Table 3. Univariate and multivariate adjusted risk estimates for wrist fractures (WF) among women in the Adventist Health Study who were postmenopausal or 45 and older at baseline

Covariates (no. of women)		No. of WF	Univariate hazard ratios		Multivariate adjusted hazard ratios[a]	
Physical activity index						
Low or none	(835)	91	1.00		1.00	
Moderate	(320)	27	0.71	(0.46, 1.08)	0.69	(0.44, 1.08)
High	(693)	52	0.63	(0.45, 0.89)	0.61	(0.41, 0.87)
				Trend: $P = 0.006$		Trend: $P = 0.004$
Hormone use						
Never	(758)	82			1.00	
Past	(387)	34	0.66	(0.44, 0.99)	0.63	(0.42, 0.96)
Current	(681)	46	0.55	(0.38, 0.79)	0.50	(0.34, 0.72)
				Trend: $P = 0.001$		Trend: $P = 0.0003$
Years since menopause[b]			1.01	(0.99, 1.03)	1.02	(1.00, 1.04)
Fracture[c] since age 35						
No	(1511)	98	1.00		1.00	
Yes	(354)	18	1.63	(1.00, 2.66)	1.75	(1.05, 2.91)
BMI						
<21.6	(627)	54	1.00		1.00	
21.6–25.0	(714)	74	1.15	(0.81, 1.63)	1.11	(0.77, 1.60)
>25.0	(524)	43	0.91	(0.61, 1.36)	0.92	(0.59, 1.42)
				Trend: $P = 0.70$		Trend: $P = 0.62$
Education						
High school graduate or less	(453)	44	1.00		1.00	
Some college	(915)	84	1.06	(0.70, 1.62)	1.00	(0.64, 1.56)
College graduate +	(491)	43	1.03	(0.71, 1.49)	1.04	(0.71, 1.52)
				Trend: $P = 0.78$		Trend: $P = 0.99$

[a] Also adjusted for diabetes, rheumatoid arthritis, ever pregnant, smoking, alcohol intake
[b] Continuous time-dependent covariate
[c] Any fracture of arm, elbow, forearm, hip, thigh, leg, or ankle

fracture with age after 40 [3], and climate and geography all contribute to the variation in incidence. Two studies that included premenopausal women as young as 28 and 34 reported incidences of 3.40 and 1.23/1000 person-years, respectively [2,4]. A study of perimenopausal women aged 45–57 years at baseline reported an incidence of 6.5/1000 person-years [13]. The years of follow-up in these three studies that included younger pre- and perimenopausal women ranged from 1 to 8 years, a relatively short follow-up compared to the 25.2 years in this study. The National Osteoporosis Risk Assessment (NORA) study, which has the largest cohort of white women in the United States to date for the study of osteoporosis, may provide the best age, ethnic, and national comparison [21]. When both study populations are directly age standardized to the 2000 U.S. population structure, the incidence of wrist fracture in women age 50–80 is 6.7/1000 in NORA and 4.5/1000 in the present study.

The low level of risk for fracture does not appear to be isolated to wrist fractures in this cohort. The risk of arm and elbow fractures (1.47/1000 person-years) and hip fracture (1.32/1000 person-years) also appear low compared to U.S. statistics [8,22]. A number of distinct lifestyle factors that distinguish this cohort from the general population may account for the low risk of fracture. Total lack of smoking over the 25 years, very low alcohol consumption, a vegetarian or low-meat diet, lower number of chronic diseases, less use of medications such as sleeping pills [23], and perhaps a somewhat higher level of customary physical activity most likely all play an important part in the reduced risk of fracture.

It is possible that this low incidence may be related to decreased chance of survival due to wrist fracture, but this is not likely. Two prospective studies investigating the impact of fractures on mortality, one a clinical trial over 3.8 years and the second a Scottish cohort of patients and age-matched population controls gathered over 10 years, have shown no increased risk of death following a wrist fracture [24,25]. Furthermore, the Scottish study concluded that elderly patients who sustain a wrist fracture have better survival than the general population. Underreporting of wrist fracture is also not a likely explanation for the low incidence. Wrist fractures have been shown to be reliably recalled and deemed useful for epidemiological studies [2,26–30]. Honkanen et al. [27] reported sensitivity and specificity of 95% and 99.5% in a validity study of 2007 cases. In a study of 251 fracture cases, only 3% of hip and wrist fractures were not reported. At the same time Joakimsen et al. [2] did find that approximately 5% recalled the wrong time period for the fracture, e.g., a fracture occurring before the beginning of the study, rather than after baseline. If we, in calculating incidence, included all fractures considered prevalent fractures in this survivor cohort, the period incidence would only increase to 4.6/1000 person-years. Although fracture recall was not validated by medical records, it should be noted that the ability to recall diet many years back in this highly educated cohort has been tested in a reliability study that found good reliability for frequency of food intake [31].

The dose–response association of vigorous leisure and occupational physical activity with risk reduction of wrist fracture in women was moderately strong and independent of age and hormonally related factors. A significant protective effect of vigorous physical activity at baseline relative to wrist fracture has been observed for a cohort of men [11]. In women, the evidence for a protective effect has been weak. Gregg et al. [15] observed a nonsignificant 12% reduction in risk with greater than 2201 kcal energy expenditure per week in women 65 and older. The same study also reported a 21% reduction in risk with 5–9 h/week of heavy chores, but a smaller nonsignificant reduction in risk for greater than 9 h/week. For the same cohort of women, an earlier study [8] showed a risk reduction of 12% associated with higher frequency of recalled physical activity in their teenage years. Similar borderline significant reduction of risk was noted in the same study for recalled levels of higher activity at ages 30 and 50. A much stronger association was seen between lifetime physical activity risk of fracture in a small case-control study by O'Neill et al. [10]. In the study noted above, a score of 5–6 on a 12-point index of lifetime physical activity based on recalled level of activity at three earlier points in life reduced the risk of wrist fracture by 70%.

The relatively strong effect of vigorous activity in this cohort may be related to the adoption of a significantly more physically active lifestyle as compared to other populations that have been studied. In a validity study of physical activity questions, both Adventist women and men had significantly greater treadmill time on a testing protocol than non-Adventist subjects of the same age and reported significantly greater frequency of exercise at sufficient intensity to "work up a sweat" than their non-Adventist counterparts [18]. An even stronger difference in frequency of "sweaty exercise" was noted between Adventist men and their age-matched neighbors [32]. This result suggests that habitual vigorous activity may be important in protection against wrist fractures, as it is for hip fractures [15,33,34]. Lack of evidence of a protective effect of physical activity and wrist fracture in previous studies could reflect a more limited range of exercise intensity in women. The lack of association could also reflect an inadequate survey, in many questionnaires, of moderately high intensity activities in which women engage [17]. Household chores, for example, have been shown to contribute a significantly larger proportion to physical activity in women than men [17,18].

The beneficial effects of exercise relative to risk of hip fracture seen in many studies have been postulated as occurring through mechanisms that enhance bone mass density and reduce the risk of falls, the two factors identified as most proximally related to any fracture event [35,36]. Indeed, in multivariable analyses, falls and femoral neck BMD were the strongest predictors of wrist and wrist fractures in the Dubbo cohort [11]. Risk of fracture has been shown repeatedly to be related to postural stability and muscle strength, both of which are strongly influenced by physical activity and exercise [35,36]. In the Dubbo cohort, lack of falling appeared to account for the borderline protective associations between quadriceps strength muscle and body sway and wrist fracture. Recent randomized clinical trials in postmenopausal women of physical strength training and aerobic exercise give evidence that those activities lead to preservation and or increases in bone mass [37–39], strength, and balance [40,41].

The positive effect of vigorous physical activity in our study contrasts with observed negative effects of walking frequency and duration that have been reported to increase the risk of wrist fracture [8,10]. In a parallel finding, Ivers et al. [12] showed that women with no vigorous exercise in the past 2 weeks were significantly less likely to experience a wrist fracture. Other researchers have found that women with impaired physical mobility have significantly less risk than those with normal mobility. In a recent case-control study of 1150 wrist fractures, Kelsey et al. [1] has shown that women with a large variety of lower extremity problems involving pain, weakness, and numbness are unmistakably at less risk than those without, which correlates well with the finding among women over 70 that those who go outdoors less than once per week are less likely to experience a wrist fracture than those who go outdoors more than three times a week [14]. The potential effect of physical disability did not appear to play a significant role in the present study because exclusion of all subjects with baseline comorbidities did not alter the protective effect of physical activity.

It has been acknowledged that physical activity may have multiple and conflicting effects on health status [36]. Although exercise has often been shown to have a beneficial impact of reducing risk of disease, it also presents an increased risk for acute events, which has been shown to be true with regard to acute coronary events [42–44]. Likewise, physical activity exposes a person to some risk of a fall. At some point there is an intersection between physical activity that promotes physical fitness and increased time involved in fall-risk behavior. Such observations argue for lifelong physical activity that maintains a level of fitness such that daily activities do not exceed the threshold for fall risk. It is possible that such lifelong activity has been responsible for the association of vigorous physical activity with reduced risk of fracture in this study. However, the assessment of physical activity was done at only one point in time. Therefore, from this study it is unknown whether the putative beneficial effect of exercise (in this study) is a result of exercise at midlife or whether the effect is associated with a true measure of lifelong physical activity in these women.

The bone-sparing effects of exogenous hormone use have been extensively investigated. Most study findings reveal a consistent moderately strong protective effect of hormone use among current users, with the effect attenuating over time after discontinuation [45–48]. In part, the relatively low incidence may be related to the high frequency and long-term use of hormones in this study population; less than 42% had never used hormones. A conservative estimate for mean duration for hormone use among past or current users at baseline was 5.1 years. In addition, data from the AHS-2 questionnaire have demonstrated a dramatic increase in use during the 25-year follow-up period, with recalled use averaging more than 15 years for ever users.

Recent meta-analysis has concluded that both current smoking and a history of smoking significantly increase the risk of fracture and that the risk from smoking is only marginally explained by lowered BMD [49]. In this cohort, with an extremely low history of smoking and no current smokers at baseline, the effect of exercise may have been more clearly observable.

