II baseline mortality cohort.[24] Most participants were aged 50–74 years at enrollment in 1992. At baseline, they completed a 10-page self-administered questionnaire that included questions on demographic, reproductive, medical, behavioral, environmental and dietary factors. Beginning in 1997, follow-up questionnaires were sent to cohort members every 2 years to update exposure information and to ascertain newly diagnosed cancers. All follow-up questionnaire response rates (after multiple mailings) among living cohort members are at least 88%. End of follow-up for the present analysis was June 30, 2003.

We excluded from this analysis 3,190 women who were lost to follow-up (*i.e.*, alive at the first follow-up questionnaire in 1997 but did not return the 1997 or any subsequent follow-up questionnaire), who reported prevalent cancer (except nonmelanoma skin cancer) at baseline ($N = 12,053$), who reported not being postmenopausal ($N = 4,291$) or who had a hysterectomy or unknown hysterectomy status at baseline ($N = 30,724$). We also excluded women with missing information on recreational physical activity

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at baseline (N = 640) or BMI at baseline (N = 756). To eliminate the strong effect of estrogen-only hormone replacement therapy (ERT) on endometrial cancer and the possibility that reports of ERT only use were in error (because this regimen is contraindicated in women with an intact uterus), we excluded women who reported current ERT use in 1992 (N = 1,583) and those with current or past postmenopausal hormone use of unknown type in 1992 (n = 1,812). Finally, we excluded reported cases of endometrial cancer that could not be verified through medical or cancer registry records (N = 33) or cases with missing or potentially unrelated histologies such as endometrial stromal sarcoma (histology code 8930), adenosarcoma (code 8933), Mullerian mixed tumor (code 8950), endometrial adenofibroma (code 8381) and carcinosarcoma (code 8980) (n = 32). The etiology of these less common tumors is thought to be different from endometrial carcinomas. Women who did not return a 1999, 2001 or 2003 questionnaire were censored at the return of their last questionnaire. Women who underwent a hysterectomy were censored when first reported on the 1997, 1999 or 2001 questionnaire. After all exclusions, the final analytic cohort consisted of 42,672 women with a mean age of 62.8 (± 6.0 SD) years when enrolled in the study.

Case ascertainment

This analysis included 466 verified incident cases of endometrial cancer diagnosed between the date of enrollment and June 30, 2003. Of these, 433 cases were identified initially by self-report on a follow-up questionnaire and subsequently verified from medical records (n = 326) or linkage with state cancer registries (n = 107). A previous study linking cohort participants with state cancer registries has shown that the Nutrition Cohort participants are highly accurate (93% sensitivity) in reporting any past cancer diagnoses.[25] An additional 9 cases were reported by participants as another type of cancer, but were found to be endometrial cancer upon examination of registry records. Lastly, 24 incident cases were initially identified as interval deaths (deaths that occurred between baseline in 1992 and the end of follow-up in 2003) through automated linkage of the entire cohort with the National Death Index,[26] and subsequently verified through linkage with state cancer registries.

Measures of physical activity and sedentary behavior

Baseline information on recreational physical activity was collected using the question "During the past year, what was the average time per week you spent at the following kinds of activities: walking, jogging/running, lap swimming, tennis or racquetball, bicycling or stationary biking, aerobics/calisthenics and dancing?" Response to each activity included "none," "1–3 hr per week," "4–6 hr per week" or "7+ hr per week." Summary MET-hr/week were calculated for each participant. A MET, or metabolic equivalent, is the ratio of metabolic rate during a specific activity to resting metabolic rate.[27] Because of the older age of this population, the summary MET score for each participant was calculated by multiplying the lowest number of hours within each category times the moderate intensity MET score for each activity according to the Compendium of Physical Activities[27] to provide conservatively estimated summary measures. The MET scores for various activities were[27]: 3.5 for walking, 7.0 for jogging/running, 7.0 for lap swimming, 6.0 for tennis or racquetball, 4.0 for bicycling/stationary biking, 4.5 for aerobics/calisthenics and 3.5 for dancing. Recreational physical activity at baseline was categorized in MET-hr/week as none, >0–<7, 7–<17.5, 17.5–<31.5 or ≥31.5. For reference, 31.5 MET-hr/week corresponds to approximately 1 hr of moderate-paced walking (3.0 mph) per day.

