testinal transit time, altered prostaglandin levels, improved immune function, changes in bile acid metabolism, and increased levels of gastrointestinal hormones that can lower gut transit time and bile acid excretion. Giovannucci (*67*) hypothesized that insulin resistance may be the factor by which other factors, such as physical inactivity and abdominal obesity, act to increase the risk of colon cancer. These factors are strong, independent determinants of insulin resistance and hyperinsulinemia (*68-73*); since insulin is an important growth factor for colonic mucosal cells and colonic cancer cells in vitro (*74-76*), hyperinsulinemia may mediate the effect of a sedentary lifestyle on the risk of colon cancer.

A major strength of this study, aside from its prospective nature, is the ability to control for other known or suspected risk factors for colon cancer. It is possible that physically active women have other healthy lifestyle factors, as was observed in this cohort of women. However, with control for these factors, the RRs were only slightly altered and remained statistically significant. Thus, leisure-time physical activity not only appears to be an indicator of a healthy lifestyle but also exerts an independent protective effect against colon cancer.

In conclusion, these prospective data show a significant reduction in the risk of colon cancer associated with a higher level of leisure-time physical activity in women. They also add to the current literature on the higher risk of colon cancer associated with a greater body size, particularly BMI. These risk factors appear to act independently of each other and of other risk factors for colon cancer. Consistent with some previous studies, these findings are stronger for left-sided colon cancer. Currently, 24% of the U.S. population engages in no physical activity (*77*). Another 54% is somewhat active but still fails to meet the current recommendations of engaging regularly in light-to-moderate physical activity for at least 30 minutes per day (*78,79*). Powell and Blair (*80*) estimate that 3500 deaths from colon cancer could be prevented if 50% of the people who are irregularly active engaged regularly in physical activity. Our own data suggest that engaging in activities of moderate intensity (i.e, walking at a normal or brisk pace) for 1 hour per day is associated with a 46% reduction in the risk of developing colon cancer. Thus, increasing physical activity levels may be an effective approach for reducing the burden of colon cancer in our society.

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Notes

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	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	30-55歳			( )		前向き研究
対象数	10000以上			( )		( )
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. Relative risk (RR) of colon cancer according to level of leisure-time physical activity (in MET-hours*) in 1986,† Nurses' Health Study, 1986-1992

	MET-hours per week					
	<2	2-4	5-10	11-21	>21	Two-sided P for trend‡
Person-years	63 734	51 413	66 435	60 769	58 817	
Colon cancer§						
No. of cases	47	26	36	29	23	
Age-adjusted RR	1.00 (referent)	0.69	0.74	0.65	0.52	
Multivariate RR‖	1.00 (referent)	0.71	0.78	0.67	0.54	.03
95% CI¶	—	0.44-1.15	0.50-1.20	0.42-1.07	0.33-0.90	
Distal colon cancer						
No. of cases	21	15	17	14	6	
Age-adjusted RR	1.00 (referent)	0.89	0.78	0.70	0.31	
Multivariate RR‖	1.00 (referent)	0.92	0.81	0.71	0.31	.01
95% CI¶	—	0.48-1.79	0.43-1.55	0.36-1.41	0.12-0.77	
Proximal colon cancer						
No. of cases	19	8	15	11	13	
Age-adjusted RR	1.00 (referent)	0.53	0.76	0.61	0.73	
Multivariate RR‖	1.00 (referent)	0.54	0.79	0.62	0.77	.67
95% CI¶	—	0.23-1.22	0.40-1.56	0.30-1.32	0.38-1.58	

*See footnote to Table 1 for definition and calculation of MET-hours.
†Data were based on 67 803 respondents. Data on leisure-time physical activity were missing for 51 case patients and 84 651 person-years.
‡Test for trend was calculated by use of the median of each MET-hours per week category as a continuous variable in the multiple regression model.
§Includes 22 cases lacking data on anatomic site.
‖Adjusted for age, cigarette smoking, family history of colorectal cancer, body mass index, postmenopausal hormone use, aspirin use, intake of red meat, and alcohol consumption.
¶CI = confidence interval.

図表掲載箇所	P950, 表2
概 要 (800字まで)	本研究は，余暇時間の身体活動，BMI，体脂肪分布と女性の大腸癌発症リスクとの関連を検討することを目的としたコホート研究である．参加者は，the Nurses' Health Studyの参加者67802名であった．身体活動は，週何時間活動をしているかについて質問され，ウォーキング，ハイキング，ジョギング，ランニング，自転車，水泳，テニス，スカッシュ，ラケットボール，健康体操，エアロビ，ローイングの種目が含まれていた．さらに，1日の階段使用回数や通常の歩行速度についても調査された．これらの調査結果より，メッツ・時/週に換算され，身体活動が評価された．大腸癌発症リスクとの関連について検討した結果，身体活動が週2メッツ・時未満の者と比較して，2-4メッツ・時/週の者の調整相対リスクは0.71(95%CI:0.44-1.15)，5-10メッツ・時/週の者では0.78(0.50-1.20)，11-21メッツ・時/週の者では0.67(0.42-1.07)，21メッツ・時/週以上の者では0.54(0.33-0.90)となり，量反応関係が認められた(trend P=0.03)．さらに，遠位大腸癌と近位大腸癌で分類して解析した結果，遠位大腸癌発症リスクと身体活動量との間には量反応関係が認められたが(trend P=0.01)，近位大腸癌の発症リスクにおいては有意な関連性が観察されなかった(trend P=0.67)．また，BMI，ウエスト・ヒップ比においても同様の検討を行った．BMIが高い者では大腸癌発症リスクが高いことが示された(trend P=0.04)．一方，ウエスト・ヒップ比では有意な関連が認められなかった．
結 論 (200字まで)	身体活動が多い女性は，大腸癌発症リスクが低いことが示唆された．
エキスパートによるコメント (200字まで)	身体活動と大腸癌の発症リスクとの関連について検討した女性を対象とした大規模なコホート研究である．身体活動を推奨する上で重要なエビデンスのひとつである．

担当者　川上諒子

ARTICLE

A Prospective Study of Age-Specific Physical Activity and Premenopausal Breast Cancer

Sonia S. Maruti, Walter C. Willett, Diane Feskanich, Bernard Rosner, Graham A. Colditz

Background Physical activity has been consistently associated with lower risk of postmenopausal breast cancer, but its relationship with premenopausal breast cancer is unclear. We investigated whether physical activity is associated with reduced incidence of premenopausal breast cancer, and, if so, what age period and intensity of activity are critical.

Methods A total of 64 777 premenopausal women in the Nurses' Health Study II reported, starting on the 1997 questionnaire, their leisure-time physical activity from age 12 to current age. Cox regression models were used to examine the relationship between physical activity, categorized by age period (adolescence, adulthood, and lifetime) and intensity (strenuous, moderate, walking, and total), and risk of invasive premenopausal breast cancer.

Results During 6 years of follow-up, 550 premenopausal women developed breast cancer. The strongest associations were for total leisure-time activity during participants' lifetimes rather than for any one intensity or age period. Active women engaging in 39 or more metabolic equivalent hours per week (MET-h/wk) of total activity on average during their lifetime had a 23% lower risk of premenopausal breast cancer (relative risk = 0.77; 95% confidence interval = 0.64 to 0.93) than women reporting less activity. This level of total activity is equivalent to 3.25 h/wk of running or 13 h/wk of walking. The age-adjusted incidence rates of breast cancer for the highest (≥54 MET-h/wk) and lowest (<21 MET-h/wk) total lifetime physical activity categories were 136 and 194 per 100 000 person-years, respectively. High levels of physical activity during ages 12–22 years contributed most strongly to the association.

Conclusions Leisure-time physical activity was associated with a reduced risk for premenopausal breast cancer in this cohort. Premenopausal women regularly engaging in high amounts of physical activity during both adolescence and adulthood may derive the most benefit.

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A quarter of all breast cancer diagnoses occur among premenopausal women (1), but few modifiable risk factors have been identified. Breast cancers among young women are more likely to have a higher grade, increased proliferation rate, and higher vascular invasion and may be more difficult to treat than breast cancers among older women (2,3). Moreover, risk factors such as body mass index (BMI) (4,5), oral contraceptive use (6), and reproductive characteristics (7) vary by menopausal status, suggesting different etiologies for pre- and postmenopausal breast cancers. An expert panel of the World Cancer Research Fund/American Institute for Cancer Research (8) and a recent systematic review (9) suggested that physical activity is associated with lower postmenopausal breast cancer incidence but that the relationship for premenopausal breast cancer is uncertain. Further unresolved questions include the role of physical activity at different age periods and intensity of activity on premenopausal breast cancer risk.

Physical activity has been hypothesized to reduce breast cancer risk through several mechanisms, including lowering the production or bioavailability of endogenous hormones such as estrogen, insulin, and insulin-like growth factor (IGF), which can act as mitogens (10,11). Estrogen stimulates the growth and division of epithelial breast cells, which can potentially increase cancer risk by allowing for the propagation of genetic errors. Insulin and IGF may raise cancer risk by increasing cellular proliferation and

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survival (12). Moreover, it has been hypothesized that the mechanism by which physical activity acts varies over time. Exposures during adolescence may be particularly relevant for breast cancer development because this period is characterized by increases in sex hormone levels and rapid proliferation of incompletely differentiated breast tissue. Among girls, strenuous activity is associated with later menarche and delayed establishment of regular menstrual cycles (13–16). Among adult women, exercise is related to decreased sex hormone levels, increased frequency of anovulation, and increased incidence of amenorrhea (17–19). Physical activity during both adolescence and adulthood may confer the greatest benefit for breast cancer risk by lowering lifetime levels of hormone risk factors (20). However, only three prospective studies (21–23), including one with only 12 breast cancer patients, have examined physical activity before adulthood, and none have examined lifetime activity in detail.

