is unknown. As postmenopausal breast cancer is associated with high estrogen levels (6), one hypothesis involves a reduction in levels of endogenous sex hormones (7). Other estrogen-independent pathways have also been proposed, including an effect of activity in modulating levels of insulin and insulin-like growth factors, enhancing immunity, and reducing chronic inflammation (8).

The plausibility of these mechanisms could be further informed by examining modification of the association between physical activity and breast cancer risk by estrogen-related factors and by breast tumor characteristics such as estrogen receptor (ER) and progesterone receptor (PR) status, tumor stage, and histology. Reports that the relation of estrogen-related factors such as parity, age at first birth, age at menarche, and postmenopausal adiposity to risk varies across breast tumor subtypes (9-11) support the idea that breast cancer subtypes represent distinct diseases with respective etiologies and prognoses (12). However, it remains unclear whether the association between physical activity and breast cancer differs by tumor characteristics. Within the large, prospective NIH-AARP Diet and Health Study, we evaluated the association between physical activity and postmenopausal breast cancer risk overall and by ER and PR status, tumor stage, and histology. We also examined effect modification by select lifestyle and reproductive factors.

Materials and Methods

Study Population. The NIH-AARP Diet and Health Study has been described previously (13). Briefly, between the years 1995 and 1996, members of the American Association of Retired Persons residing in six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) or two urban areas (Atlanta, GA, and Detroit, MI) were recruited to the study. A baseline questionnaire to assess diet, physical activity, and medical history was mailed to 3.5 million American Association of Retired Persons members and was satisfactorily completed by 566,402 individuals ages 50 to 71 years, of whom 241,228 were women. A second questionnaire distributed within 6 months of the baseline questionnaire was used to obtain additional information on histories of mammography and benign breast disease.

After excluding premenopausal women (n = 7,249) and those with unknown menopausal status (n = 1,883), women with prevalent cancers (other than nonmelanoma skin cancer; n = 23,957), those with questionnaires completed by proxy (n = 15,760), and those with missing or extreme values of height, weight, or physical activity (n = 9,517), 182,862 postmenopausal women remained for analysis. Postmenopausal status was defined as report of either natural menopause, bilateral oophorectomy, hysterectomy, or age ≥57 years. Extreme values were defined by the Box-Cox transformation. The Special Studies Institutional Review Board of the National Cancer Institute approved this study, and completion of the self-administered baseline questionnaire was considered to imply informed consent.

Cohort Follow-up and Case Ascertainment. Cohort members were followed for change of address via annual linkage to the National Change of Address database maintained by the U.S. Postal Service, by notifications of undelivered mail, through other address update services, and by direct notice from participants. Vital status was ascertained by annual linkage to the Social Security Administration Death Master File, and searches of the National Death Index Plus were used to verify vital status and to provide cause of death information.

Incident breast cancer cases were identified by linkage to 11 state cancer registries (including the addition of Texas, Arizona, and Nevada to the eight states in which baseline data were collected). Hormone receptor status was available from 7 (California, Louisiana, Georgia, North Carolina, New Jersey, Arizona, and Nevada) of the 11 reporting states, with a positive hormone receptor status recorded at a threshold of at least 10 fmol receptor/mg total protein. Although hormone receptor data were unavailable for cases from Florida, Pennsylvania, Michigan, and Texas, the distribution of risk factors considered in our study was similar for women from states with and without hormone receptor information (data not shown); thus, noncases from these states were included in analyses. Sensitivity analyses confirmed that results were unchanged when including as noncases only women from states where ER status was known.

The *International Classification of Diseases for Oncology, Third Edition* coding system was used to classify tumor histology, with ductal cases defined by code 8500 or 8523, lobular cases by code 8520 or 8524, and tumors of mixed histology by code 8522. The completeness of case ascertainment in our cohort has been reported previously, with an estimated sensitivity of ~90% and specificity of 99.5% with respect to identification of cases by cancer registry linkage (14).

Physical Activity Assessment. Physical activity was assessed in the baseline questionnaire by asking participants to report the frequency over the past year of "activities at work or home, including exercise, sports, and activities such as carrying heavy loads. . .which lasted at least 20 minutes, and caused increases in breathing or heart rate, or caused you to work up a sweat." Participants were classified into one of five activity categories: inactive; active less than once per week; active 1 to 2 times per week; active 3 to 4 times per week; and active ≥5 times per week. The questionnaire used was similar to an instrument that has been validated using objective methods (percentage agreement = 0.71; ref. 15).

Statistical Analysis. Cox proportional hazards regression with age as the time metric was used to estimate the relative risk (RR) of postmenopausal breast cancer. We tested and confirmed that the proportionality assumption was not violated. Follow-up time was calculated from the scan date of the baseline questionnaire through the date of diagnosis of breast cancer or other cancer (except nonmelanoma skin cancer), death, or the end of the study on December 31, 2003. Models were adjusted for potential confounding variables (Table 1). Analyses were done with and without inclusion of body mass index (BMI) as a covariate, because BMI could mediate the association between physical activity and breast cancer risk.

Table 1. Characteristics of the study population by level of physical activity at baseline, 182,862 postmenopausal women, NIH-American Association of Retired Persons Diet and Health Study (1995-1996)

Characteristics	Total	Physical activity (times per week)				
		Inactive	<1	1-2	3-4	≥5
Participants, *n* (%)	182,862	41,580 (22.7)	26,311 (14.4)	38,713 (21.2)	46,251 (25.3)	30,007 (16.4)
Age at baseline (y)	62.1	62.4	61.3	61.8	62.4	62.5
BMI (kg/m^2)	26.9	28.6	27.6	26.9	26.0	25.3
Race/ethnicity (%)						
White	89.9	88.5	90.2	90.6	90.0	90.8
Black	5.5	6.6	5.6	5.0	5.3	4.9
Hispanic	1.9	2.3	1.8	1.8	1.9	1.5
Asian/Pacific Islander/Native American	1.5	1.4	1.3	1.5	1.7	1.6
College education (%)	29.6	21.6	28.5	31.0	33.1	34.2
Family history of breast cancer* (%)	12.4	12.0	12.6	12.5	12.5	12.4
Current smoker (%)	14.4	19.7	17.6	14.8	10.6	9.6
Current MHT use (%)	44.9	37.8	45.3	46.0	48.9	47.0
Age at menarche (y)	12.51	12.46	12.48	12.50	12.53	12.55
Age at first birth in parous women (y)	22.88	22.68	22.78	22.94	23.02	22.97
Parity (no. children)	2.01	2.02	2.01	2.00	2.02	1.99
Age at menopause (y)	46.88	46.46	46.76	46.91	47.11	47.21
Alcohol intake (g/d)	6.0	5.8	6.1	5.8	6.1	6.3
Total energy intake† (kcal/d)	1,597.4	1,623.5	1,557.3	1,583.2	1,576.1	1,647.4

NOTE: All values, except age, are adjusted for age.
*Family history of breast cancer in a first-degree female relative.
†Adjusted for total energy intake.

In the subgroup of women who completed the second questionnaire (n = 116,159), we investigated potential confounding of the physical activity-breast cancer association by mammogram history during the preceding 3 years and by previous benign breast disease.

Interaction was explored by likelihood ratio tests comparing models with and without interaction terms. As interaction tests were not sensitive to adjustment for BMI, results are presented without inclusion of BMI in statistical models. Physical activity was modeled as an ordinal variable in all interaction tests and tests of linear trend.

In separate analyses, we investigated the relation of physical activity to distinct endpoints: ER/PR status (ER− or ER+ tumors; ER+/PR+, ER+/PR−, ER−/PR+, ER−/PR−, or unknown ER/PR tumors), tumor stage (invasive or *in situ* breast cancer; localized or regional/distant breast cancer), and histologic subtype (ductal, lobular, or mixed histology). Analyses of hormone receptor status and tumor histology were restricted to invasive cancers. Unknown ER/PR tumors (n = 3039) included borderline, missing, and unknown hormone receptor status. Heterogeneity by the above tumor characteristics was evaluated by comparison of the test of trend for each outcome using Cochran's Q statistic (16).

Analyses were done using SAS (version 9.1; SAS Institute), with all statistical tests two-sided and conducted at the 0.05 significance level.

Results

During an average of 7 years of follow-up, 6,609 cases of incident breast cancer were ascertained, including 1,176 (17.8%) *in situ* cancers. Women were an average age of 62.1 years at baseline, and 22.7% were categorized as inactive (Table 1). The majority of participants (~90%) were Caucasian, and ~30% were college educated. The most active women were more likely than the total cohort to be college educated, to report current menopausal hormone therapy (MHT) use, and to drink alcohol, and were less likely to be current smokers. BMI decreased with increasing physical activity, and women active ≥5

Table 2. RR (95% CI) for the association between physical activity and postmenopausal breast cancer incidence among 182,862 postmenopausal women

Physical activity (times per week)	Person-years	No. cases	Age-adjusted RR (95% CI)	Multivariate RR* (95% CI)	Multivariate RR† (95% CI)
Inactive	285,349	1,485	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
<1	184,682	981	1.04 (0.96-1.13)	0.99 (0.91-1.07)	1.00 (0.92-1.08)
1-2	271,497	1,391	0.99 (0.92-1.07)	0.94 (0.87-1.01)	0.96 (0.89-1.03)
3-4	325,701	1,711	1.01 (0.94-1.08)	0.93 (0.87-1.00)	0.97 (0.90-1.04)
≥5	211,557	1,041	0.94 (0.87-1.02)	0.87 (0.81-0.95)	0.92 (0.85-1.00)
P_{trend}			0.13	<0.001	0.04

*Multivariate models used age as the underlying time metric and were adjusted for race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander/American Indian), education level (<12 years or high school equivalent, 12 years or high school equivalent, post-high school vocational or technical training, some college, college graduate, postgraduate), smoking status (nonsmoker, former, current), family history of breast cancer (no, yes), menopausal hormone use (never, current, past), age at first birth (nulliparous, <20, 20-24, 25-29, ≥30 years), age at menarche (<13, 13-14, ≥15 years), age at menopause (<40, 40-44, 45-49, 50-54, ≥55 years), parity (number of children: 0, 1-2, ≥3), and alcohol intake (g/d; quintiles adjusted for total energy intake).
†Additionally adjusted for BMI (<25.0, 25.0-29.9, 30.0-34.9, ≥35.0 kg/m^2).

Table 3. Multivariate RR (95% CI) for the association between physical activity and breast cancer incidence among postmenopausal women according to selected tumor characteristics

Tumor characteristics*	No. cases	Physical activity (times per week)					P_{trend}	$P_{heterogeneity}$
		Inactive	<1	1-2	3-4	≥5		
Hormone receptor status								
ER+	2,083	1.0 (Reference)	1.03 (0.89-1.19)	0.95 (0.83-1.08)	0.98 (0.86-1.11)	0.97 (0.84-1.12)	0.64	0.07
ER−	411	1.0 (Reference)	1.10 (0.81-1.49)	0.85 (0.63-1.14)	0.85 (0.64-1.12)	0.75 (0.54-1.04)	0.03	
ER+/PR+	1,649	1.0 (Reference)	1.00 (0.84-1.18)	0.97 (0.84-1.13)	0.96 (0.83-1.11)	0.96 (0.82-1.13)	0.53	
ER+/PR−	338	1.0 (Reference)	1.29 (0.90-1.84)	0.93 (0.65-1.32)	1.17 (0.85-1.60)	1.05 (0.73-1.51)	0.85	
ER−/PR+	48	1.0 (Reference)	1.10 (0.41-2.95)	1.15 (0.47-2.78)	1.29 (0.56-2.95)	0.62 (0.21-1.86)	0.56	0.37
ER−/PR−	359	1.0 (Reference)	1.10 (0.80-1.53)	0.84 (0.61-1.15)	0.81 (0.60-1.10)	0.78 (0.55-1.10)	0.05	
Unknown ER or PR	3,039	1.0 (Reference)	0.90 (0.80-1.02)	0.95 (0.85-1.06)	0.92 (0.83-1.01)	0.81 (0.72-0.91)	0.002	
Tumor stage								
In situ	1,176	1.0 (Reference)	1.10 (0.91-1.33)	0.90 (0.75-1.08)	0.93 (0.78-1.10)	0.93 (0.77-1.13)	0.20	0.85
Invasive	5,433	1.0 (Reference)	0.97 (0.88-1.06)	0.95 (0.87-1.03)	0.94 (0.87-1.01)	0.86 (0.79-0.94)	0.001	
Localized	3,158	1.0 (Reference)	0.97 (0.86-1.09)	0.95 (0.86-1.06)	1.00 (0.90-1.10)	0.85 (0.76-0.96)	0.04	0.17
Regional/distant	1,298	1.0 (Reference)	0.99 (0.83-1.17)	0.83 (0.71-0.98)	0.74 (0.63-0.86)	0.85 (0.71-1.01)	0.003	0.36†
Tumor histology								
Ductal	3,568	1.0 (Reference)	0.98 (0.88-1.10)	0.96 (0.87-1.06)	0.93 (0.84-1.02)	0.89 (0.80-0.99)	0.02	
Lobular	550	1.0 (Reference)	1.24 (0.95-1.63)	0.92 (0.71-1.19)	0.89 (0.69-1.14)	0.87 (0.65-1.15)	0.05	0.41
Ductal-lobular	436	1.0 (Reference)	0.80 (0.58-1.12)	0.80 (0.60-1.08)	0.95 (0.73-1.24)	0.89 (0.66-1.20)	0.96	

