Table 2. Age-adjusted baseline characteristics by survival status in the Shanghai Women's Health Study ($n = 71,243$).

Characteristics	Percent Survived ($n = 68,383$)	Percent Deceased ($n = 2,860$)	p-Value[a]
Age at baseline (y)			
40–49	50.7	14.6	
50–59	24.8	19.0	
60–70	24.5	66.4	<0.01
Education			
≤Elementary	20.2	26.3	
Junior high school	37.3	41.3	
High school	28.4	22.9	
>High school	14.1	9.5	<0.01
Occupation			
Manual and agricultural workers/unknown	50.0	56.6	
Clerical	20.5	21.4	
Professional	29.5	22.0	<0.01
BMI (kg/m^2)			
<18.5	3.3	5.5	
18.5–24.99	61.8	56.2	
25.0–29.99	30.0	31.5	
≥30.0	4.9	6.7	<0.01
WHR tertiles			
<0.786	33.5	27.9	
0.786 to <0.830	33.4	30.7	
≥0.830	33.1	41.4	<0.01
Exercise participation (MET, h/d)			
None	64.5	66.8	
>0 to <1.99	24.3	23.5	
≥2.0	11.1	9.7	<0.01
Spouse smoke[b]			
Ever	61.0	65.1	
Never	39.0	34.9	<0.01
Fruit and vegetable intake tertiles (g/d)			
<404.3	33.1	37.8	
404.3–626.5	33.5	31.2	
≥626.5	33.5	31.0	<0.01

Among women who never smoked cigarettes or drank alcohol regularly. All values (except age) were directly standardized to the age distribution of the cohort.
[a]p-Value from chi-square test for general association.
[b]Excluded from the analysis were women without information on exposure to spousal smoking ($n = 7,452$).
doi:10.1371/journal.pmed.1000339.t002

conducted in rural northern Japan [34,37] and one among individuals of the Japan Collaborative Cohort Study [12]. Each of these reports demonstrated that healthier lifestyles based on several lifestyle-related factors were associated with substantial reductions in death among Asian men and women. None of these reports, however, focused on evaluating the impact of lifestyles on mortality outcomes among nonsmokers and nondrinkers.

To our knowledge, this is the first investigation of combinations of lifestyle factors and risk of mortality among Chinese women. We selected five factors that are easy to assess and interpret, based both on prior knowledge of lifestyle factors in relation to mortality and public health recommendations [1,4–9,18–24]. BMI, exercise participation, and fruit and vegetable intake have been well-studied in relation to mortality [1,5–9,24]. WHR and environmental tobacco smoke have not been studied as much, but evidence is accumulating for these two factors as important predictors of total mortality [3,4,23,40,41], and both were shown to be associated with mortality among SWHS participants [18,21]. Several large prospective cohort studies among women have shown WHR to be an important predictor of mortality independent of BMI [3,4,18,41], and in some populations, WHR may be an even stronger predictor of mortality [4,41]. Hence, on the basis of previous studies that both BMI and WHR may be independent measures of adiposity among women and our findings for independent effects of BMI and WHR after adjustment for each other and additional potential confounders, we included both BMI and WHR in the lifestyle scores. In addition, environmental tobacco smoke is a particularly important exposure for women living in China and other Asian countries

Table 3. Adjusted HRs for lifestyle-related factors and risk of all-cause, cardiovascular, and cancer mortality among nonsmoking and nondrinking women aged 40–70 y at baseline ($n = 71,243$), Shanghai Women's Health Study, 1996–2007.

Lifestyle Factor	All-Cause ($n = 2,860$ deaths)			CVD ($n = 775$)			Cancer ($n = 1,351$)		
	n Deaths/Cohort	Age and SES-Adjusted[a] HR (95% CI)	Further Adjusted[b] HR (95% CI)	*n* Deaths	Age and SES-Adjusted[a] HR (95% CI)	Further Adjusted[b] HR (95% CI)	*n* Deaths	Age and SES-Adjusted[a] HR (95% CI)	Further Adjusted[b] HR (95% CI)
BMI (kg/m^2)									
≥30 (obese)	257/3,560	1.00 (Reference)	1.00 (Reference)	104	1.00 (Reference)	1.00 (Reference)	99	1.00 (Reference)	1.00 (Reference)
<18.5 (underweight)	149/2,402	1.52 (1.24–1.86)	1.83 (1.48–2.26)	42	1.18 (0.82–1.69)	1.61 (1.10–2.35)	60	1.43 (1.03–1.97)	1.64 (1.18–2.30)
25.0–29.99 (overweight)	1,027/21,328	0.83 (0.72–0.95)	0.85 (0.74–0.98)	299	0.62 (0.50–0.77)	0.64 (0.51–0.80)	483	0.97 (0.78–1.21)	0.99 (0.80–1.23)
18.5–24.99 (normal)	1,427/43,953	0.82 (0.72–0.94)	0.91 (0.80–1.05)	330	0.53 (0.43–0.66)	0.61 (0.48–0.77)	709	0.95 (0.77–1.17)	1.02 (0.82–1.27)
WHR									
≥0.830	1,477/23,766	1.00 (Reference)	1.00 (Reference)	447	1.00 (Reference)	1.00 (Reference)	631	1.00 (Reference)	1.00 (Reference)
0.786 to <0.830	811/23,730	0.81 (0.74–0.88)	0.80 (0.73–0.87)	219	0.79 (0.67–0.93)	0.82 (0.69–0.96)	407	0.88 (0.78–1.00)	0.87 (0.76–0.99)
<0.786	572/23,747	0.74 (0.67–0.82)	0.68 (0.61–0.76)	109	0.56 (0.45–0.69)	0.52 (0.42–0.66)	313	0.84 (0.73–0.97)	0.80 (0.69–0.93)
Exercise participation (MET, h/d)									
None	1,579/46,093	1.00 (Reference)	1.00 (Reference)	417	1.00 (Reference)	1.00 (Reference)	729	1.00 (Reference)	1.00 (Reference)
>0–1.99	812/17,284	0.91 (0.83–0.99)	0.92 (0.85–1.00)	232	0.90 (0.76–1.06)	0.92 (0.78–1.08)	406	1.04 (0.92–1.18)	1.04 (0.92–1.18)
≥2.0	469/7,866	0.86 (0.77–0.96)	0.89 (0.80–0.99)	126	0.76 (0.62–0.94)	0.79 (0.65–0.97)	216	0.96 (0.82–1.12)	0.96 (0.82–1.12)
Spouse smoke[c]									
Ever	1,315/38,994	1.00 (Reference)	1.00 (Reference)	352	1.00 (Reference)	1.00 (Reference)	634	1.00 (Reference)	1.00 (Reference)
Never	987/24,797	0.92 (0.84–1.00)	0.92 (0.85–1.00)	253	0.84 (0.72–0.99)	0.86 (0.73–1.01)	479	0.93 (0.83–1.05)	0.94 (0.83–1.06)
Fruit and vegetable intake (g/d)									
<404.3	1,313/23,742	1.00 (Reference)	1.00 (Reference)	384	1.00 (Reference)	1.00 (Reference)	522	1.00 (Reference)	1.00 (Reference)
404.3 to <626.5	823/23,752	0.83 (0.76–0.91)	0.85 (0.78–0.93)	207	0.78 (0.66–0.92)	0.81 (0.68–0.96)	437	1.03 (0.91–1.18)	1.05 (0.92–1.19)
≥626.5	724/23,749	0.82 (0.75–0.90)	0.85 (0.77–0.93)	184	0.81 (0.68–0.97)	0.84 (0.70–1.00)	392	1.01 (0.89–1.16)	1.03 (0.90–1.18)

[a]HRs are estimated from Cox proportional hazards regression models using age as the time-scale and adjusted for education, occupation, and income.
[b]Additionally adjusted for other lifestyle factors in the table.
[c]Excludes women without information on exposure to spousal smoking ($n = 7,452$).
doi:10.1371/journal.pmed.1000339.t003

Table 4. Healthy lifestyle scores and risk of all-cause, cardiovascular, and cancer mortality among nonsmoking and nondrinking women aged 40–70 y at baseline ($n = 63,791$), Shanghai Women's Health Study, 1996–2007.

