Available data suggest that sex steroids, particularly androgens, play an important role in the carcinogenesis of prostate cancer.\(^1\) Although essential for normal growth and development, androgens can induce prostate cancer in animal models when given in large amounts.\(^2,3\) In a nested case-control study of 612 male physicians (222 cases of prostate cancer), high levels of circulating testosterone and low levels of sex hormone-binding globulin (SHBG) were associated with subsequent development of prostate cancer.\(^4\) On the other hand, prostate cancer often regresses when androgen stimulation is withdrawn through anti-testosterone therapy, bilateral orchidectomy, or adrenal ablations.\(^5\)

Exercise has beneficial effects on the immune system and can suppress testosterone level; thus, it has been hypothesized to lower risk of prostate cancer. Some studies have shown that basal testosterone levels are lower among men who have recently engaged in physical activity.\(^6\) Additionally, male athletes appear to have lower levels of circulating testosterone when compared to non-athletes.\(^7\) Despite plausible biological mechanisms for an association between physical activity and decreased risk of

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**Background**
Exercise can suppress androgen production and may thus decrease the risk of prostate cancer. However, findings from epidemiological studies assessing physical activity and risk of prostate cancer are inconsistent.

**Methods**
We prospectively examined the association between physical activity and prostate cancer risk in the Physicians’ Health Study (PHS), a randomized trial of low-dose aspirin and beta-carotene among 22,071 men aged 40–84 without self-reported myocardial infarction, stroke, and cancer. At baseline in 1982, men were asked about the frequency of exercise vigorous enough to work up a sweat. Physical activity was assessed in a similar fashion again at 36 months of follow-up.

**Results**
During 11.1 years of follow-up (258,779 person-years), 982 cases of prostate cancer occurred and were confirmed by medical record review. After adjustment for potential confounding factors (including age, height, randomized treatment assignment, smoking status, alcohol intake, use of multivitamins, history of diabetes, history of hypertension and history of high cholesterol), the relative risks for prostate cancer associated with exercise vigorous enough to work up a sweat were 1.0 (referent) for frequency less than once per week, 1.02 (95% CI: 0.82–1.26) for once per week, 1.07 (95% CI: 0.90–1.27) for 2–4 times per week, and 1.11 (95% CI: 0.90–1.36) for 5+ times per week. Across all subgroups of men categorized by age, body mass index, smoking status, alcohol intake, use of multivitamins, history of diabetes, history of hypertension and history of high cholesterol, there were no significant associations between frequency of exercise vigorous enough to work up a sweat and prostate cancer risk. After excluding cases of prostate cancer that occurred during the first 36 months of follow-up, again, there was no significant association. Combining physical activity assessments at baseline and at 36 months also yielded no significant association with prostate cancer risk.

**Conclusions**
These observational data from the Physicians’ Health Study do not support the hypothesis that increased physical activity reduces the risk of prostate cancer.

**Keywords**
Physical activity/exercise, vigorous, prostate cancer, prospective cohort

**Accepted**
20 July 1999
prostate cancer results from epidemiological studies assessing physical activity and risk of prostate cancer have been inconsistent. Available data have supported beneficial, neutral, and even detrimental effects of physical activity.\(^8\) In addition to the limited number of prostate cancers in some previous studies, imprecise assessment of the types and intensity of physical activity, detection bias, and failure to adjust for confounding factors may explain the inconsistency. Moreover, it remains unclear whether the relation between physical activity and prostate cancer risk differs by age and adiposity. To further understand the role of physical activity in the development of prostate cancer, we prospectively examined the relation between physical activity and risk of prostate cancer in a large cohort of US physicians, utilizing repeated assessments of physical activity.

