year in which information concerning sedentary activity level was collected.

Because our interest was in the activity–overweight relationship in healthy men, approximately 19% of the cohort with diseases that could alter activity level and/or weight were excluded from the analyses. These diseases included heart disease, stroke, arterial diseases of the leg, renal disease, cancer, and "other major illnesses" reported. Approximately 17% of the men who did not provide information concerning physical activity, height, weight, age, or smoking status were also excluded from the analyses, as were approximately 2% of the men for whom a reporting error was suspected. These were men who reported a nonsedentary activity level representing an energy expenditure exceeding 1000 calories per day, which is equivalent to running 11 miles, jogging 13 miles, or walking 14 miles *daily*. Men with a calculated body mass index below 19.4, the 5th percentile of body mass index for the reference population in NHANES II, were also excluded[25]; these were men who might have misreported their height or weight or who might have been underweight owing to chronic illnesses. The cohort for cross-sectional analyses thus included 22 076 healthy men who provided complete responses to follow-up questionnaires in 1988 and 1990. Men with a body mass index of at least 27.8 in 1988 (n = 4281) were considered already overweight and so were excluded from prospective analyses that focused on evaluating risk for becoming overweight by 1990.

Variables of Interest

Self-reported body weight (in pounds) and height (in inches) were converted to kilograms and meters and used to calculate body mass index (weight/height^2) for each survey year. The 85th percentile from the NHANES II survey[25] was used to classify as overweight cohort members with a body mass index of 27.8 kg/m^2 or greater.

Nonsedentary activity level was assessed using a question derived from the Harvard Alumni Survey.[26] Respondents indicated the average amount of time they spent per week over the past year engaged in nine activities (walking or hiking, jogging, running, bicycling, lap swimming, playing tennis, playing squash or racquetball, performing calisthenics or rowing, and doing heavy outdoor work). The number of flights of stairs they climbed each week was also included in the determination of their nonsedentary activity level. Time spent in each of the activities was multiplied by the average metabolic equivalent (MET) specific to each activity. Metabolic equivalents represent the ratio of energy expended during each specific activity relative to resting metabolic rate and are independent of body weight.[27–29] The more vigorous the activity, the more METs are attributed to it. Total weekly MET hours, a measure reflecting both the relative intensity and the time spent in all nonsedentary activities, were determined for each individual by summing all reported activities. The range of MET hours represented in the entire cohort was then divided into quintiles. For simplicity, MET hours are referred to as METS in the remainder of this paper.

Self-reported hours of TV/videocassette recorder (VCR) viewing each week was the indicator of sedentary activity level. Six time categories (0 to 1 hour; 2 to 5 hours, 6 to 10 hours, 11 to 20 hours, 21 to 40 hours, and 41 or more hours) were used.

Statistical Analyses

Multiple logistic regression models with indicator variables for each quintile of METS and for time spent watching TV/VCR were used to estimate odds ratios (ORs), which were interpreted as relative risks (RRs) when cumulative incidence rates were less than 10%. Cross-sectional analyses examined the relationships between those two variables and the prevalence and odds of being overweight in 1988. Prospective analyses evaluated the relationships between those two variables in 1988, and the cumulative incidence and relative risk of new onset of overweight between 1988 and 1990 among the 17 795 men who were not overweight in 1988. Odds ratios and relative risks were estimated using the lowest quintile of METS or time category of TV viewing as the reference category.[30] Significant monotonic trends were tested for by assigning each participant the median METS value of each quintile. Testing for an interactive effect between nonsedentary and sedentary activity level was evaluated with a log-likelihood ratio chi-square test.[31,32] To examine further the relationship between activity level and body mass index, change in METS expended in nonsedentary activity per week and change in weekly TV/VCR viewing hours between 1988 and 1990 were considered as continuous variables and entered as separate terms into linear regression models, with change in body mass index between survey years used as the dependent variable. All analyses were adjusted for age and smoking status (nonsmoker or current smoker since less than 15% of the cohort were current smokers).

Results

The mean age of the cohort in 1988 was 54.1 ± 9.3 years, with a range of 41 to 78 years. Eighty-six percent of the cohort were nonsmokers. The age-adjusted mean body mass index in 1988 (25.6 ± 3.1) was similar to the mean body mass index in 1990 (25.7 ± 3.2). The prevalence of overweight (body mass index ≥ 27.8) among the cohort was 19.4%, nearly 12% lower than the average national prevalence of overweight among men surveyed in the first phase of NHANES III.[2] The average weekly nonsedentary activity level represented by METS in 1988 was 24.8 ± 21.8, a level of activity equivalent to walking briskly or playing tennis 4 hours per week. However, the large standard deviation in METS indicated that the cohort varied greatly in its nonsedentary activity level. On average, cohort members spent 11.3 ± 8.5 hours per week watching TV/VCR in 1988, with the majority of men watching less than 10 hours per week.

Cross-Sectional Analyses

Age- and smoking-adjusted prevalence rates and odds ratios for overweight decreased as the nonsedentary activity level increased (Table 1). Men in the highest quintile of METS had lower odds of being overweight (OR = 0.50; 95% confidence interval [CI] = 0.45, 0.55) than men in the lowest quintile. Even men in the second and third quintiles with light to moderate levels of nonsedentary activity had reduced odds of being overweight relative to men in the lowest quintile of activity. In contrast, increasing time spent watching TV/VCR was associated with increased prevalence and odds ratios for overweight. Men who watched 41 or more hours of TV per week had higher odds of being overweight (OR = 4.06; 95% CI = 2.67, 6.17) than men watching 1 hour or less per week. Even men watching only 2 to 5 hours per week had increased odds of being overweight (OR = 1.42; 95% CI = 1.14, 1.77) when compared with men watching the least amount.

To determine if nonsedentary and sedentary activity levels had independent relationships with the prevalence and odds of being overweight, logistic regression models with terms for METS (for nonsedentary activity) *and* time spent

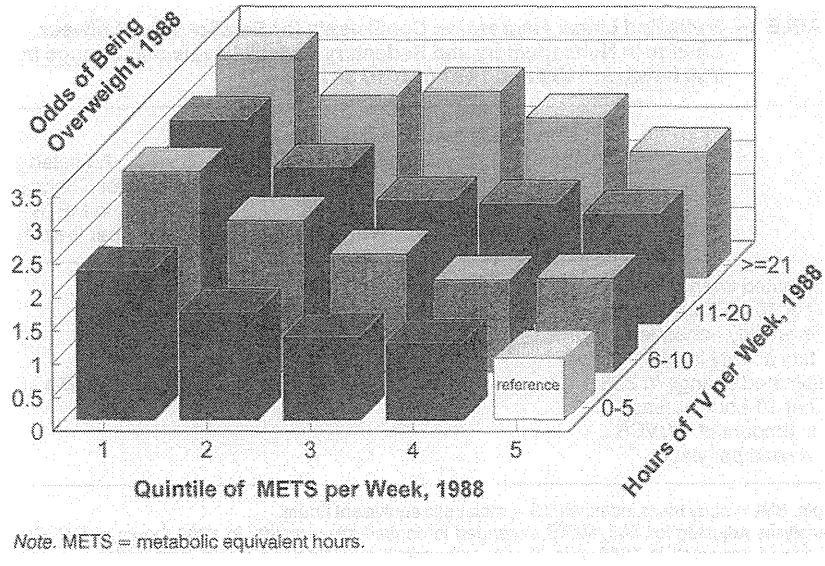
watching TV/VCR were evaluated in age- and smoking-adjusted models. Odds ratios for overweight did not change from the age- and smoking-adjusted models when the nonsedentary activity level was adjusted for time spent watching TV/VCR. Similarly, adjustment for the nonsedentary activity had little impact on the odds ratios for overweight associated with increasing time spent watching TV/VCR.

To evaluate the association between the joint classification of nonsedentary and sedentary activity levels and the odds of being overweight, quintiles of METS were retained but the TV/VCR viewing time categories were collapsed from 6 to 4 to give stability to the categories. The time categories now represented watching TV/VCR for zero to 5 hours per week, 6 to 10 hours per week, 11 to 20 hours per week, and 21 or more hours per week. Men in the highest quintile of METS and lowest time category of TV/VCR viewing were considered the most active men and served as the reference group. In comparing men in the most extreme categories of combined activity level, men with the lowest nonsedentary activity level and highest TV/VCR viewing (considered the most sedentary men) had odds of being overweight that were more than three times the odds for the most active men (Figure 1). Overall, within each quintile of METS, greater amounts of TV/VCR watching were associated with higher odds of being overweight, and at each level of TV/VCR viewing, the increasing nonsedentary activity level was generally associated with lower odds of being overweight. These trends suggest that no interaction was occurring between the nonsedentary and sedentary activity levels. A formal test for interaction was not statistically significant (χ^2 with 1 df = 3.0; $P > .05$).