Lifestyle Score	Percent	All-Cause ($n = 2,302$ deaths)			CVD ($n = 605$)			Cancer ($n = 1,113$)		
		n Deaths	HR	(95% CI)	*n* Deaths	HR	(95% CI)	*n* Deaths	HR	(95% CI)
Score 1										
0–2	13.2	507	1.00	(Reference)	163	1.00	(Reference)	204	1.00	(Reference)
3	16.6	465	0.84	(0.74–0.95)	125	0.72	(0.57–0.92)	205	0.89	(0.73–1.08)
4	22.4	497	0.78	(0.69–0.89)	132	0.70	(0.56–0.89)	241	0.88	(0.73–1.06)
5	22.1	415	0.70	(0.62–0.80)	105	0.61	(0.48–0.78)	214	0.82	(0.68–1.00)
6	15.8	270	0.66	(0.57–0.77)	55	0.47	(0.34–0.64)	154	0.85	(0.68–1.05)
7–9	10.1	148	0.53	(0.43–0.63)	25	0.31	(0.20–0.48)	95	0.76	(0.59–0.97)
Trend test				$P<0.001$			$P<0.001$			$P = 0.022$
Score 2										
0	10.8	363	1.00	(Reference)	123	1.00	(Reference)	153	1.00	(Reference)
1	29.9	801	0.93	(0.82–1.05)	219	0.77	(0.62–0.96)	376	1.00	(0.83–1.20)
2	34.6	723	0.84	(0.74–0.95)	180	0.66	(0.52–0.83)	353	0.90	(0.74–1.09)
3	19.5	343	0.75	(0.64–0.87)	72	0.51	(0.38–0.68)	186	0.87	(0.70–1.09)
4–5	5.2	72	0.57	(0.44–0.74)	11	0.29	(0.16–0.54)	45	0.76	(0.54–1.06)
Trend test				$p<0.001$			$p<0.001$			$p = 0.030$
Total PAR[a]				33.4			58.7			18.9

All HRs are estimated from Cox proportional hazards regression models with age as the time-scale and are adjusted for education, occupation, and income. Range for score 1, 0–13 possible points; range for score 2, 0–5 possible points.

[a]Estimated by summing exposure-category specific PARs from score 0 to 3 using the group with score 4–5 as the reference.

doi:10.1371/journal.pmed.1000339.t004

given the high smoking prevalence among Asian men [21,42]. No previous study included either WHR or environmental tobacco smoke in the assessment of the combined impact of lifestyle factors on mortality.

This study has several strengths, including a population-based prospective cohort study design and large overall sample size. Selection bias was minimized due to the exceptionally high response rates at recruitment (92.7%) and in the follow-up surveys (96.7%–99.8%). Baseline assessments were conducted by trained interviewers using standardized protocols, and anthropometric data were based on measurements instead of self-report.

Limitations of this study should be considered for interpretation of results. One concern is the potential for information or reverse causation bias due to the presence of subclinical disease or prevalent clinical disease. To address this concern, we analyzed the association of mortality with the lifestyle score among women without prevalent CVD, cancer, stroke, diabetes, or hypertension and also after excluding deaths in the first 3 y of follow-up. Findings for these subgroups were not appreciably different from the overall results. Women without information on exposure to spousal smoking were excluded from the lifestyle score and mortality analyses. Exclusion of these women, however, is unlikely

Table 5. Healthy lifestyle score two and risk of all-cause mortality among nonsmoking and nondrinking women aged 40–70 y by chronic disease status at baseline, Shanghai Women's Health Study, 1996–2007.

Lifestyle Score Two	Women with Potentially Fatal Diseases at Baseline[a] ($n = 6,009$)			Women with Diabetes and Hypertension only at Baseline ($n = 12,209$)			Healthy Women at Baseline[b] ($n = 45,573$)		
	n Deaths	HR	(95% CI)	*n* Deaths	HR	(95% CI)	*n* Deaths	HR	(95% CI)
0	113	1.00	(Reference)	123	1.00	(Reference)	127	1.00	(Reference)
1	241	1.02	(0.81–1.28)	250	1.02	(0.82–1.27)	310	0.87	(0.71–1.07)
2	186	0.86	(0.67–1.08)	186	0.92	(0.73–1.16)	351	0.87	(0.71–1.07)
3	96	0.82	(0.62–1.09)	69	0.77	(0.57–1.04)	178	0.79	(0.62–0.99)
4–5	17	0.53	(0.32–0.89)	16	0.69	(0.41–1.16)	39	0.61	(0.43–0.88)
Trend test			$p = 0.005$			$p = 0.024$			$p = 0.009$

All HRs are estimated from Cox proportional hazards regression models with age as the time-scale and are adjusted for education, occupation, and income.

[a]Potentially fatal chronic diseases included cancer, stroke, and coronary heart disease.

[b]No history of cancer, stroke, coronary heart disease, diabetes, or hypertension.

doi:10.1371/journal.pmed.1000339.t005

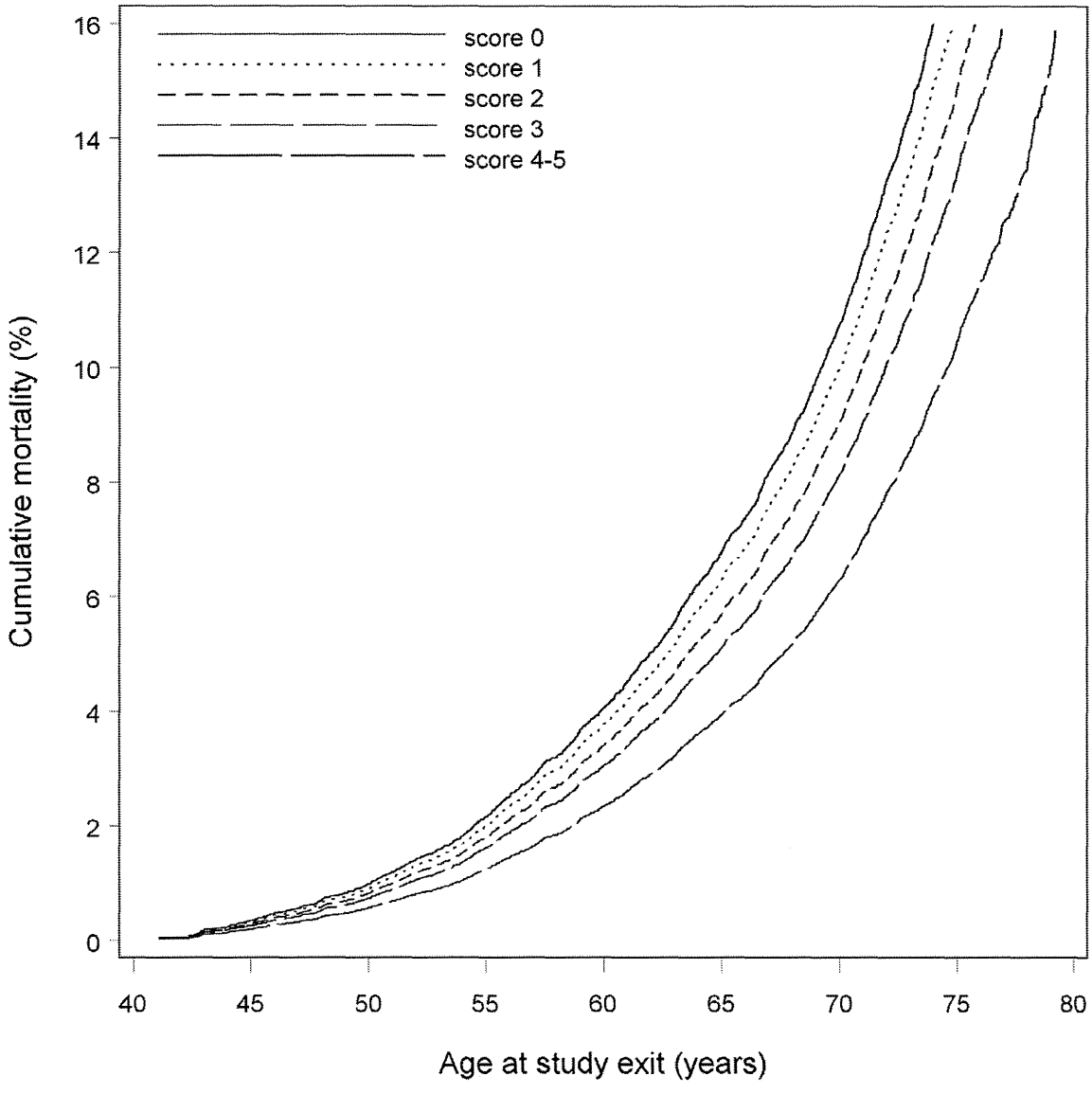

Figure 1. Mortality and healthy lifestyle score 2, adjusted for education, occupation, and income, Shanghai Women's Health Study 1996–2007.
doi:10.1371/journal.pmed.1000339.g001

to materially affect our findings, though the sample size was reduced slightly. Measurement error, particularly for self-reported data on diet and exercise, is another potential concern. However, we have previously shown good validity and reliability for diet and physical activity data from the SWHS [25,26]. Furthermore, nondifferential errors tend to attenuate the observed associations, and thus the true association between lifestyle factors and mortality may be stronger than that estimated in this study. We did not adjust for potential mediators such as blood lipid levels and hypertension in the analysis since the primary purpose of the study was to quantify the overall impact of lifestyle on mortality outcomes. Adjustment for mediators in the causal pathway between lifestyle factors and mortality would affect the quantification of the overall impact of these lifestyle factors on mortality outcomes.