NOTE: Multivariate models used age as the underlying time metric and were adjusted for race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander/American Indian), education level (<12 years or high school equivalent, 12 years or high school equivalent, post-high school vocational or technical training, some college, college graduate, postgraduate), smoking status (nonsmoker, former, current), family history of breast cancer (no, yes), menopausal hormone use (never, current, past), age at first birth (nulliparous, <20, 20-24, 25-29, ≥30 years), age at menarche (<13, 13-14, ≥15 years), age at menopause (<40, 40-44, 45-49, 50-54, ≥55 years), parity (number of children: 0, 1-2, ≥3), and alcohol intake (g/d; quintiles adjusted for total energy intake).
*Hormone receptor status and tumor histology limited to invasive cancers.
†*P* value for comparison of *in situ*, localized, and regional/distant.

times per week had the lowest average BMI despite greater total energy consumption.

Similar to previous reports (17), women diagnosed with incident breast cancer were more likely to have a first-degree female relative with breast cancer and to experience an earlier age at menarche, later age at first birth, reduced parity, later age at menopause, greater MHT use, slightly higher BMI, and increased alcohol intake relative to noncases (data not shown).

In age-adjusted models, physical activity was not statistically significantly associated with breast cancer (Table 2). However, after multivariate adjustment, the most active women experienced a 13% reduced breast cancer risk [RR, 0.87; 95% confidence interval (95% CI), 0.81-0.95] compared with inactive women. First-degree family history of breast cancer and MHT use accounted for the majority of the difference in risk estimates between age-adjusted and multivariate analyses, and the inverse relation was slightly attenuated after adding BMI to the model (RR, 0.92; 95% CI, 0.85-1.00).

Risk estimates were not sensitive to exclusion of the first 2 years of follow-up, to exclusion of women with a history of heart disease, or to adjustment for history of mammography or benign breast disease (data not shown).

Table 4. Multivariate RR (95% CI) for the association between physical activity and breast cancer incidence among postmenopausal women according to BMI, MHT use, and family history of breast cancer

	No. cases	Physical activity (times per week)					P_{trend}	$P_{heterogeneity}$
		Inactive	<1	1-2	3-4	≥5		
BMI (kg/m^2)								
≥25.0	3,787	1.0 (Reference)	0.98 (0.89-1.08)	0.98 (0.90-1.08)	0.92 (0.84-1.01)	0.86 (0.77-0.96)	0.003	0.07
<25.0	2,822	1.0 (Reference)	1.01 (0.92-1.11)	0.97 (0.89-1.05)	0.99 (0.92-1.08)	0.95 (0.87-1.05)	0.64	
MHT use								
Ever use	4,073	1.0 (Reference)	1.03 (0.93-1.15)	1.00 (0.90-1.10)	1.00 (0.92-1.10)	0.97 (0.88-1.08)	0.34	0.002
Never use	2,528	1.0 (Reference)	0.95 (0.84-1.08)	0.88 (0.79-0.99)	0.86 (0.77-0.96)	0.76 (0.67-0.86)	<0.001	
Family history								
Family history	1,193	1.0 (Reference)	0.99 (0.83-1.19)	0.92 (0.78-1.08)	0.75 (0.64-0.89)	0.75 (0.62-0.91)	<0.001	0.003
No family history	5,124	1.0 (Reference)	0.99 (0.90-1.09)	0.95 (0.87-1.03)	0.98 (0.90-1.06)	0.88 (0.81-0.97)	0.03	

NOTE: Multivariate models used age as the underlying time metric and were adjusted for race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander/American Indian), education level (<12 years or high school equivalent, 12 years or high school equivalent, post-high school vocational or technical training, some college, college graduate, postgraduate), smoking status (nonsmoker, former, current), family history of breast cancer (no, yes), menopausal hormone use (never, current, past), age at first birth (nulliparous, <20, 20-24, 25-29, ≥30 years), age at menarche (<13, 13-14, ≥15 years), age at menopause (<40, 40-44, 45-49, 50-54, ≥55 years), parity (number of children: 0, 1-2, ≥3), and alcohol intake (g/d; quintiles adjusted for total energy intake).

The physical activity-breast cancer relation appeared to differ by ER status ($P_{heterogeneity}$ = 0.07). Women in the highest versus lowest category of activity displayed a borderline statistically significant 25% lower RR of ER− tumors (RR, 0.75; 95% CI, 0.54-1.04; Table 3). In contrast, no relation was seen with ER+ breast cancers (RR, 0.97; 95% CI, 0.84-1.12). Considering joint ER/PR status, the most active women showed statistically nonsignificant reductions in ER−/PR− and ER−/PR+ breast cancer risk compared with inactive women. However, no associations were evident for ER+/PR+ or ER+/PR− breast cancers.

No statistically significant heterogeneity was observed in the relation of physical activity to breast cancer tumor characteristics (Table 3). Whereas the association with physical activity appeared weak for the small subset of *in situ* breast cancers (RR for the most active versus inactive women, 0.93; 95% CI, 0.77-1.13), inverse relations were of similar magnitude for both localized tumors (RR, 0.85; 95% CI, 0.76-0.96) and tumors with regional/distant metastases (RR, 0.85; 95% CI, 0.71-1.01). Likewise, inverse relations with physical activity were comparable for ductal (RR, 0.89; 95% CI, 0.80-0.99), lobular (RR, 0.87; 95% CI, 0.65-1.15), and mixed ductal-lobular (RR, 0.89; 95% CI, 0.66-1.20) tumors.

The relation of physical activity to breast cancer risk was suggestively modified by BMI ($P_{heterogeneity}$ = 0.07) and appeared stronger for overweight and obese women (BMI ≥25 kg/m^2) than lean women (BMI <25 kg/m^2; Table 4). MHT use statistically significantly modified the relation of physical activity to breast cancer risk ($P_{heterogeneity}$ = 0.002), so that the inverse association was more pronounced among women with no history of MHT use than those with a history of MHT use (Table 4). The association between physical activity and breast cancer was also more apparent among women with a first-degree family history of breast cancer than those without a family history ($P_{heterogeneity}$ = 0.003; Table 4).

We also reevaluated the aforementioned associations after jointly classifying exposures and including a common reference group to obtain an estimate of overall risk (Table 5). Compared with overweight or obese women who were categorized as inactive, the RR of breast cancer for the subgroup of women who were both lean and engaged in physical activity ≥5 times per week was 0.80 (95% CI, 0.72-0.88). Using women with the combination of a positive family history of breast cancer and physical inactivity as the reference group, risk reduction for women who had no family history of breast cancer and were highly physically active was nearly 50% (RR, 0.51; 95% CI, 0.44-0.58). Substantial risk reduction was also observed for women with the combination of never MHT use and high physical activity level (RR, 0.60; 95% CI, 0.53-0.68) relative to women who used MHT and were physically inactive.

The physical activity-breast cancer association was not modified by age, race, education level, age at menarche, age at first birth, parity, age at menopause, cigarette smoking, history of mammography or benign breast disease, or alcohol intake (all $P_{heterogeneity}$ > 0.10; data not shown).

Discussion

In this large, prospective study, we report a modest but statistically significant reduction in the risk of postmenopausal breast cancer with a high versus low level of physical activity. Women active ≥5 times per week displayed a 13% reduced breast cancer risk compared with inactive women. This relation persisted across tumor stage and select histologic subtypes. In particular, the inverse association appeared more pronounced for ER− breast cancers, for overweight and obese women, for those who never used MHT, and for women with a history of breast cancer in a first-degree female relative. These findings add to the current literature supporting the notion that physical activity influences the risk of this common and deleterious disease (2-4).

Our observation that a high level of activity is specifically associated with a borderline significant reduction in ER− breast cancer risk distinguishes our study from prior investigations. The majority of previous evidence supporting an association between physical activity and postmenopausal breast cancer incidence is based primarily on ER+ tumors, which account for a substantial proportion of postmenopausal breast cancers (18).

Table 5. Multivariate RR (95% CI) for the association between physical activity and breast cancer incidence among postmenopausal women according to joint effect of physical activity and BMI, joint effect of physical activity and MHT use, and joint effect of physical activity and family history of breast cancer

	No. cases	Physical activity (times per week)				
		Inactive	<1	1-2	3-4	≥5
BMI (kg/m^2)						
≥25.0	3,787	1.0 (Reference)	0.98 (0.89-1.08)	0.98 (0.90-1.08)	0.92 (0.84-1.01)	0.86 (0.77-0.96)
<25.0	2,822	0.84 (0.75-0.94)	0.85 (0.75-0.96)	0.76 (0.68-0.84)	0.84 (0.77-0.92)	0.80 (0.72-0.88)
MHT use						
Ever use	4,073	1.0 (Reference)	1.03 (0.93-1.15)	1.00 (0.90-1.10)	1.01 (0.92-1.10)	0.97 (0.88-1.08)
Never use	2,528	0.79 (0.72-0.88)	0.76 (0.67-0.85)	0.70 (0.63-0.78)	0.68 (0.61-0.76)	0.60 (0.53-0.68)
Family history						
Family history	1,193	1.0 (Reference)	0.99 (0.83-1.19)	0.92 (0.78-1.08)	0.75 (0.64-0.89)	0.75 (0.62-0.91)
No family history	5,124	0.57 (0.50-0.65)	0.57 (0.50-0.65)	0.54 (0.48-0.62)	0.56 (0.49-0.64)	0.51 (0.44-0.58)

NOTE: Multivariate models used age as the underlying time metric and were adjusted for race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander/American Indian), education level (<12 years or high school equivalent, 12 years or high school equivalent, post-high school vocational or technical training, some college, college graduate, postgraduate), smoking status (nonsmoker, former, current), family history of breast cancer (no, yes), menopausal hormone use (never, current, past), age at first birth (nulliparous, <20, 20-24, 25-29, ≥30 years), age at menarche (<13, 13-14, ≥15 years), age at menopause (<40, 40-44, 45-49, 50-54, ≥55 years), parity (number of children: 0, 1-2, ≥3), and alcohol intake (g/d; quintiles adjusted for total energy intake).

However, our results are consistent with the California Teachers Study, which found an inverse relation of physical activity to ER− breast cancer in postmenopausal women, whereas the association with ER+ tumors was null (19). A U.S. case-control study also showed a statistically nonsignificant inverse relation between adult activity and ER− tumors compared with a suggested positive association with ER+ tumors, although the study population was primarily premenopausal (20). Conversely, physical activity was selectively associated with reduced risk of ER+ postmenopausal breast cancer in the Iowa Women's Health Study (21). Furthermore, the relation of physical activity to breast cancer was not significantly modified by ER subtype in five case-control studies (22-26).