TABLE 1—Prevalence Rates and Odds Ratios for Overweight (BMI ≥ 27.8) among Male Health Professionals, by Quintile of Nonsedentary Activity Level (METS) and Average Weekly Time Spent Watching TV/VCR

	No. Men (n = 22 076)	Prevalence of Overweight, %	OR[a] (95% CI)	OR[b] (95% CI)
1988 METS/wk				
≤6.3	4370	26.5	1.00	1.00
>6.3 and ≤13.6	4460	21.4	0.76 (0.69, 0.84)	0.76 (0.69, 0.84)
>13.6 and ≤23.9	4416	17.9	0.61 (0.55, 0.67)	0.61 (0.55, 0.68)
>23.9 and ≤41.1	4419	16.2	0.54 (0.49, 0.60)	0.54 (0.49, 0.61)
>41.1	4411	15.1	0.50 (0.45, 0.55)	0.50 (0.45, 0.56)
Test for trend in ORs			P = .001	P = .001
1988 TV/VCR hrs/wk				
0–1	871	11.7	1.00	1.00
2–5	5672	15.8	1.42 (1.14, 1.77)	1.43 (1.15, 1.78)
6–10	6541	19.5	1.83 (1.48, 2.27)	1.87 (1.51, 2.32)
11–20	6591	21.3	2.04 (1.65, 2.53)	2.05 (1.66, 2.55)
21–40	2272	24.5	2.47 (1.97, 3.11)	2.40 (1.91, 3.02)
41 or more	129	34.9	4.06 (2.67, 6.17)	3.88 (2.55, 5.92)
Test for trend in ORs			P = .002	P = .002

Note. BMI = body mass index; METS = metabolic equivalent hours; OR = odds ratio; CI = confidence interval. Reference categories for estimating odds ratios are overweight at the lowest level of METS and lowest level of TV/VCR viewing.
[a]Analyses adjustd for age (5-year categories) and smoking status (nonsmoker, current smoker).
[b]Analyses for 1988 METS per week adjusted for age, smoking status, and level of TV/VCR viewing; analyses for 1988 TV/VCR hours per week adjusted for age, smoking status, and quintile of nonsedentary activity level.



Note. METS = metabolic equivalent hours.

FIGURE 1—Joint classification of quintile of METS, hours of TV/VCR viewed, and odds of being overweight among male health professionals, 1988.

Prospective Analyses

Among the 17 795 cohort members who were not overweight at the start of follow-up, the cumulative incidence of overweight between 1988 and 1990 was 4.6%. We found an inverse association (P for trend ≤ .01) between METS expended in nonsedentary activity and risk of becoming overweight by 1990 (Table 2). Compared with men in the lowest quintile of METS, men in the highest quintile had an age- and smoking-adjusted relative risk of 0.79 (95% CI = 0.64, 0.99; P for trend = .01) for becoming overweight by 1990. Men in the third and fourth quintiles of nonsedentary activity level had similar relative risks for becoming overweight, indicating that even moderate activity was associated with reduced risk. Estimated relative risks did not change appreciably when analyses were adjusted for level of TV/VCR viewing in 1988.

The cumulative incidence of overweight generally increased with increasing time spent watching TV/VCR in 1988. Although none of the estimated individual relative risks reached statistical significance, the test for trend across

TABLE 2—Cumulative Incidence Rates and Relative Risks for Becoming Overweight between 1988 and 1990, by Quintile of Nonsedentary Activity Level (METS) and Average Weekly Time Spent Watching TV/VCR

	No. Men (n = 17 795)	Cumulative Incidence of Overweight, %	Relative Risks[a] (95% CI)	Relative Risks[b] (95% CI)
1988 METS/wk				
≤6.9	3555	5.3	1.00	1.00
>6.9 and ≤14.5	3575	5.3	1.00 (0.81, 1.23)	1.01 (0.82, 1.24)
>14.5 and ≤25.3	3571	4.3	0.79 (0.63, 0.98)	0.80 (0.64, 1.00)
>25.3 and ≤42.3	3534	3.8	0.72 (0.57, 0.90)	0.73 (0.58, 0.92)
>42.3	3460	4.2	0.79 (0.64, 0.99)	0.81 (0.65, 1.01)
Test for trend in relative risks			*P* = .01	*P* = .01
1988 TV/VCR hrs/wk				
0–1	769	4.4	1.00	1.00
2–5	4773	4.5	1.04 (0.72, 1.51)	1.04 (0.72, 1.51)
6–10	5264	4.0	0.95 (0.65, 1.38)	0.95 (0.66, 1.38)
11–20	5190	4.9	1.19 (0.83, 1.72)	1.19 (0.82, 1.72)
21–40	1715	5.5	1.44 (1.04, 2.16)	1.41 (0.94, 2.12)
41 or more	84	6.0	1.56 (0.59, 4.11)	1.49 (0.57, 3.95)
Test for trend in relative risks			*P* = .001	*P* = .002

Note. METS = metabolic equivalent hours; CI = confidence interval. Reference categories for estimating relative risks are overweight at the lowest level of METS and lowest level of TV/VCR viewing.
[a]Analyses adjusted for age (5-year categories) and smoking status (nonsmoker, current smoker).
[b]Analyses for 1988 METS per week adjusted for age, smoking status, and level of TV/VCR viewing; analyses for 1988 TV/VCR hours per week adjusted for age, smoking status, and quintile of nonsedentary activity level.

TABLE 3—Estimated Linear Regression Coefficients for Relationships between Change in Nonsedentary and Sedentary Activity Levels and Change in BMI between 1988 and 1990 (n = 19 361)

	Unadjusted for Change in Hours of TV/VCR Viewed per Week[a]	Adjusted for Change in Hours of TV/VCR Viewed per Week[a]	Unadjusted for Change in METS per Week[a]	Adjusted for Change in METS per Week[a]
Estimated change in BMI per 10-MET increase in weekly nonsedentary activity level	−0.029	−0.030	...	...
Estimated change in BMI per 10-hour increase in amount of TV/VCR viewed per week	...	...	0.051	0.059

Note. BMI = body mass index; METS = metabolic equivalent hours.
[a]Analyses adjusted for BMI, METS expended in nonsedentary activity in 1988, hours of TV/VCR viewed per week in 1988, age (5-year categories), and smoking status (nonsmoker, current smoker). $P \leq .0001$ for estimated regression coefficients.

relative risks was statistically significant even when adjusted for age, smoking status, and level of nonsedentary activity in 1988. Men watching 21 or more hours of TV/VCR per week in 1988 were over 40% more likely to become overweight by 1990 than were men viewing 1 hour or less per week (RR = 1.44, 95% CI = 1.04, 2.16 for those viewing 21–40 hours; RR = 1.56, 95% CI = 0.59, 4.11 for those viewing 41 or more hours; *P* for trend <.01). Relative risks were not substantially changed after further adjustment for level of nonsedentary activity in 1988.

To explore further the relationship between activity level and body mass index, data from 19 361 cohort members who provided complete information on body mass index, nonsedentary activity level, and level of TV/VCR viewing in 1988 and 1990 were analyzed. Changes in METS and in hours of TV/VCR viewed per week between survey years were entered into linear regression models as continuous variables, and change in body mass index was entered as the dependent variable. All analyses were adjusted for body mass index, METS, hours of TV/VCR viewed, age, and smoking status in 1988. Each 10-MET increase in the nonsedentary activity level (equivalent to running or playing squash an extra hour each week) predicted a 0.03 decrease in body mass index or approximately one fifth of a pound lost in body weight (Table 3). Each 10-hour per week increase in TV/VCR viewed predicted a 0.05 increase in body mass index or approximately one third of a pound gained in body weight between 1988 and 1990. The inclusion of changes in METS and in hours of TV/VCR viewed per week simultaneously in the linear regression model did not change the regression coefficients substantially.

Discussion

The present study revealed associations between nonsedentary activity level and risk of overweight in both cross-sectional and prospective analyses; these associations persisted even when adjusted for age, smoking status, and level of weekly TV/VCR viewing. In addition, time spent watching TV, one measure of sedentary activity level, was related to risk of overweight independent of nonsedentary activity level. These findings suggest that both nonsedentary activity and sedentary activity, specifically TV viewing, may play independent roles in the genesis and persistence of overweight in adult men.

Within the cohort of male health professionals studied, prospective analyses indicate that expending an average of more than 14.5 METS per week in physical activity in 1988 was sufficient to achieve a lowered risk for development of overweight by 1990. This level of activity represents engaging in light to moderate activities such as brisk walking, jogging, and/or swimming for at least 30 minutes daily and is consistent with levels of activity recommended for the nation in *Healthy People 2000*.[33] Results from linear regression analyses suggest that each

additional hour of nonsedentary activity (assuming an expenditure of 5 METS during that hour) predicted a 0.015 decrease in body mass index, more than three times that predicted for a 1-hour reduction in time spent watching TV/VCR (0.005). These analyses indicate that change in nonsedentary activity level had an independent and greater effect on change in body mass index than change in time spent watching TV/VCR. These findings are consistent with those found cross-sectionally and prospectively by others. In the Centers for Disease Control and Prevention's Behavioral Risk Factor Surveillance System, prevalence of overweight was inversely related to physical activity level.[34] In the NHANES I Epidemiologic Follow-Up Study, recreational physical activity was inversely associated with body mass index, average 10-year weight change, and risk of developing clinical overweight; prospectively, change in activity level was inversely related to change in weight. These findings suggest that low physical activity is both a cause and a consequence of weight gain.[35]

Within the Health Professionals Follow-Up Study, time spent watching TV/VCR, as a measure of sedentary activity, was positively associated with overweight cross-sectionally and prospectively, even when analyses were adjusted for level of nonsedentary activity. The cohort of men surveyed watched, on average, only a quarter to a third the amount of TV in 1988 as men aged 35 years and older who were included in the Nielsen rating estimates for 1989.[17] Nonetheless, odds ratios for overweight were slightly higher than those found by Tucker and Friedman in their cross-sectional study of obesity in adult males.[18]

The relationship between TV/VCR viewing and risk of overweight may have been observed for several reasons. TV/VCR viewing may be associated with caloric intake; that is, time spent watching TV/VCR may be a measure of both inactivity and caloric intake. Numerous food cues appear in prime time programming and commercial advertisements.[36,37] Such cues have been correlated with eating patterns in children and may exert a greater influence in the obese.[38–40] In addition, individuals often eat while watching TV but may be less inclined to eat while involved in other types of sedentary activity. Thus, TV viewing may result not only in inactivity but also in increased food intake. Future investigations should examine the role that eating behaviors may play in influencing the TV–overweight relationship.