The findings of this study should be understood in full view of the possible limitations. The measure of physical activity was ordinal in nature and may not have included an adequate survey of the contribution of household chores to physical activity; thus, measurement error may be significant. However, substantial differential misclassification of physical activity exposure in relation to outcome is unlikely as exposure was assessed at baseline. The resulting nondifferential misclassification of exposure in the study is likely to attenuate the true relationship between physical activity and fracture risk. Survivor cohorts often differ in substantial ways from the original cohort. It is possible that the subjects who survived and chose to participate in AHS-2 were healthier or genetically better endowed than subjects who did not, which could have biased the estimates of wrist fracture incidence downward in the target population. The inference of causal relationships between physical activity and risk of wrist fracture is limited by the observational nature of this study. The possibility cannot be excluded that those who had a more active lifestyle had higher muscle mass and superior coordination by heredity which in turn lead both to the propensity to exercise and to lower potential for fracture [50]. It is of interest to note, however, that the parent cohort had the same physical activity profile as the survivor cohort, suggesting that the propensity to exercise is not linked to survivorship. And finally, the findings in this study population of Caucasian women may not be broadly generalizeable to women of other ethnicities.

To our knowledge, this is the first cohort study to demonstrate a moderately strong protective dose–response association of leisure and occupational physical activity on risk for wrist fracture in peri- and postmenopausal women. Assessment of exercise before fracture enhances the strength of this study. Replication of these results in future longitudinal studies is needed to confirm the benefit observed in this survivor cohort. Clarification is also needed on the parameters of lifelong exercise and leisure physical activity that optimizes the musculoskeletal health and minimizes the risk of falls.

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論文名	The effect of vigorous physical activity and risk of wrist fracture over 25 years in a low-risk survivor cohort
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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	平均50歳代	[redacted]		( )		前向きコホート
対象数	1000～5000			( )		( )

調査の方法	質問紙	( )

アウトカム

予 防	なし	なし	なし	転倒・骨折予防		( )
維持・改善	な し	な し	な し	なし	( )	( )

図 表

Table 3. Univariate and multivariate adjusted risk estimates for wrist fractures (WF) among women in the Adventist Health Study who were postmenopausal or 45 and older at baseline

Covariates (no. of women)		No. of WF	Univariate hazard ratios		Multivariate adjusted hazard ratios[a]	
Physical activity index						
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				Trend: $P = 0.001$		Trend: $P = 0.0003$
Years since menopause[b]			1.01	(0.99, 1.03)	1.02	(1.00, 1.04)
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College graduate +	(491)	43	1.03	(0.71, 1.49)	1.04	(0.71, 1.52)
				Trend: $P = 0.78$		Trend: $P = 0.99$

[a] Also adjusted for diabetes, rheumatoid arthritis, ever pregnant, smoking, alcohol intake
[b] Continuous time-dependent covariate
[c] Any fracture of arm, elbow, forearm, hip, thigh, leg, or ankle

図表掲載箇所	P480，表3

概 要（800字まで）

本研究は，手首の骨折のリスクと高強度の身体活動との関連について明らかにすることを目的とした．対象者は，the Adventist Health Studyの参加者で，閉経前後の女性1865名であり，1976から2002年までの25年間追跡された．身体活動の評価は，余暇時間や仕事における高強度活動について質問され，3段階に分類された．手首の骨折リスクとの関連について検討した結果，余暇時間や仕事において高強度活動がほとんどない者と比較して，余暇に15分以上の中強度活動を週3回以上実施している者，又は，仕事で時々高強度活動を行う者の調整ハザード比は0.69(95%CI:0.44-1.08)，15分以上の高強度活動を週3回以上実施している者，又は仕事に高強度活動が多く含まれている者では0.61(0.41-0.87)となり，高強度活動との間に量反応関係が認められた(trend P=0.004)．BMIや学歴については，有意な関連が認められなかった．

結 論（200字まで）

余暇時間に15分以上の高強度活動を週3回以上行っている者，或いは仕事に高強度の活動が多く含まれている者は，手首の骨折リスクが低いことが示された．

エキスパートによるコメント（200字まで）

閉経後女性の手首骨折のリスクと高強度の身体活動との関連について検討した研究である．身体活動の評価にはアンケート調査を使用しており，余暇時間と仕事の高強度活動がまざっている．どちらの活動が特に起因しているのか不明であり，今後より詳細な検討が要される．

担当者　川上諒子

ORIGINAL INVESTIGATION

Physical Activity and Risk of Breast Cancer Among Postmenopausal Women

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Background: Physical activity has many health benefits. Although greater activity has been related to lower postmenopausal breast cancer risk, important details remain unclear, including type, intensity, and timing of activity and whether the association varies by subgroups.

Methods: Within the prospective Nurses' Health Study, we assessed the associations of specific and total activity, queried every 2 to 4 years since 1986, with breast cancer risk. Cox proportional hazards models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). Activity was measured as hours of metabolic equivalent task values (MET-h).

Results: During 20 years of follow-up (1986-2006), 4782 invasive breast cancer cases were documented among 95 396 postmenopausal women. Compared with less than 3 MET-h/wk (<1 h/wk walking), women engaged in higher amounts of recent total physical activity were at lower breast cancer risk (≥27 MET-h/wk [approximately 1 h/d of brisk walking]: HR, 0.85; 95% CI, 0.78-0.93; $P<.001$ for trend). Compared with women who were least active at menopause and through follow-up (<9 MET-h/wk [approximately 30 minutes of walking at an average pace on most days of the week]), women who increased activity were at lower risk (<9 MET-h/wk at menopause and ≥9 MET-h/wk during follow-up: HR, 0.90; 95% CI, 0.82-0.98). Among specific activities modeled simultaneously, brisk walking was associated with lower risk (per 20 MET-h/wk [5 h/wk]: HR, 0.91; 95% CI, 0.84-0.98). The association with total activity did not differ significantly between estrogen and progesterone receptor–positive and –negative tumors ($P=.65$ for heterogeneity).

Conclusion: Our findings suggest that moderate physical activity, including brisk walking, may reduce postmenopausal breast cancer risk and that increases in activity after menopause may be beneficial.

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PHYSICAL ACTIVITY PROVIDES many health benefits, including weight loss and maintenance, improved insulin sensitivity, and improved lipid profile.[1] Physical activity has been shown to decrease circulating estrogen levels in postmenopausal women,[2,3] and lower circulating estrogen levels are associated with lower breast cancer risk.[4-7] Many prospective studies have investigated the association between physical activity and breast cancer risk, with most finding a 10% to 30% lower risk comparing the highest with the lowest activity levels.[8-19] In addition, a systematic review concluded that physical activity was a probable factor in reducing breast cancer risk in postmenopausal women.[20] However, the literature still contains gaps, particularly regarding the timing, type, and intensity of activity that are required to achieve a reduced breast cancer risk. Given that most prior studies had only 1 assessment of physical activity, it is unclear whether recent or past activity is important or whether an inactive postmenopausal woman can reduce her risk by initiating regular exercise. In addition, inconsistencies remain regarding whether the associations vary by other lifestyle factors, such as body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) and use of postmenopausal hormones (PMH), or by tumor hormone receptor subtype.

We examined the associations of physical activity with breast cancer risk among postmenopausal women in the prospective Nurses' Health Study. This study expands upon an earlier Nurses' Health Study analysis with follow-up through 1996 (3137 cases of breast cancer, including 2101 postmenopausal cases) that documented a lower breast cancer risk with

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moderate/vigorous activity.[21] Using data updated every 2 to 4 years and an additional 10 years of follow-up, we investigated the importance of long-term and recent activity, change in activity, and specific types of activity.

METHODS

The Nurses' Health Study began in 1976 when 121 700 female, married, registered nurses, aged 30 to 55 years, responded to a mailed questionnaire.[22,23] The study population is 97% white. Information on lifestyle factors, including many breast cancer risk factors, and new disease diagnoses was collected on the initial questionnaire and has been updated biennially throughout follow-up. This study was approved by the Committee on the Use of Human Subjects in Research at the Brigham and Women's Hospital.

STUDY POPULATION

Follow-up began in 1986 when detailed data on physical activity, including specific activities, were first collected. The analysis includes only postmenopausal women. Women were classified as postmenopausal at the first report of natural menopause or surgery with bilateral oophorectomy, which has been validated in this cohort.[24] Women who reported hysterectomy without bilateral oophorectomy or whose type of menopause was unknown were not classified as postmenopausal until they reached the age at which 90% of the cohort had reached natural menopause (54 years for current smokers and 56 years for nonsmokers). At the start of follow-up in 1986, we excluded those who had died or had previous cancers except nonmelanoma skin cancer (n=10 402) and women missing all measures of physical activity throughout follow-up (n=10 602). Of the remaining 100 697, women entered the analysis in 1986 if they were postmenopausal or in the follow-up cycle after they first reported becoming postmenopausal. We excluded deaths and cancer diagnoses at each questionnaire cycle, resulting in a study population of 95 396 women (1 203 929 person-years) (**Table 1**). Follow-up data through June 1, 2006, are available for 91.1% of the study population.