For ease of interpretation, healthy lifestyle scores were created in the analysis assuming an equal weight for each of the factors included. A weighted approach based on the effect size of each variable could improve the estimate of the overall impact of lifestyle factors on mortality. However, as demonstrated in our study, the estimates using score 1 (semi-weighted) and score 2 (nonweighted) are similar, suggesting that a weighted approach may not improve the estimates substantially. Despite an overall large sample size, the sample sizes for some cause-specific analyses were relatively small, which may affect the precision of the point estimates. In addition, the observed associations between lifestyle factors and mortality outcomes in our study may be underestimated because of the use of baseline covariate measurements only [43]. Extended follow-up of this cohort will provide the opportunity to further evaluate the impact of these lifestyle-related factors on mortality outcomes in the future.

Most of the lifestyle-related factors studied here may be improved by individual motivation to change unhealthy behaviors. For example, changes in physical activity levels and energy

expenditure to reduce adiposity can be made by increasing activity levels through walking daily or participating in group exercise classes. Increased fruit and vegetable intake is fairly straightforward for the majority of Chinese women in urban communities, given that many varieties of fruit and vegetables are readily available at the markets. However, both the physical and social environments also are important contributors to sustained lifestyle changes, and may be more significant than individual motivation for some lifestyle factors, which is particularly true for exposure to spousal smoking. Change in exposure to spousal smoking may start with increased awareness by both women and their husbands about the detrimental health effects of smoking, but also will require community-based interventions and change in the social environment (e.g., promotion of home smoking bans in communities) [44].

In conclusion, in this first study to quantify the combined impact of lifestyle-related factors on mortality outcomes among Chinese women, we found that a higher healthy lifestyle score based on five factors was associated with substantial reductions in total and cause-specific mortality among lifetime nonsmoking and nondrinking women. Reductions in premature deaths associated with higher healthy lifestyle scores were seen among women with and without preexisting comorbidities. Our study suggests that a combined healthy lifestyle—including being of normal weight, lower central adiposity, participation in physical activity, nonexposure to spousal smoking, and higher fruit and vegetable intake—can result in lower mortality among middle-aged and older women, including women with a history of severe disease. Research is needed to design appropriate interventions to increase these healthy lifestyle factors among Asian women.

Supporting Information

Table S1 Baseline characteristics for study participants before and after exclusions, Shanghai Women's Health Study.
Found at: doi:10.1371/journal.pmed.1000339.s001 (0.08 MB DOC)

Acknowledgments

We thank the participants and the research staff of the Shanghai Women's Health Study for making this study possible.

Author Contributions

ICMJE criteria for authorship read and met: SJN XOS HLL GY YBX HC WHC BJ XZ WW YTG WZ. Agree with the manuscript's results and conclusions: SJN XOS HLL GY YBX HC WHC BJ XZ WW YTG WZ. Designed the experiments/the study: XOS YBX HC BJ XZ YTG WZ. Analyzed the data: SJN WW WZ. Collected data/did experiments for the study: HLL GY YBX YTG WZ. Enrolled patients: GY YBX BJ YTG. Wrote the first draft of the paper: SJN. Contributed to the writing of the paper: SJN XOS GY HC XZ YTG WZ. Directed the overall study operation: XOS. Contributed to study design and data collection: WHC. Contributed to data interpretation and manuscript preparation: WHC. Principal investigator of the Shanghai Women's Health Study: WZ.

References

1. Whitlock G, Lewington S, Sherliker P, Clarke R, Emberson J, et al. (2009) Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Lancet 373: 1083–1096.
2. Knoops KT, de Groot LC, Kromhout D, Perrin AE, Moreiras-Varela O, et al. (2004) Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: the HALE project. JAMA 292: 1433–1439.
3. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, et al. (2008) General and abdominal adiposity and risk of death in Europe. N Engl J Med 359: 2105–2120.
4. Folsom AR, Kushi LH, Anderson KE, Mink PJ, Olson JE, et al. (2000) Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. Arch Intern Med 160: 2117–2128.
5. Oguma Y, Sesso HD, Paffenbarger RS, Jr., Lee IM (2002) Physical activity and all cause mortality in women: a review of the evidence. Br J Sports Med 36: 162–172.
6. Lollgen H, Bockenhoff A, Knapp G (2009) Physical activity and all-cause mortality: an updated meta-analysis with different intensity categories. Int J Sports Med 30: 213–224.
7. Steffen LM, Jacobs DR, Jr., Stevens J, Shahar E, Carithers T, et al. (2003) Associations of whole-grain, refined-grain, and fruit and vegetable consumption with risks of all-cause mortality and incident coronary artery disease and ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) Study. Am J Clin Nutr 78: 383–390.
8. Genkinger JM, Platz EA, Hoffman SC, Comstock GW, Helzlsouer KJ (2004) Fruit, vegetable, and antioxidant intake and all-cause, cancer, and cardiovascular disease mortality in a community-dwelling population in Washington County, Maryland. Am J Epidemiol 160: 1223–1233.
9. World Health Organization/Food and Agricultural Organization (2003) Expert report on diet, nutrition, and the prevention of chronic diseases, technical report. Series 916. Geneva: World Health Organization.
10. International Agency for Research on Cancer (2004) Tobacco smoking and involuntary smoking. Lyon: IARC (IARC monographs on the evaluation of carcinogenic risks to humans Vol. 83).
11. Danaei G, Ding EL, Mozaffarian D, Taylor B, Rehm J, et al. (2009) The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. PLoS Med 6: e1000058. doi:10.1371/journal.pmed.1000058.
12. Tamakoshi A, Tamakoshi K, Lin Y, Yagyu K, Kikuchi S (2009) Healthy lifestyle and preventable death: findings from the Japan Collaborative Cohort (JACC) Study. Prev Med 48: 486–492.
13. van Dam RM, Li T, Spiegelman D, Franco OH, Hu FB (2008) Combined impact of lifestyle factors on mortality: prospective cohort study in US women. BMJ DOI: 10.1136/bmj.a1440.
14. Khaw KT, Wareham N, Bingham S, Welch A, Luben R, et al. (2008) Combined impact of health behaviours and mortality in men and women: the EPIC-Norfolk prospective population study. PLoS Med 5: e12. doi:10.1371/journal.pmed.0050012.
15. Kvaavik E, Batty GD, Ursin G, Huxley R, Gale CR (2010) Influence of individual and combined health behaviors on total and cause-specific mortality in men and women: the United Kingdom health and lifestyle survey. Arch Intern Med 170: 711–718.
16. Kim S, Popkin BM, Siega-Riz AM, Haines PS, Arab L (2004) A cross-national comparison of lifestyle between China and the United States, using a comprehensive cross-national measurement tool of the healthfulness of lifestyles: the Lifestyle Index. Prev Med 38: 160–171.
17. Zheng W, Chow WH, Yang G, Jin F, Rothman N, et al. (2005) The Shanghai Women's Health Study: rationale, study design, and baseline characteristics. Am J Epidemiol 162: 1123–1131.
18. Zhang X, Shu XO, Yang G, Li H, Cai H, et al. (2007) Abdominal adiposity and mortality in Chinese women. Arch Intern Med 167: 886–892.
19. Zhang X, Shu XO, Chow WH, Yang G, Li H, et al. (2008) Body mass index at various ages and mortality in Chinese women: impact of potential methodological biases. Int J Obes (Lond) 32: 1130–1136.
20. Matthews CE, Jurj AL, Shu XO, Li HL, Yang G, et al. (2007) Influence of exercise, walking, cycling, and overall nonexercise physical activity on mortality in Chinese women. Am J Epidemiol 165: 1343–1350.
21. Wen W, Shu XO, Gao YT, Yang G, Li Q, et al. (2006) Environmental tobacco smoke and mortality in Chinese women who have never smoked: prospective cohort study. BMJ 333: 376–380.
22. Cai H, Shu XO, Gao YT, Li H, Yang G, et al. (2007) A prospective study of dietary patterns and mortality in Chinese women. Epidemiology 18: 393–401.
23. McGhee SM, Ho SY, Schooling M, Ho LM, Thomas GN, et al. (2005) Mortality associated with passive smoking in Hong Kong. BMJ 330: 287–288.
24. Key TJ, Thorogood M, Appleby PN, Burr ML (1996) Dietary habits and mortality in 11,000 vegetarians and health conscious people: results of a 17 year follow up. BMJ 313: 775–779.
25. Shu XO, Yang G, Jin F, Liu D, Kushi L, et al. (2004) Validity and reproducibility of the food frequency questionnaire used in the Shanghai Women's Health Study. Eur J Clin Nutr 58: 17–23.
26. Matthews CE, Shu XO, Yang G, Jin F, Ainsworth BE, et al. (2003) Reproducibility and validity of the Shanghai Women's Health Study physical activity questionnaire. Am J Epidemiol 158: 1114–1122.
27. WHO Expert Consultation (2004) Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 363: 157–163.
28. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, et al. (2000) Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 32: S498–504.

29. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR, Jr., Montoye HJ, et al. (1993) Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 25: 71–80.
30. Korn EL, Graubard BI, Midthune D (1997) Time-to-event analysis of longitudinal follow-up of a survey: choice of the time-scale. Am J Epidemiol 145: 72–80.
31. Rockhill B, Newman B, Weinberg C (1998) Use and misuse of population attributable fractions. Am J Public Health 88: 15–19.
32. Wacholder S, Benichou J, Heineman EF, Hartge P, Hoover RN (1994) Attributable risk: advantages of a broad definition of exposure. Am J Epidemiol 140: 303–309.
33. Spencer CA, Jamrozik K, Norman PE, Lawrence-Brown M (2005) A simple lifestyle score predicts survival in healthy elderly men. Prev Med 40: 712–717.
34. Tsubono Y, Koizumi Y, Nakaya N, Fujita K, Takahashi H, et al. (2004) Health practices and mortality in Japan: combined effects of smoking, drinking, walking and body mass index in the Miyagi Cohort Study. J Epidemiol 14 (Suppl 1): S39–45.
35. Haveman-Nies A, de Groot LP, Burema J, Cruz JA, Osler M, et al. (2002) Dietary quality and lifestyle factors in relation to 10-year mortality in older Europeans: the SENECA study. Am J Epidemiol 156: 962–968.
36. Meng L, Maskarinec G, Lee J, Kolonel LN (1999) Lifestyle factors and chronic diseases: application of a composite risk index. Prev Med 29: 296–304.
37. Tsubono Y, Fukao A, Hisamichi S (1993) Health practices and mortality in a rural Japanese population. Tohoku J Exp Med 171: 339–348.
38. Breslow L, Enstrom JE (1980) Persistence of health habits and their relationship to mortality. Prev Med 9: 469–483.
39. (2009) Cigarette smoking among adults and trends in smoking cessation - United States, 2008. MMWR Morb Mortal Wkly Rep 58: 1227–1232.
40. Humble C, Croft J, Gerber A, Casper M, Hames CG, et al. (1990) Passive smoking and 20-year cardiovascular disease mortality among nonsmoking wives, Evans County, Georgia. Am J Public Health 80: 599–601.
41. Lahmann PH, Lissner L, Gullberg B, Berglund G (2002) A prospective study of adiposity and all-cause mortality: the Malmo Diet and Cancer Study. Obes Res 10: 361–369.
42. Kubo M, Hata J, Doi Y, Tanizaki Y, Iida M, et al. (2008) Secular trends in the incidence of and risk factors for ischemic stroke and its subtypes in Japanese population. Circulation 118: 2672–2678.
43. Emberson JR, Whincup PH, Morris RW, Wannamethee SG, Shaper AG (2005) Lifestyle and cardiovascular disease in middle-aged British men: the effect of adjusting for within-person variation. Eur Heart J 26: 1774–1782.
44. Ji M, Ding D, Hovell MF, Xia X, Zheng P, et al. (2009) Home smoking bans in an urbanizing community in China. Am J Prev Med 37: 132–136.

Editors' Summary

Background. It is well established that lifestyle-related factors, such as limited physical activity, unhealthy diets, excessive alcohol consumption, and exposure to tobacco smoke are linked to an increased risk of many chronic diseases and premature death. However, few studies have investigated the combined impact of lifestyle-related factors and mortality outcomes, and most of such studies of combinations of established lifestyle factors and mortality have been conducted in the US and Western Europe. In addition, little is currently known about the combined impact on mortality of lifestyle factors beyond that of active smoking and alcohol consumption.

Why Was This Study Done? Lifestyles in regions of the world can vary considerably. For example, many women in Asia do not actively smoke or regularly drink alcohol, which are important facts to note when considering practical disease prevention measures for these women. Therefore, it is important to study the combination of lifestyle factors appropriate to this population.

What Did the Researchers Do and Find? The researchers used the Shanghai Women's Health Study, an ongoing prospective cohort study of almost 75,000 Chinese women aged 40–70 years, as the basis for their analysis. The Shanghai Women's Health Study has comprehensive baseline data on anthropometric measurements, lifestyle habits (including the responses to validated food frequency and physical activity questionnaires), medical history, occupational history, and select information from each participant's spouse, such as smoking history and alcohol consumption. This information was used by the researchers to create a healthy lifestyle score on the basis of five lifestyle-related factors shown to be independently associated with mortality outcomes in this population: normal weight, lower waist-hip ratio, daily exercise, never being exposed to spouse's smoking, and higher daily fruit and vegetable intake. The score ranged from zero (least healthy) to five (most healthy) points. The researchers found that higher healthy lifestyle scores were significantly associated with decreasing mortality and that this association persisted for all women regardless of their baseline comorbidities. So in effect, healthier lifestyle-related factors, including normal weight, lower waist-hip ratio, participation in exercise, never being exposed to spousal smoking, and higher daily fruit and vegetable intake, were significantly and independently associated with lower risk of total, and cause-specific, mortality.

What Do These Findings Mean? This large prospective cohort study conducted among lifetime nonsmokers and nonalcohol drinkers shows that lifestyle factors, other than active smoking and alcohol consumption, have a major combined impact on total mortality on a scale comparable to the effect of smoking—the leading cause of death in most populations. However, the sample sizes for some cause-specific analyses were relatively small (despite the overall large sample size), and extended follow-up of this cohort will provide the opportunity to further evaluate the impact of these lifestyle-related factors on mortality outcomes in the future.

The findings of this study highlight the importance of overall lifestyle modification in disease prevention, especially as most of the lifestyle-related factors studied here may be improved by individual motivation to change unhealthy behaviors. Further research is needed to design appropriate interventions to increase these healthy lifestyle factors among Asian women.

Additional Information. Please access these Web sites via the online version of this summary at http://dx.doi.org/10.1371/journal.pmed.1000339

- The Vanderbilt Epidemiology Center has more information on the Shanghai Women's Health Study
- The World Health Organization provides information on health in China
- The document Health policy and systems research in China contains information about health policy and health systems research in China
- The Chinese Ministry of Health also provides health information

論文名	Combined impact of lifestyle-related factors on total and cause-specific mortality among Chinese women: prospective cohort study
著 者	Nechuta SJ, Shu XO, Li HL, Yang G, Xiang YB, Cai H, Chow WH, Ji B, Zhang X, Wen W, Gao YT, Zheng W
雑誌名	PLoS Med
巻・号・頁	7(9) 1-11
発行年	2010
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/20856900

対象の内訳							
	ヒト	動物	地 域	アジア	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	40-70歳			( )		前向き研究	
対象数	10000以上			( )		( )	

調査の方法	質問紙	( )					
アウトカム	予 防	心疾患予防	な し	ガン予防	な し	死亡	( )
	維持・改善	な し	な し	な し	な し	( )	( )

図 表

Table 3. Adjusted HRs for lifestyle-related factors and risk of all-cause, cardiovascular, and cancer mortality among nonsmoking and nondrinking women aged 40–70 y at baseline (n = 71,243), Shanghai Women's Health Study, 1996–2007.