**Methods**

**Study population**

The Physicians’ Health Study (PHS) is a completed randomized, double blind, placebo-controlled trial of aspirin and beta-carotene among US male physicians.\(^9\) At study entry in 1982, 22,071 physicians aged 40–84 years were assigned randomly to aspirin alone, beta-carotene alone, aspirin plus beta-carotene, or both placebos, using a 2 × 2 factorial design. All men were free from a known history of myocardial infarction, stroke, or cancer (except for non-melanoma skin cancer); contraindication to the use of aspirin; or current use of aspirin, other platelet-active agents, or vitamin A supplements. These 22,071 physicians formed the observational cohort for the present investigation of physical activity and risk of prostate cancer. We then excluded 266 men with missing information on physical activity at baseline, or who provided post-randomization reports of cancer that had occurred pre-randomization, leaving 21,805 men available for the present analysis.

**Assessment of physical activity and other characteristics**

At baseline, physicians completed a mailed questionnaire that included information on physical activity. Specifically, they were asked, ‘How often do you exercise vigorously enough to work up a sweat?’ This question primarily assessed recreational physical activity since physicians at work are unlikely to exert enough energy to generate sweat or perceive their exertion at work as exercise. Response options were: rarely/never, 1–3 times/month, once/week, 2–4 times/week, 5–6 times/week, or daily. This method of assessing physical activity has been shown to correlate reasonably well with measures of physical fitness, such as maximal oxygen uptake and treadmill time during a maximal exercise test.\(^10,11\) Other information collected on the questionnaire included: age (in years), cigarette smoking (never, past, current: <20, 20+ cigarettes per day), alcohol intake (rarely/never, monthly, weekly, daily), height (in inches), history of diabetes mellitus (self-reported yes/no), history of high cholesterol (self-reported yes/no), history of hypertension (self-reported yes/no), and self-reported use of multivitamins (yes/no).\(^12\)

The physicians completed brief questionnaires mailed every 6 months during the first year and then annually. These questionnaires inquired about compliance to their assigned treatment, side effects of the study agents, the occurrence of endpoints of interest (including prostate cancer) and potential predictors of chronic diseases. At the 36-month follow-up, the questions regarding physical activity were slightly modified to further emphasize the assessment of recreational physical activity. The physicians were asked specifically, ‘Do you engage in a regular programme of exercise vigorous enough to work up a sweat?’ If an affirmative reply was given, men were asked further, ‘How many days per week?’ with response options being <1, 1–2, 3–4, 5–7 days/week. As at baseline, these questions assessed primarily recreational activity.

**Ascertainment of prostate cancer**

Non-fatal prostate cancers were reported on the semi-annual or annual questionnaires. Deaths among the physicians were usually reported by family members or postal authorities. Morbidity and mortality follow-up among physicians was more than 99% complete. An Endpoints Committee of physicians confirmed incident cases of prostate cancer only after medical records (including pathology reports) and all other relevant information were reviewed. Unconfirmed cases of prostate cancer were not used in analyses. This report includes available data as of 24 October 1995. By this date, men had been followed up for an average of 11.1 years, during which 982 incident cases of prostate cancer were confirmed.

**Statistical analysis**

Each participant accumulated follow-up time beginning at baseline and ending on the month of diagnosis of prostate cancer or censoring (death from causes other than prostate cancer or 24 October 1995, whichever came first). We calculated incidence rates of prostate cancer for men in a specific category of physical activity level at baseline by dividing the number of incident cases by the person-years of follow-up. The relative risk (RR) was estimated by dividing the incidence rate among men in the category of interest by the incidence rate among men in the specified reference category. To obtain enough data in the extreme categories of activity level, we collapsed the six exercise categories on the baseline questionnaire into four: <1 time/week, 1 time/week, 2–4 times/week, and 5+ times/week. All categories were defined before analyses were conducted. To estimate RR adjusting for multiple risk factors, we used proportional hazard regression to model the RR of prostate cancer associated with physical activity adjusted for age, randomized treatment status, cigarette smoking, alcohol intake, height, history of diabetes mellitus, history of high cholesterol, history of hypertension and use of multivitamins. We then conducted stratified analyses according to age (>70 or ≤70 years) and body mass index (BMI) (≥25 or <25 kg/m\(^2\)) to evaluate whether the relation between physical activity and prostate cancer risk differs by age or BMI. Since BMI could be an intermediate variable through which physical activity affects the risk of prostate cancer, we did not adjust for BMI in the primary model. In secondary analyses, we included BMI in the model to consider its impact on the relation between physical activity and risk of prostate cancer. Tests for trend were conducted by treating the different activity categories of physical activity as a single ordinal variable. All P-values were two-sided, and P < 0.05 was considered as statistically significant.