Our results regarding joint ER/PR status correspond to a recent systematic review (5) reporting a stronger association with ER−/PR− than ER+/PR+ tumors. In addition, our observation of a suggestive reduction in ER−/PR− cancer risk with increasing physical activity is consistent with results from the California Teachers Study (19) and a Shanghai-based case-control study (24). Physical activity was not associated with ER+/PR+ tumors in our study, in agreement with two other large cohort studies (19, 27) and two case-control studies (20, 23). In contrast, two studies (21, 24) reported an inverse association between physical activity and ER+/PR+ cancers. Associations with the less common discordant ER+/PR− and ER−/PR+ subtypes revealed no consistent pattern in our study and past studies (20, 21, 23, 24, 27).

Our study suggests a potential role of physical activity in the prevention of ER− breast cancers. This is of considerable interest because women with ER− cancers tend to be younger (28), to have tumors that are large and advanced at diagnosis (29), and to experience reduced survival (30). Moreover, there is currently a paucity of knowledge regarding risk factors for ER− tumors (18, 31).

The suggestion of a stronger relation with ER− than ER+ tumors also indicates that physical activity may influence breast cancer risk independently of estrogens. Potential alternative mechanisms include decreased levels of circulating insulin and insulin-like growth factors, reduction of chronic inflammation, and modulation of the immune response (8).

However, because estrogen may actually mediate the development of ER− tumors through growth signals produced by adjacent ER+ cells following estrogen exposure (32), physical activity could relate to ER-tumors through estrogenic mechanisms. It remains unresolved whether ER+ and ER− tumors represent two phases of one unified disease process or two distinct pathologic entities (33), although heterogeneity in correlated risk factors (9-11) and unique genetic profiles (34) for each subtype support the latter hypothesis. Moreover, estrogen metabolites may influence breast cancer risk independently of the ER via DNA damage (35).

In accordance with other reports (19, 22, 26, 36-38), we found no significant heterogeneity in the relation of physical activity to invasive versus *in situ* breast cancers, although we did note only a weak association with *in situ* tumors, similar to the Collaborative Breast Cancer Study (39). In contrast, the Cancer Prevention Study II (40) reported an inverse relation for physical activity specific to localized tumors, whereas a Polish case-control study (26) observed a stronger relation with advanced tumors. Taken together, our results along with most, but not all, epidemiologic evidence suggest that physical activity operates at all stages of breast cancer pathogenesis.

Our observation that the association with physical activity does not vary by breast tumor histology is consistent with the only other report on this relation (26), suggesting that physical activity reduces risk of both ductal and lobular carcinomas.

We found a suggestively more pronounced inverse association with physical activity for heavy than lean women, contrasting somewhat with a recent review (5) showing a greater reduction in breast cancer risk with increasing physical activity among lean than heavy women.

We observed a lower breast cancer risk among active versus inactive women who had never used MHT compared with those with past or current MHT use, similar to results for active non-Hispanic White women with no recent MHT use in one previous investigation (25). However, other studies (19, 22, 37, 38, 40-46) have not observed effect modification of the physical activity-breast cancer relation by MHT use. One possible explanation is limited statistical power to examine effect modification by MHT use in those studies (19, 22, 37, 38, 40-46). A differential association by MHT use indicates that physical activity affects breast cancer risk at least partially through a reduction in circulating sex hormones (7). Conceivably, exogenous estrogens taken by postmenopausal women may render such individuals less sensitive to any physical activity effect if physical activity most effectively reduces breast cancer risk at low estrogen levels.

In our study, physical activity was particularly associated with reduced breast cancer risk in women with a positive family history of breast cancer. This is not consistent with previous observations of either no effect modification or a stronger inverse relation for women without a family history (5). Apart from chance, one possible explanation for our finding is a greater potential for residual confounding by MHT use or other reproductive variables among women with a family history of breast cancer compared with those without a family history. If true, our finding suggests that women with hereditary risk require a lower "dose" of physical activity to alter their risk profile. This would have implications for targeting a subgroup of individuals who would most benefit from a physical activity intervention.

A major strength of our study is the large number of breast cancer cases. With nearly twice the number of incident cancers than any previous prospective study of the physical activity-breast cancer relation (3), we had ample statistical power to investigate the association by tumor characteristics and by select breast cancer risk factors. However, it is possible that some of our subgroup results emerged by chance due to multiple comparisons. The prospective nature of our data collection helped avoid recall bias, and comprehensive data on lifestyle covariates allowed extensive control for potential confounding. Because physical activity may serve as a proxy for an overall healthy lifestyle, we adjusted for numerous potentially confounding factors.

A limitation of our study includes the physical activity assessment, which queried participants' activity

by self-report and did not measure all physical activity parameters. However, bias related to misreporting of true activity levels would likely be nondifferential and would tend to underestimate the association between physical activity and breast cancer risk. In addition, our physical activity classification predicts cardiovascular mortality (47); this biologically plausible relation is consistent with the accumulated evidence and shows construct validity in the discriminatory ability of our five activity categories. An additional, although not necessarily critical, limitation is that the generalizability of our results may be limited because of the relatively low response proportion to our initial postal questionnaire.

Due to the very limited number of premenopausal participants in our cohort, we restricted the study population to postmenopausal women. Although this slightly reduced our cohort size, evidence of a stronger relation between physical activity and postmenopausal breast cancer (5), divergent associations between lifestyle factors such as BMI and risk of premenopausal versus postmenopausal breast cancer (2, 4, 5), and distinct incidence profiles for ER+ and ER− tumors by menopausal status (28) warrants our approach of excluding premenopausal women.

In summary, physical activity was associated with a modest reduction in the risk of postmenopausal breast cancer, particularly ER− tumors. In addition, the physical activity-breast cancer relation was modified by family history of breast cancer and by the estrogen-related factors MHT use and BMI. Our results suggest the potential for prevention of the comparatively aggressive ER− breast cancer subtype, and observation of a more pronounced inverse association between physical activity and breast cancer risk among certain subgroups of women may have practical implications for targeting an at-risk population. Future studies with large cohorts will be imperative for replication of our subgroup findings, and experimental studies and controlled trials will be required to elucidate the potential biological mechanisms underlying the association between physical activity and breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Ries LAG, Melbert D, Krapcho M, et al., editors. SEER cancer statistics review, 1975-2004. Based on November 2007 SEER data submission, posted to the SEER Web site, 2008. Bethesda (MD): National Cancer Institute. Available from: http://seer.cancer.gov/csr/1975_2004/.
2. Vainio H, editor. Weight control and physical activity. IARC handbooks of cancer prevention. Lyon (France): IARC Press; 2002.
3. Monninkhof EM, Elias SG, Vlems FA, et al. Physical activity and breast cancer: a systematic review. Epidemiology 2007;18:137–57.
4. World Cancer Research Fund/American Institute for Cancer Research. Food, nutrition, physical activity, and the prevention of cancer: a global perspective. Washington (DC): American Institute for Cancer Research; 2007.
5. Friedenreich CM, Cust AE. Physical activity and breast cancer risk: impact of timing, type and dose of activity and population sub-group effects. Br J Sports Med 2008;42:636–47.
6. Key T, Appleby P, Barnes I, Reeves G. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst 2002;94:606–16.
7. McTiernan A, Wu L, Chen C, et al. Relation of BMI and physical activity to sex hormones in postmenopausal women. Obesity (Silver Spring) 2006;14:1662–77.
8. McTiernan A. Mechanisms linking physical activity with cancer. Nat Rev Cancer 2008;8:205–11.
9. Ma H, Bernstein L, Pike MC, Ursin G. Reproductive factors and breast cancer risk according to joint estrogen and progesterone receptor status: a meta-analysis of epidemiological studies. Breast Cancer Res 2006;8:R43.
10. Althuis MD, Fergenbaum JH, Garcia-Closas M, Brinton LA, Madigan MP, Sherman ME. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. Cancer Epidemiol Biomarkers Prev 2004;13:1558–68.
11. Garcia-Closas M, Brinton LA, Lissowska J, et al. Established breast cancer risk factors by clinically important tumour characteristics. Br J Cancer 2006;95:123–9.
12. Potter JD, Cerhan JR, Sellers TA, et al. Progesterone and estrogen receptors and mammary neoplasia in the Iowa Women's Health Study: how many kinds of breast cancer are there? Cancer Epidemiol Biomarkers Prev 1995;4:319–26.
13. Schatzkin A, Subar AF, Thompson FE, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: the National Institutes of Health-American Association of Retired Persons Diet and Health Study. Am J Epidemiol 2001;154:1119–25.
14. Michaud DS. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. J Registry Manage 2005;32:70–5.
15. Marshall AL, Smith BJ, Bauman AE, Kaur S. Reliability and validity of a brief physical activity assessment for use by family doctors. Br J Sports Med 2005;39:294–7.
16. Cochran W. The combination of estimates from different experiments. Biometrics 1954;10:101–29.
17. Department of Health and Human Services. Risk factors. Centers for Disease Control and Prevention, 2006. Available from: http://www.cdc.gov/cancer/breast/basic_info/risk_factors.htm.
18. Gail MH, Anderson WF, Garcia-Closas M, Sherman ME. Absolute risk models for subtypes of breast cancer. J Natl Cancer Inst 2007;99:1657–9.
19. Dallal CM, Sullivan-Halley J, Ross RK, et al. Long-term recreational physical activity and risk of invasive and *in situ* breast cancer: the California Teachers Study. Arch Intern Med 2007;167:408–15.
20. Britton JA, Gammon MD, Schoenberg JB, et al. Risk of breast cancer classified by joint estrogen receptor and progesterone receptor status among women 20-44 years of age. Am J Epidemiol 2002;156:507–16.
21. Bardia A, Hartmann LC, Vachon CM, et al. Recreational physical activity and risk of postmenopausal breast cancer based on hormone receptor status. Arch Intern Med 2006;166:2478–83.
22. Bernstein L, Patel AV, Ursin G, et al. Lifetime recreational exercise activity and breast cancer risk among black women and white women. J Natl Cancer Inst 2005;97:1671–9.
23. Enger SM, Ross RK, Paganini-Hill A, Carpenter CL, Bernstein L. Body size, physical activity, and breast cancer hormone receptor status: results from two case-control studies. Cancer Epidemiol Biomarkers Prev 2000;9:681–7.
24. Adams SA, Matthews CE, Hebert JR, et al. Association of physical activity with hormone receptor status: the Shanghai Breast Cancer Study. Cancer Epidemiol Biomarkers Prev 2006;15:1170–8.
25. Slattery ML, Edwards S, Murtaugh MA, et al. Physical activity and breast cancer risk among women in the southwestern United States. Ann Epidemiol 2007;17:342–53.
26. Peplonska B, Lissowska J, Hartman TJ, et al. Adulthood lifetime physical activity and breast cancer. Epidemiology 2008;19:226–36.
27. Lee IM, Rexrode KM, Cook NR, Hennekens CH, Burin JE. Physical activity and breast cancer risk: the Women's Health Study (United States). Cancer Causes Control 2001;12:137–45.
28. Anderson WF, Matsuno RK, Sherman ME, et al. Estimating age-specific breast cancer risks: a descriptive tool to identify age interactions. Cancer Causes Control 2007;18:439–47.
29. Dunnwald LK, Rossing MA, Li CI. Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. Breast Cancer Res 2007;9:R6.
30. Anderson WF, Chen BE, Jatoi I, Rosenberg PS. Effects of estrogen receptor expression and histopathology on annual hazard rates of death from breast cancer. Breast Cancer Res Treat 2006;100:121–6.