In this study, we investigated whether physical activity is associated with reduced incidence of premenopausal breast cancer, and if so, what age period and intensity of exercise are most critical. In two earlier prospective investigations, we did not detect an association between premenopausal breast cancer and leisure-time physical activity during adolescence (22) or adulthood (24). Here, we used a more detailed measure of adolescent physical activity and investigated the role of lifetime (ages 12 years to current) physical activity. Based on proposed biologic mechanisms and some observational findings, we hypothesized that physical activity is associated with reduced risk of premenopausal breast cancer.

CONTEXT AND CAVEATS

Prior knowledge

Physical activity is associated with reduced risk of breast cancer among postmenopausal women.

Study design

Cohort study of premenopausal nurses who were surveyed about the type and duration of leisure-time physical activity they engaged in during their lifetime and were monitored for breast cancer for 6 years.

Contributions

Average lifetime physical activity equivalent to 3.25 h/wk of running or 13 hours per week of walking was associated with a reduced risk for breast cancer compared with less activity (136 vs 196 breast cancers per 100000 person-years). High amounts of physical activity during ages 12–22 were the most important.

Implications

In this cohort, women who regularly engaged in high amounts of physical activity during adolescence and early adulthood had a lower risk of premenopausal breast cancer than women who engaged in less activity.

Limitations

The results are likely to be generalizable only to premenopausal white women. Nearly 90% of the women in the cohort also regularly engaged in regular occupational physical activity (walking). Other lifestyle behaviors may also be important. In addition, the physical activity data were based on recall.

Subjects and Methods

Study Population

The Nurses' Health Study II (NHSII) is an ongoing cohort study that began in 1989, when 116608 female registered nurses (aged 25–42 years) completed a self-administered questionnaire about risk factors for cancer. Biennially, participants are sent a follow-up questionnaire to update information on lifestyle factors and to report newly diagnosed conditions; response rates are approximately 90%. Reports of death are confirmed by searches of the National Death Index (25,26).

For this analysis, we followed women for 6 years, starting in 1997, when participants, who were then 33–51 years of age, reported their adolescent and adult physical activity. Women were excluded if they died before 1997, had a report of cancer (except for nonmelanoma skin cancer) before 1997, were diagnosed with breast cancer that was not invasive, did not report their physical activity during their youth, or were postmenopausal. After these exclusions, 64777 eligible premenopausal women remained. This study was approved by the Human Subjects Committee at Brigham and Women's Hospital in Boston, Massachusetts. Written informed consent was assumed upon completion and return of the questionnaire.

Assessment of Physical Activity

In 1997, participants were asked about their walking or leisure-time activity (ie, outside of work) during five age periods: grades 7–8 (ages 12–13), grades 9–12 (ages 14–17), ages 18–22, ages 23–29, and ages 30–34. For each period, participants reported the average hours per week they engaged in each of three activity categories, with examples given for each: strenuous (eg, running, aerobics, swimming laps), moderate (eg, hiking, walking for exercise, casual cycling, and yard work), and walking to and from school or work. In 1997 and again in 2001, participants reported the average hours per week spent on the following walking or leisure-time activities in the previous year: jogging, running, bicycling (including stationary machine), racquet sports, swimming laps, walking or hiking outdoors, calisthenics or aerobics, and other aerobic activities.

Occupational activity was assessed in 1997, when participants were asked to best describe their work activity during ages 23–29 and 30–34; answer choices were: not employed, mostly sitting, mostly standing, mostly walking with little lifting, mostly walking with much lifting, and heavy manual labor. Similar questions have been used in other studies (27,28). In this investigation, we chose, a priori, to primarily examine activity outside of work because there was little variation in participants' reported occupational levels (86% reported mostly walking with little or some amount of lifting).

All these physical activity questions are available online (29). When we evaluated the leisure-time physical activity measures, they had good reproducibility and validity. Recalled activity during the first three life periods had high 4-year reproducibility in a subgroup of 160 NHSII participants (average correlation $r = 0.76$ for strenuous, $r = 0.70$ for strenuous plus moderate, and $r = 0.64$ for total activity) (30). As for validity, our measure of physical activity in the previous year performed well when compared with previous week activity recalls ($r = 0.79$, 95% confidence interval [CI] = 0.64

to 0.88) and separately, with four 7-day activity diaries (r = 0.62, 95% CI = 0.44 to 0.75) in a subsample of NHSII participants (31). Moreover, in a validation study among 238 men, higher past year vigorous activity, as self-reported on a similar activity assessment, was associated with lower resting pulse (r = −0.45) (32). Furthermore, among 50 women aged 20–59, the physical activity score, as determined on a similar questionnaire, was correlated with maximal oxygen consumption (a measure of physical fitness) (r = 0.54) (33).

Estimation of Physical Activity by Intensity and Age

To classify intensity of leisure-time activity, each past year activity was assigned a metabolic equivalent (MET) value (31) based on the categorizations by Ainsworth et al. (34). The MET value is the ratio of the metabolic rate of an activity divided by the resting metabolic rate and generally describes the effort required for that activity (34). For example, running (12 METs) requires 12 times the energy as sitting quietly. We defined jogging, running, bicycling (including stationary machine), racquet sports, and swimming laps as strenuous (≥7.0 METs). Calisthenics or aerobics and other aerobic activity were moderate (4.0–6.0 METs); walking was categorized separately, with METs assigned according to pace (average = 3 METs). The intensity categories were based on Centers for Disease Control and Prevention designations (35) and are consistent with a recent 2007 consensus (36).

In these analyses, strenuous, moderate, and walking activities were expressed in hours per week and calculated by summing the hours per week of each activity. Total activity, expressed in MET hours per week (MET-h/wk), was computed by multiplying the hours per week of strenuous, moderate, and walking activities with their corresponding MET value and summing the values. To estimate activity levels for the five life periods, we assigned strenuous, moderate, and walking categories MET values of 7.0, 4.5, and 3.0, respectively.

To obtain mean leisure-time activity (for strenuous, moderate, walking, and total) during different age periods, we averaged activity levels for specific ages and across a woman's lifetime. We used linear interpolation to calculate yearly adult activity between the last life period report for ages 30–34 and the past year assessments. For example, in the case of a woman who was 45 in 1997, linear interpolation was used to estimate her activity for each age between 34 and 45, assuming that activity changed at the same rate. Mean lifetime physical activity was calculated by averaging activity from age 12 to the participant's current age. For example, if the sum of a 45-year-old woman's total activity from ages 12 to 45 (as weekly averages for each year) was 1320 MET-h/wk, her lifetime average would be 38.8 MET-h/wk (1320 MET/34). We similarly computed mean activity levels of women at ages 12–22 (referred to as "youth" for simplicity), 23–34, and 35 and older.

For occupational activity, we assigned MET values based on the occupational activity categorizations of Ainsworth et al. (37): mostly sitting (1.5 METs), mostly standing (3.0 METs), mostly walking with little lifting (3.8 METs), mostly walking with much lifting (4.5 METs), and heavy manual labor (7.0 METs). We estimated work activity in MET-h/wk by multiplying 40 h/wk (the average work week in the United States) by the activity's corresponding MET value. Thus, if a respondent chose mostly sitting during ages 23–29, her estimated work activity would be 60 MET-h/wk (1.5 METs × 40 h/wk). Occupational activity during ages 23–34 was obtained by calculating a weighted average of activity levels from ages 23–29 and 30–34 with the weights being the number of years in each period. Leisure plus occupational activity, in MET-h/wk, was the average of the two values. Individuals who reported not being employed were excluded from the occupation-related analyses.

Assessment of Incident Breast Cancer

Self-reported diagnoses of breast cancer on biennial NHSII questionnaires were confirmed by study physicians who, blinded to patient exposure status, reviewed participants' medical records and pathology reports. Details about the diagnosis, including hormone receptor status, were also recorded. We identified 739 premenopausal women with a breast cancer diagnosis between 1997 and 2003 who had physical activity data. We excluded all in situ cancers (n = 159) and 30 unconfirmed breast cancer diagnoses, leaving 550 women with diagnoses of invasive premenopausal breast cancer during follow-up. There were too few invasive postmenopausal breast cancers (n = 129) during the follow-up period to analyze separately.

Covariates

Age at menarche, height, childhood body shape, and menstrual length and pattern during ages 18–22 years were reported on the 1989 questionnaire. Birthweight was reported in 1991, and alcohol and fat intakes were obtained on the 1995 questionnaire. Information on other risk factors used in this investigation, including parity, age at first birth (afb), history of benign breast disease, oral contraceptive use, menopausal status, use of multivitamins, smoking, and body weight, were reported on the 1997 questionnaire and updated every 2 years on subsequent questionnaires. Television watching was reported in 1997. Information about family history of breast cancer in mother and/or sister was obtained in 1989 and 1997, and data on socioeconomic status were collected in 1999 and 2001.

Statistical Analysis

Each participant contributed person-time from the return date of her questionnaire in 1997 until menopause, a diagnosis of breast cancer or other cancer (except nonmelanoma skin cancer), death, or the end of follow-up on June 1, 2003, whichever came first, giving 335 681 person-years of follow-up. Person-time was assigned to the appropriate level of physical activity and covariate categories at the beginning of each 2-year questionnaire cycle.

Spearman rank correlation coefficients between physical activity categories and their associated 95% confidence intervals were based on the arcsine transformation approach (38). For breast cancer risk, Cox proportional hazards models were used to estimate the age-adjusted and multivariable-adjusted relative risks (RRs) and their 95% confidence intervals. Age in months was the time scale. Physical activity exposures were divided into approximate quintiles and grouped into categories divisible by 3, the MET of average-paced walking. Relative risks represented the ratio of breast cancer incidence rates comparing each upper category of physical activity with the lowest group, adjusting for risk factors.