Finally, to reduce within-person variation over time and to evaluate the influence of physical activity over a period of time, we utilized another measurement of physical activity at 36
months of follow-up in addition to that measured at baseline. We defined four categories of physical activity: inactive (i.e. reporting exercise vigorous enough to work up a sweat less than once per week) both at baseline and at 36 months, inactive at baseline but active at 36 months (i.e. at least once a week), active at 36 months but inactive at baseline, or active both at baseline and at 36 months. Physical activity assessed both at the baseline and at the 36 months was then related to subsequent occurrence of prostate cancer, with follow-up starting from 36 months.

### Results

The relations between frequency of exercise vigorous enough to work up a sweat and potential risk factors for prostate cancer are shown in Table 1. At baseline in 1982, 28% of men reported exercise vigorous enough to work up a sweat less than once a week whereas 16% did so five times or more a week. Greater frequency of exercise vigorous enough to work up a sweat was associated with slightly younger age and lower BMI; it also was associated with lower prevalence of heavy smoking, a history of diabetes, hypertension or high cholesterol but higher prevalence of multivitamin supplement use. Approximately equal proportions of men in each of the physical activity categories were randomized to taking active aspirin and active beta-carotene.

During 11.1 years of follow-up (258 779 person-years), 982 cases of prostate cancer were confirmed. No significant association between frequency of exercise vigorous enough to work up a sweat and occurrence of prostate cancer was observed (Table 2). Compared to those who exercised vigorously less than once per week, those who exercised five times or more had similar risks of prostate cancer: the RR adjusted for age and treatment assignment was 1.07 (95% CI: 0.88–1.29, \( P \) for trend = 0.34). The lack of association between frequency of exercise vigorous enough to work up a sweat and prostate cancer risk remained evident after additional adjustment for cigarette smoking, alcohol intake, height, history of diabetes mellitus, history of hypertension, and history of high cholesterol and use of multivitamin supplements. Further adding BMI into the multivariate model had no impact on the null association (Table 2). In addition, the test for linear trend across ascending levels of exercise was not significant (\( P = 0.24 \)).

To evaluate possible effect modification and minimize residual confounding, we conducted several subgroup analyses where we examined the association between frequency of exercise vigorous enough to work up a sweat and prostate cancer according to age, BMI, smoking status, alcohol intake, use of multivitamin supplements, history of diabetes, history of hypertension, and history of high cholesterol. In none of these subgroups did we observe a significant association between physical activity and prostate cancer risk (Table 3).

To take into account changes in physical activity over time and to reduce within-person variation, we utilized repeated assessments of physical activity at both baseline and at 36 months of follow-up. We classified men into those inactive (i.e. frequency of exercise vigorous enough to work up a sweat less than once a week) at both baseline and at 36 months of follow-up (22%), those inactive at baseline but active (i.e. frequency of exercise vigorous enough to work up a sweat at least once a week) at 36 months (5%), those active at baseline but inactive at 36 months (22%), and those active at both times (51%). Again, there was no significant association between physical activity and prostate cancer risk (Table 3).
activity defined in this fashion and risk of prostate cancer; the null findings were essentially the same as those from analyses using baseline physical activity (Table 4). Comparing those who consistently reported exercise vigorous enough to work up a sweat at least once a week to those who consistently reported such exercise less than once per week at both times, the multivariate-adjusted RR of developing prostate cancer was 1.13 (95% CI: 0.94–1.36).