Television viewing may also be associated with overweight because it results in lower energy expenditure, particularly when compared with other types of sedentary activity. Ainsworth et al. indicate that the energy cost of sitting and watching TV is nearly comparable to that of activities done while reclining and is lower than that for other sedentary activities such as sewing, playing board games, reading, writing, and driving a car.[41] This may be partly owing to the "fidgeting" or other spontaneous physical activity that is more likely to occur with some sedentary activities but not with TV viewing.[42] Metabolic rate and observed movements in children have been found to be lower while watching TV than when at rest.[43,44]

Within the current study, the magnitude of associations between activity level and overweight in cross-sectional analyses was greater than that observed in prospective analyses. This might have been because the prevalence of overweight in the cohort (19%) was greater than the cumulative incidence of overweight (approximately 5%) in the 2-year interval. The prevalent cases of overweight accumulated excess weight over decades. Thus, men with prevalent overweight were heavier than men who became overweight only during the 2 years of follow-up. Mean body mass index among prevalent cases of overweight in 1988 was 30.4 while mean body mass index among incident cases of overweight in 1990 was 28.7. Also, in the cross-sectional analyses, there may have been a coincident measure of cause and effect. That is, the effect of overweight on activity level was simultaneously measured with the effect of activity level on overweight, a problem not encountered in the prospective analyses.

The average level of nonsedentary activity in the cohort was high, possibly because the cohort members were all health professionals and self-selected into the study. Their education, income, and occupation likely led them to engage in healthier behaviors (e.g., higher levels of nonsedentary activity and lower levels of sedentary activity) than would be expected in the general American male population. In addition, because information concerning intensity at which nonsedentary activities were performed was not collected from respondents, METS assigned to activities may have overestimated the intensity level at which each activity was actually performed and subsequently led to an overestimate of the total nonsedentary activity level. These sources of bias may limit the generalizability of prevalence rates of activity and overweight but not the validity of the relationship between activity and overweight.

The major strengths of the current study are its prospective design and its use of a quantitative measure of nonsedentary activity that accounted for the type and duration of different nonsedentary activities, as well as its assessment of a sedentary activity level.

The process of weight maintenance involves balancing energy intake with energy expenditure. Support of this physiological process comes from engaging in certain eating and activity behaviors—that is, patterns of dietary intake and composition as well as physical activity. When the energy balance is disturbed, it is assumed that these volitional behaviors can be modified to prevent or reverse weight gain. Effective treatment of weight gain occurs primarily by limiting dietary energy intake to impose the requisite caloric deficit necessary to achieve weight loss. Increases in physical activity alone are usually not sufficient to promote weight loss because exercise cannot be sustained at a high enough intensity for a long enough duration of time to achieve the necessary caloric deficit. Consistent with other studies, the current study suggests that physical activity plays a role in preventing weight gain rather than in promoting weight loss. More importantly, it suggests that attention should be focused on the role physical activity can play in preventing small insidious increases in body weight from occurring. While such increases in body weight from one year to the next may appear insignificant, when accumulated over decades they present a serious health risk for many other chronic diseases.

Given the findings in the current study, members of the general public should be encouraged to increase their activity level and decrease their time spent being sedentary. Alone or in combination, these two behavioral changes are important for effective weight control. Health benefits can be gained not only from engaging in vigorous activities such as running or jogging, but also from pursuing less strenuous activities such as walking and stair climbing.[45] The most inactive individuals should be encouraged to engage in activities such as walking, which is simple and convenient, carries low risk for injury, and promotes caloric expenditure important for weight loss and

maintenance. This may provide one of the most efficacious exercise strategies for weight control, especially when combined with a reduction in television viewing time. □

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論文名	Activity level and risk of overweight in male health professionals.						
著 者	Ching PL, Willett WC, Rimm EB, Colditz GA, Gortmaker SL, Stampfer MJ.						
雑誌名	Am J Public Health						
巻・号・頁	86(1) 25-30						
発行年	1996						
PubMedリンク	http://www.ncbi.nlm.nih.gov/entrez/8561237						
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	41－78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	肥満予防	な し	な し	( )	( )
	維持・改善	な し	な し	な し	な し	( )	( )
図 表							
図表掲載箇所							
概 要 (800字まで)	目的：男性における座位中心の活動(テレビ(TV)/ビデオ(VCR)を見る時間)と肥満のリスクとの関連を調べることを目的とした. 方法.Health Professionals Follow-up Studyに参加した者。1988年に41-78歳。ガンや冠動脈疾患、心筋梗塞、糖尿病にならなかった者、およびBMI標準値の5%ile(19.4)以上かつ27.8未満の者。横断的分析で過体重になる割合とオッズ比を、前方視的研究で、2年後の過体重になる相対危険度と累積発生率を検討した。 結果.METs・時/週が14.5以上の群でP=0.05前後。TV/VCR・時/週については、全体では有意な傾向がみられたものの、第1五分位と有意な差がある群はなし。横断的分析で過体重になる可能性は50%(95% CI＝45%、55%)である。1週間あたり41時間以上テレビ/VCRを見ている男性では、過体重の可能性は1週間あたり1時間未満見ている男性より4.06(95% CI＝2.67, 6.17)倍大きかった。座位以外の活動が多いか、テレビ/VCR視聴がより少ないと、調査期間で過体重になる相対危険度がより低い、という独立な関連があった。						
結 論 (200字まで)	身体活動の不足とテレビ/VCRの視聴時間の両方は、男性で過体重の増加に寄与する。座位中心でない活動と座位中心の活動は、過体重のリスクと独立に関与している。						
エキスパートによるコメント (200字まで)	METs・時/週で約14.5以上が必要であることが示唆され、興味深い。						

担当者 呉泰雄, 田中茂穂

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Physical activity and risk of endometrial cancer in a prospective cohort study (United States)

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Key words: activity, cohort studies, endometrial cancer, exercise, physical fitness.

Abstract

Objective: To examine the physical activity and endometrial cancer relationship in a prospective study of US women enrolled in the Breast Cancer Detection Demonstration Project (BCDDP) Follow-up Study.
Methods: We assessed past-year physical activity of all types in 23,369 women who returned the baseline questionnaire (1987–1989) and had no prior hysterectomy and/or endometrial cancer. Cox proportional hazards models were used to estimate age, education, and parity-adjusted rate ratios (RR) and 95% confidence intervals (CI) for the 253 confirmed endometrial cancer cases identified during an average 8.2 years of follow-up (ending 1995–1998).
Results: There were no dose–response relationships with either total or vigorous physical activity; however, compared to the lowest total activity quartile, the higher four quartiles had a non-significantly lower risk (RR = 0.8, CI = 0.6–1.0). The association with moderate activity varied with follow-up time: RRs (CI) for a 1 h increase in daily moderate activity within 2-year intervals of follow-up (≤2, 2.1–4.9, 5.0–8.0, > 8 years) were 1.1 (1.0, 1.2), 1.0 (0.9, 1.1), 1.0 (0.9, 1.1), 1.0 (0.9, 1.1), and 0.8 (0.7, 1.0), respectively.
Conclusion: These data suggest that recent physical activity is not strongly related to the risk of endometrial cancer, and that prolonged exposure and longer follow-up may be necessary.

Introduction

Evidence for an association between physical activity and endometrial cancer has been rather sparse and inconsistent. Of the 10 case–control and linkage studies that have examined the relationship, many showed lower risk among more active women, although the results were frequently neither statistically significant nor was there evidence of dose–response [1–10]. Two cohort investigations also provided data, one having assessed occupational activity [11], and the other recreational activity [12], and both observed a reduced risk of endometrial cancer at increased activity levels during approximately 19–20 years of follow-up. A recent review noted that although the results to date point to a 'probable' association between physical activity and endometrial cancer, the number of studies evaluating this association are insufficient to draw definitive conclusions [13]. Mechanisms that have been hypothesized to mediate such an association include changes in obesity and/or fat mass as well as a reduced exposure to endogenous estrogen [14].

Methodological issues relevant to testing this hypothesis include the need to assess many types of activity, particularly household and leisure activities that may be important contributors among the middle-aged women evaluated in most studies. Some of the previous studies

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have not modeled the association both with and without adjustment for body mass index (BMI) or body weight [2, 8, 9, 12], which may be important if, as has been suggested [13, 14], the activity–endometrial cancer association is mediated through altered body weight and resulting effects on hormonal profiles. Additionally, strong risk factors for endometrial cancer, such as hormone replacement therapy, must be carefully considered as potential confounders in these models [15].