In multivariable analyses, we adjusted for several established risk factors for breast cancer: age (months), average childhood body shape [collapsed pictogram scale from 1 to ≥5, (39)], duration and recency of oral contraceptive use (never, past <4 y, past ≥ 4 y, current < 4 y, and current ≥ 4 y), history of benign breast disease (yes, no), mother or sister with breast cancer (yes, no), parity and age at first birth (nulliparous; parity 1–2, afb < 25; parity 1–2, afb 25–29; parity 1–2, afb ≥ 30; parity ≥ 3, afb < 25; parity ≥ 3, afb 25–29; parity ≥ 3, afb ≥ 30), current alcohol consumption (none, >0.0–1.4 g/d, 1.5–4.9 g/d, 5.0–9.9 g/d, ≥ 10 g/d), and height (inches). Adjustment for other possible confounders (smoking, smoking cessation, animal fat intake, birthweight, television watching, multivitamin use, and socioeconomic status) did not change the relative risk estimates and were omitted from our final model. We did not include BMI or age at menarche as core covariates because we considered them as intermediates in the causal pathway between physical activity and breast cancer. However, these and other hypothesized intermediates were evaluated in additional models to examine potential mechanisms for the activity–breast cancer associations (discussed in "Results"). Tests for linear trend were performed by modeling the exposure as a continuous variable (there were no outliers). We examined effect modification by factors (BMI, oral contraceptive use, parity) that had biologic plausibility and for which we had sufficient numbers to conduct stratified analyses; tests of interaction were based on a Wald test of the interaction term. We observed no violation of proportional hazards by age. In ad hoc analyses to further investigate which age periods were critical for the association with breast cancer risk, we examined whether adolescent and adult activity were statistically significantly different from each other by entering both in the same regression model as continuous terms and evaluating whether the difference between their betas was statistically significant. For this, we used the test statistic (beta1 − beta2)/standard error (beta1 − beta2) and a standard normal table to evaluate the *P* value. All *P* values were two-sided. A *P* value less than .05 was considered statistically significant for all analyses. These analyses were performed using SAS version 9.0 (SAS Institute Inc, Cary, NC).

Results

We first examined the pattern of total levels of leisure-time physical activity over time when participants were between the ages 12 and 55 (eldest in 2001). Women's average total activity levels declined appreciably with age (Figure 1). At young ages, women engaged in mostly strenuous or moderate activities; for adults, walking was most common.

Several established or possible risk factors for breast cancer were associated with leisure-time physical activity at the start of follow-up in 1997 (Table 1). After adjusting for age, physically active women were more likely to currently use oral contraceptives, to be nulliparous, to be taller, to consume greater than 10 grams of alcohol (about one glass of wine) per day, to take multivitamins, and to be current smokers. They had lower BMI (childhood, at age 18, and current) and animal fat intakes. More active women also were less likely to have an early age at menarche (<12 years) and long (>40 days) menstrual cycles than less active women. The magnitudes of these associations were modest.

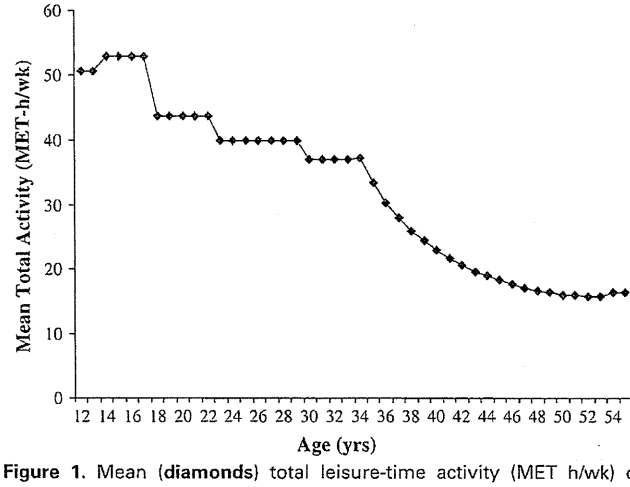

Figure 1. Mean (**diamonds**) total leisure-time activity (MET h/wk) of women ages 12–55 (eldest in 2001). There are **steps** in the figure because activity data before age 35 were obtained for specific life periods.

We investigated the role of intensity of leisure-time physical activity by conducting separate analyses of average lifetime strenuous, moderate, walking, and total activities (Table 2). The strongest association was for total activity. Risk of breast cancer was lower for women reporting 54 or greater MET-h/wk of total activity than for those reporting less than 21 MET-h/wk (RR = 0.77, 95% CI = 0.59 to 1.01; P_{trend} = .04). The age-adjusted incidence rates of breast cancer for these highest (≥54 MET-h/wk) and lowest (<21 MET-h/wk) total activity categories were 136 and 194 per 100 000 person-years, respectively. Because the results (Table 2) suggested a threshold effect, we compared women with 39 or greater MET-h/wk of total activity (equivalent to 3.25 h/wk of running) vs those with less than 39 MET-h/wk. We found a similar association (RR = 0.77, 95% CI = 0.64 to 0.93), suggesting a threshold effect. Results for strenuous, moderate, and walking activities were not statistically significant and were further attenuated when we mutually adjusted for each activity, suggesting that the association was not dependent on a single intensity but rather on total activity. The moderate correlations between the different intensities limited the ability to identify one as most important.

To evaluate the role of leisure-time physical activity during specific ages of life, we examined total activity during three different life periods (Table 3). Activity during ages 12–22 had the strongest association. Higher total activity during that period was statistically significantly associated with a 25% lower breast cancer risk (for ≥72 vs <21 MET-h/wk, RR = 0.75, 95% CI = 0.57 to 0.99; P_{trend} = .05). The relative risks were attenuated after mutually adjusting for activity at age 23 years or older (data not shown; between 12–22 and ≥23 age periods, r = 0.55, 95% CI = 0.56 to 0.57). The associations with activity during ages 12–17 years were similarly inverse (for ≥78 vs <21 MET-h/wk, RR = 0.76, 95% CI = 0.58 to 0.99; P_{trend} = .09; data not shown). We observed a suggestion of lower breast cancer risk with higher total activity during ages 23–34 (P_{trend} = .06), but no association with reduced risk was apparent after age 35.

Because activity declined with age, we modeled activity during the three age periods as continuous terms and calculated the relative

Table 1. Characteristics of 64777 women in 1997 according to categories of average lifetime total activity, Nurses' Health Study II*

Characteristic	MET-h/wk (median)					P
	<21 (14.5)	21–29.9 (25.5)	30–38.9 (34.3)	39–53.9 (45.4)	≥54 (68.2)	
No. of participants	16015	12592	11187	12390	12593	—
Age, y	42.8	42.1	41.7	41.3	41.0	<.001
Mother or sister with breast cancer, %	9.2	9.2	9.3	9.5	8.9	.82
History of benign breast disease, biopsy confirmed, %	14.7	14.5	14.8	14.9	14.7	.13
Current oral contraceptive user, %	9.0	9.5	9.6	9.5	9.9	.004
Nulliparous, %	17.9	17.7	18.5	19.6	22.7	<.001
Parity†	2.3	2.3	2.3	2.3	2.3	.009
Age at first birth, y†	26.5	26.7	26.8	26.9	26.9	<.001
Height, inches	64.7	64.9	64.9	65.0	65.1	<.001
Birthweight, ≥8.5 lbs, %	11.9	12.0	11.8	11.8	12.2	.07
Overweight during ages 5 and 10, %	6.7	6.2	5.8	5.6	5.6	<.001
BMI at age 18, kg/m²	21.5	21.3	21.2	21.1	21.0	<.001
Current BMI, kg/m²	26.7	26.0	25.6	25.5	25.2	<.001
Alcohol intake ≥10 g/d, %‡	6.7	8.7	8.9	10.3	11.1	<.001
Multivitamin use, %	46.8	50.0	52.1	52.7	55.5	<.001
Animal fat, % energy from data collected in 1995	17.9	17.2	16.9	16.5	16.1	<.001
Current smoker, %	8.6	8.5	9.1	9.0	10.2	<.001
Age at menarche, <12 y, %	25.7	23.0	23.1	22.7	22.9	.06
Irregular menstrual cycles or no periods at age 18–22 y, %	10.2	9.9	8.9	9.2	10.3	.66
Length of menstrual cycle at ages 18–22, >40 days, %	8.6	8.1	7.2	7.6	7.7	<.001
Television watching, h/wk	8.6	8.2	8.2	8.3	8.6	.50

* All means and percentages refer to data in 1997, unless otherwise noted and are standardized to the age distribution of the study population. *P* values (two-sided) were obtained using Wald tests from an age-adjusted linear regression with normalized total activity as the continuous outcome. MET-h/wk = metabolic equivalent hours per week; BMI = body mass index.

† Among parous women only.

‡ Refers to data collected in 1995.

risks for the same 21 MET-h/wk increment of total activity to be able to make direct comparisons between relative risks. The estimates for the different age periods were similar (−4% to −6%, Table 3) and not independently statistically significant. A 21 MET-h/wk increase of lifetime activity was statistically significantly associated with a 9% reduction in risk.

We next categorized activity for 12–22 years (youth) and for 23 years and older (adulthood) into tertiles and cross-classified them to examine whether a specific pattern of activity was related to breast cancer risk (Table 4). The relative risk for the high during youth and low during adulthood (high–low) activity pattern (RR = 0.63, 95% CI = 0.35 to 1.11) was similar to that of the high–high activity pattern (RR = 0.70, 95% CI = 0.53 to 0.93), suggesting that high levels of leisure-time physical activity during ages 12–22 were important, no matter the activity level during later years. However, most women were either inactive (low–low) or active (high–high) during both youth and adulthood, limiting our ability to examine specific age periods. Moreover, the associations with risk for activity during youth and adulthood were not statistically significantly different from each other when we entered each type of activity in the same regression model as continuous terms and evaluated the statistical significance of the difference between their betas.