Discussion

In this large cohort of male physicians, non-occupational vigorous exercise was not significantly related to the occurrence of prostate cancer. The null associations between physical activity and risk of prostate cancer were consistently observed across subgroups of men defined by age, cigarette smoking, intake of alcohol, BMI, history of diabetes mellitus, history of high cholesterol, history of hypertension, and use of multivitamins. These findings were also independent of potential risk factors for prostate cancer. Our analysis included a large sample of male physicians followed for a long period of time (11.1 years). The large number of confirmed prostate cancer cases provided precise estimates (narrow 95% CI) for the measures of effect and allowed us to conduct several subgroup analyses to evaluate potential effect modification and the possibility of biases. Follow-up among participants was nearly 100% complete and thus excluded the possibility of bias due to loss of follow-up. Physical activity was assessed before the occurrence of prostate cancer; thus, recall bias was unlikely to affect our findings.

Several limitations need to be considered when interpreting these null findings. One alternative explanation for our findings is residual confounding by potential risk factors. However, the null associations remained evident even after we adjusted for a large number of confounding factors. Confounding from unmeasured sources, such as diet, may be of concern. Although the diet-prostate cancer relation remains to be elucidated, diets high in fruits and vegetables and low in animal products have been associated with a lower risk of prostate cancer.13–16 Because the tendency would be for men who were physically active to consume a more ‘healthy’ diet, confounding by dietary factors, if any, would have created a spurious inverse association between physical activity and prostate cancer rather than a null one. Misclassification of physical activity was another major concern because only a single question regarding vigorous physical activity was asked at baseline. This may not have captured well the total energy expenditure associated with physical activity. Although there is no consensus regarding whether total energy expenditure, or the intensity of the activities is more important for reduced risk of prostate cancer, vigorous physical activity has been associated with a reduced risk of prostate cancer in previous studies.17 Our physical activity question assessed vigorous exercise rather than total physical activity. However, this may not be a major limitation since physicians who engage in vigorous activities are likely to be those accumulating a high level of total energy expenditure because of their relatively sedentary occupation. In addition, such a simple question has been shown to relate reasonably well to other measures of physical fitness such as maximal oxygen uptake (r = 0.54 in men).10

Detection bias may be another alternative explanation for the null findings between physical activity and risk of prostate cancer. If men who reported exercise vigorous enough to work up a sweat were more health conscious and were more likely to be screened for prostate cancer, the rates of prostate cancer might have been underestimated among those who were more active because of a high rate of detection of early-stage lesions among them. If such an under-diagnosis differed across levels of physical activity, it could have obscured an inverse relation between exercise and prostate cancer. We were unable to address these concerns directly. However, participants in this study were all physicians and, compared to the general population, access to medical care is expected to be fairly homogeneous. This homogeneity was likely to have minimized biases due to extraneous factors. In addition, the null findings were consistently observed across subgroups and were essentially the same after excluding cases during the first 36 months of follow-up, further arguing against bias from differences in access to medical care. Furthermore, using this same physical activity assessment, we previously found that physical activity is a strong predictor for both type 2 diabetes18 and stroke19 in this cohort, consistent with the findings of other epidemiological studies.20

A number of cohort studies have evaluated the relations of either occupational or leisure time physical activity to prostate cancer risk. Overall, neither occupational nor leisure time physical activity was associated with a lower risk of prostate cancer.
physical activity has shown consistent associations with risk of developing prostate cancer. Among the few studies that suggest an inverse association between physical activity and risk of prostate cancer, most have reported a small magnitude of relation without linear dose-response. Moreover, the inverse relation is often not statistically significant after taking into account potential confounding factors, and only evident among subgroups of men who are extremely active. Conflicting reports also suggest the inverse relation between exercise and prostate cancer may be limited to either younger or older men. In a cohort study of 47,542 male health professionals followed for 8 years in the US, physical activity has shown consistent associations with risk of developing prostate cancer.8 Among the few studies that suggest an inverse association between physical activity and risk of prostate cancer, most have reported a small magnitude of relation without linear dose-response. Moreover, the inverse relation is often not statistically significant after taking into account potential confounding factors, and only evident among subgroups of men who are extremely active. Conflicting reports also suggest the inverse relation between exercise and prostate cancer may be limited to either younger or older men. In a cohort study of 47,542 male health professionals followed for 8 years in the US,
Table 4 Relative risks (RR) (95% CI) of prostate cancer according to frequency of vigorous exercise assessed both at baseline and at 36 months of follow-up in the US Physicians’ Health Study