Lifestyle Factor	All-Cause (n = 2,860 deaths)			CVD (n = 775)			Cancer (n = 1,351)		
	n Deaths/Cohort	Age and SES-Adjusted[a] HR (95% CI)	Further Adjusted[b] HR (95% CI)	n Deaths	Age and SES-Adjusted[a] HR (95% CI)	Further Adjusted[b] HR (95% CI)	n Deaths	Age and SES-Adjusted[a] HR (95% CI)	Further Adjusted[b] HR (95% CI)
BMI (kg/m²)									
≥30 (obese)	257/3,560	1.00 (Reference)	1.00 (Reference)	104	1.00 (Reference)	1.00 (Reference)	99	1.00 (Reference)	1.00 (Reference)
<18.5 (underweight)	149/2,402	1.52 (1.24–1.86)	1.83 (1.48–2.26)	42	1.78 (0.82–1.69)	1.61 (1.10–2.35)	60	1.43 (1.03–1.97)	1.64 (1.18–2.30)
25.0–29.99 (overweight)	1,027/21,328	0.83 (0.72–0.95)	0.85 (0.74–0.98)	299	0.62 (0.50–0.77)	0.64 (0.51–0.80)	483	0.97 (0.76–1.23)	0.99 (0.80–1.23)
18.5–24.99 (normal)	1,427/43,953	0.82 (0.72–0.94)	0.91 (0.80–1.05)	330	0.53 (0.43–0.66)	0.61 (0.48–0.77)	709	0.95 (0.77–1.17)	1.02 (0.82–1.27)
WHR									
≥0.830	1,477/23,766	1.00 (Reference)	1.00 (Reference)	447	1.00 (Reference)	1.00 (Reference)	631	1.00 (Reference)	1.00 (Reference)
0.786 to <0.830	811/23,730	0.81 (0.74–0.88)	0.80 (0.73–0.87)	219	0.79 (0.67–0.93)	0.82 (0.69–0.96)	407	0.88 (0.78–1.00)	0.87 (0.76–0.99)
<0.786	572/23,747	0.74 (0.67–0.82)	0.68 (0.61–0.76)	109	0.56 (0.45–0.69)	0.52 (0.42–0.66)	313	0.84 (0.73–0.97)	0.80 (0.69–0.93)
Exercise participation (MET, h/d)									
None	1,579/46,093	1.00 (Reference)	1.00 (Reference)	437	1.00 (Reference)	1.00 (Reference)	729	1.00 (Reference)	1.00 (Reference)
>0–1.99	812/17,284	0.91 (0.83–0.99)	0.92 (0.85–1.00)	232	0.90 (0.76–1.06)	0.92 (0.78–1.08)	406	1.04 (0.92–1.18)	1.04 (0.92–1.18)
≥2.0	469/7,866	0.86 (0.77–0.96)	0.89 (0.80–0.99)	126	0.76 (0.62–0.94)	0.79 (0.65–0.97)	216	0.96 (0.82–1.12)	0.96 (0.82–1.12)
Spouse smoke[c]									
Ever	1,315/38,994	1.00 (Reference)	1.00 (Reference)	352	1.00 (Reference)	1.00 (Reference)	634	1.00 (Reference)	1.00 (Reference)
Never	987/24,797	0.92 (0.84–1.00)	0.92 (0.85–1.00)	253	0.84 (0.72–0.99)	0.86 (0.73–1.01)	479	0.93 (0.83–1.05)	0.94 (0.83–1.06)
Fruit and vegetable intake (g/d)									
<404.3	1,313/23,742	1.00 (Reference)	1.00 (Reference)	384	1.00 (Reference)	1.00 (Reference)	522	1.00 (Reference)	1.00 (Reference)
404.3 to <626.5	823/23,752	0.83 (0.76–0.91)	0.85 (0.78–0.93)	207	0.78 (0.66–0.92)	0.81 (0.68–0.96)	437	1.03 (0.91–1.18)	1.05 (0.92–1.19)
≥626.5	724/23,749	0.82 (0.75–0.90)	0.85 (0.77–0.93)	184	0.81 (0.68–0.97)	0.84 (0.70–1.00)	392	1.01 (0.89–1.16)	1.03 (0.90–1.18)

[a]HRs are estimated from Cox proportional hazards regression models using age as the time scale and adjusted for education, occupation, and income.
[b]Additionally adjusted for other lifestyle factors in the table.
[c]Excludes women without information on exposure to spousal smoking (n = 7,452).
doi:10.1371/journal.pmed.1000339.t003

図表掲載箇所	P6, Table3
概 要 (800字まで)	本研究は、1996年から2000年までにShanghai Women's Health Study(SWHS)に参加した74,942名の女性を対象に平均9.1年間の追跡調査を行い、生活習慣と総死亡、心血管疾患による死亡、がんによる死亡の関連について検討したものである。運動量、WHO classifications、インタビューで過去5年間の定期的運動習慣について尋ねた。定期的運動習慣の定義は3ヶ月以上継続し週一回以上実施していることとした。運動のタイプ、時間、頻度を調べた。運動タイプから強度をメッツで当てはめ、メッツ時/日で運動量を定量化した。また、生活習慣についての5項目をスコア化し、得点の高い者がより健康的で低い者がより不健康であるとした。運動量に関して、2.0メッツ時/日以上の運動習慣のある者は運動習慣のない者と比較すると、総死亡リスクが0.89(95%信頼区間:0.80-0.99)に減少し、心血管疾患死亡リスクが0.79(0.65-0.97)に減少した。がん死亡リスクでは有意な減少はみられなかった。また、生活習慣スコアが高いほど総死亡と心血管疾患死亡リスクは有意に減少したが、がん死亡リスクには有意な減少はみられなかった。
結 論 (200字まで)	中高年齢の中国人女性において、2メッツ時/日以上の運動習慣のある女性は運動習慣のない女性と比較して、総死亡リスク、心血管疾患死亡リスクが有意に低いことが明らかとなった。しかし、がん死亡リスクに関しては、有意な関連はみられなかった。
エキスパートによるコメント (200字まで)	身体活動基準の策定に用いられた研究の1つである。これまで多くのコホート研究により、喫煙や運動、食事が死亡や様々な疾患発症にかかわることが報告されているものの、複合的な影響をみた研究は少ない。これら複合的生活習慣の影響を、アジア人にて、約7万5000名の大規模な集団で検討していることは非常に重要な研究である。生活習慣は国により異なることから、日本においても、大規模な集団を対象に複合的影響を長期に追う研究が期待される。

担当者 久保絵里子・村上晴香・宮地元彦

Int. J. Cancer: **119,** 2943–2947 (2006)

Recreational physical activity and risk of prostate cancer: A prospective population-based study in Norway (the HUNT study)

Tom I.L. Nilsen*, Pål R. Romundstad and Lars J. Vatten

Department of Public Health and General Practice, Faculty of Medicine, Norwegian University of Science and Technology, NO-7489 Trondheim, Norway

Physical activity has been studied in relation to prostate cancer risk, but the findings have been inconclusive. We prospectively examined the association between self-reported recreational physical activity and overall risk of prostate cancer, risk of advanced disease and risk of prostate cancer death in a cohort of 29,110 Norwegian men. Incident prostate cancers were obtained from the Norwegian Cancer Registry, and prostate cancer deaths were obtained from the national Cause of Death Registry. During 17 years of follow-up, 957 incident cases were identified, 266 of them were advanced (*i.e.* metastases at diagnosis) and 354 of the incident cases died from prostate cancer. In multivariable analysis, frequency and duration of exercise were inversely associated with the risk of advanced prostate cancer (p for trend = 0.04 and 0.02). We computed a summary score that combined frequency, duration and intensity of exercise, and this score showed inverse associations with advanced prostate cancer risk and mortality (p for trend = 0.02 and 0.07). Compared to men who reported no activity, the relative risks (95% confidence intervals) among men in the highest category of physical exercise was 0.64 (0.43–0.95) for advanced prostate cancer and 0.67 (0.48–0.94) for prostate cancer death. We found no association between physical activity and overall risk of prostate cancer. We conclude that recreational physical exercise is associated with reduced risk of advanced prostate cancer and prostate cancer death.