Table 1. Age and Age-Standardized Characteristics of 95 396 Postmenopausal Women by Total Activity in the Nurses' Health Study, 1986-2006[a]

	Total Activity, MET-h/wk		
Characteristic	<3	3 to <18	≥18
Person-years	270 364	536 372	397 193
Age, y	64.1 (7.8)	63.5 (7.4)	63.6 (7.1)
Age at menarche, y	12.5 (1.4)	12.6 (1.4)	12.6 (1.4)
Nulliparous, %	5.7	5.5	5.8
Parity, No. of children[b]	3.3 (1.6)	3.3 (1.6)	3.2 (1.5)
Age at first birth, y[b]	25.3 (3.5)	25.2 (3.4)	25.1 (3.3)
Age at menopause, y[c]	48.5 (5.7)	48.8 (5.6)	48.9 (5.7)
Current PMH use, %	33.6	38.0	40.5
Mammography within past 2 y, %	73.4	79.8	82.9
Family history of breast cancer, %	13.4	13.7	14.0
History of benign breast disease, %	42.2	44.4	46.3
BMI	27.9 (6.1)	26.4 (5.0)	25.3 (4.4)
Weight gain since age 18 y, kg	16.6 (14.9)	13.6 (12.4)	10.9 (11.4)
Height, m	1.64 (0.06)	1.64 (0.06)	1.64 (0.06)
Alcohol intake, g/d	4.9 (10.4)	5.2 (9.6)	6.1 (9.9)
Total physical activity, MET-h/wk	1.3 (0.9)	9.1 (4.3)	37.6 (19.6)
Moderate/vigorous physical activity, MET-h/wk	0.1 (0.4)	1.5 (3.0)	9.4 (13.4)
Brisk walking, MET-h/wk	0.1 (0.4)	1.4 (2.9)	8.5 (12.3)
Easy walking, MET-h/wk	0.6 (0.8)	3.1 (3.8)	5.4 (9.0)
Jogging/running, MET-h/wk	0.0 (0.4)	0.1 (1.0)	0.9 (5.2)
Biking, MET-h/wk	0.1 (1.0)	0.9 (2.5)	4.0 (9.1)
Swimming, MET-h/wk	0.0 (0.7)	0.3 (1.7)	2.0 (6.9)
Tennis, MET-h/wk	0.0 (0.3)	0.1 (0.9)	1.5 (7.3)
Calisthenics, MET-h/wk	0.1 (0.9)	0.8 (2.5)	4.3 (8.7)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MET-h, hours of metabolic equivalent task values; PMH, postmenopausal hormone.

[a] Indicates age standardized to the age distribution of the study population during follow-up from 1986 through 2006. Unless otherwise indicated, data are expressed as mean (SD).

[b] Among parous women only.

[c] Among women with natural menopause or bilateral oophorectomy.

PHYSICAL ACTIVITY ASSESSMENT

Beginning in 1986, participants reported their average time per week (in 10 categories ranging from 0 minutes to ≥11 hours) during the preceding year spent doing any of the following activities: walking or hiking outdoors, jogging, running, bicycling, lap swimming, tennis, calisthenics/aerobics/aerobic dance/rowing machine, and squash or racquet ball. In addition, participants reported their usual walking pace (easy/casual, <2.0 mph; normal/average, 2.0-2.9 mph; brisk, 3.0-3.9 mph; or very brisk/striding, ≥4.0 mph) and the number of flights of stairs climbed daily. These questions were repeated, with minor modifications, in 1988, 1992, 1996, 1998, 2000, and 2004 (questionnaires are available at http://www.nurseshealthstudy.org). To compare each activity by intensity and to create a score of total activity weighted by intensity, metabolic equivalent task (MET) values were assigned to each activity according to previously established criteria.[25] The MET scores for walking were assigned on the basis of pace, and an intensity score was selected for each of the other activities. We calculated MET hours (MET-h) per week for each activity by multiplying the MET score and reported hours per week; values from individual activities were summed for total MET-h per week. Because women may expend different amounts of energy in some activities, such as bicycling and tennis, moderate/vigorous activity was defined as brisk or very brisk walking, jogging, or running. Physical activity data were carried forward when not included on biennial questionnaires (eg, 1988 data used in the 1990-1992 follow-up), but data were not carried forward when women failed to answer physical activity questions (eg, 1996 data were not carried forward if a woman was missing 1998 data).

The validity of this physical activity assessment has been tested among 151 participants in the Nurses' Health Study II, a cohort of younger women.[26] Although the questionnaire underestimated moderate/vigorous activity compared with four 7-day activity diaries, the correlation for MET-h per week of moderate/vigorous activity was fairly good ($r=0.62$), suggesting that the questionnaire is reasonably valid for ranking participants. For walking, the primary activity among the participants in our analysis, the correlation was 0.70.

BREAST CANCER CASE ASCERTAINMENT

Invasive breast cancer cases, diagnosed from 1986 through May 2006, were identified on the biennial questionnaires; the National Death Index was searched for those who did not respond. To confirm cancer reports and abstract information on tumor characteristics, medical records were reviewed by investigators blinded to exposure status. Records were unavailable for 248 (5.2%) of 4782 cases. Given that pathology re-

Table 2. Risk of Postmenopausal Breast Cancer According to Physical Activity, Follow-up 1986-2006

	Activity, MET-h/wk, HR (95% CI)					*P* Value for Trend	HR (95% CI) per 20 MET-h/wk
	<3	3 to <9	9 to <18	18 to <27	≥27		
Total Physical Activity							
Baseline (1986)							
No. of cases	1218	1146	864	480	624		
Age-adjusted	1 [Reference]	0.96 (0.89-1.05)	1.01 (0.92-1.10)	1.02 (0.92-1.14)	0.95 (0.86-1.05)	.71	0.99 (0.93-1.05)
Multivariate[a]	1 [Reference]	0.94 (0.86-1.02)	0.96 (0.88-1.05)	0.97 (0.87-1.08)	0.91 (0.83-1.01)	.20	0.96 (0.91-1.02)
Simple update							
No. of cases	1126	1170	997	586	903		
Age-adjusted	1 [Reference]	1.01 (0.93-1.09)	0.97 (0.89-1.06)	0.94 (0.85-1.04)	0.91 (0.83-0.99)	.01	0.93 (0.88-0.98)
Multivariate[a]	1 [Reference]	0.98 (0.90-1.06)	0.92 (0.85-1.01)	0.88 (0.80-0.97)	0.85 (0.78-0.93)	<.001	0.90 (0.85-0.95)
Cumulative average							
No. of cases	666	1313	1294	717	792		
Age-adjusted	1 [Reference]	1.03 (0.94-1.13)	1.01 (0.91-1.11)	1.00 (0.90-1.11)	0.94 (0.85-1.05)	.09	0.95 (0.90-1.01)
Multivariate[a]	1 [Reference]	0.99 (0.90-1.09)	0.95 (0.86-1.04)	0.93 (0.84-1.04)	0.88 (0.79-0.98)	.003	0.92 (0.87-0.97)
Moderate/Vigorous Physical Activity							
Baseline (1986)							
No. of cases	3224	409	313	232	154		
Age-adjusted	1 [Reference]	1.09 (0.98-1.21)	0.96 (0.86-1.08)	1.04 (0.91-1.19)	0.93 (0.79-1.10)	.66	0.98 (0.91-1.07)
Multivariate[a]	1 [Reference]	1.03 (0.93-1.14)	0.91 (0.81-1.02)	1.00 (0.87-1.14)	0.92 (0.78-1.09)	.24	0.95 (0.88-1.03)
Simple update							
No. of cases	3723	302	353	270	134		
Age-adjusted	1 [Reference]	0.98 (0.87-1.10)	1.00 (0.89-1.11)	0.96 (0.85-1.09)	0.86 (0.72-1.02)	.12	0.94 (0.87-1.02)
Multivariate[a]	1 [Reference]	0.93 (0.83-1.05)	0.94 (0.84-1.05)	0.91 (0.80-1.03)	0.83 (0.70-0.98)	.007	0.89 (0.82-0.97)
Cumulative average							
No. of cases	3201	843	479	167	92		
Age-adjusted	1 [Reference]	1.01 (0.94-1.09)	0.96 (0.87-1.06)	0.93 (0.80-1.09)	0.89 (0.72-1.09)	.12	0.93 (0.85-1.02)
Multivariate[a]	1 [Reference]	0.96 (0.89-1.03)	0.91 (0.82-1.00)	0.89 (0.76-1.04)	0.85 (0.69-1.05)	.009	0.88 (0.80-0.97)

Abbreviations: CI, confidence interval; HR, hazard ratio; MET-h, hours of metabolic equivalent task values.

[a] Adjusted for age at menarche (≤12 years, 13 years, ≥14 years, or missing), body mass index (calculated as weight in kilograms divided by height in meters squared) at age 18 years (<19, 19 to <21, 21 to <23, ≥23, or missing), height (<160, 160 to <163, 163 to <168, or ≥168 cm), parity and age at first birth (nulliparous, 1-2 children at <25 years, 1-2 children at 25-29 years, 1-2 children at ≥30 years, 3-4 children at <25 years, 3-4 children at 25-29 years, 3-4 children at ≥30 years, ≥5 children at <25 years, ≥5 children at 25-29 years, ≥5 children at ≥30 years, or missing), alcohol intake (none, <5 g/d, 5 to <15 g/d, ≥15 g/d, or missing), postmenopausal hormone use (never, past, current for <5 years, current for ≥5 year, or missing), age at menopause (continuous), missing age at menopause (yes vs no), family history of breast cancer (yes vs no), and history of benign breast disease (yes vs no).

ports confirmed 99% of the reported cases, diagnoses confirmed by the participant but missing medical record confirmation were included as cases in this analysis.

COVARIATE ASSESSMENT

Age was calculated from birth date to questionnaire return date. Age at menarche, height, and age at first birth were queried in 1976. Weight at 18 years of age was assessed in 1980. Information on parity was collected biennially until 1984. History of breast cancer in the participants' mothers and sisters was queried in 1976, 1982, and every 4 years since 1988. Alcohol consumption was assessed with a semiquantitative food frequency questionnaire every 4 years from 1986. Information on mammograms was collected biennially starting in 1988. Current weight, menopausal status, age at menopause, PMH use, and diagnosis of benign breast disease were assessed biennially.

STATISTICAL ANALYSIS

We calculated person-years from the baseline questionnaire return date to the first date of diagnosis of breast or other cancer (except nonmelanoma skin cancer), death, or June 1, 2006. Cox proportional hazards models, stratified jointly by age in months and follow-up year at the beginning of each 2-year questionnaire cycle, were used to calculate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). Multivariate models controlled for several breast cancer risk factors (see the footnote in **Table 2**), using time-dependent covariates for exposures updated throughout follow-up; missing indicators accounted for missing data (11% for BMI at 18 years of age, 6% for PMH use, and ≤2% for age at menarche, age at menopause, parity and age at first birth, and alcohol consumption). The proportional hazards assumptions were tested by including interaction terms between exposure and time or age and comparing the interaction model with the model without the interaction terms by means of a likelihood ratio test. In all cases, the likelihood ratio test findings were not significant, indicating that the proportional hazards assumptions were met.