Because error in self-reporting can bias results, we corrected for measurement error by regression calibration (40,41) using past year adult activity from an earlier validation study (31). With the correction, we observed a 39% lower breast cancer risk for total lifetime physical activity comparing the most with the least active women, suggesting that our original estimate of a 23% lower risk was an underestimate of reduced risk.

We also evaluated the relationship between total lifetime physical activity and breast cancer risk by hormone receptor status. We observed a non–statistically significant inverse association for both estrogen receptor (ER)–positive (RR = 0.76, 95% CI = 0.54 to 1.06; P_{trend} = .15, for 363 patients) and ER-negative (RR = 0.89, 95% CI = 0.48 to 1.63; P_{trend} = .21, for 103 patients) breast cancers for the highest vs lowest categories of activity. Moreover, there were similar, non–statistically significant inverse associations for breast cancers with concordant ER and progesterone receptor (PR) status (comparing the most vs least active women: for ER+/PR+, RR = 0.80, 95% CI = 0.56 to 1.15, and for ER–/PR–, RR = 0.86, 95% CI = 0.46 to 1.61). There were too few patients to examine discordant receptor status (eg, ER–/PR+ or ER+/PR–).

Physical activity has been hypothesized to influence breast cancer risk by changing menstrual characteristics or BMI. Thus, we assessed the association between total lifetime activity and breast cancer risk after adjusting for age at menarche, regularity and length of menstrual cycle during youth and adulthood, and BMI (at age 18, current, and cumulatively updated). Relative risks were not appreciably different.

Lastly, we examined whether the relationship between total lifetime activity and breast cancer risk varied according to BMI, parity, or oral contraceptive use (Table 5, stratified analyses). Among women with a BMI of less than 25.0 kg/m² in 1997, the most active women had a 32% lower risk compared with the least active women (RR = 0.68, 95% CI = 0.48 to 0.98; P_{trend} = .02). However, among overweight women (BMI ≥ 25 kg/m²), activity was not statistically significantly associated with breast cancer risk (RR = 0.85, 95% CI = 0.56 to 1.30; P_{trend} = .60). In addition, we observed a statistically

Table 2. RR of premenopausal breast cancer by intensity of lifetime physical activity, Nurses' Health Study II, 1997–2003*

Type of activity	Person-years	No. of cancers	Age-adjusted RR	Multivariable-adjusted RR† (95% CI)
Strenuous, h/wk				
<1.0	69517	129	1.00 (referent)	1.00 (referent)
1.0–1.9	82780	149	1.03	1.01 (0.79 to 1.28)
2.0–2.9	68541	109	0.98	0.94 (0.72 to 1.22)
3.0–3.9	46098	65	0.89	0.86 (0.64 to 1.17)
≥4.0	68746	98	0.96	0.90 (0.68 to 1.18)
P_{trend}				.14
Moderate, h/wk				
<1.0	38066	70	1.00 (referent)	1.00 (referent)
1.0–1.9	86284	159	1.07	1.06 (0.80 to 1.41)
2.0–2.9	76046	133	1.04	1.01 (0.75 to 1.36)
3.0–3.9	53755	81	0.92	0.91 (0.66 to 1.26)
≥4.0	81530	107	0.82	0.81 (0.59 to 1.10)
P_{trend}				.08
Walking, h/wk				
<0.5	63008	98	1.00 (referent)	1.00 (referent)
0.5–0.9	67493	132	1.16	1.14 (0.88 to 1.49)
1.0–1.4	59723	86	0.86	0.85 (0.63 to 1.14)
1.5–2.4	74012	135	1.08	1.04 (0.80 to 1.36)
≥2.5	71445	99	0.83	0.79 (0.59 to 1.05)
P_{trend}				.09
Total activity, MET-h/wk				
<21.0	81563	158	1.00 (referent)	1.00 (referent)
21.0–29.9	65264	121	1.00	0.98 (0.77 to 1.25)
30.0–38.9	58299	97	0.95	0.93 (0.72 to 1.20)
39.0–53.9	64947	85	0.76	0.74 (0.56 to 0.97)
≥54.0	65609	89	0.83	0.77 (0.59 to 1.01)
P_{trend}				.04

* RR = relative risk; CI = confidence interval; MET-h/wk = metabolic equivalent hours per week.

† Adjusted for the following covariates: age (months), average childhood body shape (collapsed pictogram scale from 1 to ≥5), duration and recency of oral contraceptive use (never, past <4 y, past ≥ 4 y, current < 4 y, and current ≥ 4 y), history of benign breast disease (yes, no), mother or sister with breast cancer (yes, no), parity and age at first birth (afb) (nulliparous; parity 1–2, afb < 25; parity 1–2, afb 25–29; parity 1–2, afb ≥ 30; parity ≥ 3, afb < 25; parity ≥ 3, afb 25–29; parity ≥ 3, afb ≥ 30), current alcohol consumption (none, >0.0–1.4 g/d, 1.5–4.9 g/d, 5.0–9.9 g/d, ≥10 g/d), and height (inches). P_{trend} values (two-sided) were computed using the Wald test statistic.

significant inverse activity–breast cancer risk association among parous women (most vs least active; RR = 0.72, 95% CI = 0.53 to 0.98; P_{trend} = .02) but not among nulliparous women (RR = 1.08; P_{trend} = .68). However, formal tests for interaction with current BMI (P = .10) and parity (P = .45) were not statistically significant. Moreover, there were no substantial differences by subgroups of BMI at age 18 (<20.5 kg/m², ≥20.5 kg/m², approximate median) or by oral contraceptive use (never, past, present use) in stratified analyses.

There was little variation in work-related activity, with 86% of participants reporting mostly walking. The association of occupational activity during ages 23–34 years with breast cancer risk was non–statistically significantly inverse (for >171 vs <114 MET-h/wk, RR = 0.83, 95% CI = 0.63 to 1.09; P_{trend} = .42). The relative risk for leisure plus occupational activity during ages 23–34 years was 0.80 (for ≥216 vs <147 MET-h/wk, 95% CI = 0.61 to 1.04, P_{trend} = .07). The correlation between occupational and total leisure-time activity during ages 23–34 years was low (r = 0.10, 95% CI = 0.10 to 0.11).

Discussion

In this large prospective study, total activity was most strongly associated with lower risk of premenopausal breast cancer. Women who had engaged in at least 39 MET-h/wk of total activity on average from ages 12 years onward had a 23% lower risk of premenopausal breast cancer than the least active women. This activity level translates to about 3.25 h/wk of running or 13 h/wk of walking. High quantities of total activity during youth (12–22 years) appeared to contribute most to this benefit.

Epidemiological results for the association of physical activity with premenopausal breast cancer risk have been inconsistent (8,9). Direct comparisons between investigations are particularly challenging due to the diversity in physical activity assessments, types of activity (eg, leisure time, occupational, household, total), units of activity, and the various study populations examined (42). For adolescent or lifetime leisure-time activity, there have been at least three prospective studies (21–23) and 15 case–control studies (20,43–56) examining premenopausal breast cancer risk. Wyshak and Frisch (21) observed a very strong association between physical activity and reduced risk for breast cancer (RR = 0.16, 95% CI = 0.04 to 0.64) in a prospective analysis comparing US college athletes vs nonathletes, but results were unstable, based on 12 patients. In a Swedish cohort, Margolis et al. (23) did not detect a relationship for physical activity at age 14 or for consistently high activity levels at ages 14 and 30 and enrollment and premenopausal breast cancer risk. In an earlier NHSII analysis, we did not

Table 3. RR of premenopausal breast cancer by age periods of total physical activity, Nurses' Health Study II, 1997–2003*

Activity, MET-h/wk	Person-years	No. of cancers	Age-adjusted RR	Multivariable-adjusted RR* (95% CI)
		Ages 12–22 y		
<21	63582	128	1.00 (referent)	1.00 (referent)
21.0–35.9	76770	136	0.95	0.94 (0.74 to 1.21)
36.0–47.9	55607	86	0.85	0.82 (0.62 to 1.09)
48.0–71.9	73251	112	0.85	0.82 (0.63 to 1.06)
≥72.0	66471	88	0.76	0.75 (0.57 to 0.99)
P_{trend}				.05
For 21 MET h/wk increase†				–6%
		Ages 23–34 y		
<15	58559	91	1.00 (referent)	1.00 (referent)
15.0–26.9	75723	155	1.38	1.38 (1.06 to 1.80)
27.0–38.9	62353	102	1.13	1.12 (0.84 to 1.49)
39.0–56.9	70410	110	1.08	1.04 (0.78 to 1.39)
≥57.0	68636	92	0.93	0.88 (0.65 to 1.19)
P_{trend}				.06
For 21 MET h/wk increase†				–6%
		Ages ≥ 35 y		
<9.0	75004	117	1.00 (referent)	1.00 (referent)
9.0–14.9	61015	115	1.15	1.19 (0.92 to 1.55)
5.0–20.9	53001	90	1.02	1.02 (0.77 to 1.35)
21.0–32.9	71402	99	0.81	0.80 (0.61 to 1.05)
≥33.0	71943	128	1.05	1.00 (0.77 to 1.30)
P_{trend}				.27
For 21 MET h/wk increase†				–4%

* P_{trend} values (two-sided) were computed using the Wald test statistic. Adjusted for covariates listed in second footnote of Table 2. RR = relative risk; CI = confidence interval; MET-h/wk = metabolic equivalent hours per week.