In addition to recreational leisure activity at baseline, nonrecreational leisure activity was also examined based on information collected from the question "During the past year, what was the average time per week you spent at the following kinds of activities: gardening/mowing/planting, heavy housework/vacuuming, heavy home repair/painting and shopping?" The above algorithm was used to calculate MET-hr/week using the following values for each activity[27]: 3.0 for gardening/mowing/planting, 2.5 for heavy housework/vacuuming, 3.0 for heavy home repair/painting and 2.5 for shopping. Baseline nonrecreational leisure activity was categorized in quartiles of MET-hr/week as none, >0–5.0, >5.0–<10.0, 10.0–<18.5 or ≥18.5.

For both recreational and nonrecreational physical activity, women who reported being inactive were not used as the referent group because of the possibility that their complete inactivity may be due to underlying conditions related in some way to endometrial cancer risk. If inactive women suffer from other health conditions that are hormone-related and impair their ability to engage in physical activity (such as severe osteoporosis), the association between inactivity and endometrial cancer risk may be confounded.

We assessed sedentary behavior based on the question "During the past year, on an average day, (not counting time spent at your job) how many hours per day did you spend sitting (watching TV, reading, etc.)?" Responses included "none, less than 3, 3–5, 6–8, more than 8 hr per day." Sedentary behavior at baseline was categorized as 0–<3, 3–5, ≥6 or missing hr/day.

The baseline questionnaire also asked participants to recall physical activity at age 40 using the question, "At age 40, what was the average time per week you spent at the following kinds of activities: walking, jogging/running, lap swimming, tennis or racquetball, bicycling or stationary biking, aerobics/calisthenics and dancing?" A summary MET score at age 40 was created using the same method for baseline recreational activity described above. Recreational physical activity at age 40 was categorized in MET-hr/week as none, >0–<7, 7–<17.5, 17.5–<31.5, 31.5–<42.0 or ≥42.0. Another measure of past physical activity was obtained from a questionnaire completed in 1982 when participants in the CPS-II Nutrition Cohort were enrolled in the larger CPS-II mortality study. The 1982 questionnaire asked "How much exercise do you get (work or play)?" with possible responses: "none, slight, moderate or heavy." Although crude, this measure of physical activity has been shown to correlate with all-cause mortality rates.[28] The self-reported activity level in 1982 was combined with the more detailed information on 1992 recreational physical activity to examine whether risk of endometrial cancer was reduced among women who consistently reported being physically active in both 1982 and 1992. Women who reported being "none or slight" in 1982 and <17.5 MET-hr/week in 1992 were categorized as "consistently low," those reporting "moderate or heavy" in 1982 and 17.5+ MET-hr/week in 1992 were categorized as "consistently high," those reporting "none or slight" in 1982 and 17.5+ MET-hr/week in 1992 were categorized as "increasing low to high" and those reporting "moderate or heavy" in 1982 and <17.5 MET-hr/week in 1992 were classified as "decreasing high to low."

Statistical analysis

We used Cox proportional hazards modeling[29] to calculate hazards rate ratios (RR) and corresponding 95% confidence intervals (CI) to examine the relationship between measures of physical activity (recreational and nonrecreational), sedentary behavior and endometrial cancer risk. Statistical Analysis Software (SAS), v 9.1 was used for all analyses. For each exposure variable, we assessed risk in 3 models, one adjusted only for age, the second adjusted for age and other potential confounding factors except BMI and the third adjusting for all potential confounding factors including BMI. All Cox models were stratified on exact year of age at enrollment, and follow-up time in days was used as the time-axis. We tested the Cox proportional hazards assumption for each exposure measure and found no violations. Potential confounders included in the multivariate models were BMI [weight (kg)/height (m^2)] (<25.0, 25.0–<27.5, 27.5–<30.0, ≥ 30.0), oral contraceptive use (never, <5 years, 5+ years, ever use with unknown duration, missing), parity (nulliparous, 1–2, 3+, missing), age at men-

TABLE I – SELECTED STUDY PARTICIPANT CHARACTERISTICS[1] IN RELATION TO RECREATIONAL PHYSICAL ACTIVITY AT BASELINE AMONG 42,672 WOMEN IN THE CPS-II NUTRITION COHORT, 1992–2001