We evaluated the association between physical activity and endometrial cancer in a cohort study of US women originally enrolled in the Breast Cancer Detection Demonstration Project (BCDDP). Activity of all types during the previous year was evaluated, and the analysis carefully considered potential confounding factors and effect modifiers of the association.

Materials and methods

Study design and subjects

The study subjects were participants in the BCDDP, a breast cancer screening program conducted in 27 cities throughout the US between 1973 and 1980. A follow-up study of a selected subset (n = 64,182) of the 283,222 BCDDP participants was initiated by the National Cancer Institute in 1979, and has been previously described [16]. The follow-up study included (1) all screening participants who underwent breast surgery during the screening period, but had no evidence of malignancy (n = 25,114); (2) all subjects who had recommendations by the project for surgical consultation, but did not have either a biopsy or aspiration performed (n = 9628); (3) all subjects diagnosed with breast cancer during the screening program (n = 4275) and (4) a sample of women who had neither surgery nor recommendation for surgical consultation during screening participation (n = 25,165). The follow-up study was approved by the Institutional Review Board at the National Cancer Institute, and informed consent was obtained from all participants.

Annual telephone interviews were conducted between 1979 and 1986, and one mailed questionnaire was self-administered during each of the following time periods: 1987–1989, 1993–1995, and 1995–1998. Pathology reports were sought for all self-reported cancers. In addition the cohort was periodically linked to the National Death Index to ascertain date and cause of death. Approximately 80% of the cohort was also linked to state cancer registries using the state of last known residence at the time of the 1995–1998 questionnaire mailing.

Information on physical activity habits was collected only in the 1987–1989 postal questionnaire, which is therefore used as the baseline for this analysis (from 7 to 16 years after participation in the original BCDDP screening program, and 8–10 years after the start of the follow-up study). This questionnaire also obtained information regarding smoking status, dietary habits, diabetes, and current body weight. Information on menstruation and menopause, including hysterectomy status, and hormone replacement therapy was collected on all questionnaires. Information on oral contraceptive use was obtained during the annual telephone interviews conducted between 1979 and 1986, while information on menarche, parity, and age at first live birth was collected on the baseline follow-up interview in 1979. Information on race, education, and income was collected on entry into the original screening program. For 213 women who did not report their body weight in the 1987–1989 questionnaire, weight measured during the screening program was used (Pearson correlation between reported weight on questionnaire and measured weight during the screening trial for all women was $r = 0.87$).

Physical activity assessment

Participants were asked to estimate how many hours per typical weekday and weekend day in the past year they spent in each of four categories of activity by intensity: sleeping, light, moderate, and vigorous activity, and were instructed that the total for each day should add up to 24 h. Numerous examples of light, moderate, and vigorous activities that included occupational, leisure-time, household, and sports activities were listed on the questionnaire under the appropriate heading (*e.g.*, office work as a light activity, recreational tennis as a moderate activity, running as a vigorous activity). Acceptable ranges for reported hours by category were set at: sleep, 4–14; light, 0–20; moderate, 0–18, vigorous, 0–12; and total hours, 20–28. In order for the data to be considered valid, the sleep and total hours had to be in range, and the light, moderate, and vigorous hours had to be either in range or missing. If missing, a zero value was imputed. Women with invalid data were excluded from the analysis.

For women with valid physical activity data (see 'analytical cohort' below), the hours in each category of activity were then proportionalized to total 24 h/day. Weekly averages were obtained using the following formula: [(weekday h*5) + (weekend h*2)]/7. Substantially more women reported valid weekday data (n = 42,684) than weekend data (n = 39,764). Given the high correlation between the weekday and weekly

averages of activity (Spearman correlations: moderate activity, $r = 0.97$; vigorous activity, $r = 0.97$; total activity, $r = 0.96$; all $p < 0.001$), the weekday data were used for this analysis under the assumption that it adequately represents regular, daily activity.

To examine total time spent in moderate and vigorous activity with consideration for intensity level, a Physical Activity Index (PAI) was created using literature-based relative metabolic equivalent unit (MET) values for moderate and vigorous activities [17]. MET values of four for moderate and seven for vigorous were used to create a weighted score [MET-h/week = (h/week moderate activity × 4.0) + (h/week vigorous activity × 7.0)]. The analysis of the total physical activity and endometrial cancer relationship was also examined using both weekend and weekday data, in those who provided it.

Analytical cohort

Of the original 64,182 women invited into the follow-up study, 51,691 (84%) completed the 1987–1989 postal questionnaire, which contained information on physical activity. The 1987–1989 questionnaire was not completed by participants due to death (n = 4605), refusal to respond (n = 2287), illness (n = 505), or being otherwise unreachable or unavailable (n = 5094). Of the 51,691 who completed a questionnaire, 275 were previously diagnosed with endometrial cancer, and 22,959 had reported a hysterectomy that occurred before the date on which they completed the 1987–1989 questionnaire and were excluded from the analysis. Also excluded were women with unknown menopausal status (n = 285), those who never menstruated (n = 8), women with missing or invalid physical activity information (n = 4599), or those missing information on education, parity, or body weight (n = 191). A total of 23,374 participants were therefore available for this analysis, and they were predominantly white (88%). There were small percentages of black (3%), Hispanic (2%), and Asian American women (5%), along with those of other or unknown race/ethnicity (2%). The participants in the analysis were similar to the 38,054 from the follow-up who were excluded in regards to parity, body weight, and physical activity (for those who reported it). The excluded women were less likely to have used oral contraceptives (26 *versus* 32%) or have obtained at least some college education (41 *versus* 50%) while many more had used estrogen-only hormone replacement therapy (62 *versus* 38%). Additionally, they were more likely to have been diagnosed with breast cancer (7 *versus* 5%) or have had breast surgery with no malignant disease (41 *versus* 38%) and less likely to have been in the group not recommended for any surgical procedure (38 *versus* 41%) in the original BCDDP study.

Case identification

Endometrial cancer cases were initially identified through self-reports, death certificates, or from searches in state cancer registries. Pathology reports were sought for all self-reported cases. Because the accuracy of self-reported diagnoses among those with pathology reports was not high (79%), cases supported only by self-reports were not considered cases in the main analyses. A total of 258 confirmed endometrial cancer cases were identified, of which five were determined to be of non-epithelial origin and excluded. Thus, 253 epithelial endometrial cancers were included in the final analysis; 182 (72%) based on pathology reports, 66 (26%) from state registries, and 5 (2%) from death certificates. Of the 253 cases, 94% were adenocarcinomas. Analyses were repeated including the 24 women who self-reported endometrial cancer, but for whom no confirmation was available.

Statistical analysis

Follow-up time began at the date of the 1987–1989 questionnaire that included physical activity, and ended at the earliest of the following dates: self-reported hysterectomy (5.6%), diagnosis of endometrial cancer (1.1%), death (7.9%), the date of completion of the last questionnaire, 1995–1998 (76.5%), date of last contact during 1995–1998 (2.5%), or, if status was otherwise unknown, the date at which the last questionnaire should have been completed (6.5%). Incident endometrial cancers were considered events, while individuals were censored for all other events noted.

Quintiles of total activity PAI were created based on the whole cohort. For daily hours spent in moderate and vigorous activities, categories of ≤2, 2.1–4.9, 5.0–8.0, and >8.0; and 0, 0–1, 1.1–2, and >2 h; respectively, were created. The categories of moderate activity were approximate quartiles, while the vigorous activity categorization was chosen to allow comparison of smaller increments to no participation in vigorous activity. In our examination of moderate activity, women who reported any vigorous activity were excluded from the analysis in order to prevent potential confounding by vigorous activity.

Statistical analyses were performed using Statistical Analysis Systems (SAS) software (SAS Institute, Cary, NC). Cox proportional hazards models were used to estimate the rate ratios (RR) and 95% confidence

intervals (CI) of endometrial cancer associated with level of physical activity, with person-years of follow-up time as the underlying time metric. Likelihood ratio tests were used to test for overall effects, effect modification, and deviations from the proportional hazards assumption. All tests were two-sided and $p < 0.05$ was used as the cut-off for statistical significance.

Covariate information was obtained from interviews up to and including the 1987–89 questionnaire on which physical activity was reported. All covariates shown in Table 2 were evaluated as confounders of the associations in addition to age at first live birth, race, a history of other cancers, duration of estrogen use, and menopausal status. Women were considered menopausal if they had not menstruated for at least three months prior to their baseline interview because of natural menopause or bilateral oophorectomy. Final models included age and variables (*i.e.*, parity and education) that produced a greater than 10% change in any of the β-coefficients for the physical activity variables.

As body weight may lie in the causal pathway of the physical activity–endometrial cancer association, separate models were also run with adjustment for weight. Effect modification of the association between endometrial cancer and total activity was assessed by including variables and their cross-product terms in the models. Proportional hazards assumptions were assessed by including cross-product terms for physical activity and total follow-up time (person-years) in the models. There were no departures from the hazard assumptions for total PAI or vigorous activity, but the cross-product term was significant for follow-up time and moderate activity ($p = 0.002$). Consequently, the association with moderate activity was assessed by estimating the RR for two-year intervals of follow-up time, and by looking at the risk estimates for quartiles of moderate activity in those with > 6 years of follow-up.