† Percent change in relative risk for a 21 MET-h/wk increase in total physical activity during the specific age period, from regression models with activity as a continuous term. For total activity averaged across the lifetime (ages 12 to present), a 21 MET-h/wk increase in activity was statistically significantly associated with a −9% risk (P_{trend} = .04).

detect statistically significant associations between strenuous activity during high school or ages 18–22 and risk of premenopausal breast cancer (22); however, the two-question activity measure used for the analysis was probably not sufficiently detailed. Among case–control studies reporting on premenopausal breast cancer, six observed statistically significant associations (20,43–48), ranging from moderate to strong decreased relative risks, and one (49) reported borderline, non–statistically significant inverse associations. Our study is consistent with these findings. Other case–control studies (50–56) have not found statistically significant associations.

For adult leisure-time activity, previously conducted cohort studies (23,24,27,57–63) have not observed statistically significant associations with premenopausal breast cancer risk, consistent with the current study and an earlier NHSII analysis (24). This finding may be due, in part, to declining levels of physical activity after age 35; for example, few participants in our study reported very vigorous activities such as running. Few studies have examined associations between occupational physical activity and breast cancer risk. Among four cohort studies, two observed statistically significantly decreased risks (27,64) with occupational activity whereas two reported no statistically significant associations (63,65). Among six case–control studies (47,49,52,66–68), no statistically significant associations with occupational activity were reported. Studies have varied in the quality and completeness of their assessments of physical activity, and in some investigations sample sizes have been small.

Table 4. RR of premenopausal breast cancer by patterns of total physical activity during youth (12–22 years) and adulthood (≥23 years), Nurses' Health Study II, 1997–2003*

Activity by age group	Person-years	No. of cancer	Multivariable-adjusted RR (95% CI)
Low youth/low adulthood	59947	118	1.00 (referent)
Low youth/high adulthood	13945	22	0.83 (0.53 to 1.32)
High youth/low adulthood	11874	13	0.63 (0.35 to 1.11)
High youth/high adulthood	69462	89	0.70 (0.53 to 0.93)

* Adjusted for covariates listed in second footnote of Table 2. The "low youth" category consisted of women in the bottom tertile of total activity (average of <8 MET-h/wk) during ages 12–22, whereas "high youth" represented those in the top tertile of total activity (average of >43 MET h/wk) during that age. The "low adulthood" category consisted of women in the top tertile of total activity (average of <13 MET h/wk) from ages 23 years to present, whereas "high adulthood" represented women in the top tertile of total activity (>26 MET h/wk) during that age. Not included in this table are 308 breast cancer patients and 180454 person-years of women in the other cross-classifications of low, medium, and high categories of activity during youth and adulthood. RR = relative risk; CI = confidence interval; MET-h/wk = metabolic equivalent hours per week.

Table 5. RRs of breast cancer by total lifetime activity, stratified by adult body mass index and parity, Nurses' Health Study II, 1997–2003*

	BMI < 25 kg/m²		BMI ≥ 25 kg/m²		Nulliparous		Parous	
Activity, MET-h/wk	No. of cancers	RR (95% CI)	No. of cancers	RR (95% CI)	No. of cancers	RR (95% CI)	No. of cancers	RR (95% CI)
<21.0	86	1.00 (referent)	72	1.00 (referent)	29	1.00 (referent)	128	1.00 (referent)
21.0–29.9	66	0.88 (0.63 to 1.22)	55	1.14 (0.80 to 1.63)	19	0.79 (0.43 to 1.45)	99	1.01 (0.77 to 1.32)
30.0–38.9	62	0.95 (0.68 to 1.32)	35	0.92 (0.61 to 1.38)	20	1.09 (0.60 to 1.97)	76	0.91 (0.68 to 1.21)
39.0–53.9	52	0.72 (0.50 to 1.02)	33	0.76 (0.49 to 1.16)	19	0.84 (0.45 to 1.55)	65	0.72 (0.53 to 0.97)
≥54.0	53	0.68 (0.48 to 0.98)	35	0.85 (0.56 to 1.30)	26	1.08 (0.61 to 1.90)	63	0.72 (0.53 to 0.98)
P_{trend}		.02		.60		.68		.02

* P_{trend} values (two-sided) were calculated using the Wald test statistic. Adjusted for covariates listed in second footnote of Table 2. RR = relative risk; CI = confidence interval; MET-h/wk = metabolic equivalent hours per week; BMI = current body mass index, as reported in 1997.

Our study adds to the current literature by being, to our knowledge, the first prospective study to collect data for a broad range of etiologically relevant ages (in this study, from ages 12 to a maximum of 55) and to prospectively examine the role of activity throughout life. Further strengths of this investigation include its relatively large number of premenopausal invasive breast cancers and the medical confirmation of cancer diagnoses. In addition, the age- and multivariable-adjusted relative risks were similar, suggesting no major sources of confounding.

This study also has some limitations. First, we relied on self-reported activity, which will inevitably be imperfect. In our previous investigations, these physical activity questions had good reproducibility (30) and validity as compared with 7-day activity diaries in a subgroup of NHSII participants (31). Moreover, self-reported physical activity using a similar questionnaire was well correlated with lowered resting pulse in men (32) and maximal oxygen consumption in women (33). Second, adult activity between questionnaire cycles was linearly interpolated. Although errors due to reporting and estimation of activity levels are inevitable, when we corrected for such errors in the analysis, we observed a stronger risk reduction (39%), indicating that our original estimate may have underestimated the association. Third, physical activity was correlated across different ages and intensities, as has been seen in other studies (69,70); this limited the ability to statistically identify one age period and intensity with the strongest association.

Our results are applicable to premenopausal white women. Although participants were registered nurses at the initiation of the study, previous exposure–disease relationships in this cohort, including those for breast cancer, have been confirmed in other populations, suggesting that our findings are generalizable on a population level. Although this study focused primarily on leisure-time activity, we did not observe much variation in physical activity at work (most reported walking) or a statistically significant association between occupational physical activity and breast cancer risk. Despite homogeneity in occupation levels, there was sufficient variation in leisure-time activity to examine associations with breast cancer risk.

Physical activity has been hypothesized to lower breast cancer incidence through several hormone-related mechanisms (71). Estrogen is strongly implicated in breast cancer etiology (72,73). Physical activity can delay menarche or change menstrual cycle characteristics (71,74) and thus alter women's lifetime exposure to the mitogenic effects of sex hormones (16). We observed modest changes in menstrual characteristics with increasing activity levels. Furthermore, among NHSII women, physical activity during adulthood has been inversely associated with plasma concentrations of luteal phase estrodiol, free estradiol, and estrogen (75). Second, physical activity is known to lower insulin concentrations (76). Insulin can increase hepatic production of IGF (12,77) and may raise levels of bioactive IGF and estrogen by lowering hepatic secretion of their respective binding proteins. IGF has been associated with increased premenopausal breast cancer risk (78), but results are conflicting (79,80). We observed suggestive inverse associations for both ER+ and ER− breast cancers, as had a previous study (81), suggesting that both ovarian and nonovarian hormonal mechanisms could be involved.

Although most studies suggest that physical activity during adulthood is associated with at least a 20% reduced risk of postmenopausal breast cancer (9,82), this and other investigations indicate that women need to regularly engage in physical activity starting at a young age to achieve a comparable benefit for premenopausal breast cancer. Unresolved questions for future investigations include whether higher physical activity during adolescence is associated with reduced risk of postmenopausal breast cancer, the role of physical activity at earlier ages such as during childhood, the role of occupational activity, and the mechanisms underlying a potential association with breast cancer risk. Only a handful of case–control studies have reported results in African American (46,48) and Hispanic (48,83) populations, and it is unclear whether the physical activity–breast cancer association differs by ethnicity.

In conclusion, these results suggest that consistent physical activity during a woman's lifetime is associated with decreased breast cancer risk. Unlike many risk factors for breast cancer, physical activity is an exposure that can be modified. This association, if found to be causal, has public health implications for prevention. Moreover, physical activity at any age promotes health in many ways (84,85), and even walking has several well-documented benefits (86). Although the underlying mechanisms require further study, this research supports the benefits of regular exercise during all ages among women.

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対象の内訳	ヒト	動物	地 域	欧米	研究の種類	縦断研究
対象	一般健常者	空白		( )		コホート研究
性別	女性	( )		( )		( )
年齢	25-42歳	[redacted]		( )		前向きコホート
対象数	10000以上			( )		( )
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. RR of premenopausal breast cancer by intensity of lifetime physical activity, Nurses' Health Study II, 1997–2003*

Type of activity	Person-years	No. of cancers	Age-adjusted RR	Multivariable-adjusted RR† (95% CI)
Strenuous, h/wk				
<1.0	69517	129	1.00 (referent)	1.00 (referent)
1.0–1.9	82780	149	1.03	1.01 (0.79 to 1.28)
2.0–2.9	68541	109	0.98	0.94 (0.72 to 1.22)
3.0–3.9	46098	65	0.89	0.86 (0.64 to 1.17)
≥4.0	68746	98	0.96	0.90 (0.68 to 1.18)
P_{trend}				.14
Moderate, h/wk				
<1.0	38066	70	1.00 (referent)	1.00 (referent)
1.0–1.9	86284	159	1.07	1.06 (0.80 to 1.41)
2.0–2.9	76046	133	1.04	1.01 (0.75 to 1.36)
3.0–3.9	53755	81	0.92	0.91 (0.66 to 1.26)
≥4.0	81530	107	0.82	0.81 (0.58 to 1.10)
P_{trend}				.08
Walking, h/wk				
<0.5	63008	98	1.00 (referent)	1.00 (referent)
0.5–0.9	67493	132	1.16	1.14 (0.88 to 1.49)
1.0–1.4	59723	86	0.86	0.85 (0.63 to 1.14)
1.5–2.4	74012	136	1.08	1.04 (0.80 to 1.36)
≥2.5	71445	99	0.83	0.79 (0.59 to 1.05)
P_{trend}				.09
Total activity, MET-h/wk				
<21.0	81563	158	1.00 (referent)	1.00 (referent)
21.0–29.9	65264	121	1.00	0.98 (0.77 to 1.25)
30.0–38.9	58299	97	0.95	0.93 (0.72 to 1.20)
39.0–53.9	64947	85	0.76	0.74 (0.56 to 0.97)
≥54.0	65609	89	0.83	0.77 (0.59 to 1.01)
P_{trend}				.04

* RR = relative risk; CI = confidence interval; MET-h/wk = metabolic equivalent hours per week.