Physical activity was modeled categorically (<3, 3 to <9, 9 to <18, 18 to <27, and ≥27 MET-h/wk) and continuously, using MET-h per week to assess the magnitude of the association per 20 MET-h/wk or the midpoints of the categories to perform a Wald test for trend. Categories were chosen to correspond to the equivalent of less than 1, 1 to less than 3, 3 to less than 6, 6 to less than 9, and at least 9 hours of walking at an average pace per week. We assessed the importance of timing of activity by modeling baseline activity (1986) and activity updated throughout follow-up. Activity was updated in the following 2 ways: simple update, using the most recently reported activity, and cumulative average, using the mean MET-h per week from all previous physical activity assessments as a measure of long-term physical activity. Change in activity after menopause was assessed by cross-classifying activity level at the time a woman became postmenopausal (or 1986 for women already postmenopausal at baseline) with activity at each questionnaire cycle through follow-up (1988-2006), using a dichotomous measure (<9 or ≥9 MET-h/wk). This cut point was chosen because 9 MET-h/wk is equivalent to 3 hours of walking at an average pace per week or 30 minutes on most days of the week. Specific types of activity were modeled simultaneously using continuous MET-h per week.

To assess whether the association between physical activity and breast cancer risk varied across levels of other risk factors, we tested interaction terms between activity and the potential modifier in multivariate models using the Wald test. To assess whether the associations differed by estrogen and progesterone receptor (ER/PR) status of the tumor, we used a competing risks Cox proportional hazards regression model stratified by 3 end points (ER/PR-positive, ER/PR-negative, and no breast cancer) as well as age and time period.[27] We used a likelihood ratio test to compare a model with separate physical activity estimates in each case group with a model with common estimates. We also assessed the association with physical activity by ER status alone and ductal and lobular status. Although our main analysis was restricted to invasive cases, we performed a secondary analysis that included invasive and in situ cases. All analyses were conducted using SAS statistical software (version 9; SAS Institute, Inc, Cary, North Carolina). All *P* values were based on 2-sided tests and considered statistically significant at $P \leq .05$.

RESULTS

During follow-up, we documented 4782 cases of invasive breast cancer. Women who were more physically active were more likely to use PMH, to have had a recent mammogram, and to have a history of benign breast disease (Table 1). Physically active women also tended to have a lower BMI, to have gained less weight since 18 years of age, and to consume more alcohol. Brisk walking was the most frequent activity in the highest category of physical activity throughout follow-up.

We did not observe an association between baseline total activity and breast cancer risk (≥27 MET-h/wk [the equivalent of approximately 7 h/wk of brisk walking] vs <3 MET-h/wk: multivariate HR, 0.91; 95% CI, 0.83-1.01; $P = .20$ for trend) (Table 2). However, significantly lower breast cancer risks were associated with higher activity using both the simple update and cumulative average assessments, with comparable HRs (≥27 vs <3 MET-h/wk: multivariate HR, 0.85; 95% CI, 0.78-0.93; $P < .001$ for trend for simple update, and HR, 0.88; 95% CI, 0.79-0.98; $P = .003$ for trend for cumulative average). Multivariate-adjusted HRs were slightly lower than age-adjusted HRs. No covariate changed the HR greater than 2%, but adjusting for BMI at 18 years of age, PMH use, age at menopause, alcohol consumption, and history of benign breast disease accounted for most of the differences in HRs. As with baseline total activity, baseline moderate/vigorous activity was not related to breast cancer risk. Hazard ratios for both simple updated and cumulative average moderate/vigorous activity were slightly stronger than for total activity (≥27 vs <3 MET-h/wk: HR, 0.83; 95% CI, 0.70-0.98; $P = .007$ for trend for simple update, and HR, 0.85; 95% CI, 0.69-1.05; $P = .009$ for trend for cumulative average).

We assessed the association of change in activity by cross-classifying women by activity levels at the time they became postmenopausal (or 1986 for those who were postmenopausal at baseline) and current activity levels, updated throughout follow-up (**Table 3**). Compared with the least active women at both periods (<9 MET-h/wk), women who increased activity from less than 9 MET-h/wk at menopause to at least 9 MET-h/wk during follow-up were at a reduced breast cancer risk (HR, 0.90; 95% CI, 0.82-0.98). In addition, those who were most active at menopause and during follow-up (≥9 MET-h/wk) had a suggested lower risk (HR, 0.93; 95% CI, 0.86-1.00). However, women who were active at menopause but became less active during follow-up were not at a reduced risk (HR, 0.97; 95% CI, 0.87-1.07).

Table 3. Multivariate Risk of Postmenopausal Breast Cancer According to Change in Total Physical Activity Since Menopause, Follow-up 1988-2006[a]

	Current Activity, MET-h/wk			
	<9		≥9	
Baseline Activity, MET-h/wk[b]	No. of Cases	Multivariate HR (95% CI)	No. of Cases	Multivariate HR (95% CI)
<9	1041	1 [Reference]	622	0.90 (0.82-0.98)
≥9	528	0.97 (0.87-1.07)	1215	0.93 (0.86-1.00)

Abbreviations: CI, confidence interval; HR, hazard ratio; MET-h, hours of metabolic equivalent task values.
[a] Multivariate models were adjusted for all factors listed in Table 2.
[b] Indicates at menopause or 1986 if postmenopausal at baseline.

To assess the importance of individual types of activities, we included all specific activities in a single statistical model. Only brisk walking was associated significantly with a lower breast cancer risk (per 20 MET-h/wk [equivalent to 5 h/wk]: HR, 0.91, 95% CI, 0.84-0.98; $P = .01$). Hazard ratios for most other activities were less than 1.00, but the 95% CIs for each activity overlapped the HR for brisk walking.

The association between total activity and breast cancer risk did not differ significantly between ER/PR-positive (n=2632 cases) and ER/PR-negative (n=690 cases) tumors ($P = .65$ for heterogeneity). Although the trend was statistically significant for ER/PR-positive tumors ($P = .004$) but not for ER/PR-negative tumors ($P = .18$), estimates for at least 27 vs less than 3 MET-h/wk were similar between the 2 subtypes (HR, 0.86; 95% CI, 0.76-0.97 for ER/PR-positive, and HR, 0.85; 95% CI, 0.68-1.07 for ER/PR-negative tumors). The association also did not differ when evaluated by status of ER alone ($P = .51$ for heterogeneity) or by ductal or lobular subtype ($P = .60$ for heterogeneity) (data not shown). Results were not appreciably different when in situ cases (n=943) were included (data not shown).

Because body weight is a potential mechanism by which activity may exert an effect on breast cancer risk, we did not include weight change or current BMI in our multivariate model. When we added weight change since 18 years of age to the multivariate models, HRs were attenuated but the inverse associations remained (eg, for simple update total activity ≥27 vs <3 MET-h/wk: HR, 0.90; 95% CI, 0.82-0.98; $P = .006$ for trend). Nearly identical results were observed when we used BMI instead of weight change (data not shown). Adjustment for weight change slightly attenuated the associations with ER/PR-positive and ER/PR-negative tumors, although the attenuation was greater for ER/PR-positive tumors (data not shown). To ensure that preclinical disease did not affect the association observed, we repeated the analyses using a 2-year lag (eg, 1986 activity for the 1988-1990 follow-up period); results were essentially unchanged (data not shown). To examine whether increased screening associated with healthy behaviors affected our results, we adjusted for mammograms in the past 2 years; results were unchanged.

We investigated whether other factors modified the association between total activity and breast cancer risk, including BMI (<25 vs ≥25), weight change since 18 years of age (<10 vs ≥10 kg), PMH use (never vs ever), family history of breast cancer (yes vs no), and mammograms in the past 2 years (yes vs no) (data not shown). We observed similar associations between activity and risk in each of these comparisons ($P \geq .30$ for interactions). For example, HRs for at least 27 vs less than 3 MET-h/wk were comparable in each strata comparing BMI of less than 25 vs at least 25 (HR, 0.88 and 0.91, respectively; $P = .70$ for interaction) and PMH use never vs ever (0.89 and 0.88, respectively; $P = .54$ for interaction).

COMMENT

In this large prospective study with 20 years of follow-up, higher levels of both recent and long-term total and moderate/vigorous physical activity were associated with lower breast cancer risk among postmenopausal women. The main activity observed in this population, brisk walking, was associated with a reduced breast cancer risk. Women who engaged in low activity levels at the menopause transition and increased their activity levels were at a reduced breast cancer risk compared with those who remained sedentary. Weight change since 18 years of age, BMI, PMH use, and family history of breast cancer did not modify the association between total activity and breast cancer risk. In addition, the association did not differ by ER/PR status or by ductal or lobular subtype.

Many other large (>500 cases) prospective studies have assessed the association between physical activity and breast cancer risk among postmenopausal women, and most,[8-13,16,17,19] but not all,[14,15,18] have observed lower risks overall with activity. Our results have confirmed this association, and we have elaborated on the relationship between activity and breast cancer risk in several important ways.

Whether past or recent physical activity is important in the etiology of breast cancer among postmenopausal women has not been thoroughly explored until now. Although some studies have assessed long-term activity or activity in early adult years,[9-11,17,28] few studies have focused on the importance of recent activity, which is most relevant for public health recommendations for women who are currently postmenopausal. Although previous studies have used baseline or recalled measures of physical activity,[8-19,28] ours is the first large study, to our knowledge, to assess updated physical activity measures among postmenopausal women and change in activity since menopause. Although most studies using baseline assessments of activity have observed lower risk with higher activity, follow-up for most of these studies was less than 10 years.[9-11,17,19,28] We did not observe an association between baseline activity and breast cancer risk during a 20-year follow-up, nor did 3 other studies with follow-up of more than 10 years,[14,15,18] suggesting that baseline measures may not accurately predict risk over longer periods. Our finding of lower risk with higher recent activity in postmenopausal women suggests that activity appears to exert a protective effect during postmenopausal years. Indeed, our finding of reduced risk with increased activity since menopause suggests that it is not too late for postmenopausal women to modify their activity habits to influence breast cancer risk.

Several studies have isolated moderate and/or vigorous activity to assess the association with intensity, with most finding stronger associations with more strenuous activities, similar to our findings.[12,17,18] To our knowledge, no other studies have assessed specific types of activity. Although we cannot clearly determine the benefits of other activities, our finding that brisk walking is associated with lower breast cancer risk suggests that women do not need to engage in intense activities to appreciate a benefit.