Variable	Baseline recreational activity MET-hr/week (total n = 42,672)				
	None (n = 3,854)	0–<7 (n = 13,445)	7–<17.5 (n = 14,365)	17.5–<31.5 (n = 8,112)	31.5+ (n = 2,896)
Median recreational activity MET-hr/week	0	3.5	11.5	24.0	39.5
Median nonrecreational MET-hr/week	8.0	8.0	8.0	12.5	13.0
Median recreational MET-hr/week, age 40	3.5	3.5	9.5	18.0	28.5
Moderate or high exercise in 1982 (%)	56.9	65.8	73.6	81.5	88.4
Median hr/day spent sedentary	4.0	4.0	4.0	4.0	1.5
BMI[1] (mean ± SE)	26.9 ± 0.08	25.9 ± 0.04	25.2 ± 0.04	24.7 ± 0.05	24.1 ± 0.09
Age at menopause[1] (mean ± SE)	50.0 ± 0.09	50.4 ± 0.05	50.5 ± 0.04	50.5 ± 0.06	50.6 ± 0.10
Age at menarche[1] (mean ± SE)	12.8 ± 0.02	12.8 ± 0.01	12.8 ± 0.01	12.8 ± 0.02	12.8 ± 0.03
Estimated kcal/day[1] (SE)	1,374 (7.9)	1,358 (4.2)	1,353 (4.1)	1,370 (5.4)	1,411 (9.0)
Race[1] (% White)	97.2	97.8	97.8	97.7	97.7
Parity[1] (%)					
0	8.5	8.0	7.7	7.6	7.3
1–2	34.1	32.7	32.5	33.5	32.5
3+	55.1	57.5	57.9	56.8	58.2
Missing	2.2	1.8	1.8	2.1	1.9
Oral contraceptive use[1] (%)					
Never use	65.6	64.2	62.2	64.0	61.4
<5 years	17.0	17.7	18.7	17.8	19.0
5+ years	14.0	15.6	16.7	15.8	17.5
Ever use/years unknown	1.7	1.3	1.2	1.2	1.2
Missing	1.6	1.2	1.1	1.1	0.9
Ever use of HT[1] (%)	36.3	41.3	43.2	42.2	43.4
Ever smoked[1]	50.1	42.6	44.6	46.2	51.9
History of diabetes[1] (%)	7.6	5.9	5.3	5.1	4.6

[1]Values are standardized to the age distribution of the study population.

opause (<45, 45–49, 50–54, 55+, unknown), age at menarche (<12, 12+, missing), postmenopausal hormone therapy use (HT) (never, current, former, other, missing/unknown), personal history of diabetes (yes, no), smoking status (never, current, former, ever unknown status, missing) and total energy intake (in quartiles). HT use and history of diabetes were modeled as time-varying covariates using information obtained in 1992, 1997, 1999 and 2001.

Trend tests for baseline recreational and nonrecreational activity, physical activity at age 40 and duration of sedentary behavior were calculated by assigning the median value within each category to that category. Trend tests for physical activity in 1982 were obtained by using an ordinal variable corresponding to each level of physical activity. To test whether physical activity across multiple time points was associated with endometrial cancer risk, we combined baseline recreational physical activity with physical activity in 1982 as an index of consistency in the 10-years prior to baseline. To test whether any of the potential confounders described above modified the association between the main effect measures and endometrial cancer risk, we examined each factor in a separate model by constructing multiplicative interaction terms with each risk factor and comparing the interaction model to the base model without the interaction terms. Because of small numbers in some strata, categories of potential effect modifiers were sometimes combined. Statistical interaction was assessed in multivariate models using the likelihood ratio test and a p-value <0.05 was considered statistically significant.[30]

Results

Approximately 9% (n = 3,854) of women reported no recreational physical activity at baseline (Table I). Among physically active women (defined as those reporting any recreational physical activity at baseline), the median MET expenditure was 8.0 MET-hr/week, corresponding to approximately 2 hr of moderately paced walking per week. Physically active women, regardless of level of energy expenditure, engaged primarily in activities judged to be of low to moderate intensity (walking, biking, aerobics or dancing) rather than higher intensity (jogging/running, swimming, tennis/racquetball). Physically active women were more likely to be lean and have ever used oral contraceptives and postmenopausal HT. Physically active women were also more likely to have been physically active in the past (both as measured in 1982 and recalled from age 40) and to engage in various household (nonrecreational) activities (Table I).