31. Chlebowski RT, Anderson GL, Lane DS, et al. Predicting risk of breast cancer in postmenopausal women by hormone receptor status. J Natl Cancer Inst 2007;99:1695–705.
32. Dontu G, El-Ashry D, Wicha MS. Breast cancer, stem/progenitor cells and the estrogen receptor. Trends Endocrinol Metab 2004;15:193–7.
33. Zhu K, Bernard LJ, Levine RS, Williams SM. Estrogen receptor status of breast cancer: a marker of different stages of tumor or different entities of the disease? Med Hypotheses 1997;49:69–75.
34. Gruvberger S, Ringner M, Chen Y, et al. Estrogen receptor status in breast cancer is associated with remarkably distinct gene expression patterns. Cancer Res 2001;61:5979–84.
35. Yager JD, Davidson NE. Estrogen carcinogenesis in breast cancer. N Engl J Med 2006;354:270–82.
36. Bernstein L, Henderson BE, Hanisch R, Sullivan-Halley J, Ross RK. Physical exercise and reduced risk of breast cancer in young women. J Natl Cancer Inst 1994;86:1403–8.
37. Gammon MD, Schoenberg JB, Britton JA, et al. Recreational physical activity and breast cancer risk among women under age 45 years. Am J Epidemiol 1998;147:273–80.
38. McTiernan A, Kooperberg C, White E, et al. Recreational physical activity and the risk of breast cancer in postmenopausal women: the Women's Health Initiative Cohort Study. JAMA 2003;290:1331–6.
39. Sprague BL, Trentham-Dietz A, Newcomb PA, Titus-Ernstoff L, Hampton JM, Egan KM. Lifetime recreational and occupational physical activity and risk of *in situ* and invasive breast cancer. Cancer Epidemiol Biomarkers Prev 2007;16:236–43.
40. Patel AV, Calle EE, Bernstein L, Wu AH, Thun MJ. Recreational physical activity and risk of postmenopausal breast cancer in a large cohort of US women. Cancer Causes Control 2003;14:519–29.
41. Moore DB, Folsom AR, Mink PJ, Hong CP, Anderson KE, Kushi LH. Physical activity and incidence of postmenopausal breast cancer. Epidemiology 2000;11:292–6.
42. McTiernan A, Stanford JL, Weiss NS, Daling JR, Voigt LF. Occurrence of breast cancer in relation to recreational exercise in women age 50-64 years. Epidemiology 1996;7:598–604.
43. Rockhill B, Willett WC, Hunter DJ, Manson JE, Hankinson SE, Colditz GA. A prospective study of recreational physical activity and breast cancer risk. Arch Intern Med 1999;159:2290–6.
44. Friedenreich CM, Bryant HE, Courneya KS. Case-control study of lifetime physical activity and breast cancer risk. Am J Epidemiol 2001;154:336–47.
45. Tehard B, Friedenreich CM, Oppert JM, Clavel-Chapelon F. Effect of physical activity on women at increased risk of breast cancer: results from the E3N cohort study. Cancer Epidemiol Biomarkers Prev 2006; 15:57–64.
46. Lahmann PH, Friedenreich C, Schuit AJ, et al. Physical activity and breast cancer risk: the European Prospective Investigation into Cancer and Nutrition. Cancer Epidemiol Biomarkers Prev 2007;16: 36–42.
47. Leitzmann MF, Park Y, Blair A, et al. Physical activity recommendations and decreased risk of mortality. Arch Intern Med 2007;167: 2453–60.

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対象の内訳	ヒト	動物	地 域	欧米	研究の種類	縦断研究
対象	一般健常者	空白		( )		コホート研究
性別	女性	( )		( )		( )
年齢	50～71(62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	( )
	維持・改善	な し	な し	な し	なし	( )

図 表

Table 2. RR (95% CI) for the association between physical activity and postmenopausal breast cancer incidence among 182,862 postmenopausal women

Physical activity (times per week)	Person-years	No. cases	Age-adjusted RR (95% CI)	Multivariate RR* (95% CI)	Multivariate RR† (95% CI)
Inactive	285,349	1,485	1.0 (Reference)	1.0 (Reference)	1.0 (Reference)
<1	184,682	981	1.04 (0.96-1.13)	0.99 (0.91-1.07)	1.00 (0.92-1.08)
1-2	271,497	1,391	0.99 (0.92-1.07)	0.94 (0.87-1.01)	0.96 (0.89-1.03)
3-4	325,701	1,711	1.01 (0.94-1.08)	0.93 (0.87-1.00)	0.97 (0.90-1.04)
≥5	211,557	1,041	0.94 (0.87-1.02)	0.87 (0.81-0.95)	0.92 (0.85-1.00)
P_{trend}			0.13	<0.001	0.04

*Multivariate models used age as the underlying time metric and were adjusted for race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander/American Indian), education level (<12 years or high school equivalent, 12 years or high school equivalent, post-high school vocational or technical training, some college, college graduate, postgraduate), smoking status (nonsmoker, former, current), family history of breast cancer (no, yes), menopausal hormone use (never, current, past), age at first birth (nulliparous, <20, 20-24, 25-29, ≥30 years), age at menarche (<13, 13-14, ≥15 years), age at menopause (<40, 40-44, 45-49, 50-54, ≥55 years), parity (number of children: 0, 1-2, ≥3), and alcohol intake (g/d; quintiles adjusted for total energy intake).
†Additionally adjusted for BMI (<25.0, 25.0-29.9, 30.0-34.9, ≥35.0 kg/m^2).

図表掲載箇所	
概 要 (800字まで)	<目的>身体活動と乳がん発症リスクとの関係をあきらかにすること。<方法>コホート名:NIH-AARP Diet and Health Study、対象者数:182862人、追跡期間:7年、身体活動評価方法詳細:直近の1年間に"汗をかいたり、心拍数が上がるような20分以上の身体活動を生活活動、勤労活動余暇で週何回行いましたかの質問に対し、なし 1回未満 1～2回 3～4回 5回以上の回答に基づき5つの分位わけた。<結果>高強度身体活動回数と女性の乳がん発症との関連は、分位1:1、分位2:0.99(0.91-1.07)、分位3:0.94(0.87-1.01)、分位4:0.93(0.87-1)、分位5:0.87(0.81-0.95であった。
結 論 (200字まで)	週5回以上の汗をかいたり 心拍数の上がるような20分以上の高強度運動は閉経後女性の乳がんリスクを減少させる。
エキスパートによるコメント (200字まで)	女性の乳がん発症リスクを減らすためにはかなりの高強度活動を実施する必要がある。身体活動による乳がん発症予防の難しさを示す研究。

担当者 宮地元彦

ORIGINAL ARTICLE

Adiposity Compared With Physical Inactivity and Risk of Type 2 Diabetes in Women

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OBJECTIVE — The relative contribution of adiposity and physical inactivity to the risk of developing type 2 diabetes remains controversial.

RESEARCH DESIGN AND METHODS — We prospectively examined the individual and joint association of obesity and physical activity with the development of type 2 diabetes in 68,907 female nurses who had no history of diabetes, cardiovascular disease, or cancer at baseline. Adiposity was measured by BMI and waist circumference. Physical activity was assessed through average hours of moderate or vigorous exercise and computation of an MET score.

RESULTS — We documented 4,030 incident cases of type 2 diabetes during 16 years of follow-up (from 1986 to 2002). In a multivariate model including age, smoking, and other diabetes risk factors, risk of type 2 diabetes increased progressively with increasing BMI ($P < 0.001$) and waist circumference ($P < 0.001$) and with decreasing physical activity levels ($P < 0.001$). In joint analyses of BMI and physical activity, using women who had a healthy weight (BMI <25 kg/m^2) and were physically active (exercise ≥21.8 MET h/week) as the reference group, the relative risks of type 2 diabetes were 16.75 (95% CI 13.99–20.04) for women who were obese (BMI ≥30 kg/m^2) and inactive (exercise <2.1 MET h/week), 10.74 (8.74–13.18) for women who were active but obese, and 2.08 (1.66–2.61) for women who were lean but inactive. In combined analyses of waist circumference and physical activity, both variables were significant predictors of type 2 diabetes, but the association for waist circumference was substantially stronger than that for physical inactivity.

CONCLUSIONS — Obesity and physical inactivity independently contribute to the development of type 2 diabetes; however, the magnitude of risk contributed by obesity is much greater than that imparted by lack of physical activity.

Diabetes Care 30:53–58, 2007

Type 2 diabetes is a major cause of morbidity and mortality and has become an important public health issue worldwide (1). Obesity and physical inactivity are well-known risk factors for the development of type 2 diabetes (2–6). It has been suggested that higher levels of physical activity can mitigate the impact of overweight and obesity on morbidity and mortality, and, thus, obesity may not be detrimental to those who are physically fit (7). However, our recent analyses indicated that both obesity and physical activity were independent predictors of all-cause mortality (8) and coronary heart disease (9), and being physically active did not abolish the excess risk associated with obesity. For type 2 diabetes, a recent study (10) suggested that the magnitude of association with BMI was much greater than that with physical inactivity and that physical activity was less predictive of diabetes in overweight and obese individuals than in those with normal weight. In addition, a recent Finnish study (11) showed that increasing physical activity was associated with a significantly reduced risk for type 2 diabetes, especially in obese patients. In this study, we evaluated the individual and combined association of obesity and physical inactivity with the incidence of type 2 diabetes among 68,907 participants in the Nurses' Health Study.

RESEARCH DESIGN AND METHODS

The Nurses' Health Study cohort was established in 1976, when 121,700 female registered nurses aged 30–55 years completed a mailed questionnaire about their medical history and lifestyle. Women have provided information regarding lifestyle and health conditions biennially since 1976. The 1980 questionnaire asked about weight at 18 years of age; ~80% of the participants provided the information. Diet and physical activity were assessed by validated questionnaires starting from 1980 (12). For this study, we included 68,907 women in the analyses after excluding those who reported cardiovascular disease, diabetes, or cancer at baseline in 1986. We chose 1986 as the baseline since we had more detailed information regarding physical activity and waist circumference along with BMI. The study was approved by the Human Research Committees at the Brigham and Women's Hospital.

Assessment of overall and abdominal adiposity

BMI was calculated as weight in kilograms divided by the square of height in meters to assess overall obesity. Self-reported weights were validated among 184 participants in the Nurses' Health Study living in the Boston area and were highly correlated with measured weights ($r = 0.96$, mean difference [self-reported − measured weight] = −1.5 kg) (13).

In 1986, Nurses' Health Study participants measured and reported measurements of their waist (at the umbilicus) and hip (the largest circumference) to the near-

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est quarter of an inch. In a validation study, the correlation between self-reported and technician-measured circumferences was 0.89 for the waist (14). We had information on waist circumference on 63.8% of the participants followed.

Assessment of physical activity

In 1986, 1988, 1992, 1996, 1998, and 2000, women were asked to report the average time spent per week on the following activities: walking, jogging, running, bicycling, lap swimming, playing tennis or squash, and participating in calisthenics. Using this information, we calculated the average amount of time per week spent in moderate-to-vigorous activities (requiring three or more METs per hour, including brisk walking) at each time point (15). We divided physical activity by quintiles such that the current physical activity recommendation of ≥150 min or 10 MET h/week of moderate-intensity physical activity was met by women in the fourth and fifth quintiles. Our validation study indicated relatively good validity and reproducibility for the questionnaire. The correlation between physical activity reported on 1-week recalls and that reported on the questionnaire was 0.79. The correlation between moderate-to-vigorous activity reported in diaries and that reported on the questionnaire was 0.62.

Walking, a moderate-intensity activity, was by far the most prevalent physical activity in our cohort. In 1986, women were also asked about their usual walking pace, specified as easy (<3.2 km/h) or normal (3.2–4.8 km/h). Because only 2% of women reported a very brisk (≥6.4 km/h) pace, we combined it with the brisk (4.8–6.2 km/h) category in the analyses of walking pace. For this information, weekly walking energy expenditure in MET hours was calculated to differentiate between moderate and vigorous activity (16).

Ascertainment of end point

The primary end point for this study was type 2 diabetes. At each 2-year questionnaire cycle, participants were asked whether they had a diagnosis of diabetes. For each self-reported diagnosis of diabetes, a supplemental questionnaire was sent asking about diabetes symptoms, diagnostic tests, and treatments. A diagnosis of diabetes was made when any one of the following criteria were met: *1*) one or more classic symptoms of diabetes and elevated plasma glucose levels (fasting plasma glucose 7.8 mmol/l or randomly measured plasma glucose 11.1 mmol/l), 2) elevated plasma glucose on at least two occasions in the absence of symptoms, or 3) treatment with oral hypoglycemic medication or insulin. Our criteria for the diagnosis of diabetes are consistent with those proposed by the National Diabetes Data Group (17) for cases that were diagnosed before 1997. For diagnoses of diabetes established after 1998, the new American Diabetes Association criteria (fasting plasma glucose ≥7 mmol/l) were used. We excluded women with type 1 diabetes or gestational diabetes. The diagnosis of type 2 diabetes by the use of the supplemental questionnaire has been validated (5).