Results

The average follow-up time for the 23,369 study subjects was 8.2 years, with a maximum of 10.9 years and a minimum of less than a year. The women reported an

Table 1. Baseline characteristics of BCDDP participants by quintile of PAI, 1987–1998, US[a,b]

	PAI quintile (median MET-h/day[b])				
	Q1 (8.0)	Q2 (20.0)	Q3 (32.0)	Q4 (40.5)	Q5 (56.0)
Characteristic[c]	n = 4617	n = 4693	n = 4560	n = 4607	n = 4892
Physical activity (h/day)					
Sleep	7.5 ± 1.2	7.6 ± 1.1	7.6 ± 1.0	7.5 ± 1.0	7.2 ± 1.0
Light	14.9 ± 1.7	11.7 ± 1.5	9.1 ± 1.4	7.3 ± 1.5	4.3 ± 1.9
Moderate	1.5 ± 1.1	4.2 ± 1.3	6.5 ± 1.6	7.7 ± 2.1	9.3 ± 3.3
Vigorous	0.1 ± 0.3	0.4 ± 0.6	0.7 ± 0.8	1.5 ± 1.2	3.0 ± 2.4
Age (years)	60.7 ± 8.6	61.6 ± 8.2	61.8 ± 7.8	61.8 ± 7.5	61.9 ± 7.6
Height (cm)	162.7 ± 6.9	162.5 ± 6.6	162.7 ± 6.5	162.4 ± 6.5	162.3 ± 6.4
Weight (kg)	66.7 ± 14.0	66.3 ± 13.0	65.9 ± 12.4	65.2 ± 11.9	64.6 ± 11.4
BMI (kg/m^2)	25.2 ± 5.1	25.1 ± 4.7	24.9 ± 4.4	24.7 ± 4.3	24.5 ± 4.1
Education $\geqslant$ college (%)	58.5	52.9	49.8	48.7	42.7
Current smoker (%)	14.3	12.3	12.6	11.9	13.5
Age at menarche (years)	12.7 ± 1.4	12.8 ± 1.4	12.8 ± 1.4	12.8 ± 1.4	12.9 ± 1.5
Age at menopause (years)	49.9 ± 4.1	49.9 ± 4.2	49.9 ± 4.2	50.0 ± 4.0	49.8 ± 4.2
Parous (%)	81.8	83.8	86.7	86.3	87.6
OC use[d] (%)	36.1	32.4	31.5	30.5	28.6
Estrogen HRT use[d] (%)	35.7	38.2	37.7	39.2	36.7
Hypertension[e] (%)	2.9	2.9	3.0	3.0	2.5
Diabetes[e] (%)	5.8	4.9	4.1	4.0	4.0
Energy intake (kcal/day)	1275 ± 524	1280 ± 512	1292 ± 508	1295 ± 513	1296 ± 534
Fat intake (g/day)	51.1 ± 26.7	51.0 ± 26.7	50.8 ± 26.3	51.0 ± 26.5	50.8 ± 27.2
Alcohol intake (g/day)	0.43	0.24	0.22	0.22	0.04

[a] Values presented as mean ± standard deviation (SD) or % of group, with the exception of alcohol (median).

[b] The PAI was created using reported hours of moderate and vigorous activity/day and the approximate MET level for the type of activity reported: (moderate h × 4) + (vigorous h × 7).

[c] Abbreviations used: BMI – body mass index; OC – oral contraceptives; HRT – hormone replacement therapy.

[d] Reported ever using OC or estrogen-only HRT.

[e] Self-reported.

average of 9.5, 5.9, and 1.2 h/day of light, moderate, and vigorous activity, respectively. Baseline participant characteristics according to PAI quintile are shown in Table 1. Age, height, age at menarche, or age at menopause did not materially differ by level of total physical activity, while body weight and BMI decreased slightly with increasing level of activity. Women who reported more hours of moderate and vigorous physical activity were less likely to have attained higher levels of education, and slightly more likely to have borne children. Reported use of oral contraceptives decreased somewhat with increasing physical activity, while estrogen-replacement therapy was not related to activity level. Smoking, hypertension, and intake of energy and fat were not appreciably related to activity, while alcohol consumption and the proportion of women with diabetes were higher among the least active.

We examined the risk of endometrial cancer according to PAI quintile. There was no significant association between endometrial cancer and PAI adjusted for age, parity, and education, and there was no apparent dose response (Table 2). There were, however, non-statistically significant 10–30% lower RR in each of the four higher quintiles compared to the first. We compared the women in these four highest quintiles to those in the lowest quintile of activity and found an overall 20% reduction in risk that was of borderline significance (RR = 0.8; CI = 0.6, 1.0). Further adjustment for body weight did not appreciably change the quintile risk estimates (RR = 1.0, 0.8, 0.9, 0.8, 0.8 for quintiles 1–5, respectively), even though body weight itself was highly associated with endometrial cancer risk ($p < 0.001$). There was no evidence for effect modification of the PAI association by age, weight, BMI, menopausal status, parity, or reported use of estrogen-replacement therapy (data not shown). Including self-reported cases in the analysis (see Methods), yielded similar results (RR = 1.0, 0.7, 0.8, 0.7, 0.8 for quintiles 1–5, respectively; $p_{trend} = 0.17$), as did the PAI calculated using both weekend and weekday data in those who provided it (RR = 1.0, 0.8, 0.7, 0.8, 0.8 for quintiles 1–5, respectively; $p_{trend} = 0.26$). The analysis was also repeated excluding those women who came into the follow-up study with a history of breast cancer, and the results were similar (RR = 1.0, 0.8, 0.8, 0.7, 0.8 for quintiles 1–5, respectively; $p_{trend} = 0.21$).

Amount of time spent in vigorous and moderate activities was also evaluated. Vigorous activity was not associated with endometrial cancer risk (Table 2), and further adjustment for body weight did not appreciably alter these results. Because the assumption of proportional hazards for hours of moderate activity was not met (*i.e.*, time * moderate activity cross-product term, $p = 0.002$), we examined the association by two-year intervals of follow-up time (Figure 1). There was a small, non-significant increase in risk associated with each 1 h per day increase in moderate activity during the first two years of follow-up, little association from two to eight years of follow-up, and lower risk with increased moderate activity after eight or more years of follow-up. The RR by quartile of activity during the complete follow-up were 1.0 (referent), 1.0 (0.6, 1.6), 0.8 (0.5, 1.3), and 0.8 (0.4, 1.3) for ≤2, 2.1–4.9, 5.0–8.0, and >8 h of moderate activity/day, respectively ($p_{trend} = 0.23$). Given the suggestion of a beneficial association with longer follow-up shown in Figure 1, we also examined quartiles of moderate activity among women with more than six years of follow-up only (six years was chosen to

Table 2. RRs (95% CI) of endometrial cancer by PAI[a] (total moderate and vigorous physical activity) and vigorous activity alone, BCDDP cohort, 1987–1998, US

	PAI quintile (median MET-h/day[a])					p_{trend}
	Q1 (8.0)	Q2 (20.0)	Q3 (32.0)	Q4 (40.5)	Q5 (56.0)	
# Cases	60	47	51	45	50	
Person-years	36,942	38,332	37,427	37,963	40,525	
RR (CI)[b]	1.0	0.8 (0.5, 1.1)	0.9 (0.6, 1.2)	0.7 (0.5, 1.1)	0.8 (0.5, 1.1)	0.24
	Vigorous activity [h/day, median (range)]					
	0	1.0 (0.10–1.00)	2.0 (1.01–2.00)	4.0 (2.01–12.0)		
# Cases	124	57	29	43		
Person-years	91,981	41,061	26,841	31,305		
RR (CI)[b]	1.0	1.1 (0.8, 1.5)	0.8 (0.6, 1.2)	1.1 (0.7, 1.5)		0.94

[a] The PAI was created using reported hours of moderate and vigorous activity/day and the approximate MET level for the type of activity reported: (moderate h × 4) + (vigorous h × 7).

[b] Adjusted for age, parity, and education.

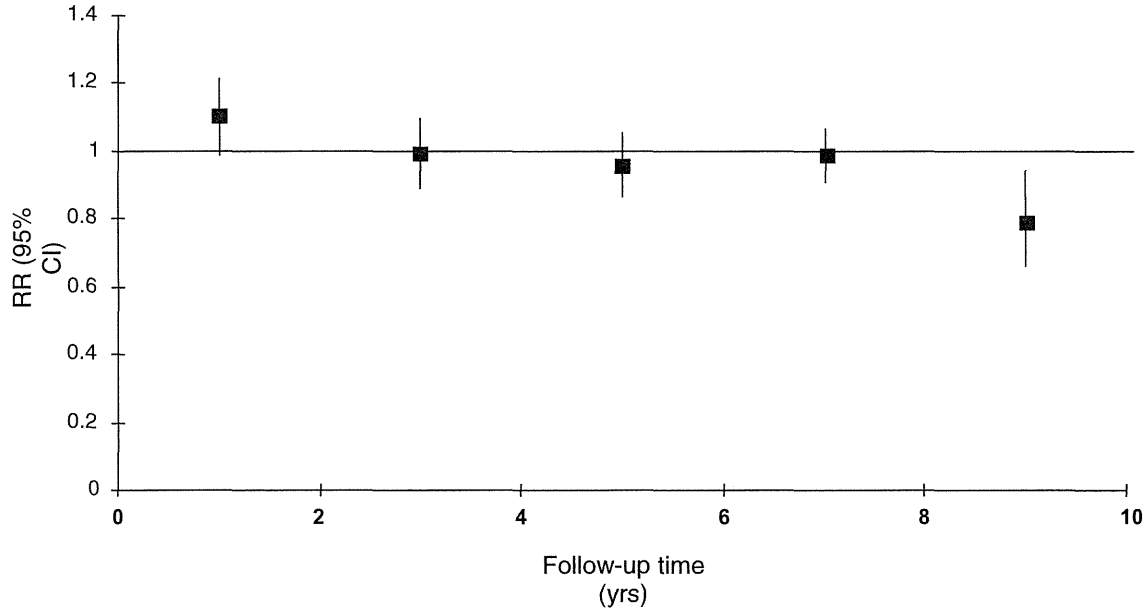

Fig. 1. RRs (95% CI) of endometrial cancer for moderate hours of physical activity by follow-up time, BCDDP cohort, 1987–1998, US. RR were calculated in 2-year intervals of follow-up (≤2, >2–≤4, >4–≤6, >6–≤8, and >8 years) and represent the change in risk for each 1 h increase in moderate physical activity.

allow adequate cases in both time periods for the analysis). RR for the increasing quartiles were 1.0, 0.7, 0.7, and 0.3, but these estimates are based on only 53 cases for this restricted analysis.