Whether the association between activity and breast cancer risk differs by risk factor status is unclear from the literature to date. For instance, while some studies have observed stronger associations among leaner women,[11,16,18] some have observed stronger associations among overweight women,[19] and others have found no differences by BMI.[9,12,28] We observed similar risk reductions among active lean and overweight women. Similar to our findings, most[11,12,16,28] but not all[10,19] studies have observed similar associations between activity and breast cancer risk by PMH use. Our findings suggest that women of all sizes and hormonal therapy status will benefit from daily moderate-intensity activity.

The relation between activity and breast cancer by hormone receptor subtype has been investigated in a few studies, with conflicting results. Although stronger associations with ER-negative breast tumors were observed in the California Teachers Cohort (highest vs lowest category of strenuous activity: relative risk [RR], 0.89; $P = .23$ for trend for ER-positive tumors [1879 cases], and RR, 0.45; $P = .003$ for trend for ER-negative tumors [345 cases])[17] and the National Institutes of Health–AARP (formerly known as the American Association of Retired Persons) cohort (highest vs lowest category of activity: RR, 0.97; $P = .64$ for trend for ER-positive tumors [2083 cases], and RR, 0.75; $P = .03$ for trend for ER-negative tumors [411 cases]),[19] we did not detect a significant difference by ER or ER/PR status. It is possible that adjustment for BMI in the California Teachers Cohort contributed to this finding because adjustment for BMI attenuated the association with ER/PR-positive more than with ER/PR-negative tumors in the Iowa Women's Health Study[13] and our own analysis.

Studies among postmenopausal women consistently show that higher circulating estrogen and androgen levels are related to higher breast cancer risk.[4-7] Physical activity has been shown to reduce levels of these hormones in postmenopausal women,[2,3] which suggests that a steroid-hormone pathway may play a role in the association between activity and breast cancer risk. However, the similar associations we observed for hormone receptor–positive and –negative tumors suggest that additional pathways also may be responsible, for example, by improving insulin sensitivity and reducing circulating insulin levels, enhancing immune function, or reducing chronic inflammation.[1]

This study has several strengths, including the large cohort size and long follow-up. Validated, updated information on physical activity allowed us to assess recent and long-term activity and change in activity throughout follow-up. In addition, extensive and updated information on other risk factors allowed us to adjust for potential confounding factors. However, there are also limitations. Physical activity was self-reported and aimed to assess average annual activity. Although this is an imperfect measure, previous validation of this questionnaire suggests that this is a reasonable way to rank individuals. In addition, we have observed significant associations between this measure of physical activity and other chronic diseases, including diabetes, stroke, and coronary heart disease.[29-31] Given that the correlation between the questionnaire and four 7-day activity diaries was 0.62,[26] it is likely that we have underestimated the true association between physical activity and breast cancer risk. Although the homogeneity of the study population is another potential limitation, it is unlikely that the observed associations between activity and risk differ substantially from the general population.

In conclusion, our results confirm the association between higher levels of physical activity and lower postmenopausal breast cancer risk and suggest that recent activity is important. The equivalent of 5 h/wk of brisk walking was sufficient to reduce the risk of breast cancer, an amount consistent with the US government's guidelines for adults to achieve additional health benefits beyond minimal activity.[32] The lack of significant difference by ER/PR status, BMI, and PMH use and the attenuation but not elimination of the association with adjustment for weight change suggest that activity may be acting, at least in part, on a nonhormonal pathway. Our findings suggest that moderate physical activity, including brisk walking, may reduce postmenopausal breast cancer risk and that increases in activity after menopause may be beneficial.

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対象の内訳

	ヒト	動物				
対象	一般健常者	空白	地 域	欧米	研究の種類	縦断研究
性別	女性	(　　)		(　　)		コホート研究
年齢	40-65歳	[redacted]		(　　)		(　　)
対象数	10000以上			(　　)		前向きコホート
				(　　)		(　　)

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		(　　)
アウトカム　維持・改善	な し	な し	な し	なし	(	(　　)

図 表

Table 2. Risk of Postmenopausal Breast Cancer According to Physical Activity, Follow-up 1986-2006

	Activity, MET-h/wk, HR (95% CI) <3	3 to <9	9 to <18	18 to <27	≥27	*P* Value for Trend	HR (95% CI) per 20 MET-h/wk
Total Physical Activity							
Baseline (1986)							
No. of cases	1218	1146	864	480	624		
Age-adjusted	1 [Reference]	0.96 (0.89-1.05)	1.01 (0.92-1.10)	1.02 (0.92-1.14)	0.95 (0.86-1.05)	.71	0.99 (0.93-1.05)
Multivariate[a]	1 [Reference]	0.94 (0.86-1.02)	0.96 (0.88-1.05)	0.97 (0.87-1.08)	0.91 (0.83-1.01)	.20	0.96 (0.91-1.02)
Simple update							
No. of cases	1126	1170	997	586	903		
Age-adjusted	1 [Reference]	1.01 (0.93-1.09)	0.97 (0.89-1.06)	0.94 (0.85-1.04)	0.91 (0.83-0.99)	.01	0.93 (0.88-0.98)
Multivariate[a]	1 [Reference]	0.98 (0.90-1.06)	0.92 (0.85-1.01)	0.88 (0.80-0.97)	0.85 (0.78-0.93)	<.001	0.90 (0.85-0.95)
Cumulative average							
No. of cases	666	1313	1294	717	792		
Age-adjusted	1 [Reference]	1.03 (0.94-1.13)	1.01 (0.91-1.11)	1.00 (0.90-1.11)	0.94 (0.85-1.05)	.09	0.95 (0.90-1.01)
Multivariate[a]	1 [Reference]	0.99 (0.90-1.09)	0.95 (0.86-1.04)	0.93 (0.84-1.04)	0.88 (0.79-0.98)	.003	0.92 (0.87-0.97)
Moderate/Vigorous Physical Activity							
Baseline (1986)							
No. of cases	3224	409	313	232	154		
Age-adjusted	1 [Reference]	1.09 (0.98-1.21)	0.96 (0.86-1.08)	1.04 (0.91-1.19)	0.93 (0.79-1.10)	.66	0.98 (0.91-1.07)
Multivariate[a]	1 [Reference]	1.03 (0.93-1.14)	0.91 (0.81-1.02)	1.00 (0.87-1.14)	0.92 (0.78-1.09)	.24	0.95 (0.88-1.03)
Simple update							
No. of cases	3723	302	353	270	134		
Age-adjusted	1 [Reference]	0.98 (0.87-1.10)	1.00 (0.89-1.11)	0.96 (0.85-1.09)	0.86 (0.72-1.02)	.12	0.94 (0.87-1.02)
Multivariate[a]	1 [Reference]	0.93 (0.83-1.05)	0.94 (0.84-1.05)	0.91 (0.80-1.03)	0.83 (0.70-0.98)	.007	0.89 (0.82-0.97)
Cumulative average							
No. of cases	3201	843	479	167	92		
Age-adjusted	1 [Reference]	1.01 (0.94-1.09)	0.96 (0.87-1.06)	0.93 (0.80-1.09)	0.89 (0.72-1.09)	.12	0.93 (0.85-1.02)
Multivariate[a]	1 [Reference]	0.96 (0.89-1.03)	0.91 (0.82-1.00)	0.89 (0.76-1.04)	0.85 (0.69-1.05)	.009	0.88 (0.80-0.97)

図表掲載箇所	P1760, Table2
概 要 (800字まで)	Nurses' Health Studyの閉経後女性95396名を対象とした研究である。追跡期間は20年であった。身体活動の評価は、質問紙から推定された。前年におけるウォーキング、ハイキング、ジョギング、ランニング、サイクリング、水泳、テニス等の時間が調査され週当たりのメッツ・時が算出された。また、歩くスピードについても調査された。ベースライン時における身体活動を3メッツ・時/週未満、3-9メッツ・時/週、9-18メッツ・時/週、18-27メッツ・時/週、27メッツ・時/週以上の5分位に分類した場合、追跡期間中の乳がん発症リスクは、それぞれ1.0、0.94(0.86-1.02)、0.96(0.88-1.05)、0.97(0.87-1.08)、0.91(0.83-1.01)であり、有意な低下を示さなかった。しかしながら、最も近年の身体活動量を上記メッツ・時/週に分類し、乳がんのリスクを検討したところ、18メッツ・時/週以上を行っている者は有意なリスク低下が認められた(RR, 0.88; 95%CI, 0.80-0.97)。また20年間の追跡期間中の積算の身体活動量において評価したところ、身体活動量の蓄積が多いほど、乳がんのリスク低下が認められた。
結 論 (200字まで)	閉経後の女性において、身体活動量を高く保つことは、乳がんのリスクを減少させることが明らかとなった。またこの身体活動量は、蓄積されることでよりリスク低下と関連している。
エキスパートによるコメント (200字まで)	身体活動量と乳がんの関連については、これまでの先行研究と一致しており、本研究では更に身体活動の変化との関連についても検討を行っている。身体活動量が低い集団においても、身体活動量を増加させることで乳がんのリスク低下が認められることは、乳がん予防のための身体活動支援を推進する上で重要なエビデンスである。

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Walking and Leisure-Time Activity and Risk of Hip Fracture in Postmenopausal Women

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Context Physical activity can reduce the risk of hip fractures in older women, although the required type and duration of activity have not been determined. Walking is the most common activity among older adults, and evidence suggests that it can increase femoral bone density and reduce fracture risk.

Objective To assess the relationship of walking, leisure-time activity, and risk of hip fracture among postmenopausal women.

Design, Setting, and Participants Prospective analysis begun in 1986 with 12 years of follow-up in the Nurses' Health Study cohort of registered nurses within 11 US states. A total of 61 200 postmenopausal women (aged 40-77 years and 98% white) without diagnosis of cancer, heart disease, stroke, or osteoporosis at baseline.

Main Outcome Measures Incident hip fracture resulting from low or moderate trauma, analyzed by intensity and duration of leisure-time activity and by time spent walking, sitting, and standing, measured at baseline and updated throughout follow-up.