<table>
<thead>
<tr>
<th>Frequency of vigorous exercise (times per week)</th>
<th>Baseline</th>
<th>36 months</th>
<th>No. of cases</th>
<th>Person-years</th>
<th>Age and treatment adjusted RR (95% CI)</th>
<th>Multivariate-adjusted RRa (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>&lt;1</td>
<td>191</td>
<td>40 561</td>
<td></td>
<td>1.0 (referent)</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>&lt;1</td>
<td>1+</td>
<td>186</td>
<td>39 931</td>
<td></td>
<td>1.00</td>
<td>0.96</td>
</tr>
<tr>
<td>1+</td>
<td>&lt;1</td>
<td>37</td>
<td>9932</td>
<td></td>
<td>(0.82–1.22)</td>
<td>(0.78–1.20)</td>
</tr>
<tr>
<td>1+</td>
<td>1+</td>
<td>424</td>
<td>93 819</td>
<td></td>
<td>0.91</td>
<td>0.97</td>
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<td></td>
<td></td>
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<td></td>
<td>(0.64–1.29)</td>
<td>(0.62–1.32)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.10</td>
<td>1.13</td>
</tr>
</tbody>
</table>

a Adjusted for age, randomized treatment status, cigarette smoking, alcohol intake, height, history of diabetes mellitus, history of high cholesterol, history of hypertension, and use of multivitamins.

Giovannucci et al. reported no overall association between either vigorous or non-vigorous physical activity and risk of prostate cancer. In contrast to previous findings from a case-control study that suggested a positive association between exercise and risk of aggressive prostate cancer, 27 the authors found an increased risk of prostate cancer associated with high levels of physical activity among men aged ≥70. 28 Although our findings were generally consistent with these previous studies showing no overall effect of physical activity on prostate cancer risk, our data showed neither negative nor positive association among subgroups of men with different age and BMI (Table 3).

It has been hypothesized that exercise can reduce risk of prostate cancer by suppressing levels of testosterone. However, the exact mechanism whereby exercise may exert its effect in the complex aetiology of prostate cancer remains unclear. 17 In a recent study of nine healthy men, growth hormone and testosterone were significantly elevated immediately after exercise, 29 raising the possibility of an adverse effect associated with exercise. Moreover, it is still unclear why cancer of the prostate is much more prevalent than cancers of other adjacent sexual glands with similar exposure to testosterone. 30 Another paradox is that the incidence of prostate cancer increases with age while endogenous production of testosterone tends to decline with age. Perhaps local metabolites of testosterone such as 5α-dihydrotestosterone (17 beta-hydroxy-5α-androstan-3-one, DHT) and 5α-androstanediols may be the relevant hormones in the aetiology of prostate cancer, 31,32 and factors that can modulate the metabolism of testosterone should be the focus of further investigation.

The reported incidence of prostate cancer has been increasing; at present, prostate cancer is the most frequently diagnosed cancer among men within the US, accounting for approximately 180 000 new cancer cases in 1997. 33 The mortality from prostate cancer is estimated at over 28 000 annually, making it the second leading cause of cancer death. Despite the public health significance of this cancer, few risk factors have been identified. Although a positive family history is significantly associated with increased risk of prostate cancer, 34 available data suggest that hereditary factors may only account for less than 10% of the cases, 35 indicating strong influences of environmental determinants. From a public health perspective, identifying modifiable risk factors is of critical importance for the development of appropriate preventive measures. Until recently, physical activity has been one such candidate factor. However, findings from the present study add to the accumulating body of evidence that physical activity is not related to risk of prostate cancer. Thus, for the prevention of prostate cancer, research efforts need to be directed to evaluate effects of other modifiable risk factors such as diet. Meanwhile, regular physical activity should still be recommended since it is important in the prevention of obesity, type 2 diabetes and cardiovascular disease.

References