Discussion

In contrast to some previous cohort and case–control investigations, our prospective study did not find an overall association between average time spent in recent physical activity and the risk of developing endometrial cancer. We also saw no evidence of a dose–response relationship, with our estimates suggesting lower risk among those reporting any but the lowest level of activity, a potential threshold effect that was found on further categorical analysis to be of borderline statistical significance. While risk was somewhat decreased with increased time spent in moderate activities, this association only appeared in later years of follow-up. Additionally, vigorous activity was not related to endometrial cancer. Our results were not modified by BMI, weight, age, menopausal status, parity or use of estrogen-replacement therapy.

One possible interpretation of our finding of a modest risk reduction in women spending greater time in moderate activities that was evident only with longer follow-up time is that sustained, long-term participation in such physical activity is necessary for a beneficial impact on endometrial cancer. The two previously published cohort studies of physical activity and endometrial cancer that found significant associations had substantially longer follow-up than did the present study (~20 *versus* ~8 years) [11, 12]. Evidence regarding the importance of lifetime versus recent activity from case–control studies is mixed, with some showing larger inverse associations with more recent activity [2, 10], others supporting both recent and lifetime levels [3, 9], and one finding stronger associations with earlier life activity [7]. One issue complicating these time-related comparisons is that the past year physical activity assessed by such questionnaires can correlate with activity levels in preceding years in middle-aged women [18], such that the estimates reflect more than one period. Another possibility for the delayed association we noted is that the women who were more active at baseline may have been more likely to seek medical care if they were experiencing any unusual symptoms such as irregular bleeding, thus leading to a detection bias among the more active women. The stronger reduction in risk from moderate activity with prolonged follow-up may also simply be a chance finding.

The majority of prior studies have observed risk reductions of 30–40% for the highest average activity levels compared to lowest [13]. A lack of a dose–response relationship has been noted in some [4, 7, 10],

but not all [11, 12] studies. Other studies have shown significant associations between endometrial cancer and more moderate intensity activities compared to vigorous activities, as we did here. Levi *et al.* [2] found women who were sedentary *versus* most active in sports and leisure activities to have elevated risk of endometrial cancer (RR = 1.9, CI = 0.9, 4.0), but even higher risk estimates for women who were sedentary compared to the most active in housework (RR = 4.2, CI = 2.4, 7.5). Similarly, Sturgeon *et al.* [3] reported that RRs were higher for sedentary women compared to those actively engaged in housework than for sedentary women compared to those actively engaged in sports. It is not clear why greater levels of moderate, but not vigorous, activity might be associated with endometrial cancer.

Biologically, one would postulate that vigorous activity would afford greater inhibition of carcinogenesis than moderate activity, particularly if the association is mediated through a hormonal pathway. Cross-sectional data from postmenopausal women suggests that serum hormones such as androstenedione and estrone are lowest among women reporting the most activity [19], and in general, more intense activity or physical training is associated with more severe disruptions of menstrual function and/or hormone level [14]. This apparent inconsistency will require data from studies having more detailed activity data.

Given the variety of questionnaires that have been used to assess physical activity in studies of endometrial cancer, it is difficult to make comparisons between the level of activity in our participants *versus* those in prior studies. The women in our study reported relatively high levels of daily activity. Compared to data from the Behavioral Risk Factor Surveillance System (BRFSS) in 1990, for example, which found that only 24% of US women ages 18 and older get at least 30 min of moderate leisure-time activity most days of the week or at least 20 min of vigorous activity three days/week [20], our study participants reported significantly more activity. In the study by Littman *et al.* [10], only 11% of their similarly aged women reported more than 6 h per week of any leisure-time physical activity. The difference in these reports may be due to the fact that BRFSS and Litman *et al.* [10] queried only leisure-time activity. Greater overall levels of activity may have resulted from our questionnaire's intentional inclusion of household activities, important when assessing the activity of women in particular [21].

Data in Table 1 show that the more active women in this cohort tended to have had less education, were more likely to have had children, drank less alcohol, and were only slightly leaner than the less active women, patterns generally opposite those observed for higher levels of leisure exercise or recreational activity [22]. This suggests that our study subjects may have been reporting more housework, or less likely, occupational activity, although we are unable to determine this from the format of the questionnaire we used. It is also possible that our cohort of women, who were initially enrolled in a breast cancer screening trial in the 1970s and responded to our activity questionnaire in the late 1980s, may have been more health conscious and active than women sampled in BRFSS. That the reported body weights and BMIs of the BCDDP women were quite low is consistent with greater activity and health consciousness (but may also have resulted from the necessary exclusion of women with prior hysterectomy). It is also possible, however, that over-reporting contributed to some of the daily averages of 1.2 vigorous hours and 5.9 moderate hours of activity observed. For example, our physical activity questionnaire instructed the women to account for 24 h of total daily activity, including sleep. Having been incorporated into a broader BCDDP mailed questionnaire, the activity questions were self-administered, which may have resulted in the inflation of the reported time spent in more strenuous activity levels compared to more open-ended, interviewer-administered questionnaires [23].

Strengths of our study include its prospective design, cohort size, and the relatively large number of cases for analysis. The activity instrument queried typical weekend and weekday activities including occupational, recreational, and housework activities. We were also able to use updated information on hysterectomies, which was accurately reported by BCDDP women [24], to censor those who were no longer at risk during the course of follow-up, and were able to assess numerous potential confounding factors in our analyses. As in many studies of physical activity and cancer, few factors, including body weight, were found to empirically confound our data [14].

Our analysis is limited by the fact that the BCDDP Follow-up Study was not conducted specifically to evaluate physical activity in relation to endometrial cancer. These results may not generalize to the US population as a whole, as these were women who volunteered to participate in the original BCDDP study and agreed to continue in the follow-up study, in which those with prior breast cancers and biopsies were oversampled. It is possible that the women in our analysis who had breast cancer and/or breast surgery many years prior to physical activity ascertainment may have altered their physical activity patterns following those diagnoses and treatment; however, our study was focused on activity during the previous year, and so our results should not have been biased in this respect. Further, our

results were unchanged when we excluded women with breast cancer, suggesting that the results are internally valid. Another potential limitation is that the sample we used for analysis excluded women who had more breast surgical procedures, had a higher prevalence of estrogen use, and were less educated, which may have resulted in a sample with endometrial cancer risk that was different from that in the original population sample. Importantly, the physical activity level in those who were excluded (which was available for most of the women) was similar to the level of those included in the study, suggesting that our results were not materially biased by these exclusions. Although our questionnaire was designed to capture typical activity of all types, its necessary simplicity restricted our ability to examine activity by subtype, and the format may have resulted in some over-reporting of activity. Additionally, measurement error in our questionnaire may have attenuated the risk estimates we observed.

In contrast to many previously published studies, we observed no significant overall relationship between physical activity and endometrial cancer in this study. We did, however, observe a 20% lower risk among women who were engaged in any but the lowest level of total physical activity, and a lower risk for higher moderate physical activity in particular, but only with longer follow-up. Future studies designed to directly address the role of detailed components of physical activity and periods of exposure in the development of endometrial and other women's cancers should help clarify the associations. In particular, the potential difference between long-term *versus* recent activity on endometrial cancer should be further explored.

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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	61.6歳			( )		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 2　Relative Risk for Uterine Associated with Physical Activity

Table 2. RRs (95% CI) of endometrial cancer by PAI[a] (total moderate and vigorous physical activity) and vigorous activity alone, BCDDP cohort, 1987–1998, US

	PAI quintile (median MET-h/day[a])					P_{trend}
	Q1 (8.0)	Q2 (20.0)	Q3 (32.0)	Q4 (40.5)	Q5 (56.0)	
# Cases	60	47	51	45	50	
Person-years	36,942	38,332	37,427	37,963	40,525	
RR (CI)[b]	1.0	0.8 (0.5, 1.1)	0.9 (0.6, 1.2)	0.7 (0.5, 1.1)	0.8 (0.5, 1.1)	0.24
	Vigorous activity [h/day, median (range)]					
	0	1.0 (0.10–1.00)	2.0 (1.01–2.00)	4.0 (2.01–12.0)		
# Cases	124	57	29	43		
Person-years	91,981	41,061	26,841	31,305		
RR (CI)[b]	1.0	1.1 (0.8, 1.5)	0.8 (0.6, 1.2)	1.1 (0.7, 1.5)		0.94

[a] The PAI was created using reported hours of moderate and vigorous activity/day and the approximate MET level for the type of activity reported: (moderate h × 4) + (vigorous h × 7).
[b] Adjusted for age, parity, and education.