Every measure of baseline physical activity and the avoidance of sedentary behavior were associated with lower endometrial cancer risk (Table II). Recreational physical activity at baseline was associated with a 33% lower risk (RR = 0.67, 95% CI 0.44–1.03 for 31.5+ *vs.* <7 MET-hr/week, trend p = 0.007) in the multivariate model without adjustment for BMI (Table II). However, the association was attenuated when BMI was added to the model (RR = 0.79, 95% CI 0.52–1.22 for 31.5+ *vs.* <7 MET-hr/week, trend p = 0.18). Similarly, baseline household activity was marginally associated with lower endometrial cancer risk (RR = 0.79, 95% CI, 0.61–1.03 for >18.5 MET-hr/week *vs.* >0–<5 MET-hr/week; trend p = 0.07); further adjustment for BMI only slightly attenuated this association (Table II). Finally, adjustment for BMI greatly influenced the relationship between endometrial cancer and sedentary behavior at baseline (6+ *vs.* <3 hr/day sitting RR = 1.40, 95% CI 1.03–1.89 without adjustment for BMI *versus* RR = 1.18, 95% CI 0.87–1.59 with adjustment for BMI).

With regard to past measures of physical activity, prospectively reported exercise in 1982 showed a similar reduction in risk of endometrial cancer as baseline recreational physical activity, before adjusting for BMI (RR = 0.67, 95% CI 0.42–1.07 heavy *vs.* none/slight). Recreational physical activity at age 40 (as recalled in 1992) was not associated with endometrial cancer risk (Table II). There were no appreciable changes in any risk estimates when simultaneously adjusting for recreational physical activity, nonrecreational activity or sedentary behavior in multivariate models (data not shown). Consistently high levels of physical activity over the 10-years prior to baseline (1982 and 1992) were associated with lower risk of endometrial cancer even after adjustment for BMI (RR = 0.75, 95% CI, 0.56–0.99 for consistently high *vs.* consistently low activity levels) (Table II).

When we tested for potential effect modification by other endometrial cancer risk factors, we found evidence of effect modification by BMI (heterogeneity of trends p = 0.01). In normal weight women (BMI < 25.0), we observed no association between rec-

TABLE II – HAZARD RATE RATIOS (RR) AND 95% CONFIDENCE INTERVALS (CI) FOR MEASURES OF PHYSICAL ACTIVITY AT VARIOUS POINTS IN TIME AND ENDOMETRIAL CANCER, CPS-II NUTRITION COHORT, 1992–2001

	Cases	*p*-years	RR[1] (95% CI)	RR[2] (95% CI)	RR[3] (95% CI)
Baseline recreational activity MET-hr/week					
None	43	34,622	0.92 (0.66–1.28)	0.93 (0.67–1.30)	0.84 (0.60–1.17)
0<–<7	170	124,302	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
7–<17.5	157	133,553	0.86 (0.69–1.07)	0.86 (0.70–1.07)	0.92 (0.74–1.14)
17.5–<31.5	72	75,456	0.70 (0.53–0.92)	0.70 (0.53–0.93)	0.80 (0.60–1.05)
31.5+	24	27,264	0.65 (0.42–1.00)	0.67 (0.44–1.03)	0.79 (0.52–1.22)
				p-trend = 0.007	*p*-trend = 0.18
Baseline nonrecreational activity MET-hr/week[4]					
None	11	5,473	1.45 (0.78–2.69)	1.44 (0.78–2.66)	1.31 (0.71–2.44)
>0–5.0	132	96,620	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
>5.0–<10.0	110	93,290	0.87 (0.67–1.11)	0.87 (0.67–1.12)	0.91 (0.70–1.17)
10.0–<18.5	103	96,592	0.77 (0.60–1.00)	0.77 (0.60–1.00)	0.79 (0.61–1.02)
18.5+	106	99,250	0.78 (0.60–1.01)	0.79 (0.61–1.03)	0.83 (0.64–1.07)
				p-trend = 0.07	*p*-trend = 0.13
Baseline sitting[4] (hr/day)					
<3	195	184,173	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
3–5	203	165,561	1.13 (0.93–1.38)	1.13 (0.92–1.38)	1.02 (0.83–1.25)
6+	56	36,584	1.40 (1.04–1.89)	1.40 (1.03–1.89)	1.18 (0.87–1.59)
				p-trend = 0.05	*p*-trend = 0.41
Exercise in 1982[4]					
None/Slight	156	105,260	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Moderate	285	264,391	0.71 (0.58–0.86)	0.74 (0.60–0.90)	0.83 (0.68–1.02)
Heavy	20	20,608	0.64 (0.40–1.02)	0.67 (0.42–1.07)	0.80 (0.50–1.28)
				p-trend = 0.003	*p*-trend = 0.08
Recreational activity MET-hr/week at age 40[4]					
None	64	57,878	0.91 (0.67–1.23)	0.93 (0.68–1.26)	0.92 (0.68–1.25)
0<–<7	119	97,393	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
7–<17.5	146	115,712	1.02 (0.80–1.30)	1.02 (0.80–1.30)	1.03 (0.81–1.32)
17.5–<31.5	78	74,574	0.84 (0.63–1.12)	0.83 (0.63–1.11)	0.81 (0.61–1.08)
31.5–<42	28	20,991	1.09 (0.73–1.65)	1.11 (0.73–1.68)	1.11 (0.73–1.68)
42+	25	22,236	0.92 (0.60–1.42)	0.94 (0.61–1.45)	0.96 (0.63–1.49)
				p-trend = 0.74	*p*-trend = 0.72
Long-term exercise[4,5]					
None/consistently low	142	90,185	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Low 1982, High 1992	14	15,075	0.58 (0.34–1.01)	0.58 (0.34–1.01)	0.65 (0.37–1.13)
High 1982, Low 1992	229	203,277	0.69 (0.56–0.86)	0.72 (0.58–0.89)	0.81 (0.65–1.00)
Consistently high	76	81,722	0.58 (0.44–0.76)	0.61 (0.46–0.80)	0.75 (0.56–0.99)