Results From 1986 to 1998, 415 incident hip fracture cases were identified. After controlling for age, body mass index, use of postmenopausal hormones, smoking, and dietary intakes in proportional hazards models, risk of hip fracture was lowered by 6% (95% confidence interval [CI], 4%-9%; $P<.001$) for each increase of 3 metabolic equivalent (MET)–hours per week of activity (equivalent to 1 h/wk of walking at an average pace). Active women with at least 24 MET-h/wk had a 55% lower risk of hip fracture (relative risk [RR], 0.45; 95% CI, 0.32-0.63) compared with sedentary women with less than 3 MET-h/wk. Even women with a lower risk of hip fracture due to higher body weight experienced a further reduction in risk with higher levels of activity. Risk of hip fracture decreased linearly with increasing level of activity among women not taking postmenopausal hormones ($P<.001$), but not among women taking hormones ($P=.24$). Among women who did no other exercise, walking for at least 4 h/wk was associated with a 41% lower risk of hip fracture (RR, 0.59; 95% CI, 0.37-0.94) compared with less than 1 h/wk. More time spent standing was also independently associated with lower risks.

Conclusion Moderate levels of activity, including walking, are associated with substantially lower risk of hip fracture in postmenopausal women.

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Despite varying populations and diversity in methods of assessing physical activity, evidence from epidemiological studies suggests that the risk of hip fracture can be reduced by 20% to 50% for active compared with sedentary adults.[1,2] Most hip fractures result from a fall,[3] and several clinical trials have demonstrated that regular activity can reduce fall occurrence[4-6] through improvements in muscle strength[7-11] and balance.[12-14] Physical activity can also reduce fracture risk by increasing the mechanical load on bone, which promotes remodeling. Clinical trials have demonstrated that femoral bone density can be increased with weight-bearing exercise or resistance training.[15-17]

Although physical activity has definite benefits for bone health, its relative contributions to fracture reduction by type, frequency, intensity, and duration of activity have been difficult to define. In this analysis, we examined associations between exercise and leisure-time activities and the risk of hip fracture among postmenopausal women in the Nurses' Health Study, considering type, intensity, and duration of activity. We also assessed the concurrent influences of body mass index, postmenopausal hormone use, smoking, and diet.

METHODS

The Nurses' Health Study is an ongoing cohort of 121 700 women who in 1976 (time of initial mail questionnaire) were registered nurses between the ages of 30 and 55 years and resided in 1 of 11 US states. Approximately 98% of the cohort is white. Follow-up questionnaires are sent every 2 years and the response rate is at least 90% in each cycle. Deaths are confirmed through the National Death Index.[18] On the initial questionnaire, participants provided a medical history and information on lifestyle and other risk factors related to cancer and heart disease. Subsequent questionnaires updated these data and were expanded to include other diseases and relevant risk factors. Time spent in specific exercise or leisure-time activities was added to the questionnaire in 1986.

This analysis began in 1986 with the postmenopausal women who responded to the specific activity questions and had not reported a previous

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hip fracture or a diagnosis of cancer, heart disease, stroke, or osteoporosis. Eligible women entered the analysis after menopause. A total of 61 200 women, aged 40 to 77 years, contributed to this analysis with follow-up through 1998.

Hip Fracture Outcomes

In 1982, participants reported all previous hip fractures with the date and circumstances leading to fracture. Incident fractures were reported on subsequent biennial questionnaires. Only fractures due to low or moderate trauma (eg, slipping on ice, falling from the height of a chair) were included as cases in this study. Those associated with high trauma (eg, skiing, falling off a ladder) were excluded from analysis (about 15% of reported hip fractures). During the 12 years of follow-up, 415 cases were identified among the women in this study. The median age at fracture was 67 years (range, 46-75 years). Although we relied on self-reports of hip fractures, we expected reliable information in a cohort of registered nurses. Specificity was demonstrated in a small validation study in which all 30 reported hip fractures were confirmed by medical records.[19]

Activity and Inactivity

In 1986, participants were asked to report the average amount of time spent per week during the previous year in each of 7 activities: walking or hiking outdoors, jogging (>10 min/mile), running, bicycling (including stationary machine), racquet sports, lap swimming, and other aerobic activity (eg, aerobic dance, rowing machine). These activities were the most common ones reported by women in the University of Pennsylvania Alumni Health Study. For each activity, women chose one of 11 duration categories that ranged from zero to 11 h/wk or more. Walking pace was also reported as either easy (<2 mph), average (2-2.9 mph), brisk (3-3.9 mph), very brisk (≥4 mph), or unable to walk. Activity was reassessed in 1988, 1992, 1994, and 1996. The last 3 activity questionnaires included 2 additional items: other vigorous activities (eg, lawn mowing) and lower intensity exercise (eg, yoga, stretching).

Each activity on the questionnaire was assigned a metabolic equivalent (MET) score based on the classification by Ainsworth et al.[20] One MET is the energy expenditure for sitting quietly. MET scores for specific activities are defined as the ratio of the metabolic rate associated with that activity divided by the resting metabolic rate. For example, walking at an average pace was assigned a MET score of 3; jogging, 7; and running, 12. MET scores for walking were assigned based on walking pace; for other activities, a leisurely to moderate intensity score was selected. The scores for MET-hours per week for each activity were calculated from the reported hours per week engaged in that activity multiplied by the assigned MET score, and the values from the individual activities were summed for a total MET-hours per week score. To obtain the best long-term measure of physical activity, total values were cumulatively averaged in analyses. That is, at the beginning of each 2-year follow-up cycle, the MET-hours per week is the mean of all MET-hours per week calculated from responses to the questionnaires up to that time.

We also assessed inactivity with hours per week spent sitting and standing (at home, at work, and other time away from home). These items were on the questionnaires in 1988, 1990, and 1992, and hours of standing were cumulatively averaged over follow-up in this analysis. For sitting, the data were collected with one general question in 1988, which was later expanded to 2 (in 1990) and 3 (in 1992) more specific questions. Predictably, the total reported hours per week of sitting in the cohort increased as the number of questions increased. Therefore, separate category cut points were created for each year of data collection and hours of sitting were updated, but not cumulatively averaged, over follow-up.

The ability of the activity questionnaire to assess total activity and inactivity over the previous year was tested in a sample of 151 white women.[21] Compared with four 7-day activity diaries, the questionnaire underascertained total activity by approximately 20% and inactivity by 35%. However, the correlations for total MET-hours per week of activity (r=0.62; 95% confidence interval [CI], 0.44-0.75) and total hours of inactivity (r=0.41; 95% CI, 0.25-0.54) suggest that the questionnaire is a reasonably valid tool for categorical ranking of respondents. The activity questionnaire was also compared with 4 past-week questionnaires collected seasonally during the year. For walking, the primary activity among postmenopausal women, the correlation was 0.70 (95% CI, 0.49-0.84).

In 1980, participants were asked to report the number of hours per week spent in moderate and vigorous activity as well as the frequency in which they engaged in any regular activity long enough to work up a sweat. From the responses to these questions, we estimated the number of hours per week that participants engaged in leisure-time activities in 1980. This was used with the 1986 hours per week from the activity questionnaire to determine a 6-year change in activity level.

Covariates

Weight was requested on all biennial questionnaires and body mass index (BMI) was calculated using the height reported on the initial 1976 questionnaire. Postmenopausal hormone use (never, past, or current) and smoking (never, past, or current, with time since quitting for past smokers and number of cigarettes per day for current smokers) were also assessed every 2 years. Diet was measured at least every 4 years beginning in 1980 with a semiquantitative food frequency questionnaire, and intakes of calcium, vitamin D, retinol, protein, vitamin K, alcohol, and caffeine were calculated from the reported consumption of foods and use of multivitamins and specific vitamin or mineral supplements. The BMI and nutrient intakes were cumulatively averaged over follow-up in this analysis.

Statistical Analysis

Study participants contributed person-time from the return date of their 1986 questionnaire or the questionnaire on which they first became postmenopausal until the occurrence of a hip fracture, death, or the end of follow-up on June 1, 1998. A total of 576518 person-years was accrued from the 61200 women in this analysis. Median follow-up time per woman was 11.6 years.

Person-time was allocated to the appropriate category for each exposure and covariate variable at the beginning of every 2-year follow-up cycle. Age-adjusted incidence rates were calculated within exposure categories and relative risks (RRs) are the ratio of the rate in each upper category compared with the rate in the lowest category. Cox proportional hazards models were used to calculate multivariate RRs adjusted for other risk factors for hip fracture. *P* values for linear trend and for interaction in stratified analyses were determined using continuous exposure variables in the models. Statistical analysis was conducted using SAS statistical software (Version 6.12; SAS Institute Inc, Cary, NC) and $P<.05$ was used as the level of significance.

RESULTS

The postmenopausal women in this analysis were fairly sedentary. From the 7 activity questions in 1986, the median total activity was 7 MET-h/wk (equivalent to 2.3 h/wk of walking at an average pace), while 19% of the women reported zero or minimal leisure-time activity (ie, <15 min/wk). In the general US population, 29% of adults engage in no leisure-time activity.[22] Walking was by far the most popular activity in this cohort, contributing 66% of the total MET-hours per week. The median duration among walkers was 1.25 h/wk. Biking (14%) and other aerobic activity (11%) were contributors toward total activity.