† Adjusted for the following covariates: age (months), average childhood body shape (collapsed pictogram scale from 1 to ≥5), duration and recency of oral contraceptive use (never, past <4 y, past ≥ 4 y, current < 4 y, and current ≥ 4 y), history of benign breast disease (yes, no), mother or sister with breast cancer (yes, no), parity and age at first birth (afb) (nulliparous; parity 1–2, afb < 25; parity 1–2, afb 25–29; parity 1–2, afb ≥ 30; parity ≥ 3, afb < 25; parity ≥ 3, afb 25–29; parity ≥ 3, afb ≥ 30), current alcohol consumption (none, >0.0–1.4 g/d, 1.5–4.9 g/d, 5.0–9.9 g/d, ≥10 g/d), and height (inches). P_{trend} values (two-sided) were computed using the Wald test statistic.

図表掲載箇所	P733, 表2
概 要 (800字まで)	本研究は，身体活動と閉経前の女性における乳癌発症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，Nurses' Health Study Ⅱに参加する閉経前女性64777名とし，6年間追跡された．身体活動の調査として，ランニング，エアロビ，水泳などの激しい活動，ハイキング，ウォーキング，サイクリングなどの中等度の活動，通勤，通学などの歩行の3つの活動に分けられ，週あたりの実施時間が評価された．また，12-13歳，14-17歳，18-22歳，23－29歳，30－34歳の5つの期間における身体活動についても同様に調査された．身体活動と乳癌発症との関連についてみると，週21メッツ・時未満の者と比較して，21.0-29.9メッツ・時/週の者の調整相対リスクは0.98(95%CI:0.77-1.25)，30.0-38.9メッツ・時/週の者では0.93(0.72-1.2)，39.0-53.9メッツ・時/週の者では0.74(0.56-0.97)，54メッツ・時/週以上の者では0.77(0.59-1.01)となり，量反応関係が認められた(trend P=0.04)．さらに，22歳以下の時と23歳以上の身体活動量がともに低い者と比較して，どちらの時期もともに高い者の調整相対リスクは0.70(0.53-0.93)であり，乳癌発症リスクが低いことが示された．
結 論 (200字まで)	身体活動量が多いことは閉経前における乳癌発症のリスクを低下させることが示された．
エキスパートによるコメント (200字まで)	乳癌発症に関する研究は，閉経後女性を対象としたものが多いが，この研究では青年期における身体活動との関係についても検討したものである．成人になってからの身体活動量だけでなく，青年期における身体活動量が十分にあることも乳癌予防のために重要であることを示した意義深い研究である．

担当者　川上諒子

Physical Activity, Obesity, Height, and the Risk of Pancreatic Cancer

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Context Diabetes mellitus and elevated postload plasma glucose levels have been associated with an increased risk of pancreatic cancer in previous studies. By virtue of their influence on insulin resistance, obesity and physical inactivity may increase risk of pancreatic cancer.

Objective To examine obesity, height, and physical activity in relation to pancreatic cancer risk.

Design and Setting Two US cohort studies conducted by mailed questionnaire, the Health Professionals Follow-up Study (initiated in 1986) and the Nurses' Health Study (initiated in 1976), with 10 to 20 years of follow-up.

Participants A total of 46648 men aged 40 to 75 years and 117041 women aged 30 to 55 years who were free of prior cancer at baseline and had complete data on height and weight.

Main Outcome Measures Relative risk of pancreatic cancer, analyzed by self-reported body mass index (BMI), height, and level of physical activity.

Results During follow-up, we documented 350 incident pancreatic cancer cases. Individuals with a BMI of at least 30 kg/m^2 had an elevated risk of pancreatic cancer compared with those with a BMI of less than 23 kg/m^2 (multivariable relative risk [RR], 1.72; 95% confidence interval [CI], 1.19-2.48). Height was associated with an increased pancreatic cancer risk (multivariable RR, 1.81; 95% CI, 1.31-2.52 for the highest vs lowest categories). An inverse relation was observed for moderate activity (multivariable RR, 0.45; 95% CI, 0.29-0.70 for the highest vs lowest categories; P for trend <.001). Total physical activity was not associated with risk among individuals with a BMI of less than 25 kg/m^2 but was inversely associated with risk among individuals with a BMI of at least 25 kg/m^2 (pooled multivariable RR, 0.59; 95% CI, 0.37-0.94 for the top vs bottom tertiles of total physical activity; P for trend=.04).

Conclusion In 2 prospective cohort studies, obesity significantly increased the risk of pancreatic cancer. Physical activity appears to decrease the risk of pancreatic cancer, especially among those who are overweight.

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CANCER OF THE PANCREAS REPresents the fifth leading cause of cancer-related mortality in the United States.[1] Nonetheless, other than cigarette smoke, few environmental factors have been linked to the risk of pancreatic cancer.[2,3] An association between diabetes and pancreatic cancer has been shown in many studies. In a meta-analysis including more than 20 epidemiologic studies, the pooled relative risk (RR) of pancreatic cancer among those diagnosed with diabetes for at least 5 years was 2.0 (95% confidence interval [CI], 1.3-2.2).[4] Recently, a positive association between postload plasma glucose concentration and pancreatic cancer risk was found in 2 studies, supporting the hypothesis that impaired glucose tolerance, insulin resistance, and hyperinsulinemia play a role in pancreatic cancer etiology.[5,6]

Obesity has been linked to significant metabolic abnormalities including insulin resistance, glucose intolerance, and diabetes mellitus.[7-10] Epidemiologic findings on obesity and the risk of pancreatic cancer have been conflicting.[5,11-18] To date, suggestive associations have been observed for height and pancreatic cancer risk in 3 studies.[15-17] Height has been associated with elevated risks of other cancers[19-21] and may be a marker for exposure levels to growth factors or a proxy for net energy intake during childhood and early adolescence.

Because physical activity improves glucose tolerance, even in the absence of weight loss,[22,23] we hypothesized that physical activity would reduce the risk of pancreatic cancer. However, to our knowledge no study has examined the association between physical activity and pancreatic cancer risk.

We therefore examined the relationship between body mass index (BMI), height, and physical activity and the risk of pancreatic cancer in 2 large prospective cohort studies of men and women. In both studies, weight and physical activity data were measured prior to pancreatic cancer detection, thus avoiding potential biases that may occur when obtaining such information from pancreatic cancer patients and next-of-kin.

For editorial comment see p 967.

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METHODS

Cohorts

Two ongoing cohort studies provided data for our analyses, the Health Professionals Follow-up Study (HPFS) and the Nurses' Health Study (NHS). The HPFS was initiated in 1986 when 51 529 US men aged 40 to 75 years responded to a mailed questionnaire. The NHS began in 1976 when 121 700 female registered nurses aged 30 to 55 years responded to a mailed questionnaire. Detailed information on individual characteristics and habits was obtained from the mailed questionnaires at baseline and subsequently every 2 years. Most of the deaths in this cohort were reported by family members or by the postal service in response to the follow-up questionnaires. In addition, the National Death Index was searched for nonrespondents; this method has been shown to have a sensitivity of 98%.[24]

For those analyses using anthropometric measurements, a total of 46 648 HPFS men and 117 041 NHS women were eligible after excluding participants diagnosed with cancer (other than nonmelanoma skin cancer) prior to baseline or with missing weight data at baseline. In the NHS, detailed data on physical activity were not obtained until 1986. A total of 77 559 women completed the physical activity questions on the 1986 questionnaire and were free of cancer.

Assessment of Anthropometric Variables

Baseline height, current weight, weight at 21 years old, and weight change in past 5 years were reported by men participating in the HPFS in 1986. Similarly, women in the NHS reported their baseline height and current weight in 1976. Weight at 18 years old was collected in 1980. In addition, participants of the 2 cohorts reported their current weight on the biennial mailed questionnaires. We estimated BMI from weight and height (weight in kilograms divided by square of height in meters) as a measure of total adiposity. We evaluated the precision of self-reported anthropometric measures among 123 HPFS participants by having trained technicians visit those participants twice (6 months apart) to measure current weight.[25] After adjustment for age and within-person variability, the Pearson correlation between self-report and the average of the 2 technician measurements was 0.97 for weight. Among women in the NHS, the correlation between self-reported and measured weight was 0.96, although self-reported weight averaged 1.5 kg less than directly measured weight.[25]

Assessment of Physical Activity

In 1986, the questionnaires mailed to the 2 cohorts included a section assessing physical activity. Participants were asked to average the time spent per week in each of the following 8 activities over the previous year: walking or hiking outdoors; jogging (<10 minutes per mile); running (≥10 minutes per mile); bicycling (including on stationary machines); lap swimming; tennis; squash or racquetball; and calisthenics (use of a rowing machine [HPFS] or aerobics, aerobic dance [NHS]). A total of 10 possible answers were available for each of the exercises, ranging from 0 to 11 or more hours per week. In addition, individuals reported their usual walking pace (<2.0, 2.0-2.9, 3.0-3.9, or ≥4.0 mph [<3.2, 3.2-4.6, 4.8-6.2, or ≥6.4 km/h]) and the number of flights of stairs climbed daily. Our calculations did not include household activities or occupational physical activity. The reliability and validity of the assessment of physical activity as used in these 2 cohorts were tested among 147 participants of the Nurses' Health Study II, a similar cohort to the NHS but participants were younger nurses. The correlation between physical activity reported on the questionnaire and that recorded in the 4 1-week diaries was 0.62.[26] The validity of the physical activity questionnaire used in the HPFS in 1986 was assessed among 238 randomly selected participants by comparisons with 4 1-week activity diaries, 4 1-week activity recalls, and resting and postexercise pulse rates.[27] The correlation for vigorous physical activity with the activity diaries was 0.58. Vigorous activity assessed by the questionnaire was correlated with resting pulse (r=–0.45) and postexercise pulse (r=–0.41).