Key words: prostate cancer; advanced; mortality; physical activity; epidemiology

If it were to work, physical activity would be an attractive means of cancer prevention, especially since physical activity reduces the risk of other diseases, most notably, cardiovascular disease and diabetes.[1,2] There is some evidence that physical activity may protect against cancer of the colon and breast,[3] but for prostate cancer, the evidence is inconclusive. A recent review found that 16 out of 27 studies conducted between 1979 and 2002 reported a decreased risk of prostate cancer, with an average risk reduction between 10 and 30%, for the most physically active men[4] The authors concluded that there is a probable link between increased physical exercise and decreased prostate cancer risk,[4] whereas previous reviews have concluded that the effect is uncertain and probably negligible.[5,6] Nonetheless, the results of 2 recent cohort studies from the United States suggest that physical activity may be associated with reduced risk of advanced prostate cancer.[7,8]

We have prospectively studied the association between recreational physical activity, measured as frequency, duration and intensity of exercise, and risk of prostate cancer in a cohort of 29,110 Norwegian men who participated in a population-based study between 1984 and 2003 (the HUNT study). This study represents an extension and update of analyses previously reported from a follow-up through 1996.[9] Specifically, we examined the association between recreational physical exercise and advanced prostate cancer, defined as metastatic disease at diagnosis, and between exercise and prostate cancer mortality.

Material and methods

Study population

In Nord-Trøndelag County in Norway, the adult population 20 years of age and older was invited to participate in the HUNT study in 1984–1986. Among 42,532 male individuals who were eligible to participate in the cohort, 36,522 (85.9%) accepted the invitation and attended a clinical examination between 1984 and 1986. They filled in a questionnaire that was included with the invitation, and received a second questionnaire upon attendance to the clinical examination. The second questionnaire included items on recreational physical activity, and was to be filled in at home and returned in a pre-stamped envelope. This information was not updated throughout the follow-up period. The study has been described in detail elsewhere.[10] Among the 36,522 men who participated, 790 men with prevalent cancer (of any site) were excluded from analysis. Among the remaining 35,732 men, 6,622 failed to return the second questionnaire, leaving 29,110 men eligible for prostate cancer follow-up.

Follow-up

The unique 11-digit identity number of Norwegian citizens was used to link information from the HUNT study to information on incidence of prostate cancer from the Cancer Registry of Norway. Prostate cancer was registered according to the International Classification of Diseases, 7th edition (ICD-7, code 177). We also used information in the Registry to identify cases with advanced prostate cancer, defined as those who presented with regional invasion (*i.e.* extended into regional lymph nodes or the surrounding tissue) or distant metastases (*i.e.* spread to other lymph nodes or remote organs) at the time of diagnosis. For solid tumors, this information is based on mandatory reporting from all pathology laboratories in Norway (biopsy, cytology and autopsy). Information on deaths where prostate cancer was registered as the underlying cause was obtained by linkage to the Cause of Death Registry at Statistics Norway (ICD-9, code 185 and ICD-10, code C61). The study was approved by the Norwegian Data Inspectorate, the Norwegian Board of Health and the Regional Committee for Ethics in Medical Research.

For the analyses of prostate cancer incidence, each participant contributed person-time from the date of clinical examination until the date of a cancer diagnosis (of all sites), until death, emigration or to the end of follow-up at December 31, 2002, whichever occurred first. For the analysis of prostate cancer mortality, participants contributed person-years until death or to December 31, 2002.

Physical activity

At baseline, the participants were asked to respond to questions about their average frequency of recreational physical exercise in a week (*i.e.* walking, skiing, swimming or other sports), with 5 response choices (0, <1, 1, 2–3 and ≥4 times). Participants who reported exercising at least once a week were also asked about the average duration (<15, 15–30, 30–60 and >60 min) and intensity (light, moderate and vigorous) of the activity. Among men who

***Correspondence to:** Department of Public Health and General Practice, Medical Research Centre, NTNU, N-7489 Trondheim, Norway. Fax: +47-73-59-75-77. E-mail: tom.i.nilsen@ntnu.no
Received 26 January 2006; Accepted 7 June 2006
DOI 10.1002/ijc.22184
Published online 3 October 2006 in Wiley InterScience (www.interscience.wiley.com).

Publication of the International Union Against Cancer

TABLE I – BASELINE CHARACTERISTICS OF THE STUDY POPULATION (N = 29110 NORWEGIAN MEN)

Characteristic	Frequency of recreational physical activity (average number of sessions per week)				
	No activity	<1	1	2–3	≥4
No. of participants	3855	8183	6776	6362	3934
Mean physical activity score[1]			1.8	2.1	2.2
Mean age at baseline (years)	52.3	44.8	46.8	47.2	58.0
Mean body-mass index (kg/m^2)	25.4	25.4	25.3	25.0	25.1
Obesity (% ≥30 kg/m^2)	10.6	8.6	7.0	5.6	6.8
Smoking (% current)	47.9	44.2	34.8	25.4	29.6
Alcohol (% drinking last two weeks)	46.8	60.8	61.0	58.6	40.0
Education (% college/university)	4.1	9.6	13.9	16.9	8.9
Marital status (% married)	65.6	71.0	73.1	69.6	68.2

[1]Physical activity score calculated from a weighted sum of frequency, intensity and duration among participants who reported a frequency of once per week or more.

exercised once a week or more, we also constructed a summary score of frequency, duration and intensity of physical activity. The score was calculated by summarizing each participant's response to the frequency, duration and intensity questions, giving equal weight to each variable according to the following equation: 1/5 × frequency + 1/3 × intensity + 1/4 × duration. This gave a score variable with a median value of 2.02, ranging from 1.18 to 3.00. The participants were then divided into 4 separate categories (no activity, low, moderate and high activity). Men whose summary score was equal to or above the median were classified as highly active, men with score values below the median were classified as moderately activity, whereas men who exercised less than once a week was categorized as having low activity. In the baseline questionnaire, the participants were asked to average over all types of activities, and thus, no information on specific activities was obtained. The questions related to duration and intensity have been validated against measured oxygen uptake (VO_{2max}) and heart rate (HF_{max}), and shown to perform well.[11]

Statistical analyses

We used the Cox proportional hazards model to computed age-adjusted relative risks (RRs) with 95% confidence intervals (CIs) of total prostate cancer, advanced prostate cancer or prostate cancer death among men within any level of recreational physical activity compared to men in the reference category of no physical activity. Trend tests across categories of physical activity were calculated by treating the categories as ordinal variables in the Cox model. Departure from the proportional hazards assumption was evaluated by Schoenfeld residuals. Further adjustments were made for body mass index (<18.5, 18.5–24.9, 25.0–29.9 and ≥30.0 kg/m^2), smoking status (never, former and current), use of alcohol (frequency last 2 weeks: 0, 1–4, ≥5, total abstainer and missing), marital status (married, unmarried, widower and divorced/separated) and level of education (elementary school, high school, college/university and missing).

In subsequent analyses, we excluded the first 5 years of follow-up in order to evaluate the potential effect of existing but undiagnosed disease (*i.e.* preclinical prostate cancer) on the association of physical activity and prostate cancer risk. To test whether other baseline factors such as age (<65 or ≥65 years), smoking status (never or ever smoker), education (elementary school or high school and above) and body mass index (<25 or ≥25 kg/m^2) modified the association between physical activity and prostate cancer risk, we constructed interaction terms between the physical activity score and these variables. All statistical tests were two-sided, and all statistical analyses were performed using the statistical software Stata for Windows (Version 9.0 (StataCorp LP, 1985–2005).

Results

During a median of 17.5 years (range, 0–19 years) of follow-up, 957 men were diagnosed with prostate cancer and 266 of them had metastatic disease at diagnosis. Median age at diagnosis was 75 years (range, 41–100 years), both for all and for metastatic prostate cancers. During the follow-up period, 354 men with incident prostate cancer died from the disease. Baseline characteristics of the study population are given in Table I.

We found no association between frequency of physical activity and the overall risk of prostate cancer (p for trend = 0.64, Table II). The age-adjusted relative risk of men who reported exercising on average 4 times or more each week was 1.04 (95% CI, 0.84–1.30) compared to men who reported no activity. Adjustment for body mass index, smoking status, alcohol consumption, marital status and level of education did not substantially alter this association (RR, 1.01; 95% CI, 0.81–1.27). Also duration and intensity of physical activity showed no association with overall risk of prostate cancer, but there was a moderate inverse association among men in the highest score that combined all 3 measures of physical activity (multivariable RR, 0.86; 95% CI, 0.68–1.07).