Table 1. Characteristics of Postmenopausal Women (N = 61 200) by Metabolic Equivalent (MET)–Hours per Week of Activity in the Nurses' Health Study, 1986-1998*

	Activity, MET-h/wk†				
	<3	3-8.9	9-14.9	15-23.9	≥24
Age, y	60	61	61	61	61
Type of activity, h/wk					
Walking	0.2	0.6	1.0	1.6	2.7
Standing	30	33	35	37	39
Sitting‡	38	37	37	36	36
Body mass index	25.6	25.1	24.7	24.3	23.6
Current use, %					
Hormone replacement therapy	29	36	40	40	40
Cigarettes	23	17	14	13	13
Thiazide diuretic	17	15	14	13	12
Calcium supplement	37	43	36	48	50
Multivitamin	38	43	36	47	48
Daily intake					
Calcium, mg	868	917	953	978	1007
Vitamin D, µg	7.5	7.9	8.3	8.5	8.8
Retinol, µg	1255	1302	1359	1397	1453
Vitamin K, µg	165	175	186	194	210
Protein, g	73	74	75	75	76
Alcohol, g	6.1	5.8	6.1	6.5	7.0
Caffeine, mg	336	320	310	308	299
Total energy, kcal	1663	1688	1699	1709	1729
Hip fracture incidence/100 000 women per year					
Age-standardized	118	82.4	70.2	52.7	46.6
Adjusted§	230	184	155	124	100

*Values are standardized to the age distribution of the study population over follow-up from 1986 to 1998.
†Calculated from time spent in exercise and leisure-time activities in 1986, 1988, 1992, 1994, and 1996. Values were cumulatively averaged in analyses.
‡Data are for 1992 only.
§Hip fracture incidence estimated for white women 65 years old who have never smoked, do not use postmenopausal hormones, do not drink alcohol, and are at the median level for all other covariates.

TABLE 1 outlines the characteristics of the study population by level of activity. Active women spent more time walking and standing, but sitting was unrelated to activity. Active women also had a lower BMI, were less likely to smoke, were more likely to take postmenopausal hormones, and were more likely to take a calcium supplement and a multivitamin, although diet in general was not strongly related to activity. Although thiazide diuretic use was somewhat higher among less active women, this factor was not included in multivariate models because it did not confound results. Hip fracture incidence rates for this cohort are also presented.

Among the postmenopausal women in this study, both activity and BMI exhibited significant inverse associations with risk of hip fracture (TABLE 2). These associations were independent of one another and showed little confounding by the other measured risk factors. Compared with the women in the lowest category of less than 3 MET-h/wk, those with 24 MET-h/wk or higher had a significantly lower (55%) hip fracture risk (RR, 0.45; 95% CI, 0.32-0.63) in the multivariate analysis. Risk declined in a dose-dependent manner with a 6% decrease in risk (95% CI, 4%-9%) for every 3 MET-h/wk increase in activity (equivalent to 1 h/wk of walking at an average pace). Risks of hip fracture among women with BMIs between 25.0 and 29.9 were not different from that of the reference group with BMIs between 23 and 24.9. A BMI of 30 or higher was associated with 50% the hip fracture risk of women in the reference group, and women with a BMI of less than 23 had significantly higher risk (45%-83%; Table 2). These inverse associations between activity, BMI, and risk of hip fracture were unchanged when women were excluded during follow-up because of diagnosis of cancer, heart disease, stroke, or diabetes. We also found that fracture risks were unchanged when women who reported balance problems in 1990 (5% of the study population) were excluded from analysis.

Based on our risk estimates, we calculated the percentage of hip fractures

Table 2. Relative Risks of Hip Fracture by Metabolic Equivalent (MET)–Hours per Week of Activity and by Body Mass Index (BMI)

	Activity, MET-h/wk*					
	<3	3-8.9	9-14.9	15-23.9	≥24	*P* for Trend
Cases	110	124	73	54	54	
Person-years (1986-1998)	112 029	153 167	101 091	98 841	111 389	
Relative risk (95% confidence interval)						
Age-adjusted	1.00	0.74 (0.57-0.95)	0.63 (0.46-0.85)	0.47 (0.34-0.65)	0.41 (0.29-0.57)	<.001
MET-hours, BMI, and age	1.00	0.74 (0.57-0.97)	0.62 (0.46-0.84)	0.46 (0.33-0.64)	0.38 (0.27-0.53)	<.001
Multivariate†	1.00	0.79 (0.60-1.03)	0.67 (0.49-0.92)	0.53 (0.37-0.74)	0.45 (0.32-0.63)	<.001

	BMI‡						
	<21	21-22.9	23-24.9	25-26.9	27-29.9	≥30	*P* for Trend
Cases	134	86	63	49	48	25	
Person-years (1986-1998)	116 730	105 492	106 775	82 688	77 790	77 479	
Relative risk (95% confidence interval)							
Age-adjusted	1.89 (1.40-2.56)	1.42 (1.03-1.97)	1.00	0.99 (0.68-1.44)	1.04 (0.71-1.51)	0.58 (0.37-0.93)	<.001
MET-hours, BMI, and age	1.91 (1.41-2.57)	1.45 (1.05-2.01)	1.00	0.97 (0.67-1.41)	0.99 (0.68-1.44)	0.52 (0.33-0.83)	<.001
Multivariate†	1.83 (1.35-2.48)	1.45 (1.05-2.01)	1.00	0.97 (0.67-1.41)	0.98 (0.67-1.43)	0.50 (0.31-0.80)	<.001

*Calculated from time spent in exercise and leisure-time activities in 1986, 1988, 1992, 1994, and 1996. Values were cumulatively averaged in analyses.
†Adjusted for MET-hours, BMI, age, smoking, postmenopausal hormone use, and intakes of calcium, vitamin D, retinol, protein, vitamin K, alcohol, and caffeine.
‡Assessed every 2 years during follow-up. Values were cumulatively averaged in analyses.

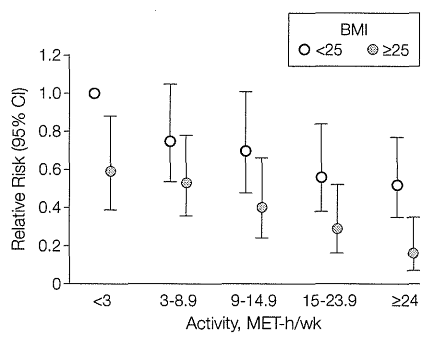
in the Nurses' Health Study cohort that could have been prevented if all participants had exercised at a higher level. If all had exercised at 9 MET-h/wk or higher, 23% (95% CI, 15%-34%) of the hip fractures could have been prevented; at 15 MET-h/wk or higher, 32% (95% CI, 21%-44%) could have been prevented; and if all exercised at 24 MET-h/wk or higher, 42% (95% CI, 27%-59%) of the hip fractures could have been prevented.

Higher levels of physical activity were significantly protective against hip fractures among both the leaner (BMI <25; *P* for trend <.003) and heavier women (BMI ≥25; *P* for trend <.001). However, the heavier women had a lower fracture risk in every activity category (FIGURE 1). Even among the leanest (BMI <21) and heaviest (BMI ≥30) women, we observed significant inverse linear associations between activity and risk of hip fracture (*P* for trend=.04 in both BMI strata).

The association between activity and hip fractures appeared dissimilar for users and nonusers of postmenopausal hormones (FIGURE 2). However, a test for interaction was not statistically significant (*P*=.12). Among the nonusers, there was a steep decline in risk (*P* for trend <.001) with higher levels of activity. For the postmenopausal hormone users, risk was significantly lower compared with nonusers in the lowest activity category of less than 3 MET-h/wk (RR, 0.45; 95% CI, 0.26-0.78) and there was little further risk reduction with higher activity levels (*P* for trend=.24). In the highest activity category of 24 MET-h/wk or higher, the reduced risk of hip fracture was essentially the same for the hormone users (RR, 0.29; 95% CI, 0.16-0.51) and nonusers (RR, 0.33; 95% CI, 0.22-0.50) when both were compared with nonusers in the lowest activity category. We also examined the association between physical activity and hip fracture stratified by median years of age and by median intakes of calcium, vitamin D, and retinol, but did not find any evidence that the association differed in the upper and lower strata of these variables.

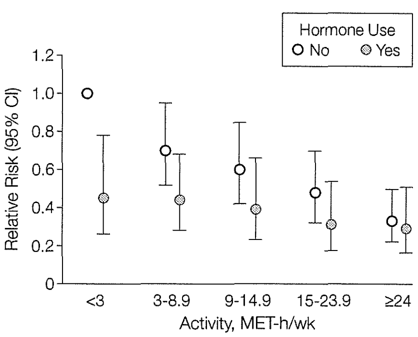
We explored the risk of hip fracture among women who increased or decreased their level of activity based on the differences in hours per week reported on the 1980 and 1986 questionnaires (TABLE 3). Consistent with our primary analyses, risk was assessed from 1986-1998 and women with a diagnosis of cancer, heart disease, stroke, or osteoporosis were excluded at baseline.

Figure 1. Hip Fracture Among Postmenopausal Women in the Nurses' Health Study, 1986-1998, by Body Mass Index (BMI)



Analyses were adjusted for the covariates in the Table 2 multivariate model. *P* for interaction=.002. CI indicates confidence interval; MET, metabolic equivalent.

Figure 2. Hip Fracture Among Postmenopausal Women in the Nurses' Health Study, 1986-1998, by Hormone Use



Analyses were adjusted for the covariates in the Table 2 multivariate model. *P* for interaction=.12. CI indicates confidence interval; MET, metabolic equivalent.

Among women who reported a low activity of less than 1 h/wk in 1980, those who increased their activity to 4 h/wk or more by 1986 had an RR of 0.53 (95% CI, 0.27-1.04) compared with those who remained in the low-activity category. Risk appeared to decrease as the 1986 activity level increased (*P* for trend=.07). Among women who reported a high activity level of 4 h/wk or more in 1980, risk of hip fracture was doubled among those who decreased to less than 1 h/wk in 1986 (RR, 2.08; 95% CI, 1.20-3.61) compared with those who remained in the high activity category. Risk increased linearly with increasing reduction of activity (*P* for trend=.004). Similar results were found when comparing change in activity between 1986 and 1992. For those who increased activity from less than 3 to 15 MET-h/wk or higher from 1986 to 1992, the adjusted RR for hip fracture was 0.34 (95% CI, 0.13-0.88) and for those who decreased activity from 15 MET-h/wk or more to less than 3 MET-h/wk, the RR was 1.84 (95% CI, 0.86-3.92).

Since walking was the primary activity for the postmenopausal women in this cohort, we examined whether walking was associated with a lower risk of hip fracture. No other activity was reported with sufficient frequency for an individual analysis. To focus only on walking, we excluded women at baseline and during follow-up when they reported engaging in any other activity for 20 min/wk or more. Compared with women who reported no activity or who walked for less than 1 h/wk, those who walked 4 h/wk or more had a significantly lower risk of hip fracture (RR, 0.59; 95% CI, 0.37-0.94) and there was a significant dose-response of lower risk with longer duration of walking (*P* for trend=.02; TABLE 4). Walking pace was also a significant predictor of hip fracture. Compared with an easy pace, women reporting an average pace had 49% lower risk and women reporting a brisk to very brisk pace had 65% lower risk. When both duration and pace were analyzed in the same multivariate model, the RRs for pace did not change while those for duration were attenuated (RR, 0.72; 95% CI, 0.45-1.16 for ≥4 h/wk).