Statistical analysis

We grouped women into nine categories of BMI measured in 1986, which included standard cutoffs for overweight (BMI ≥25 kg/m^2), class 1 obesity (BMI ≥30 kg/m^2), class 2 obesity (BMI ≥35 kg/m^2), and class 3 obesity (BMI ≥40 kg/m^2). Participants contributed person-time from the date they returned the 1986 questionnaires (BMI and waist circumference analyses) until the date of death or June 1, 2002, whichever came first. The relative risk (RR) was calculated as the rate for a given category of BMI compared with the referent category. Age-adjusted analyses were conducted using 5-year age categories by the Mantel-Haenszel method. Cox proportional hazard regression was used to adjust for age or other potential confounders, including smoking status (never; past; or current smoker of 1–14, 15–24, and ≥25 cigarettes/day), alcohol consumption (0, 1–4, 5–14, or ≥15 g/day), menopausal status and postmenopausal hormone use, and parental history of diabetes. Analysis of BMI and risk of type 2 diabetes was additionally adjusted for physical activity in five categories.

To best represent long-term physical activity levels and to reduce measurement error, we created measures of cumulative average of hours of moderate-to-vigorous activities from all available questionnaires up to the start of each 2-year follow-up interval (18). In a secondary analysis, we also controlled for a dietary score reflecting high intakes of the ratio of polyunsaturated fat to saturated fat, cereal fiber, low intakes of trans fat, and glycemic load (19). We examined the joint associations of physical activity and BMI and waist circumference with risk of type 2 diabetes. Statistical analyses were conducted using SAS version 8.2 (Cary, NC). All *P* values were two sided.

RESULTS — During 16 years of follow-up from 1986 to 2002, 4,030 incident cases of type 2 diabetes were identified. Table 1 shows RRs of type 2 diabetes according to BMI categories at baseline in 1986. The risk of type 2 diabetes increased progressively with increasing BMI. Women with BMI ≥40 kg/m^2 had an ~28-fold higher risk of type 2 diabetes than those with BMI <21 kg/m^2. Similarly, the risk of type 2 diabetes increased progressively with increasing quintiles of waist circumference (*P* for trend <0.001). Further adjustment for dietary score did not change the association.

We assessed physical activity according to the intensity and amount of exercise (MET hours per week). There was a progressive increment in the multivariable-adjusted RR of diabetes with decreasing quintiles of total MET hours per week (Table 2). This inverse gradient, although attenuated, still remained statistically significant after adjustment for BMI (RRs across quintiles were 1.66, 1.56, 1.30, 1.27, and 1.0, respectively; *P* for trend <0.001).

In Table 3, we present joint associations of BMI and physical activity with the risk of type 2 diabetes. Both higher BMI and lower physical activity levels were associated with increased risk of type 2 diabetes (*P* for interaction was 0.22 between physical activity and BMI). Compared with women who were physically active and had a BMI <25 kg/m^2, women who were lean but physically inactive had an RR for type 2 diabetes of 2.08 (95% CI 1.66–2.61). Obese women (BMI ≥30 kg/m^2) who were physically active had an RR of 10.74 (8.74–13.18), and obese women who were inactive had an RR of 16.75 (13.99–20.04). Thus, increasing BMI in the same category of physical activity markedly increased the risk for type 2 diabetes. Even in the physically active group, the RR increased 11-fold in obese participants compared with lean participants. Further adjustment for dietary score did not appreciably alter these results.

In joint analyses of physical activity and abdominal adiposity, the highest risk of type 2 diabetes was among women in the lowest category of physical activity and the highest tertile of waist circumference (RR 22.26 [95% CI 15.75–31.45]). The associations of physical activity and abdominal obesity with type 2 diabetes were independent of each other (*P* for interaction was 0.85 between physical ac-

Table 1—*Baseline BMI, waist circumference, and RR of type 2 diabetes in the Nurses' Health Study from 1986 through 2002*

	BMI (kg/m^2) (n = 68,907)							
	<21	21–22.9	23–24.9	25–26.9	27–29.9	30–32.9	33–34.9	35–39.9	40	P for trend
n	95	224	438	555	944	730	328	482	234	
Person-years (1,034,808)	165,274	229,913	224,553	150,502	137,714	67,443	22,615	26,277	10,567	
Age-adjusted RR (95% CI)	1.00	1.68 (1.32–2.13)	3.32 (2.66–4.14)	6.26 (5.04–7.79)	11.67 (9.45–14.41)	18.62 (15.04–23.07)	25.31 (20.14–31.81)	32.56 (26.12–40.57)	40.28 (31.73–51.13)	<0.001
Multivariate RR (95% CI)*	1.00	1.65 (1.30–2.10)	3.10 (2.48–3.87)	5.51 (4.43–6.86)	9.80 (7.93–12.11)	14.83 (11.96–18.39)	19.11 (15.19–24.06)	23.98 (19.21–29.95)	27.96 (21.97–35.58)	<0.001
	Waist circumference (inches) (n = 43,986)									
	20–28	28–29.9	30–31.9	32–34.9	≥35	P for trend				
n	58	156	248	584	1,096					
Person-years (664,976)	149,922	156,197	125,540	131,638	101,633					
Age-adjusted RR (95% CI)	1.00	2.55 (1.89–3.45)	5.03 (3.78–6.69)	11.25 (8.58–14.75)	27.69 (21.24–36.09)	<0.001				
Multivariate RR (95% CI)*	1.00	2.48 (1.83–3.35)	4.62 (3.47–6.15)	9.51 (7.25–12.47)	21.44 (16.42–28.00)	<0.001				

*Adjusted for age (<49, 50–54, 55–59, 60–64, and 65 years), smoking status (never, past, or current [1–14, 15–24, or 25 cigarettes/day]), family history of diabetes, postmenopausal status and hormone use (pre- and postmenopausal status and hormone use as never, past, or current), physical activity (quintiles), and alcohol consumption (0, 0.1–4.9, 5–14.9, or 15 g/day).

tivity and waist circumference). Further adjustment for BMI attenuated these results, but the increased risk associated with abdominal obesity remained significant (Table 3).

We also examined the combined association of BMI with walking pace among the women (n = 47,358) who did not perform vigorous exercise. When we compared the pace of the moderate-intensity physical activity of walking, we found that slower pace of walking was associated with higher risk of diabetes within the same BMI category (Fig. 1). The inverse association between pace and intensity of walking and risk of diabetes was most evident in overweight and obese patients. Among overweight women, slower pace was associated with nearly double the risk of developing type 2 diabetes compared with brisk or very brisk pace.

CONCLUSIONS — In this large prospective cohort, we found that obesity and physical inactivity independently contributed to the development of type 2 diabetes. The magnitude of risk contributed by obesity appeared to be much greater than the risk imparted by physical inactivity.

Data on the relative influence of obesity and physical inactivity on risk of development of diabetes are sparse and controversial (10,11,20). A recent study (10) indicated that physical activity had relatively small effects on diabetes in overweight and obese patients. The Medical Expenditure Panel Survey (20) showed that inactive normal weight individuals had lower risk than obese and active individuals. However, due to the cross-sectional nature of the data, any temporal effect of activity versus obesity on risk of type 2 diabetes could not be demonstrated; whereas a Finnish study (11) showed that increasing physical activity was associated with a significantly reduced risk for type 2 diabetes, especially in obese patients.

Our study had several strengths. We had a much larger sample size and a longer follow-up. We assessed both obesity and physical activity in several ways. For adiposity, we examined both overall obesity and central obesity. For physical activity, we assessed both the amount and intensity of activity according to MET hours per week. Finally, we examined the most common form of exercise, walking (20), and the relative effect of its intensity or pace versus adiposity and the risk of

Table 2—*RR of type 2 diabetes according to physical activity from 1986 through 2002 (n = 68,907)*

MET hours of activity per week	<2.1	2.1–4.6	4.7–10.4	10.5–21.7	≥21.8	*P* for trend
n	1,010	784	769	796	671	
Person-years (1,034,808)	161,509	165,568	206,597	229,903	271,231	
Age-adjusted RR	2.66 (2.41–2.94)	2.10 (1.89–2.33)	1.57 (1.42–1.74)	1.43 (1.29–1.59)	1.00	<0.001
Multivariate RR*	2.37 (2.15–2.16)	1.92 (1.73–2.13)	1.48 (1.34–1.64)	1.40 (1.26–1.55)	1.00	<0.001
Multivariate RR including continuous BMI*	1.66 (1.50–1.83)	1.56 (1.41–1.74)	1.30 (1.17–1.44)	1.27 (1.15–1.41)	1.00	<0.001

Data are RR (95% CI). *Adjusted for age (5-year interval), smoking status (never, past, or current [1–14, 15–24, or 25 cigarettes/day]), alcohol consumption (0, 0.1–4.9, 5–14.9, or ≥15 g/day), menopausal status and postmenopausal hormone use, and family history of diabetes.

type 2 diabetes. In the joint analyses, higher physical activity within each BMI category was associated with decreased risk of diabetes, whereas elevated BMI even in the highest category of physical activity markedly increased the risk for type 2 diabetes. Similarly, increased walking pace decreased the risk of diabetes within each weight category, although the risk was still 13-fold among obese brisk walkers versus normal-weight brisk walkers.

Physical activity is known to decrease the risk of type 2 diabetes (5,6). Although physical activity has multiple beneficial effects that can improve insulin and glucose delivery to muscle (21), it may not fully abolish the adverse effects of obesity (22). Obesity is known to increase peripheral insulin resistance and reduce β-cell sensitivity to glucose (23). Production of adipokines from adipocytes is known to influence insulin sensitivity and type 2 diabetes (24). The increased plasma concentration of inflammatory mediators, such as tumor necrosis factor-α and interleukin-6 induced by obesity (25), may interfere with insulin action by suppressing insulin signal transduction. Weight loss may therefore be a key mechanism to reduce the secretion of these factors by decreasing adipose tissue volume and subsequently reducing the risk of diabetes. Even moderate weight loss (5% of body weight) can improve insulin action, decrease fasting blood glucose concentrations, and reduce the need for diabetes medications (26–28).

The current study has some potential limitations. Some under-diagnosis of diabetes is likely because screening for blood glucose was not feasible, given the size of the cohort. Our participants are all health professionals and have ready access to care; over 98% of them reported fasting glucose screening in the past 4 years. Thus, undiagnosed diabetes should be relatively low in our cohort. However, we cannot exclude the possibility that obese people were more likely to be diagnosed than nonobese people. Moreover, underascertainment of cases, if not associated with exposure, would not be expected to affect the RR estimates (29).

We did not assess cardiorespiratory fitness. However, physical activity is the primary modifiable determinant of fitness, and even modest levels of physical activity (e.g., 30 min/day of brisk walking) can achieve levels of cardiorespiratory fitness that have been associated with a significant reduction in mortality risk (30). Our physical activity variable included only leisure time activity. Other activities such as household chores and occupational activities may also affect the risk for diabetes. Measurement errors in self-reported physical activity are inevitable, and nondifferential misclassification may have biased the association of physical activity with risk of type 2 diabetes toward the null. However, this should not substantially affect the analyses stratified according to physical activity levels. Our validation studies using physical activity diaries indicated good reproducibility and validity of self-reported physical activity. Our previous analysis showed that physical activity predicted the risk of diabetes (5) and other chronic diseases (18). Moreover, physical activity was assessed regularly during follow-up, and use of the repeated measures in the analyses not only dampened measurement errors but also took into account real changes in physical activity levels over time.