A weekly physical activity score expressed in metabolic equivalent tasks (METs) was derived by multiplying the time spent in each activity per week by its typical energy-expenditure requirements.[28] The MET is the caloric expenditure per kilogram of body weight per hour of activity divided by the equivalent per hour at rest. One MET, which is the energy expended by sitting quietly, is equivalent to 3.5 mL of oxygen uptake per kilogram of body weight per minute for a 70-kg adult. Body weight was excluded from the derivation of energy expenditure from physical activity to avoid confounding the expenditure variable by body weight. We further classified activities into vigorous (≥6 METs) and moderate (<6 METs). Accordingly, moderate activities included walking or hiking outdoors and stair climbing, and all other activities were classified as vigorous (eg, MET values of 7 were assigned to swimming and bicycling).

Smoking History and Other Risk Factors

Smoking status and history of smoking were obtained at baseline and in all subsequent questionnaires in both cohorts. Current smokers also reported intensity of smoking (average number of cigarettes smoked per day) on each questionnaire. Past smokers reported when they last smoked and time since quitting was also calculated for those who quit during follow-up. In a previous publication,[29] we examined the relationship between smoking and pancreatic cancer risk in detail; the strongest associations were observed in analyses of pack-years smoked within the previous 15 years.

Participants were asked about history of diabetes at baseline and in all subsequent questionnaires. In 1986 (HPFS) and in 1982 (NHS), and biennially thereafter, participants were asked about their history of cholecystectomy.

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Identification of Pancreatic Cancer Cases

In both cohorts, participants were asked to report specified medical conditions including cancers that were diagnosed in the 2-year period between each follow-up questionnaire. Whenever a participant (or next-of-kin for decedents) reported a diagnosis of pancreatic cancer, we asked for permission to obtain related medical records or pathology reports. If permission to obtain records was denied, we attempted to confirm the self-reported cancer with an additional letter or telephone call to the participant. If the primary cause of death as reported on a death certificate was a previously unreported pancreatic cancer case, we contacted a family member to obtain permission to retrieve medical records, or at least to confirm the diagnosis of pancreatic cancer. In the HPFS cohort, we were able to obtain pathology reports confirming the diagnosis of pancreatic cancer for 95% of cases. For the other 5% of cases, we obtained confirmation of the self-reported cancer from a secondary source (eg, death certificate, physician, or telephone interview of a family member). In the NHS cohort, we were able to obtain pathology reports confirming the diagnosis of pancreatic cancer for 85% of cases. For the other 15% of cases, we obtained confirmation of the self-reported cancer from a secondary source (eg, death certificate, physician, or telephone interview of a family member). In both cohorts, all medical records had complete information on histology (hospitals were recontacted if the original information sent was incomplete). In our analyses, associations were examined including and excluding cases with missing medical records; because no differences were observed between these 2 types of analyses, we included cases without medical records.

In the HPFS cohort, 140 confirmed incident cases of pancreatic cancer were diagnosed between 1986 and 1998 (after exclusions); 139 cases were available with data on physical activity at baseline. In the NHS, 210 confirmed incident pancreatic cancer cases, diagnosed between 1976 and 1996, were available for the anthropometric analyses (after exclusions); 110 confirmed cases were available for analyses on physical activity (1986-1996).

Statistical Analysis

We computed person-time of follow-up for each participant from the return date of the baseline questionnaire to the date of pancreatic cancer diagnosis, death from any cause, or the end of follow-up (January 31, 1998, for men and June 30, 1996, for women), whichever came first. Incidence rates of pancreatic cancer were calculated by dividing the number of incident cases by the number of person-years in each category of exposure. We computed the RR for each of the upper categories by dividing the rates in these categories by the rate in the lowest category.

We estimated the power to detect trends across quintiles for specified RRs comparing highest vs the lowest quintile, assuming a linear relationship and fixing the 2-tailed $\alpha = .05$.[30] We found an 80% power to detect an RR of 1.5 between the highest and lowest quintiles; a 95% power to detect an RR of 1.75 between the highest and lowest quintiles; and a greater than 99% power to detect an RR of 2.0 between the highest and lowest quintiles.

For each cohort, RRs adjusted for potential confounders were estimated using pooled logistic regression analyses with 2-year time increments. With short intervals between questionnaires and the low rates of events, this approach yields results similar to those of a Cox regression analysis with time-varying covariates.[31] In these models, age was categorized into 5-year age groups and cigarette smoking was categorized as follows (based on a previous analysis of these cohorts[29]): never smoker, quit more than 15 years ago, quit less than 15 years ago and smoked less than 25 pack-years in past 15 years, quit less than 15 years ago and smoked more than 25 pack-years in past 15 years, current smoker with less than 25 pack-years in past 15 years, and current smoker with more than 25 pack-years in past 15 years (age and smoking variables were updated biennially). In addition, we controlled for history of diabetes and cholecystectomy updating these variables biennially in the analyses.[4,32,33] We categorized men and women into 5 groups of BMI using whole number cutpoints that included widely used definitions of overweight and obesity.[34,35] BMI was not updated in the main analyses because pancreatic cancer is frequently associated with profound weight loss. In addition, we performed analyses with a 2-year lag to exclude preclinical cases at baseline. We used quintiles of total, vigorous, and moderate physical activity in both cohorts and did not update these variables over time since preclinical symptoms could affect activity levels. For height, whole cutpoints were made to approximate increments of 2.54 to 5.08 cm and keeping person-years fairly evenly distributed across the categories. All P values are based on 2-sided tests.

We pooled the data from the 2 cohorts using a random-effects model for the log of the RRs.[36] Tests of heterogeneity using the Q statistic[36] were obtained for continuous variables to evaluate the overall trend before pooling. All statistical procedures were performed using SAS version 6.12 (SAS Institute Inc, Cary, NC). The Human Research Committee at the Brigham and Women's Hospital approved the NHS and the Harvard School of Public Health Human Subjects Committee approved the HPFS.

RESULTS

We examined BMI and physical activity in relation to potential confounders for both men and women (TABLE 1). History of diabetes or cholecystectomy was higher among individuals with elevated BMI or with low physical activity. Men and women with low BMI or low physical activity were more likely to be current smokers, although men with high BMI had smoked more cigarettes in the past. Height and age were not substantially different by BMI or physical activity level. Caloric intake was slightly higher and percentage of total calories from fat was slightly lower among those in the top quintile

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of physical activity. As expected, physically active individuals tended to be leaner whereas heavier individuals tended to be more sedentary.

During 2 800 837 person-years of follow-up from the 2 cohorts, we identified 140 men and 210 women who were diagnosed as having pancreatic cancer. A statistically significant association between BMI and the risk of pancreatic cancer was observed in both cohorts (TABLE 2). After adjusting for known risk factors, men and women with a BMI of 30 or higher had a 72% increase in the risk of pancreatic cancer compared with men and women with a BMI of less than 23. In multivariable analyses, an increment of 1 BMI unit (1 kg/m^2) was associated with a 5% increased risk of pancreatic cancer in the HPFS (RR, 1.05; 95% CI, 1.00-1.11) and a 3% increased risk in the NHS (RR, 1.03; 95% CI, 1.00-1.07). Of all the pancreatic cancer cases, only 24 women and 14 men were diabetic prior to diagnosis. Controlling for smoking history using cumulative (lifetime) pack-years did not change the results for BMI and pancreatic cancer risk.

To eliminate preclinical cases that might have experienced weight loss before completing the baseline questionnaires, we performed analyses that excluded the first 4 years of follow-up. In both cohorts, associations with BMI were strengthened in lag analyses in top vs bottom category comparison (multivariable RR, 1.94; 95% CI, 1.26-2.98 in women and multivariable RR, 2.03; 95% CI, 0.90-4.57 in men).