* Controlled for age, weight, smoking, estrogen replacement therapy, dietary calcium, falls, alcohol intake, self-rated health, and functional difficulty.

図表掲載箇所	P563, Table 2
概 要 (800字まで)	The Breast Cancer Detection Demonstration Project(BCDDP) Follow-up Studyに参加している女性23369名の女性を対象に、平均8.2年間の追跡調査を行い、日常の身体活動量と子宮内膜がん発症との関連を検討した研究である。身体活動は、過去1年間における典型的な週の身体活動時間を聞き取った。身体活動は、職業、余暇活動、家事、スポーツなどにおいて、4つのカテゴリーの強度(睡眠、低強度、中強度、高強度)により分類された。身体活動量が、8.0メッツ・時/日と比較して、20.0, 32.0, 40.5, 56.0メッツ・時/日の群は、子宮内膜がんの発症リスクが、それぞれ0.8(0.5-1.1), 0.9(0.6-1.2), 0.7(0.5-1.1), 0.8(0.5-1.1)であり、有意な関連は認められなかった。しかしながら、追跡年数でのサブ解析を行ったところ、8年以上追跡している群で有意な関連が認められた。
結 論 (200字まで)	子宮内膜がん発症には、近々の身体活動は関連しておらず、長期の身体活動が関連している可能性が示唆された。
エキスパートによるコメント (200字まで)	本研究では、子宮内膜がん発症に身体活動が関与しているという結果は得られていないものの、追跡年数でのサブ解析を行ったところ、長期間の高いレベルでの身体活動への暴露が子宮内膜がん発症を抑制する可能性が示唆された。つまり、身体活動が子宮内膜がん発症を抑制するか否かは、より長期の追跡を行った研究により確認していくことが必要である。

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ORIGINAL ARTICLE

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The effect of vigorous physical activity and risk of wrist fracture over 25 years in a low-risk survivor cohort

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Abstract Recent studies have suggested that a high level of recent physical activity increases the risk of a wrist fracture in postmenopausal women. The relationship of more distant past physical activity to wrist fracture is less clear, and most studies have relied on recall of physical activity much earlier in life. The aim of this study was to assess the risk of wrist fracture in a subset of women who had completed a recent questionnaire and also had participated in a cohort study 25 years earlier, 1865 women who were perimenopausal and postmenopausal in 1976 and had completed the 1976 and 2002 Adventist Health Study lifestyle questionnaires. Data on risk factors including physical activity were collected from the 1976 survey. Subjects reported wrist fractures occurring since baseline, and the approximate time of fracture, in the 2002 questionnaire. Incidence of wrist fracture was 3.7/1000 person-years of follow up. There was a dose–response inverse relationship between level of physical activity and wrist fracture with a 37% reduction of risk for the highest level of physical activity with respect to the lowest level (HR, 0.63; 95% CI, 0.45, 0.89). The effect of physical activity changed little in the final multivariable model (HR, 0.61; 95% CI, 0.43, 0.87). In this cohort of women with a relatively low incidence of wrist fracture, higher levels of physical activity at baseline were protective against risk of fracture during 25 years of follow-up.

Key words cohort study · physical activity · survivor cohort · wrist fracture

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Introduction

A wrist fracture (WR) is the most commonly occurring fracture in women under 75 in the United States and northern Europe [1]. There is a rapid increase in the fracture rate among premenopausal, perimenopausal, and early postmenopausal women in the United States until age 65, after which the rate of acceleration tends to slow [2,3]. In the Nurses Health study, the rate of wrist fractures rose from 5 per 10,000 person-years in women aged 35–39 to 19.4 in women aged 60–64 [4]. The estimated lifetime risk of a WR in women is 16%. Contrary to the common belief that a WR is a short-term and fairly benign problem, serious complications, such as persistent neuropathies, tendon ruptures, arthrosis of the radiocarpal or radioulnar joint, malposition or malunion of the fracture, pain, and decreased function of the hand that may persist for years after the fracture, occur surprisingly frequently [5]. Although the consequences of these fractures are often less severe as compared to the outcomes for hip fracture, they nevertheless account for significant morbidity as well as causing a major outlay of medical expenditures [2,6]. In some, pain and loss of grip strength lead to diminished hand function, which in turn can ultimately herald a loss of independence [7].

Although studies on physical activity and risk of wrist fracture have been steadily accumulating over the past decade, the effects of physical activity are far from clear [8–15]. O'Neill et al. [10] showed a 60%–70% reduction in risk with increasingly high lifetime activity score, whereas others report no significant effect of physical activity [11,13]. Some have observed that wrist fractures tend to occur in women who are healthy and often report higher levels of physical activity, such as frequency and duration of walking and going outdoors, raising the concern that physical activity may be a risk factor for wrist fracture in peri- and early postmenopausal women [1,8,10,14].

Studies on the relationship of physical activity at a time period much earlier than the occurrence of a wrist fracture are case-control studies and have relied on recall of physical activity at those earlier times. To date, most prospective

studies of risk of wrist fracture have reported findings with 10 or fewer years of follow-up. In this survivor cohort, recreational and occupational physical activity was reported at baseline in 1976 and the subjects were followed for 25 years. The aim of the study was to examine the effect of self-reported physical activity on risk of wrist fracture in women who were perimenopausal and postmenopausal at baseline and who are part of a group that regularly encourage healthy lifestyle choices.

Methods and materials

Adventist Health Study 1 (1976–1988)

The survivor cohort is composed of Seventh-Day Adventist (SDA) female respondents to two lifestyle questionnaires, the first administered in 1976–1977 and the second in 2002–2004. The first Adventist Health Study (AHS-1) was a prospective cohort study designed to examine the risk of cancer, coronary heart disease, and all-cause mortality among SDAs, a population that encourages adoption of a healthy lifestyle. In 1974 a census of the California SDA membership was undertaken to identify all non-Hispanic whites residing in California. A lifestyle questionnaire was sent in 1976 to the 59 081 non-Hispanic white census respondents who were 25 years and older. The 34 198 respondents to the lifestyle questionnaire formed the cohort that was followed for 12 years. The details of the census and Adventist Health Study have been described elsewhere [16].

Adventist Health Study 2 (2001–)

The purpose of the second Adventist Health Study is to extend the investigation of the effects of lifestyle choices on health in the black as well as white membership of the SDA church throughout the United States. A 5-year recruitment plan included announcements and media presentations made at weekly church services, as well as advertisements in SDA periodicals, brochures, and interviews on SDA television networks. Those who were interested responded through distributed enrollment cards. The lifestyle questionnaire II was then sent to each enrollee. The campaign was carried out across the country in phases, with the earliest phase including the churches in the state of California. By the summer of 2004, it was determined that the campaign in California was largely complete.

Record linkage

In an effort to identify respondents who may have participated in both the first and second lifestyle surveys, the AHS-2 Lifestyle questionnaire asked if the respondent recalled participating in the 1976 survey. A request for a maiden name and the last name that was used in 1988 (the last annual follow-up of AHS-1) was also made of female respondents. A matching process involving several steps was developed to link the appropriate records from the AHS-1 and AHS-2 surveys, because the AHS-1 survey did not have a common numerical identifier such as a social security number. Ultimately, 14 variables were used to determine a match of records: first, middle, and last name; month, day, and year of birth; state or country of birth; recalled age at baptism into the church, recalled participation in AHS-1; marital status, maiden name, last name used in 1988; birthyear of first child; and last name of contact person. The first 7 variables were considered most important in determining probable matching records. In the first step of the matching process, computer software was used to identify records from both AHS-1 and AHS-2 databases that matched perfectly on the first 8 variables, regardless of whether respondents indicated participating in the AHS-1 study. In the second step, 12 algorithms that allowed for imperfect matches on the first 9 variables were computerized. From these algorithms, lists of possible matching records with the 10 variables were generated.

The lists were first reviewed by one of the authors (D.L.T.) to identify highly probable matches, such as records that differed only in the use of a first or middle name versus a matching first or middle initial, or minor spelling differences. If more than one critical variable differed between potential matching records, the pair remained on the list to be reviewed in the final step by a panel of two faculty members of the Department of Epidemiology and one graduate student. Before the final determination by consensus among the panel members, information on the last 5 variables was retrieved on respondents not yet declared as matches to aid in the deliberations. This matching process yielded 3209 matching records on female respondents to both the AHS-1 and AHS-2 questionnaires.

Of the 3209 women, 1406 were menopausal at baseline; this number included women who experienced surgical menopause as well as early but natural menopause. An additional 459 women were not yet menopausal but were 45 years and older. They were considered perimenopausal in that age 45 was 2 SD below the reported current mean age for menopause in AHS-2; this is consistent with the definition for the perimenopausal period used in other studies [1,13]. Thus, a total of 1865 women comprised the study population.