Our analyses of the combined effects of physical activity and obesity have direct public health implications. The adverse effects of body fatness on type 2 diabetes

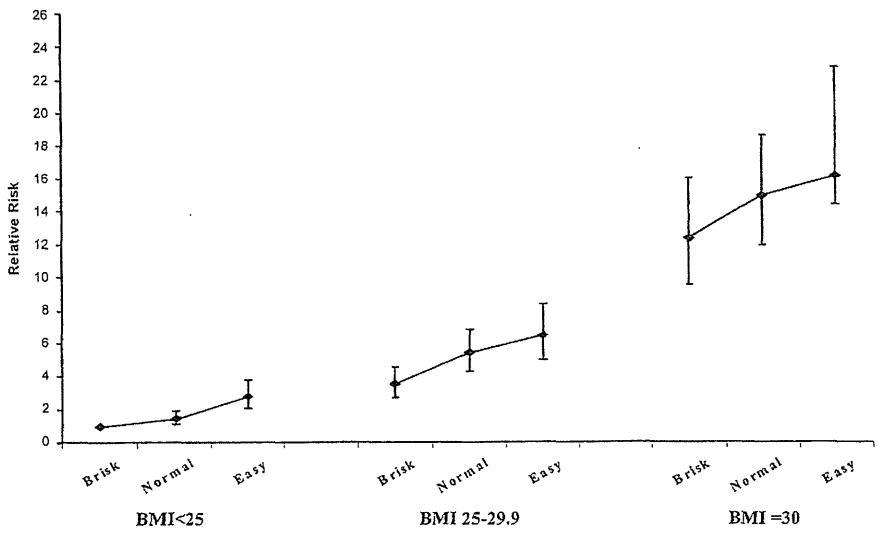

Figure 1—*RRs of type 2 diabetes according to usual walking pace among women who did not perform vigorous (<6 METs) activities and categories of BMI in the Nurses' Health Study 1986–2002. Data are adjusted for age (5-year interval), smoking status (never; past; or current smoker of 1–14, 15–24, and ≥25 cigarettes/day), alcohol consumption (0, 1–4, 5–14, or ≥15 g/day), menopausal status and postmenopausal hormone use, and family history of diabetes. Walking pace was specified as easy (<3.2 km/h), normal (3.2–4.8 km/h), brisk (4.8–6.2 km/h), and very brisk (≥6.4 km/h).*

Table 3—*Multivariate RRs of type 2 diabetes according to categories of BMI, waist circumference, and physical activity from the Nurses' Health Study from 1986 through 2002*

	MET hours of activity per week					
	<2.1	2.1–4.6	4.7–10.4	10.5–21.7	≥21.8	*P* for trend
BMI (kg/m^2)						
<25						
Multivariate-adjusted RR*	2.08 (1.66–2.61)	1.64 (1.29–2.08)	1.50 (1.20–1.88)	1.58 (1.28–1.96)	1 (Ref.)	<0.001
25–29.9						
Multivariate-adjusted RR*	6.87 (5.67–8.33)	6.30 (5.18–7.66)	5.10 (4.20–6.21)	5.35 (4.41–6.48)	4.76 (3.92–5.79)	<0.001
30						
Multivariate-adjusted RR*	16.75 (13.99–20.04)	15.76 (13.06–19.01)	13.01 (10.74–15.75)	12.93 (10.64–15.71)	10.74 (8.74–13.18)	<0.001
	MET hours of activity per week					
	Inactive (<2)		Moderate (2.0–5.9)		Vigorous (≥6)	
Waist circumference tertiles (inches)						
<28						
Multivariate-adjusted RR*	2.01 (1.08–3.73)		1.20 (0.58–2.49)		1 (Ref.)	
Multivariate RR further adjusted for continuous BMI*	2.16 (1.15–4.04)		0.99 (0.44–2.24)		1 (Ref.)	
29–31						
Multivariate-adjusted RR*	5.24 (3.52–7.82)		4.57 (3.08–6.79)		3.73 (2.62–5.32)	
Multivariate RR further adjusted for continuous BMI*	4.22 (2.79–6.36)		3.75 (2.50–5.64)		3.10 (2.15–4.46)	
≥32						
Multivariate-adjusted RR*	22.26 (15.75–31.45)		19.87 (14.04–28.11)		15.92 (11.34–22.35)	
Multivariate RR further adjusted for continuous BMI*	10.26 (7.14–14.74)		9.74 (6.78–13.98)		8.22 (5.77–11.71)	

Data are RR (95% CI). *Adjusted for age (5-year interval), smoking status (never, past, or current [1–14, 15–24, or 25 cigarettes/day]), alcohol consumption (0, 0.1–4.9, 5–14.9, or ≥15 g/day), menopausal status and postmenopausal hormone use, and family history of diabetes.

risk were persistent in both lower and higher physical activity categories. Conversely, the benefits of physical activity were not limited to lean women; among those who were overweight and obese, physically active women tended to have lower type 2 diabetes risk than sedentary women. Our findings are in line with Finnish Diabetes Prevention Study (32) and the Diabetes Prevention Program study (33) that found that even modest weight loss led to substantial reduction in diabetes risk. Given the difference in the magnitude of risk contribution of adiposity versus physical activity to the development of type 2 diabetes, weight loss and maintenance of healthy weight should be emphasized as an eventual goal to prevent the onset of type 2 diabetes.

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References

1. Perkins I: Diabetes mellitus epidemiology-classification, determinants, and public health impacts. *J Miss State Med Assoc* 45:355–362, 2004
2. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC: Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 17:961–969, 1994
3. Colditz GA, Willett WC, Rotnitzky A, Manson JE: Weight gain as a risk factor for clinical diabetes mellitus in women. *Ann Intern Med* 122:481–486, 1995
4. Koh-Banerjee P, Wang Y, Hu FB, Spiegelman D, Willett WC, Rimm EB: Changes in body weight and body fat distribution as risk factors for clinical diabetes in US men. *Am J Epidemiol* 159:1150–1159, 2004
5. Manson JE, Rimm EB, Stampfer MJ, Colditz GA, Willett WC, Krolewski AS, Rosner B, Hennekens CH, Speizer FE: Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet* 338:774–778, 1991
6. Hu FB, Sigal RJ, Rich-Edwards JW, Colditz GA, Solomon CG, Willett WC, Speizer FE, Manson JE: Walking compared with vigorous physical activity and risk of type 2 diabetes in women: a prospective study. *JAMA* 282:1433–1439, 1999
7. Lee CD, Blair SN, Jackson AS: Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. *Am J Clin Nutr* 69:373–380, 1999
8. Hu FB, Willett WC, Li T, Stampfer MJ,

Colditz GA, Manson JE: Adiposity as compared with physical activity in predicting mortality among women. *N Engl J Med* 351:2694–2703, 2004
9. Li YT, Rana JS, Manson JE, Willet WC, Stampfer MJ, Colditz GA, Rexrode KM, Hu FB: Obesity as compared with physical activity in predicting risk of coronary heart disease in women. *Circulation* 113: 499–506, 2006
10. Weinstein AR, Sesso HD, Lee IM, Cook NR, Manson JE, Buring JE, Gaziano JM: Relationship of physical activity vs body mass index with type 2 diabetes in women. *JAMA* 292:1188–1194, 2004
11. Hu G, Lindstrom J, Valle TT, Eriksson JG, Jousilahti P, Silventoinen K, Qiao Q, Tuomilehto J: Physical activity, body mass index, and risk of type 2 diabetes in patients with normal or impaired glucose regulation. *Arch Intern Med* 164:892–896, 2004
12. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, Hennekens CH, Speizer FE: Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol* 122:51–65, 1985
13. Willett W, Stampfer MJ, Bain C, Lipnick R, Speizer FE, Rosner B, Cramer D, Hennekens CH: Cigarette smoking, relative weight, and menopause. *Am J Epidemiol* 117:651–658, 1983
14. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC: Validity of self-reported waist and hip circumferences in men and women. *Epidemiology* 1:466–473, 1990
15. Rockhill B, Willett WC, Manson JE, Leitzmann MF, Stampfer MJ, Hunter DJ, Colditz GA: Physical activity and mortality: a prospective study among women. *Am J Public Health* 91:578–583, 2001
16. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR Jr, Montoye HJ, Sallis JF, Paffenbarger RS Jr: Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc* 25:71–80, 1993
17. National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. *Diabetes.* 28:1039–1057, 1979
18. Hu FB, Stampfer MJ, Colditz GA, Ascherio A, Rexrode KM, Willett WC, Manson JE: Physical activity and risk of stroke in women. *JAMA* 283:2961–2967, 2000
19. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, Willett WC: Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med* 345:790–797, 2001
20. Sullivan PW, Morrato EH, Ghushchyan V, Wyatt HR, Hill JO: Obesity, inactivity, and the prevalence of diabetes and diabetes-related cardiovascular comorbidities in the U.S., 2000–2002. *Diabetes Care* 28: 1599–1603, 2005
21. Holloszy JO, Hansen PA: Regulation of glucose transport into skeletal muscle. *Rev Physiol Biochem Pharmacol* 128:99–193, 1996
22. Goodyear LJ, Kahn BB: Exercise, glucose transport, and insulin sensitivity. *Annu Rev Med* 49:235–261, 1998
23. Kahn BB, Flier JS: Obesity and insulin resistance. *J Clin Invest* 106:473–481, 2000
24. Arner P: Insulin resistance in type 2 diabetes: role of the adipokines. *Curr Mol Med* 5:333–339, 2005
25. Dandona P, Aljada A, Bandyopadhyay A: Inflammation: the link between insulin resistance, obesity and diabetes. *Trends Immunol* 25:4–7, 2004
26. Goldstein DJ: Beneficial health effects of modest weight loss. *Int J Obes Relat Metab Disord* 16:397–415, 1992
27. Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L: XENical in the Prevention of Diabetes in Obese Subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 27:155–161, 2004
28. U.K. Prospective Diabetes Study 7: Response of fasting plasma glucose to diet therapy in newly presenting type II diabetic patients, UKPDS Group. *Metabolism* 39:905–912, 1990
29. Rothman KJ, Greenland S: *Modern Epidemiology*. 2nd ed. Philadelphia, Lippincott-Raven, 1998
30. Stofan JR, DiPietro L, Davis D, Kohl HW 3rd, Blair SN: Physical activity patterns associated with cardiorespiratory fitness and reduced mortality: the Aerobics Center Longitudinal Study. *Am J Public Health* 88:1807–1813, 1998
31. Church TS, Cheng YJ, Earnest CP, Barlow CE, Gibbons LW, Priest EL, Blair SN: Exercise capacity and body composition as predictors of mortality among men with diabetes. *Diabetes Care* 27:83–88, 2004
32. Lindstrom J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, Uusitupa M, Tuomilehto J, the Finnish Diabetes Prevention Study Group, the Finnish Diabetes Prevention Study Group: The Finnish Diabetes Prevention Study (DPS): lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care* 26:3230–3236, 2003
33. Hamman RF, Wing RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L, Hoskin M, Kriska AM, Mayer-Davis EJ, Pi-Sunyer X, Regensteiner J, Venditti B, Wylie-Rosett J: Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care* 29:2102–2107, 2006

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	ヒト	動物		欧米		縦断研究
対象	一般健常者	空白		( )		コホート研究
性別	女性	( )	地 域	( )	研究の種類	( )
年齢	40-65歳			( )		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	糖尿病予防	なし	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 type 2 diabetes according to physical activity from 1986 through 2002 (n = 68,907)*

MET hours of activity per week	<2.1	2.1–4.6	4.7–10.4	10.5–21.7	≥21.8	P for trend
n	1,010	784	769	796	671	
Person-years (1,034,808)	161,509	165,568	206,597	229,903	271,231	
Age-adjusted RR	2.66 (2.41–2.94)	2.10 (1.89–2.33)	1.57 (1.42–1.74)	1.43 (1.29–1.59)	1.00	<0.001
Multivariate RR*	2.37 (2.15–2.16)	1.92 (1.73–2.13)	1.48 (1.34–1.64)	1.40 (1.26–1.55)	1.00	<0.001
Multivariate RR including continuous BMI*	1.66 (1.50–1.83)	1.56 (1.41–1.74)	1.30 (1.17–1.44)	1.27 (1.15–1.41)	1.00	<0.001

Data are RR (95% CI). *Adjusted for age (5-year interval), smoking status (never, past, or current [1–14, 15–24, or 25 cigarettes/day]), alcohol consumption (0, 0.1–4.9, 5–14.9, or ≥15 g/day), menopausal status and postmenopausal hormone use, and family history of diabetes.