For advanced (metastatic) prostate cancer, however, there was an inverse association with each measure of physical exercise (Table II). Compared to men who reported no activity, the multivariable relative risk among men exercising once a week was 0.68 (95% CI, 0.46–1.02), and for men who reported four times of exercise or more, the RR was 0.66 (95% CI, 0.44–0.99). There was a statistically significant trend across frequency categories (p for trend = 0.04). In relation to duration of exercise, there was also an inverse trend (p for trend = 0.02), and the adjusted RR among men who reported exercising on average more than 1 hr at each session was 0.65 (95% CI, 0.42–1.00), compared to men who reported no activity. The relative risk of men who reported moderate to high intensity when they exercised was 0.80 (95% CI, 0.54–1.18), compared to men who reported no activity. The summary score of physical activity, combining frequency, duration and intensity of physical exercise also showed an inverse association with metastatic prostate cancer (p for trend = 0.02). Compared to men who reported no activity, the adjusted RR for men in the highest score category was 0.64 (95% CI, 0.43–0.95).

In relation to prostate cancer mortality, we found an inverse association with duration of physical activity (p for trend = 0.04) (Table III). The multivariable RR of men who reported exercising more than 1 hr at each session was 0.68 (95% CI, 0.47–0.98) compared to inactive men. The summary score that combined frequency, duration and intensity of physical exercise showed a weak inverse association with prostate cancer mortality (p for trend = 0.07), and the adjusted RR of men in the highest score category was 0.67 (95% CI, 0.48–0.94), compared to men with no activity.

We also excluded the first 5 years of follow-up to evaluate whether undiagnosed prostate cancer at baseline could have influenced the estimates, but the results remained unchanged. Compared to those who were inactive, men in the highest score category had a RR of 0.68 (95% CI, 0.44–1.06) for advanced prostate cancer and a RR of 0.67 (95% CI, 0.46–0.96) for prostate cancer death (data not shown). Further, we explored whether the associa-

TABLE II – PHYSICAL ACTIVITY AND RELATIVE RISK (RR) OF INCIDENT PROSTATE CANCER, AND SPECIFICALLY ADVANCED PROSTATE CANCER, AMONG 29,110 NORWEGIAN MEN DURING 17 YEARS OF FOLLOW-UP

Physical activity	No. of person-years	All incident prostate cancers				Advanced[1] prostate cancer			
		No. of cases	RR[2]	RR[3] (95% CI)	p-trend[4]	No. of cases	RR[2]	RR[3] (95% CI)	p-trend[4]
No activity (reference)	53,081	127	1.00	1.00 (Reference)		47	1.00	1.00 (Reference)	
Frequency per week									
<1	130,221	206	1.08	1.05 (0.84–1.32)		61	0.87	0.83 (0.57–1.22)	
1	107,073	226	1.15	1.11 (0.89–1.39)		53	0.73	0.68 (0.46–1.02)	
2–3	99,146	192	0.99	0.94 (0.75–1.18)		55	0.77	0.72 (0.48–1.07)	
≥4	51,961	206	1.04	1.01 (0.81–1.27)	0.64	50	0.69	0.66 (0.44–0.99)	0.04
Duration per episode of exercise (minutes)									
<15	25,331	87	1.13	1.12 (0.85–1.47)		25	0.89	0.88 (0.54–1.42)	
15–30	85,589	242	1.15	1.12 (0.90–1.39)		65	0.84	0.80 (0.55–1.17)	
31–60	121,982	237	1.03	0.99 (0.79–1.23)		60	0.71	0.66 (0.45–0.98)	
>60	75,983	148	0.97	0.93 (0.73–1.19)	0.30	39	0.69	0.65 (0.42–1.00)	0.02
Intensity									
Low	131,248	477	1.05	1.01 (0.85–1.26)		122	0.73	0.70 (0.50–0.98)	
Moderate/high	171,089	246	1.13	1.07 (0.85–1.33)	0.56	68	0.86	0.80 (0.54–1.18)	0.39
Summary score[5]									
Low	130,221	206	1.08	1.05 (0.84–1.32)		61	0.87	0.83 (0.57–1.22)	
Medium	133,036	389	1.17	1.12 (0.92–1.38)		95	0.77	0.73 (0.51–1.04)	
High	117,129	201	0.90	0.86 (0.68–1.07)	0.20	56	0.68	0.64 (0.43–0.95)	0.02

CI denotes confidence interval.
[1]Advanced prostate cancer is defined as those who presented with regional or distant metastases at diagnosis.–[2]Adjusted for age in 5-year categories (<40, 40–44, ... , 75–79, ≥80 years).–[3]Adjusted for age in 5-year categories (<40, 40–44, ... , 75–79, ≥ 80 years), body mass index (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m^2), marital status (married, unmarried, widower, divorced/separated), education (<10, 10–12, ≥13 years), alcohol consumption (frequency last 2 weeks) and smoking status (never, former, current).–[4]p-value from linear trend test when exposure categories were treated as an ordinal variable in the Cox model.–[5]Summary score combining information on frequency, duration and intensity for men who exercised once a week or more; classified into medium an high activity by the median score value, and low activity includes men with a frequency of <1 week.

TABLE III – PHYSICAL ACTIVITY AND RELATIVE RISK (RR) OF DEATH FROM PROSTATE CANCER AMONG 29,110 NORWEGIAN MEN DURING 17 YEARS OF FOLLOW-UP

Physical activity	No. of person-years	No. of cases	RR[1]	RR[2] (95% CI)	p-trend[3]
No activity (reference)	57,712	64	1.00	1.00 (Reference)	
Frequency per week					
<1	133,324	62	0.70	0.71 (0.50–1.01)	
1	110,038	68	0.72	0.74 (0.52–1.04)	
2–3	101,736	64	0.65	0.67 (0.47–0.95)	
≥4	54,127	96	0.84	0.85 (0.62–1.17)	0.49
Duration per episode of exercise (minutes)					
<15	26,289	32	0.76	0.79 (0.52–1.21)	
15–30	88,323	89	0.81	0.83 (0.60–1.14)	
31–60	125,237	82	0.73	0.75 (0.55–1.05)	
>60	78,003	55	0.68	0.68 (0.47–0.98)	0.04
Intensity					
Low	136,660	183	0.74	0.75 (0.56–1.00)	
Moderate/high	174,664	78	0.79	0.81 (0.57–1.14)	0.28
Summary score[4]					
Low	133,324	62	0.71	0.71 (0.50–1.02)	
Medium	137,483	137	0.79	0.81 (0.60–1.10)	
High	120,079	77	0.66	0.67 (0.48–0.94)	0.07

CI denotes confidence interval.
[1]Adjusted for age in 5-year categories (<40, 40–44, ... , 75–79, ≥80 years).–[2]Adjusted for age in 5-year categories (<40, 40–44, ... , 75–79, ≥80 years), body mass index (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m^2), marital status (married, unmarried, widower, divorced/separated), education (<10, 10–12, ≥13 years), alcohol consumption (frequency last 2 weeks) and smoking status (never, former, current).–[3]p-value from linear trend test when exposure categories were treated as an ordinal variable in the Cox model.–[4]Summary score combining information on frequency, duration and intensity for men who exercised once a week or more; classified into medium an high activity by the median score value, and low activity includes men with a frequency of <1 week.

tion of physical activity and risk of advanced prostate cancer could be modified by some of the other baseline factors, but we found no statistically significant interaction with variables such as age (p = 0.46), smoking status (p = 0.54), education (p = 0.27) or body mass index (p = 0.95) (data not shown).

Discussion

In this prospective, population-based study of Norwegian men, the risk of advanced prostate cancer and the risk of prostate cancer death was lower among men who reported moderate to high levels of physical exercise, compared to men who reported no physical activity. These findings are in accordance with those of 2 recent prospective studies from the United States.[7,8] The investigators of these studies reported lower risk of advanced/aggressive prostate cancer among the most physically active, but for prostate cancer risk overall, they found no association with physical activity.

In one of the studies,[8] the reduced risk of advanced disease was only observed among men in the highest category of vigorous activity, and was confined to men who were 65 years of age or older.