In each cohort, we examined the effect of body size at a younger age using BMI at ages 18 years (NHS) and 21 years (HPFS). Women with a BMI of 24 or greater at age 18 years had a nonsignificant elevation in the risk of pancreatic cancer when compared with a BMI of less than 20 among women at age 18 years (RR, 1.45; 95% CI, 0.92-2.31). After adjusting for current BMI and other risk factors, the risk of pancreatic cancer asso-

Table 1. Baseline Characteristics Among Men in the HPFS and Women in the NHS Cohorts According to Category of BMI or Physical Activity*

	Health Professionals Follow-up Study			Nurses' Health Study		
	BMI, kg/m^2†			BMI, kg/m^2†		
Characteristic	<23.0	23.0-29.9	≥30.0	<23.0	23.0-29.9	≥30.0
No. of individuals	8477	34 348	3823	60 567	46 606	9868
Age, y, mean (SD)	53.9 (10)	54.4 (9.7)	54.0 (9.0)	41.6 (7.1)	44.1 (7.1)	44.4 (6.9)
Height, cm, mean (SD)	178.3 (6.9)	178.3 (6.6)	176.8 (10.4)	164.1 (6.1)	163.6 (6.1)	163.1 (6.1)
BMI, kg/m^2, mean (SD)	21.7 (1.0)	25.7 (1.7)	32.6 (3.0)	21.0 (1.3)	25.4 (1.9)	33.6 (3.5)
MET, h/wk, mean (SD)‡	24.3 (30)	20.0 (25)	12.9 (22)	15.6 (23)	12.9 (19)	9.9 (16)
History of diabetes, %	2.7 (16)	2.9 (17)	5.7 (23)	1.0 (10)	1.7 (13)	5.9 (24)
Cholecystectomy, %	1.9 (13)	3.0 (17)	4.9 (21)	3.6 (18)	6.7 (25)	14.7 (36)
Current smokers, %	10.5 (30)	9.3 (29)	9.1 (29)	36.8 (48)	30.6 (46)	25.0 (43)
Pack-years of cigarettes, mean (SD)§	11.2 (18)	13.2 (19)	16.7 (22)	6.5 (8.5)	5.9 (8.5)	5.3 (8.5)
Daily intake, mean (SD)						
Calories, kcal	2006 (609)	1977 (618)	2018 (654)	1565 (498)	1560 (502)	1604 (527)
Total fat, % of kcal	30.7 (6.8)	32.1 (6.2)	33.9 (12)	38.8 (1.6)	38.9 (7.9)	39.5 (8.0)
Alcohol, g	10.7 (14)	11.6 (15)	10.2 (16)	7.5 (11)	5.6 (10.2)	3.1 (7.8)
	Health Professionals Follow-up Study			Nurses' Health Study		
	Physical Activity, quintiles‖			Physical Activity, quintiles		
	≤2.8	2.9-33.9	≥34.0	≤2.0	2.1-21.7	≥21.8
No. of individuals	9015	27 760	9340	13 538	48 638	15 383
Age, y, mean (SD)	54.9 (9.7)	54.6 (9.7)	53.2 (9.6)	52.9 (7.1)	52.9 (7.2)	53.0 (7.2)
Height, cm, mean (SD)	177.8 (8.6)	178.1 (8.4)	178.1 (8.6)	163.6 (8.4)	163.8 (8.1)	163.8 (7.6)
BMI, kg/m^2, mean (SD)	26.2 (3.6)	25.5 (3.1)	24.8 (2.8)	24.5 (4.8)	23.7 (4.0)	23.1 (3.6)
MET, h/wk, mean (SD)‡	1.20 (0.8)	13.8 (8.4)	57.2 (35)	0.72 (0.4)	8.6 (5.7)	43.3 (31)
History of diabetes, %	4.2 (20)	3.1 (17)	2.2 (14)	5.0 (22)	4.0 (19)	3.0 (17)
Cholecystectomy, %	3.9 (20)	2.8 (17)	2.6 (15)	11.6 (32)	9.6 (29)	8.0 (27)
Current smokers, %	14.5 (35)	9.1 (29)	6.4 (25)	28.8 (45)	20.5 (40)	17.5 (38)
Pack-years of cigarettes, mean (SD)§	16.5 (23)	12.9 (19)	10.7 (17)	7.2 (9.4)	5.6 (8.1)	5.2 (7.5)
Daily intake, mean (SD)						
Calories, kcal	1933 (618)	1983 (613)	2049 (636)	1704 (538)¶	1774 (520)¶	1798 (533)¶
Total fat, % of kcal	33.3 (6.3)	32.0 (6.2)	30.5 (8.4)	33.9 (5.9)	32.8 (5.5)	31.5 (5.8)
Alcohol, g	10.8 (16)	11.2 (15)	12.2 (15)	5.9 (12)	6.0 (10)	7.0 (11)

*All variables (except age) are age-standardized means. BMI indicates body mass index; and MET, metabolic equivalents.
†Baseline: 1986 for HPFS, 1976 for NHS (dietary values from 1980 food frequency questionnaire).
‡MET, h/wk, sum of the average time/week spent in each activity times MET value of each activity (1986 for NHS).
§Pack-years are calculated for current and past smokers.
‖Baseline: 1986 for both cohorts. Physical activity was categorized according to quintile 1, quintile 2 through 4, and quintile 5.
¶Caloric intake is higher on average in the 1986 questionnaire because the food frequency questionnaire had more items than in the 1980 food frequency questionnaire.

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ciated with BMI at age 18 years was attenuated (multivariable RR, 1.09; 95% CI, 0.66-1.80). Men with a BMI of 27 or higher at age 21 years had an RR of 1.80 (95% CI, 0.97-3.34) compared with men who had a BMI of less than 21 at age 21 years, but controlling for current BMI also attenuated the association (multivariable RR, 1.50; 95% CI, 0.75-3.00).

We also examined the relation of weight loss to risk of pancreatic cancer. Compared with individuals whose weight had not changed by more than 2.25 kg between 2 consecutive biennial questionnaires, individuals who reported losing 6.75 or more kg between 2 consecutive biennial questionnaires had an RR of 4.56 (95% CI, 2.35-8.84) among men and 2.44 (95% CI, 1.46-4.06) among women. In both cohorts, only recent weight loss was associated with risk suggesting an influence of preclinical disease. Compared with those who had not lost 6.75 kg, the RR of pancreatic cancer was 3.66 (95% CI, 2.00-6.70) and 2.60 (95% CI, 1.53-4.40) in men and women, respectively, for a 6.75-kg weight loss within the past 2 years.

We observed an association between height and risk of pancreatic cancer in both cohorts (Table 2). Although cutpoints for the categories of height were different for men and women, both cohorts had similar increases in RR when comparing the highest and lowest categories. When men and women were combined, individuals in the highest vs lowest category of height had an RR of 1.81 (95% CI, 1.31-2.52) adjusting for potential confounders and BMI. The age-adjusted RRs were very similar, however, and including BMI in the multivariable model did not change the association. In multivariable analyses, an additional 2.54 cm of height increased the risk of pancreatic cancer by 6% in the HPFS (RR, 1.06; 95% CI, 0.99-1.12) and by 10% in the NHS (RR, 1.10; 95% CI, 1.04-1.16).

A total of 1 277 183 person-years and 249 pancreatic cancer cases (139 men, 110 women) were available for the physical activity analyses. We detected a slight inverse association between total physical activity and pancreatic cancer risk, but associations were not statistically significant in either cohort (TABLE 3). Vigorous activity was not related to the risk of pancreatic cancer in men or women in the multivariable models. In contrast, we observed inverse associations for moderate activity and pancreatic cancer risk in both cohorts. In the multivariable pooled analysis, men and women in the highest quintile of moderate activity had a significant reduction in the risk of pancreatic cancer (RR, 0.45; 95% CI, 0.29-0.70; $P<.001$ for trend) compared with those in the lowest quintile (Table 3). Additional control for total fat, pro-

Table 2. Relative Risk (RR) for Pancreatic Cancer by Height and Body Mass Index (BMI) in the NHS and HPFS*

	Category					*P* Value for Trend
	1	2	3	4	5	
	BMI, kg/m²					
	<23.0	23.0-24.9	25.0-26.9	27.0-29.9	≥30.0	
Men						
Cases/person-years	19/95 809	32/149 749	44/143 405	29/97 164	16/43 370	
Age-adjusted RR†	1.00	1.06 (0.60-1.87)	1.45 (0.85-2.49)	1.41 (0.79-2.51)	1.83 (0.94-3.56)	.04
Multivariable RR†‡	1.00	1.07 (0.61-1.89)	1.48 (0.86-2.54)	1.38 (0.77-2.48)	1.76 (0.90-3.45)	.05
	<23.0	23.0-24.9	25.0-26.9	27.0-29.9	≥30.0	
Women						
Cases/person-years	85/1 178 921	41/437 651	29/264 451	24/201 117	31/189 200	
Age-adjusted RR†	1.00	1.05 (0.73-1.53)	1.16 (0.76-1.78)	1.25 (0.79-1.97)	1.77 (1.17-2.68)	.01
Multivariable RR†‡	1.00	1.10 (0.75-1.59)	1.18 (0.77-1.80)	1.25 (0.79-1.99)	1.70 (1.09-2.64)	.02
Pooled multivariable RR†‡	1.00	1.09 (0.79-1.49)	1.29 (0.92-1.80)	1.30 (0.91-1.87)	1.72 (1.19-2.48)	.003
	Height, cm					
	≤172.7	175.3	177.8-180.3	182.9	≥185.4	
Men						
Cases/person-years	34/140 138	14/62 516	45/162 667	18/72 553	29/91 623	
Age-adjusted RR†	1.00	1.00 (0.54-1.87)	1.34 (0.86-2.10)	1.32 (0.75-2.35)	1.88 (1.14-3.10)	.01
Multivariable RR†‡	1.00	1.01 (0.54-1.88)	1.34 (0.86-2.10)	1.34 (0.75-2.38)	1.88 (1.14-3.11)	.01
	<157.5	157.7-160.0	160.3-163.8	164.1-167.6	>167.6	
Women						
Cases/person-years	36/513 468	20/274 705	41/384 421	63/638 454	50/460 291	
Age-adjusted RR†	1.00	1.04 (0.60-1.80)	1.59 (1.02-2.49)	1.51 (1.00-2.27)	1.76 (1.14-2.70)	.006
Multivariable RR†‡	1.00	1.04 (0.60-1.79)	1.61 (1.03-2.51)	1.52 (1.01-2.29)	1.77 (1.15-2.72)	.006
Pooled multivariable RR†‡	1.00	1.03 (0.68-1.53)	1.47 (1.07-2.02)	1.46 (1.04-2.03)	1.81 (1.31-2.52)	.001

*NHS indicates Nurses' Health Study; HPFS, Health Professionals Follow-up Study; and CI, confidence interval.
†Data presented as RR (95% CI).
‡Relative risks are from a multivariable model that included height, BMI (assessed at baseline), age in 5-year categories, pack-years of smoking (past 15 years; current and past smokers separately), history of diabetes mellitus, and history of cholecystectomy.

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