図表掲載箇所	P56, 表2
概 要 (800字まで)	本研究は，2型糖尿病発症と肥満および少ない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．the Nurses' Health Studyの参加者68907名の女性ナースを対象とし，1986年から2002年まで16年間追跡された．身体活動は，ウォーキング，ジョギング，ランニング，サイクリング，スイミング，テニス，スカッシュ，健康体操の実施について，週当たりの時間が質問され，メッツ・時/週に換算された．2型糖尿病発症の調整相対リスクは，身体活動が週21.8メッツ・時以上の者と比較して，10.5-21.7メッツ・時/週の者で1.27(1.15-1.41)，4.7-10.4メッツ・時/週の者で1.30(1.17-1.44)，2.1-4.6メッツ・時/週の者で1.56(1.41-1.74)，2.1メッツ・時/週未満の者で1.66(1.5-1.83)となり，量反応関係が認められた(trend P<0.001)．同様に，BMI，腹囲に関しても2型糖尿病発症リスクとの間に量反応関係が示された(trend P<0.001)．さらに，身体活動量が21.8メッツ・時/週以上であり，かつBMI25未満の者と比較した場合，身体活動量が2.1メッツ・時/週未満かつBMI30以上の者の調整相対リスクは16.75(13.99-20.04)と，2型糖尿病発症のリスクが有意に高いことが示された．
結 論 (200字まで)	肥満と少ない身体活動は，2型糖尿病発症の独立した寄与因子であることが示された．
エキスパートによるコメント (200字まで)	女性における2型糖尿病発症リスクと身体活動，BMIとの関連について検討した大規模コホート研究である．2型糖尿病予防に向けた活発な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．また，活動量を増大させるだけでなく，それによって適正体重を維持することが重要であることを示唆しており，意義深い研究である．

担当者 川上諒子

Physical Activity, White Blood Cell Count, and Lung Cancer Risk in a Prospective Cohort Study

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Abstract

Previous studies have suggested that physical activity may lower lung cancer risk. The association of physical activity with reduced chronic inflammation provides a potential mechanism, yet few studies have directly related inflammatory markers to cancer incidence. The relation among physical activity, inflammation, and lung cancer risk was evaluated in a prospective cohort of 4,831 subjects, 43 to 86 years of age, in Beaver Dam, Wisconsin. A total physical activity index was created by summing up kilocalories per week from sweat-inducing physical activities, city blocks walked, and flights of stairs climbed. Two inflammatory markers, WBC count and serum albumin, were measured at the baseline examination. During an average of 12.8 years of follow-up, 134 incident cases of lung cancer were diagnosed. After multivariable adjustment, participants in the highest tertile of total physical activity index had a 45% reduction in lung cancer risk compared with those in the lowest tertile (hazard ratio, 0.55; 95% confidence interval, 0.35-0.86). Participants with WBC counts in the upper tertile ($\geq 8 \times 10^3/\mu L$) were 2.81 (95% confidence interval, 1.58-5.01) times as likely to develop lung cancer as those with counts in the lowest tertile ($<6.4 \times 10^3/\mu L$). Serum albumin was not related to lung cancer risk. There was no evidence that inflammation mediated the association between physical activity and lung cancer risk, as the physical activity risk estimates were essentially unchanged after adjustment for WBC count. Although the potential for residual confounding by smoking could not be eliminated, these data suggest that physical activity and WBC count are independent risk factors for lung cancer. (Cancer Epidemiol Biomarkers Prev 2008;17(10):2714–22)

Introduction

Lung cancer is the leading cause of cancer death among men and women in the United States (1). Strategies to reduce lung cancer risk besides smoking prevention and cessation are poorly understood. A number of epidemiologic studies have suggested that physical activity may reduce the risk of lung cancer (2-13), with a recent meta-analysis concluding that higher levels of leisure-time physical activity protect against lung cancer (14). In 2002, however, the IARC concluded that the evidence for an association between physical activity and lung cancer remained inconclusive, and two large studies recently found no consistent association between physical activity and lung cancer risk (15, 16).

The value of molecular biomarkers in discerning the relation between physical activity and cancer has recently been recognized (17, 18). The incorporation of biomarkers can be particularly helpful in clarifying inconclusive epidemiologic evidence and investigating potential mechanisms by which physical activity exerts its effects (17). A number of potential mechanisms through which physical activity may offer protection from lung cancer have been proposed. Physical activity and physical fitness are consistently observed to be associated with reduced chronic inflammation, reflected in lower levels of the inflammatory markers serum C-reactive protein, fibrinogen and WBC count, and increased levels of serum albumin (a negative acute-phase protein; refs. 19-23). Chronic inflammation has been hypothesized to be a risk factor for a wide range of cancers (24-26). Thus, physical activity could reduce lung cancer risk by reducing chronic inflammation. Yet few studies have directly evaluated markers of inflammation in relation to lung cancer incidence (27-30).

We investigated the relation between self-reported physical activity and lung cancer in an established cohort of older adults. Additionally, we measured two inflammatory markers, WBC count and serum albumin, in baseline blood samples to evaluate whether inflammation mediates the relation between physical activity and lung cancer.

Materials and Methods

Study Population. Descriptions of the population and the methods used to identify the population have been previously published (31-33). Briefly, a private census of the population living in Beaver Dam, Wisconsin, was done by the University of Wisconsin Extension-Survey Research Laboratory between September 15, 1987, and May 4, 1988. Eligibility requirements for entry into the study included living in the city or township of Beaver

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Dam and being 43 to 84 y of age at the time of the census. A total of 5,925 eligible individuals were identified who met the criteria.

Of the 5,925 eligible individuals, 4,926 (83.1%) participated in the study examination, including 2,166 men and 2,760 women. The reasons for nonparticipation included 225 deaths (3.8%) before the examination, moving out of the area by 91 people (1.5%), failure to locate 23 people (0.4%), and refusal to participate by 391 (6.6%). Eligible participants who completed telephone interviews but were not examined (n = 269; 4.5%) were not included in this analysis, so that data were available for 4,926 participants who consented to examinations.

Case Identification. Incident cases of lung cancer (International Classification of Diseases for Oncology codes C34.0-34.9; ref. 34) diagnosed in study participants through July 2004 were identified through linkages with the Wisconsin Cancer Reporting System (the statewide mandatory tumor registry), Wisconsin death certificates, and the National Death Index. Deaths due to lung cancer identified through death records that were not also identified by the tumor registry (n = 7) were assigned a date of diagnosis equal to the average length of time from diagnosis to death for lung cancer cases in the Wisconsin tumor registry subtracted from their date of death (13 mo).

Data Collection. All participants provided signed informed consent at the time of the examination. Study questionnaires elicited information on comorbidities, reproductive and menstrual histories (for females), lifestyle factors, health history, medication histories, and demographics. Lifestyle factors on the questionnaires included physical activity, alcohol and caffeinated beverage consumption, smoking history, vitamin and mineral supplement use, and occupational history. Participants reported histories of diagnosis with major chronic medical conditions and surgical history. Collected demographic information included race/ethnicity and education, and participants were asked to report their marital status and income category.

To assess smoking history, subjects were asked if they had smoked more than 100 cigarettes in their lifetime, how many years they have smoked cigarettes, whether they smoke now, how long ago they stopped, and how many cigarettes they smoked per day (currently, or "usually" during smoking history for former smokers).

To assess physical activity, subjects were asked to report the number of city blocks walked per day (12 blocks = 1 mile), flights of stairs climbed per day, and the number of episodes of "regular activity long enough to work up a sweat" each week (35). A summary measure of total physical activity was created by summing the kilocalories (kcal) per week from blocks walked, flights of stairs climbed, and episodes of sweat-inducing activities. For 1 block walked per day and 1 flight of stairs climbed per day, we assigned 56 kcal/wk and 28 kcal/wk, respectively, as previously

Table 1. Selected participant characteristics at baseline according to physical activity levels

Characteristics at baseline	Episodes of sweat-inducing activities/wk (%)*		City blocks walked/d (%)*		Flights of stairs climbed/d (%)*	
	None (n = 3,215)	1 or more (n = 1,614)	None (n = 2,204)	1 or more (n = 2,610)	0-2 (n = 2,187)	3 or more (n = 2,639)
Age, y						
43-49	16	20	16	18	12	22
50-59	26	30	25	29	24	30
60-69	27	30	28	28	28	28
70-79	23	17	22	20	27	16
80-86	9	3	9	5	10	4
Sex						
Male	43	45	37	49	39	47
Female	57	55	63	51	61	53
Smoking status						
Never	45	45	47	43	46	44
Former	32	41	33	38	36	35
Current	23	14	21	19	18	21
Body mass index tertile (kg/m^2)						
1 (<26.2)	32	36	32	34	31	35
2 (26.2-30.3)	33	36	31	36	32	35
3 (>30.3)	35	29	36	30	36	30
Alcohol drinks/wk						
None	53	45	56	46	56	46
<5	20	28	20	25	21	24
≥5	26	27	24	29	23	29
Education, y						
<12	34	19	33	25	36	23
12	44	43	44	43	42	45
>12	22	38	23	32	22	32
Mean (SD) heart rate†	38.6 (5.9)	37.5 (5.8)	38.5 (6.0)	38.0 (5.8)	38.5 (6.0)	38.0 (5.8)
Mean (SD) WBC count (×10^3/μL)	7.5 (2.2)	7.1 (1.9)	7.5 (2.2)	7.3 (2.1)	7.6 (2.3)	7.2 (2.0)
Mean (SD) albumin (g/dL)	4.6 (0.4)	4.7 (0.3)	4.6 (0.4)	4.7 (0.4)	4.6 (0.4)	4.7 (0.4)

*Information regarding episodes of activity was missing for 2 participants, blocks walked was missing for 17 participants, and stairs climbed was missing for 5 participants.
†Thirty-second heart rate.

Table 2. HR and 95% CI of lung cancer according to physical activity levels and inflammatory markers

	No. cases	Person-years*	HR (95% CI)†	P_{trend}†	HR (95% CI)‡	P_{trend}‡
Episodes of sweat-inducing activities/wk						
0	105	36,753	1		1	
1-3	10	10,862	0.44 (0.23-0.85)		0.45 (0.23-0.87)	
≥4	19	9,611	0.75 (0.45-1.24)	0.08	0.76 (0.46-1.26)	0.09
City blocks walked/d						
0	73	25,117	1		1	
1-11	44	19,633	0.93 (0.63-1.37)		0.92 (0.62-1.35)	
≥12	17	12,292	0.53 (0.31-0.90)	0.03	0.52 (0.30-0.89)	0.02
Flights of stairs climbed/d						
0-1	44	17,715	1		1	
2-5	60	20,224	1.53 (1.02-2.29)		1.53 (1.02-2.29)	
>5	30	19,254	0.84 (0.52-1.36)	0.58	0.86 (0.53-1.40)	0.67
Total physical activity index (kcal/wk)§						
0-174	65	18,531	1		1	
175-874	38	19,120	0.72 (0.47-1.09)		0.72 (0.48-1.09)	
≥875	31	19,358	0.55 (0.35-0.86)	0.01	0.56 (0.35-0.87)	0.01
Heart rate (30 s)						
21-33	27	12,065	1		1	
34-42	70	33,925	0.93 (0.59-1.46)		0.95 (0.60-1.49)	
>42	37	11,235	1.30 (0.80-2.16)	0.27	1.25 (0.75-2.09)	0.35
WBC tertile ($\times 10^3/\mu L$)						
<6.4	16	19,605	1		—	
6.4-7.9	50	19,421	2.74 (1.53-4.90)		—	
≥8	68	18,019	2.81 (1.58-5.01)	0.001	—	
Albumin tertile (g/dL)						
<4.6	52	19,307	1		—	
4.6-4.8	51	20,321	1.02 (0.69-1.52)		—	
≥4.9	31	17,427	0.85 (0.54-1.34)	0.52	—	

*Total person-years for cases and noncases in category of activity.
†Models are adjusted for age, sex, pack-years of smoking, time since smoking cessation, body mass index, alcohol intake, and education.
‡Models are adjusted for all variables in †, plus WBC count.
§Kilocalories per week from city blocks walked, flights of stairs climbed, and sweat-inducing activities (see Materials and Methods).

used in the analyses of the Harvard Alumni Health Study (5, 6, 36). The duration and intensity of participation in sweat-inducing activities were not ascertained; a typical duration of 30 min at a multiple of resting metabolic rate of 7 was assumed (equivalent to jogging or tennis; ref. 37). Given a resting metabolic rate of 1 kcal/kg/h and the median subject weight of 76 kg, each sweat-inducing activity episode per week was assigned 266 kcal [= 7 × (1 kcal/kg/h) × (76 kg) × (0.5 h)].