[1]Age-adjusted Hazard rate ratio and corresponding 95% confidence interval.–[2]Multivariate-adjusted RR and corresponding 95% CI adjusted for age, age at menarche, age at menopause, duration of OC use, parity, smoking, total caloric intake, personal history of diabetes and postmenopausal HT use.–[3]Multivariate-adjusted RR and corresponding 95% CI also adjusted for BMI.–[4]Numbers may not equal total due to missing information.–[5]Combination of exercise prospectively collected in 1982 and recreational physical activity at baseline 1992.

reational physical activity and endometrial cancer risk (RR = 1.01, 95% CI, 0.69–1.48 for >17.5 MET-hr/week *vs.* <7 MET-hr/week; trend $p = 0.51$), whereas risk of endometrial cancer was significantly lower in active women who were overweight or obese (BMI $\geq$ 25.0) than in inactive women (RR = 0.59, 95% CI, 0.42–0.83; trend $p = 0.003$) (Table III). We examined the associations while adjusting more finely for BMI and did not observe any appreciable differences in results (data not shown). Thus, in an effort to provide the most stable risk estimates, without compromising quality, we collapsed BMI categories. Results for overweight and obese women also did not differ appreciably and were therefore combined to provide more stable risk estimates. We also examined effect modification by BMI with both nonrecreational activity and sedentary behavior; however, did not observe any statistically significant interactions (data not shown). This was likely due to our limited power to examine associations in the highest levels of these exposures when stratifying by BMI. We found no suggestion of interactions between measures of physical activity or sedentary behavior and any of the other potential risk factors included in this analysis (data not shown).

Discussion

Results from this prospective study provide further support for a role of recent light and moderate physical activity (recreational and household) in lowering risk of endometrial cancer. Previous studies have reported a decrease in risk among the most physically active study subjects ranging from 20 to 90%, with a recent meta-analysis showing a pooled average of approximately 25% reduction in risk.[8] Our results are consistent with this pooled estimate for recreational physical activity. Additionally, our results agree with 4 of 5 previous studies that have shown associations between endometrial cancer and nonrecreational (daily life, household) activity[9,11,17,18] as well as sedentary behavior.[11,19]

There is strong biologic rationale to support the role of physical activity in lowering endometrial cancer risk. Exposure to unopposed estrogen is the major determinant of endometrial carcinogenesis,[2,31] and physical activity has been shown to decrease postmenopausal estrogen levels directly or indirectly through reducing peripheral fat stores, the major source of postmenopausal estrogen synthesis.[32–35] Hyperinsulinemia has also been implicated in endometrial carcinogenesis through several proposed mechanisms (reviewed in Ref. 2). Higher levels of insulin are associated with decreased levels of SHBG, resulting in increased levels of free estradiol.[36] Insulin may also act directly on endometrial tissue as a mitogenic growth factor, and may downregulate IGFBP-1 leading to a greater bioavailability of free IGF-1.[2] Independent of its effects on body mass, physical activity increases insulin sensitivity and decreases plasma insulin levels in postmenopausal women who engage in low to moderate levels of activity.[37]