Baseline data collection

The AHS-1 lifestyle questionnaire provided baseline demographic data on education, height, weight, practitioner-diagnosed medical conditions (coronary, stroke, high blood pressure, diabetes, diverticulitis, cancer, rheumatoid arthritis, other arthritis, enlarged prostate, breast cyst, ulcers of the stomach, duodenum or small bowel, menopausal status, age at menopause, parity, hormone use, alcohol use, smoking, and physical activity. Body mass index (BMI) was calculated using reported height and weight. Women less than 60 years of age who indicated they were still menstruating regularly or irregularly were accepted as perimenopausal

status. Women older than 59 who still reported menstruating were considered postmenopausal. For women who failed to respond to questions regarding menopausal status at baseline, age of menopause earlier than age 60 was accepted if provided on the AHS-2 questionnaire. Baseline hormone use, alcohol use, and smoking were assessed as never, past, or current.

For physical activity, the questionnaire included 10 items on work, recreational, and leisure-related physical activity. Eight of these items pertained to participation in any of a list of vigorous leisure activities, such as cycling and gardening for at least 15 min three or more times a week, or any other activity for the same duration and frequency. The last two items assessed participation in regular vigorous activity for less than 15 min and the frequency of work-related vigorous activity. From these items, a four-level index for occupational and leisure exercise was developed:

1 = Little or none. No vigorous leisure exercise and daily work never or rarely involves vigorous activity.
2 = Low. Some vigorous leisure exercise for less than 15 min three or more times per week. Work rarely or occasionally involves vigorous activity, OR no vigorous leisure exercise but daily work involves frequent vigorous activities.
3 = Moderate. Regular moderate level leisure exercise for 15 or more min three times or more per week. Activities included tennis and gardening. Work involves vigorous activities "frequently" or less often, OR some vigorous leisure exercise for less than 15 min three or more times per week, but daily work involves frequent vigorous activities.
4 = Regular high-level exercise for 15 or more min three or more times per week. Activities included cycling and swimming, among others, OR daily work involves vigorous activity "very often."

This measure of physical activity is similar to other indices constructed from questions on heavy or vigorous physical activity. Such indices have been validated by fitness measures such as the maximum volume of oxygen uptake and maximal treadmill time, with modest correlation coefficients (r) ranging from 0.3 to 0.6 [17–19]. As expected, this index has also been shown to be predictive of coronary heart disease during follow-up in this cohort [20].

Follow-up data collection

Data on fractures experienced since age 35 were retrieved from the AHS-2 lifestyle questionnaire. Respondents who indicated that they had experienced any fracture due to minor trauma since age 35 were asked to specify the approximate time frame for the first occurrence of each of the following six categories of fractures: arm or elbow, wrist, hip, thigh, leg, and ankle. The seven closed-ended responses for how long ago the fracture occurred were <1 year, 1–4 years, 5–9 years, 10–14 years, 15–19 years, 20–25 years, and >25 years. Fractures that were reported to have occurred more than 25 years ago were considered prevalent fractures at baseline.

Statistical methods

Differences in demographic and lifestyle variables between cases and non-cases were tested using independent t test (means) or Pearson's chi-square test. The effects of physical activity and other covariates on fracture risk were assessed using Cox proportional-hazard regression with attained age as the time variable. Attained age for wrist fracture cases were estimated as the midpoint of the time interval specified for the event.

Covariates were entered as dummy variables, except for years since menopause, which was entered as a time-dependent covariate. The dummy variables included BMI, education, any fracture since age 35, nulliparity, hormone use, smoking status, alcohol use, presence of diabetes mellitus, presence of rheumatoid arthritis, and physical activity. All variables were measured at baseline except for fracture since age 35 and years since menopause. A base model with hormone use, any fracture since age 35, BMI, education, and physical activity was first constructed. The first two were selected based on their consistently strong association with risk of fracture as reported in the literature. BMI, often associated with development of pathology, and education, a variable designated to control for socioeconomic status, were forced into the model. The other correlates were added to the model one at a time. Correlates that altered the main effect of physical activity by 10% or that showed an independent effect on wrist fracture ($P < 0.05$) were retained in the final multivariate model for all subjects. SAS (Statistical Analysis System, version 8.0) was used for all analyses.

Results

A total of 216 wrist fractures occurred after the age of 35 in the cohort. Of these, 35 were considered prevalent fractures as they were reported as occurring more than 25 years earlier (i.e., before completion of the AHS-I lifestyle questionnaire). The remaining 171 cases and 46 534 person-years of follow-up yield a period incidence rate for wrist fracture of 3.7 per 1000 person-years. The incidence rate by decade detailed in Table 1 shows a continuously increasing risk

Table 1. Incidence of first wrist fracture per 1000 person-years by age group among women who were either 45 years of age and older or postmenopausal at baseline

Age group	No. of subjects	Person-years	No. of fractures	Incidence per 1000 person-years
<35	27	683	1	1.5
35–39	66	1683	3	1.8
40–44	115	2919	5	1.7
45–49	525	13113	48	3.7
50–54	494	12338	45	3.6
55–59	375	9294	40	4.3
60–64	175	4372	15	3.4
65–69	74	1792	12	6.7
70–74	12	294	1	3.4
75–79	1	26	0	0.0
>80	1	20	1	50.0

Table 2. Selected demographic and lifestyle characteristics of wrist fracture cases and non-cases at baseline in 1976 among women in the Adventist Health Study who were menopausal or 45 years of age or older

Characteristic	Cases (n = 171)	Non-cases (n = 1694)	P
Age, years; mean (SD)	53.9 (7.2)	52.0 (7.3)	<0.0001[a]
Height, cm; mean (SD)	163.3 (6.4)	64.5 (2.6)	0.21[a]
Weight, kg; mean (SD)	63.5 (11.4)	142.1 (24.0)	0.82[a]
BMI Body mass index; mean (SD)	23.9 (4.1)	24.0 (3.9)	0.13[a]
Education			
<High school graduate or less	44 (25.7)	409 (24.1)	0.88[b]
Some college	84 (49.1)	831 (49.1)	
College graduate or higher	43 (23.2)	448 (26.4)	
Hormone *use*, n (%)			
Never	82 (48.0)	676 (39.9)	0.03[b]
Past	34 (19.9)	353 (20.8)	
Current	46 (26.9)	635 (37.5)	
Years since menopause, n (%)			
Perimenopausal	41 (24.0)	418 (24.7)	0.006[b]
1–15 years	88 (51.5)	1010 (59.6)	
>15 years	42 (24.6)	256 (15.1)	
Physical activity index, n (%)			
Low or none	91 (53.2)	744 (43.9)	0.06[b]
Moderate	27 (15.8)	293 (17.3)	
High	52 (30.4)	641 (37.8)	
History of fractures, n (%)	18 (10.5)	98 (5.8)	0.01[b]
Nulliparity, n (%)	25 (14.6)	190 (11.2)	0.19[b]
Comorbidities, n (%)			
Asthma	10 (5.8)	100 (5.9)	0.97[b]
Coronary	1 (0.6)	19 (1.1)	0.52[b]
Cancer	11 (6.4)	87 (5.1)	0.41[b]
Hypertension	30 (18.2)	268 (16.4)	0.55[b]
Rheumatoid arthritis	5 (2.9)	69 (4.1)	0.46[b]
Stroke	0 (0.0)	1 (0.06)	0.75[b]
Use alcohol, n (%)	6 (3.5)	91 (5.4)	0.30[b]
Smoker, n (%)	20 (11.7)	199 (11.8)	0.98[b]

[a] Independent t test
[b] Chi-square

with age. Table 2 compares cases to non-cases on selected variables. Cases were more likely to be older, have a history of fractures, report low or no vigorous physical activity, have experienced menopause more than 15 years earlier, and have never used hormones. There were no significant differences on baseline height, weight, BMI, level of education, prevalence of any comorbidity, ever use of alcohol, or ever smoked.

Physical activity, hormone use, years since menopause, and history of fractures since age 35 were all determinants of wrist fracture after adjusting for age. Physical activity was inversely associated with risk of fracture (P for trend = 0.006), with high level of activity reducing the risk of fracture by 37% [hazard ratio (HR), 0.63; 95% confidence interval (CI) 0.45, 0.89] (Table 3). Both current and past hormone use had a positive impact in reducing the risk of fracture (P for trend = 0.001), with a significant reduction of 45% (HR, 0.55; 95% CI, 0.38, 0.79) for current use. There was also 1% increase in risk of fracture for every year following menopause. As expected, any fracture since age 35 was a fairly strong predictor of a future wrist fracture (HR, 1.84; 95% CI, 1.33, 2.55).

All significant age-adjusted variables were entered into multivariate models along with BMI and education (surrogate for socioeconomic status and access to healthcare). The final multivariate model revealed that physical activity, hormone use, years since menopause, and history of fractures since age 35 were significant and independent determinants of wrist fractures in the cohort (see Table 3). There was little change in the effect estimates for each of the determinants when adjusted for the others, except for the risk of years since menopause, which increased to 2% per year, suggesting confounding by the other variables. To determine if the effect of physical activity was confounded by disease that may have limited physical activity, a sensitivity analysis was done excluding all subjects with baseline comorbidities. This step did not alter the strength of the dose–response effect of physical activity.

Discussion

The incidence of low-trauma WR of 3.7/1000 in this cohort appears to be low, although an appropriate basis for comparison is not readily apparent, as these are survivors. Cohort studies that have identified low-energy WR have reported incidences that range from 1.2 to 12.5/1000 person-years in women [2,4,6,13,21]. Differing age range and ethnicities in the cohorts studied, the increasing risk of wrist