Objective measures of comorbidity were collected in addition to self-reported chronic health conditions. Standardized procedures were used to measure height, weight, heart rate, vision, hearing, and blood pressure during the examination (31).

Laboratory Analysis. Casual venous blood specimens were obtained at the baseline examination for laboratory analysis. The collection, storage, and laboratory methods for the analysis of serum inflammatory markers have been previously described (38). Immediately after obtaining the baseline blood sample, WBC count was determined using the Coulter counter method, and serum albumin levels were determined by Technicon, Inc.

Statistical Analysis. Cox proportional hazards regression was used to estimate the hazard ratio (HR) and 95% confidence intervals (95% CI) of lung cancer associated with levels of physical activity and inflammatory markers. We tested proportionality assumptions and found no evidence of violation. Regression models were fitted according to the number of episodes of sweat-inducing activities, the number of blocks walked, the number of flights of stairs climbed, total physical activity index, heart rate, WBC count, and serum albumin level. With the exception of heart rate, the physical activity and inflammatory marker variables were categorized roughly by person-year tertiles, using round numbers as cutpoints. For sweat-inducing activities and city blocks walked per week, more than one third of person-years had zero activities. All models were adjusted for age (<50, 50-59, 60-69, 70-79, ≥80 y), sex, pack-years of smoking (none, tertiles), time since smoking cessation (never smoker, current smoker, quartiles), body mass index (kg/m^2, tertiles), alcohol intake (none, <5 drinks/wk, ≥5 drinks/wk), and education (<high school, high school degree, > high school). *P* values for trend were evaluated by including categorical variables in the models as continuous linear terms. Age and other covariates were assessed as effect modifiers of the association between physical activity and lung cancer by evaluating the change in the log-likelihood after including their cross-product terms in the regression models. In analyses stratified by smoking history, subjects were considered current smokers if they responded affirmatively to the questionnaire item "Do you smoke now?" and former smokers if they responded negatively but had smoked more than 100 cigarettes in their lifetime. Never and former smokers were combined in the stratified analysis because of insufficient numbers of each separately. Plots of cumulative lung cancer incidence according to the total physical activity index and WBC count were produced using the Kaplan-Meier method.

Least squared means and P values comparing WBC count and serum albumin according to tertiles of total physical activity index were calculated using multivariable ANOVA including covariates for smoking history. The mean levels of WBC count and serum albumin at baseline among participants who subsequently developed lung cancer were compared with levels corresponding to participants without lung cancer during the follow-up period using t tests. The values of albumin and WBC count were not transformed for the t tests because they were approximately normally distributed. P values using Wilcoxon nonparametric tests were essentially identical to those obtained using t tests, and are not shown.

Study participants reporting a personal history of lung cancer at the baseline examination ($n = 7$), or identified as a case of lung cancer within 12 mo of the baseline examination ($n = 6$), were excluded from the analysis. An additional 82 people who died within 12 mo of their baseline examination were also excluded from this analysis.

Results

During 62,062 person-years of follow-up (an average of 12.8 years per person), 134 cases of lung cancer were diagnosed among the 4,831 subjects without a personal history of lung cancer who survived at least 1 year after the baseline examination. Among cases, the mean time between baseline examination and diagnosis was 8.0 years (SD, 3.8; range, 1.2-16.3 years). According to

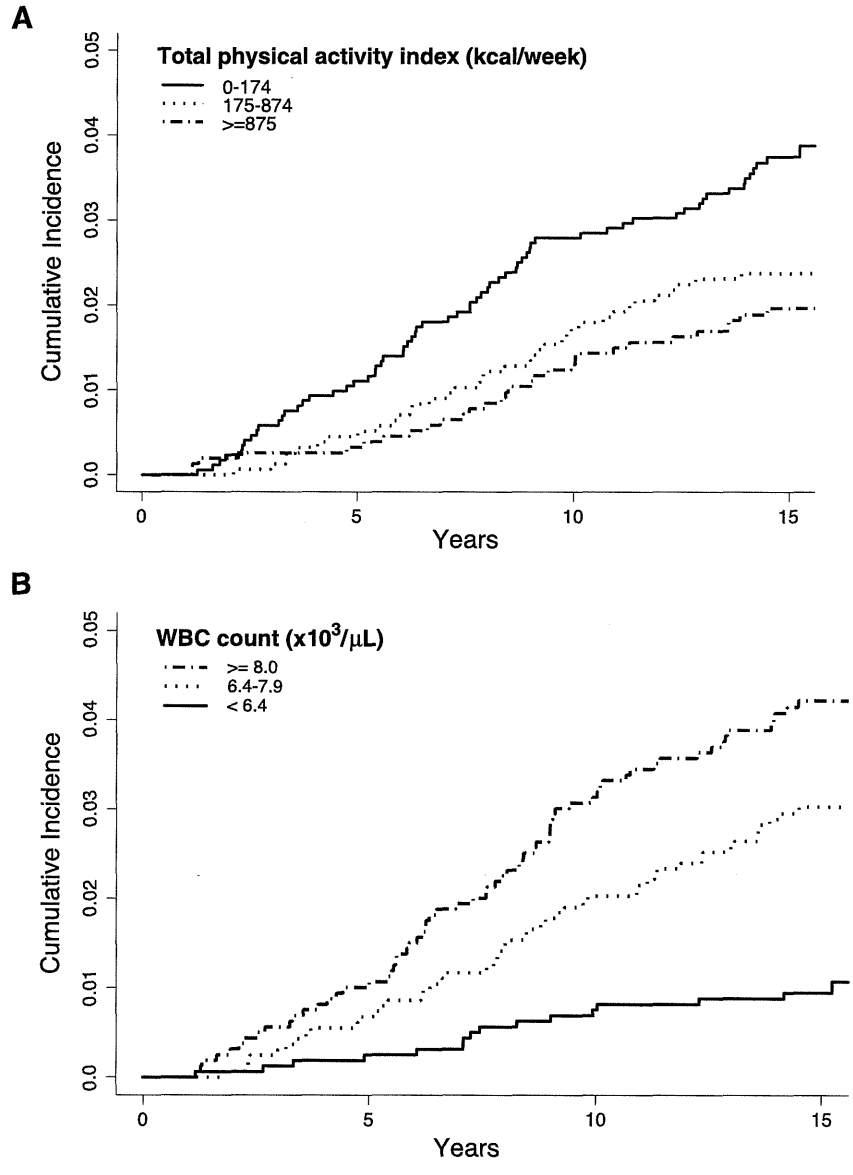

Figure 1. Lung cancer cumulative incidence according to total physical activity index (**A**) and WBC count (**B**). Note that lung cancer cases diagnosed within the first year following the baseline exam were excluded.

Table 3. HR and 95% CI of lung cancer according to physical activity by smoking status and gender

Total physical activity index (kcal/wk)*	No. cases	Person-years†	HR (95% CI)‡	P_{trend}‡
Current smokers				
0-174	36	4,052	1	
175-874	15	4,026	0.48 (0.26-0.91)	
≥875	12	3,107	0.49 (0.25-0.97)	0.02
Never/former smokers				
0-174	29	14,477	1	
175-874	23	15,081	0.97 (0.55-1.71)	
≥875	19	16,236	0.60 (0.33-1.11)	0.10
Females				
0-174	28	11,941	1	
175-874	17	10,737	1.02 (0.54-1.95)	
≥875	10	10,166	0.66 (0.30-1.44)	0.35
Males				
0-174	37	6,590	1	
175-874	21	8,383	0.56 (0.33-0.97)	
≥875	21	9,192	0.50 (0.29-0.87)	0.01

*Kilocalories per week from city blocks walked, flights of stairs climbed, and sweat-inducing activities (see Materials and Methods).
†Total person-years for cases and noncases in category of activity.
‡Models are adjusted for age, sex, pack-years of smoking, time since smoking cessation, body mass index, alcohol intake, and education.

tumor registry reports, 51% of the cases were non–small-cell type (23% adenocarcinoma, 14% squamous, 10% large cell, and 4% not otherwise specified), 12% were small-cell type, and 37% were unspecified-cell types. Of the cases, 23 (17%) were local, 27 (20%) were regional, 45 (34%) were distant, and 39 (29%) were unknown stage at diagnosis.

Physical activity variables are summarized according to other selected covariates in Table 1. In general, participants who were more active tended to be younger, have lower body mass, drink more alcohol, and report more years of education than less active participants. The distribution of participants according to smoking status within levels of physical activity depended upon the type of activity: current smokers were less likely to report vigorous activities that caused a sweat but more likely to climb stairs. Participants who were more active had lower heart rates and WBC counts than less active participants. After adjusting for smoking status, pack-years, and time since cessation, WBC counts declined in successive total physical activity index tertiles (7.6, 7.4, and 7.1 $\times$ $10^3/\mu L$, respectively; $P < 0.001$). No differences were observed in serum albumin according to physical activity levels.

Higher levels of physical activity at baseline were inversely associated with lung cancer incidence (Table 2; Fig. 1A). After multivariable adjustment for demographic and lifestyle factors (first column of HR), the risk of lung cancer was reduced by over 40% among participants reporting 12 or more city blocks walked per day (P_{trend} = 0.03) and those in the highest tertile of the total physical activity index (≥875 kcal/wk; P_{trend} = 0.01). There was a negative association between lung cancer risk and the weekly number of episodes of activity vigorous enough to cause a sweat, although a dose-response pattern was not observed (P_{trend} = 0.08). Flights of stairs climbed each day (P_{trend} = 0.58) and heart rate (P_{trend} = 0.27) were both not associated with lung cancer risk. Although power was limited to detect a difference, these associations between physical activity measures and lung cancer did not seem to differ strongly according to sex, age, body mass index, smoking status, or pack-years smoked. Reductions in lung cancer risk were observed with increasing total physical activity index scores in both current and never/former smokers, although the risk reduction was somewhat stronger and statistically significant only in current smokers (Table 3; $P_{interaction}$ = 0.99). Similarly, lung cancer risk appeared to decline with increasing total physical activity index scores among both men and women, although the risk reduction was stronger and statistically significant only in men (Table 3; $P_{interaction}$ = 0.55). The mean WBC count for lung cancer cases was significantly higher at baseline (mean, 8.2 $\times$ $10^3/\mu L$; SD, 2.2 $\times$ $10^3/\mu L$) than for participants who did not develop lung cancer (mean, 7.4 $\times$ $10^3/\mu L$; SD, 2.1 $\times$ $10^3/\mu L$; $P < 0.0001$). After multivariable adjustment, the HR for lung cancer was 2.8 times as high in participants with WBC counts ≥8 $\times$ $10^3/\mu L$ compared with those having counts <6.4 $\times$ $10^3/\mu L$ (Table 2; Fig. 1B). The mean levels of albumin at baseline among the lung cancer cases were essentially the same (mean, 4.6 g/dL; SD, 0.4 g/dL) as for noncases (mean, 4.7 g/dL; SD, 0.4 g/dL; P = 0.17), and no association was observed after multivariable adjustment.

The variables in Table 2 were similarly associated with lung cancer incidence and lung cancer mortality (data not shown), although for WBC count the relation was somewhat stronger for lung cancer mortality (HR, 3.75; 95% CI, 1.89-7.42 for tertile 3 versus tertile 1).

The results shown in Table 2 were negligibly affected by further adjustment for the presence of diabetes and emphysema at baseline (data not shown). Similarly, the further exclusion of 7 cases diagnosed between 12 and 24 months after the baseline examination had a negligible effect on the results. The relations among lung cancer risk, physical activity, and WBC count did not seem to be modified by time since the baseline examination. In analyses stratified by the median time between baseline exam and diagnosis (7.9 years), lung cancer risk was associated with physical activity and WBC count for both time frames (data not shown). There was limited power to examine these relations by histologic subtype. Compared with subjects in the lowest total physical activity index tertile, subjects in the highest tertile were 0.73 (95%