Excess weight is a strong risk factor for endometrial cancer and is also associated with sedentary behavior. Therefore, we assessed whether the relationship between physical activity and endometrial cancer was confounded or modified by BMI. Adjustment for

TABLE III – HAZARD RATE RATIOS (RR) AND 95% CONFIDENCE INTERVALS (CI) FOR BASELINE RECREATIONAL PHYSICAL ACTIVITY AMONG NORMAL AND OVERWEIGHT/OBESE WOMEN IN RELATION TO ENDOMETRIAL CANCER, CPS-II NUTRITION COHORT, 1992–2001

	Baseline recreational activity MET-hr/week			
	None	>0–<7	7–<17.5	17.5+
BMI < 25.0				
Cases	6	52	58	53
Person-years	14,958	62,636	74,888	64,369
RR[1] (95% CI)	0.52 (0.22–1.21)	1.00 (ref.)	0.94 (0.64–1.36)	1.01 (0.69–1.48)
		trend $p = 0.51$		
BMI 25+				
Cases	37	118	99	43
Person-years	19,664	61,666	58,666	38,350
RR[1] (95% CI)	0.99 (0.68–1.43)	1.00 (ref.)	0.88 (0.67–1.15)	0.59 (0.42–0.83)
		trend $p = 0.003$		
		Heterogeneity of trends $p = 0.01$		

[1]Multivariate-adjusted RR and corresponding 95% CI adjusted for: age, age at menarche, age at menopause, duration of OC use, parity, smoking, total caloric intake, personal history of diabetes and postmenopausal HT use.

BMI in the multivariate analyses greatly attenuated the association between physical activity and endometrial cancer risk. However, a modest inverse association between physical activity and endometrial cancer remained even after adjustment for BMI. This suggests that physical activity has an effect on endometrial cancer that is not entirely mediated by BMI.

Furthermore, physical activity was strongly associated with lower risk of endometrial cancer only among overweight and obese women in our study. Our findings are consistent with 3[17,18,21] of 11 previous studies[9,11,12,15,17–23] that reported a greater risk reduction with regular physical activity among overweight or obese women compared to normal weight women. It is unclear whether the other studies observed interactions on less than a multiplicative scale, *i.e.* an additive scale, or were not adequately powered to detect an interaction based on data provided. Since physical activity, even in the absence of weight loss, significantly improves insulin sensitivity and has direct effects on bioavailable estrogen,[37] it is biologically plausible that overweight or obese women engaging in regular physical activity may experience a greater risk reduction compared to active, normal weight women.

Our study has several limitations. We have no information on the intensity with which individuals engage in each behavior thus increasing the likelihood of misclassifying true energy expenditure. While the physical activity questions we used have not been validated and are subject to misreporting, they are very similar to those used and validated in another prospective study.[38] Wolf *et al.* found strong correlations between activity reported on past-week activity recalls and 7-day diaries and that reported on the questionnaire (0.79 and 0.62, respectively).[38] Despite the limitations in our physical activity measures, these measures have also been associated with lower risk of breast and colon cancer in this cohort.[39,40] We had limited statistical power to examine higher intensity activities since most highly active women engaged in walking with the addition of modest amounts of the other 6 reportable activities.

Strengths of our study include the prospective design which eliminated the possibility of recall bias and our ability to control for potential confounding by known endometrial cancer risk factors. The relatively homogenous characteristics of women in our study reduced the likelihood of residual confounding by unknown factors even though it also reduced the range of the physical activity exposure variables.

In summary, our results add to the growing body of evidence that light and moderate levels of physical activity, including daily life activities like household chores, may reduce the risk of endometrial cancer, especially among overweight and obese women. Our study also suggests that in addition to its effects mediated through BMI, physical activity may have an independent effect on lowering risk of endometrial cancer possibly through directly suppressing estrogen or increasing insulin sensitivity. Future studies should further examine the association between light-intensity activities and endometrial cancer risk to strengthen public health recommendations in this regard.

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