Sitting and standing were assessed as measures of inactivity in this cohort. Sitting was not significantly associated with risk of hip fracture (TABLE 5), although a nonsignificant increase in risk was observed among the women sitting 55 h/wk or more (RR, 1.29; 95% CI, 0.85-1.96) compared with those sitting for less than 10 h/wk after controlling for hours of standing, total MET-hours per week, BMI, and the other measured risk factors. In contrast to sitting, we observed a significant dose-response relationship between standing and risk of hip fracture (*P* for trend=.01). Compared with women who stood for less than 10 h/wk, women standing for 55 h/wk or more had a significantly lower (46%) risk. Standing for any duration of 10 h/wk or more was associated with a significantly lower (28%) fracture risk (RR, 0.72; 95% CI, 0.53-0.97).

Table 3. Relative Risks (RRs) of Hip Fracture by Change in Hours of Activity Between 1980 and 1986*

	Activity in Hours per Week in 1986				
	<1	1	2-3	≥4	*P* Value
	Activity in 1980 <1 h/wk				
Cases	57	22	16	10	
Person-years (1986-1998)	55 268	25 642	20 357	18 024	
RR (95% CI)	1.00	0.86 (0.52-1.43)	0.79 (0.45-1.38)	0.53 (0.27-1.04)	.07
	Activity in 1980 ≥4 h/wk				
Cases	28	18	29	26	
Person-years (1986-1998)	32 833	29 816	40 318	55 764	
RR (95% CI)	2.08 (1.20-3.61)	1.47 (0.80-2.71)	1.73 (1.02-2.95)	1.00	.004

*Adjusted for age, body mass index, smoking, postmenopausal hormone use, and intakes of calcium, vitamin D, retinol, protein, vitamin K, alcohol, and caffeine. CI indicates confidence interval.

COMMENT

In this 12-year prospective study among postmenopausal women, total physical activity from exercise and leisure-time activities was associated with a significantly lower risk of hip fracture. Our primary measure of activity was a MET-hour, which combined an assessment of duration and intensity. Risk of hip fracture declined 6% for every increase of 3 MET-h/wk (equivalent to 1 h/wk of walking at an average pace).

Table 4. Relative Risks (RRs) of Hip Fracture by Hours per Week of Walking and by Walking Pace*

	Walking, h/wk†				*P* for Trend	Walking Pace‡		
	<1	1	2-3	≥4		Easy	Average	Brisk/Very Brisk
Cases	115	41	36	22		65	99	30
Person-years (1986-1998)	130 807	55 575	45 044	36 215		47 887	142 912	68 683
RR (95% CI)								
Age-adjusted	1.00	0.75 (0.53-1.08)	0.75 (0.51-1.09)	0.57 (0.36-0.90)	.009	1.00	0.56 (0.41-0.77)	0.39 (0.25-0.61)
Multivariate§	1.00	0.79 (0.55-1.14)	0.78 (0.53-1.14)	0.59 (0.37-0.94)	.02	1.00	0.51 (0.37-0.71)	0.35 (0.22-0.55)

*Women were excluded when they reported engaging in an exercise or leisure-time activity other than walking for 20 min/wk or more. This analysis included 34 592 women and 214 hip fractures. CI indicates confidence interval.
†Asssessed in 1986, 1988, 1992, 1994, and 1996 and values were cumulatively averaged.
‡Assessed in 1986, 1988, 1990, 1992, and 1996 and status was updated in analysis.
§Adjusted for age, body mass index, smoking, postmenopausal hormone use, and intakes of calcium, vitamin D, retinol, protein, vitamin K, alcohol, and caffeine.

Previous prospective studies using differing measures of activity among older men and women have reported a 25% to 39% lower risk of hip fracture in the active vs inactive participants.[23-25]

As observed in this and other studies,[26,27] higher BMI is also associated with a reduced risk of hip fracture, likely due to its weight-bearing effect on bone, the protection supplied by padding around the hips in the event of a fall, and the conversion of androgens to estrogen in fatty tissues.[28] However, we found that heavier women could further reduce their fracture risk by engaging in more physical activity. Though lean women also appeared to benefit from activity, the very elderly or those with involuntary weight loss may be at higher risk of fractures due to general frailty.[29]

Even during adult years, initiation of regular physical activity can reduce fracture risk, but activity must be maintained to preserve the benefits. We found that risk of hip fracture decreased among sedentary women who increased their activity to 4 h/wk or more compared with those who remained sedentary. Conversely, risk increased among those who were actively exercising but became sedentary. Although women with a major chronic disease were removed from this analysis, we cannot exclude the possibility that other medical conditions or underlying disease contributed to both the reduced activity and increased fracture risk. Similar to our finding, Hoidrup et al[25] reported that risk of hip fracture increased among moderately active men and women who were sedentary 6 years later compared with those who remained in the moderately active group.

Several studies have reported an interaction between activity and postmenopausal hormone use. In clinical research, a combination of estrogen supplementation plus exercise was more effective than exercise alone in increasing trabecular bone mineral density in older women.[30] Population studies have observed a reduced risk of hip fracture with postmenopausal hormone use among sedentary women, but not among physically active women.[31,32] In our cohort, we found that active women not taking supplemental estrogen had similar protection against hip fractures as that provided by hormone use. Interactions reported between the effects of calcium intake and physical activity on bone density[33,34] were not supported by our data.

Based on accumulated evidence for all health outcomes, at least 30 minutes to 1 hour of moderate intensity exercise on most days of the week is recommended for adults.[35,36] However, recommendations for bone health may be different from those focused on cardiovascular fitness in which intensity of activity to raise heart rate is a critical factor. A high peak load or impact may be more important than endurance.[37,38] Also, vigorous exercise is associated with a higher risk of fall-related fractures,[2] particularly in the elderly and those with functional limitations.[39] For bone, activities that improve balance or flexibility are important to reduce the risk of falling,[40] while weight-bearing activities and resistance training can increase muscle size and strength[7,10] and lead to higher bone mineral density at the muscle site.[17,41]

Walking may increase femoral bone density,[42] and it is a relatively safe and easy activity and already the most common exercise among older adults.[35] In our cohort, walking for 4 h/wk or more was associated with a 41% lower risk of hip fracture. A faster pace was also associated with lower risk, perhaps because of a greater impact on the bone. Several cross-sectional studies have reported positive correlations between walking and bone density.[43-45] A prospective study reported a 30% lower risk of hip fracture among women who walked for exercise.[46] In relatively short-term clinical trials, brisk walking attenuated femoral bone loss, but increased the risk of falling,[47] while a walking program increased spinal bone mineral density, but had no effect at the femoral site.[48]

Table 5. Relative Risks (RRs) of Hip Fracture by Hours of Sitting and Standing per Week*

	Hours per Week					
	<10	10-24	25-39	40-54	≥55	*P* for Trend
Sitting†						
Cases	37	92	77	63	71	
Person-years (1988-1998)	45878	131416	122053	110762	88090	
RR (95% CI)						
Age-adjusted	1.00	0.85 (0.57-1.25)	0.81 (0.54-1.20)	0.74 (0.49-1.11)	1.03 (0.69-1.54)	.83
Sitting, standing, and age-adjusted	1.00	0.93 (0.62-1.37)	0.94 (0.62-1.43)	0.88 (0.58-1.35)	1.21 (0.80-1.84)	.26
Multivariate‡	1.00	0.96 (0.65-1.43)	1.02 (0.67-1.55)	0.96 (0.62-1.47)	1.29 (0.85-1.96)	.16
Standing§						
Cases	66	95	90	54	33	
Person-years (1988-1998)	61786	122646	127141	98117	85246	
RR (95% CI)						
Age-adjusted	1.00	0.73 (0.53-1.01)	0.73 (0.53-1.01)	0.62 (0.43-0.90)	0.51 (0.34-0.78)	.004
Sitting, standing, and age-adjusted	1.00	0.73 (0.53-1.02)	0.73 (0.52-1.02)	0.62 (0.42-0.90)	0.51 (0.33-0.79)	.006
Multivariate‡	1.00	0.77 (0.55-1.07)	0.77 (0.55-1.09)	0.66 (0.45-0.97)	0.54 (0.35-0.84)	.01

*CI indicates confidence interval.
†Assessed in 1988, 1990, and 1992 and values were updated in analyses. Cut points were specific for each year due to the differing number of questions used in data collection.
‡Adjusted for sitting, standing, age, MET-hours, body mass index, smoking, postmenopausal hormone use, and intakes of calcium, vitamin D, retinol, protein, vitamin K, alcohol, and caffeine.
§Assessed in 1988, 1990, and 1992 and values were cumulatively averaged in analyses.

Standing was also associated with a lower risk of hip fracture in our cohort, independent of body weight and time spent in leisure-time activities. As a weight-bearing activity, standing could confer benefits to balance and muscle that may translate into improved bone strength and protection against hip fracture. Although prior research is limited, the prospective Study of Osteoporotic Fractures[46] reported a 70% increased risk of hip fracture among postmenopausal women who stood for less than 4 h/d, and a cross-sectional study[49] found that active nurses had higher femoral bone mineral densities compared with clerks sitting at a desk.

The results of this study are applicable to white postmenopausal women and may not be generalizable to men, to women of other racial or ethnic backgrounds, or to a more elderly or frail population. Also, we lacked prospective data on frequency of falling and it is possible that women who experienced a bad fall but did not break a bone were more cautious and therefore limited their activity.

In conclusion, more leisure-time activity is associated with a lower risk of hip fractures in postmenopausal women. Walking is the most common exercise and is a suitable activity for lowering fracture risk. Both lean and heavy women can reduce their fracture risk by increasing their level of activity.

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Obtained funding: Willett, Colditz.
Administrative, technical, or material support: Colditz.

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