In comparison, we found that the inverse association of physical activity was consistent across age groups, and also, that increasing level of physical activity was related to a gradual reduction in risk for advanced prostate cancer. The gradual reduction in risk was consistent for exercise measured as frequency per week and duration of exercise per session. It also displayed a gradual inverse association with advanced prostate cancer risk related to the summary score combining frequency, duration and intensity of physical exercise.

Results from other epidemiologic studies have not been consistent. A systematic review summarized the results of 27 studies that assessed the association between physical activity and prostate cancer risk.[4] More than half of the studies suggested an inverse association, some studies reported no overall association, whereas a few studies reported a positive association between physical activity and risk of prostate cancer. Some subsequent studies have reported weak negative associations with occupational and recreational physical activity.[12,13]

This cohort consists of the majority of adults in a stable, homogeneous population in Norway. The participants come from a county that is mainly rural, where income is dominated by agriculture, small industries, education and small scale trade. The population is well suited for follow-up studies, partly because of excellent endpoint registries in the country and partly because of the unique identification number allocated to each citizen. The reporting of cancer is mandatory and regulated by law, and to achieve a high degree of completeness and high data quality, the material of the Cancer Registry is matched against the Cause of Death Registry. Evaluation of the quality of prostate cancer data reported to the Cancer Registry has shown a completeness of nearly 100%,[14] and the close collaboration between the registries has resulted in highly reliable information on prostate cancer as underlying cause of death.[15]

Our information on recreational physical activity was based on questionnaires that allows for subjective interpretation of the questions and individual perception of the activity, and thus, misclassification of physical activity can be influenced by many factors, such as age, social context and seasonal variations.[16] However, validation studies have shown that questionnaires may be able to classify people into broad categories of physical activity (*e.g.* low, moderate or highly active), but may not be appropriate to quantify energy expenditure.[17] Information on occupational physical activity was not available in these data, and hence the effect of total physical activity could not be assessed.

The precision of the relative risk estimates, and the consistency of the gradual reduction in risk of metastatic prostate cancer with increasing level of physical activity, speak against chance as a likely explanation for our results. It could be argued that preclinical disease could have influenced the measures of physical activity, and distorted the estimated associations with prostate cancer. To investigate this possibility, we excluded the first 5 years of follow-up, but the results remained nearly unchanged.

It is also conceivable that differential health seeking behavior could have biased our results. Testing for prostate cancer with PSA could be unevenly distributed among men in different categories of physical activity, and therefore, could have biased the estimates of relative risk. However, in a previous follow-up of this population, restricted to a period before PSA testing became prevalent (before 1993), we reported similar results as in the present study.[9] Biased estimates due to residual confounding cannot be excluded in this type of study, but at least 2 factors suggest that residual confounding may not be a major concern in this study. First, adjustment for age and multivariable adjustment (*i.e.* controlling for body mass index, smoking, alcohol consumption, education and marital status) yielded similar estimates of relative risk, and second, few risk factors for prostate cancer have been established.

Protective mechanisms that may be attributed to physical activity are not clear, but it has been suggested that circulating levels of insulin, insulin-like growth factors (IGFs) and androgens may play a role.[18–20] Physical activity may reduce the level of circulating testosterone,[21,22] and although the association between sex hormones and prostate cancer risk is inconsistent, some studies have shown that low levels of testosterone may be associated with reduced risk for prostate cancer.[20–23] There is also evidence that exercise may reduce serum insulin and IGF-I levels.[24,25] Insulin appears to regulate the production and metabolism of testosterone,[26] whereas IGF-I stimulates proliferation and inhibits apoptosis in prostate cancer cells, and has been associated with increased prostate cancer risk in some,[19,27] but not all epidemiologic studies.[28,29] A recent cohort study from Sweden showed an almost threefold higher risk of advanced prostate cancer among men in the highest compared to the lowest quartile of IGF-I.[30] Another part of the IGF-axis, the IGF binding proteins (IGFBPs), are also influenced by physical activity[24,25] and it has been shown that IGFBP-3 stimulates apoptosis in human prostate cancer cells.[31] Most of the factors above are thought to be related to cancer progression rather than initiation, and hence, this may explain why we find an effect of physical activity for aggressive prostate cancer and not for total prostate cancer. Moreover, autopsy studies have shown a high prevalence of occult prostate cancer in the general population (70% among men in their seventies),[32] and thus, risk factors may be different for the clinically important prostate cancers versus those who could have been left untreated.

In conclusion, recreational physical activity was not associated with overall prostate cancer incidence, buy may reduce the risk of advanced prostate cancer, and possibly, protect against prostate cancer death. We found that men who reported 1 weekly bout of exercise had a 30% lower risk of being diagnosed with metastatic prostate cancer compared to men who reported no activity. A higher frequency of exercise did not further reduce the risk, but a summary score incorporating frequency, intensity and duration showed an inverse dose-response relationship.

References

1. Berlin JA, Colditz GA. A meta-analysis of physical activity in the prevention of coronary heart disease. Am J Epidemiol 1990;132:612–28.
2. Bassuk SS, Manson JE. Epidemiological evidence for the role of physical activity in reducing risk of type 2 diabetes and cardiovascular disease. J Appl Physiol 2005;99:1193–204.
3. Bianchini F, Kaaks R, Vainio H. Weight control and physical activity in cancer prevention. Obes Rev 2002;3:5–8.
4. Torti DC, Matheson GO. Exercise and prostate cancer. Sports Med 2004;34(6):363–9.
5. Lee IM. Physical activity and cancer prevention—data from epidemiologic studies. Med Sci Sports Exerc 2003;35:1823–7.
6. Friedenreich CM, Thune I. A review of physical activity and prostate cancer risk. Cancer Causes Control 2001;12:461–75.
7. Patel AV, Rodriguez C, Jacobs EJ, Solomon L, Thun MJ, Calle EE. Recreational physical activity and risk of prostate cancer in a large cohort of U.S. men. Cancer Epidemiol Biomarkers Prev 2005;14:275–9.
8. Giovannucci EL, Liu Y, Leitzmann MF, Stampfer MJ, Willett WC. A prospective study of physical activity and incident and fatal prostate cancer. Arch Intern Med 2005;165:1005–10.
9. Lund Nilsen TI, Johnsen R, Vatten LJ. Socio-economic and lifestyle factors associated with the risk of prostate cancer. Br J Cancer 2000; 82:1358–63.
10. Holmen J, Forsen L, Hjort PF, Midthjell K, Waaler HT, Bjørndal A. Detecting hypertension: screening versus case finding in Norway. BMJ 1991;302:219–22.
11. Wisløff U, Nilsen TIL, Drøyvold WB, Mørkved S, Slørdahl SA, Vatten LJ. A single weekly bout of exercise may reduce cardiovascular mortality: how little pain for cardiac gain? The HUNT Study, Norway. Eur J Cardiovasc Prev Rehabil, in press.
12. Friedenreich CM, McGregor SE, Courneya KS, Angyalfi SJ, Elliott FG. Case-control study of lifetime total physical activity and prostate cancer risk. Am J Epidemiol 2004;159:740–9.

13. Pierotti B, Altieri A, Talamini R, Montella M, Tavani A, Negri E, Franceschi S, La Vecchia C. Lifetime physical activity and prostate cancer risk. Int J Cancer 2005;114:639–42.
14. Harvei S, Tretli S, Langmark F. Quality of prostate cancer data in the cancer registry of Norway. Eur J Cancer 1996;32A:104–10.
15. Hernes E, Harvei S, Glattre E, Gjertsen F, Fossa SD. High prostate cancer mortality in Norway: influence of Cancer Registry information? APMIS 2005;113:542–9.
16. Vanhees L, Lefevre J, Philippaerts R, Martens M, Huygens W, Troosters T, Beunen G. How to assess physical activity? How to assess physical fitness? Eur J Cardiovasc Prev Rehabil 2005;12:102–14.
17. Shephard RJ. Limits to the measurement of habitual physical activity by questionnaires. Br J Sports Med 2003;37:197–206.
18. Hsing AW, Chua S, Jr, Gao YT, Gentzschein E, Chang L, Deng J, Stanczyk FZ. Prostate cancer risk and serum levels of insulin and leptin: a population-based study. J Natl Cancer Inst 2001;93:783–9.
19. Chan JM, Stampfer MJ, Giovannucci E, Gann PH, Ma J, Wilkinson P, Hennekens CH, Pollak M. Plasma insulin-like growth factor-I and prostate cancer risk: a prospective study. Science 1998;279:563–6.
20. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst 1996;88:1118–26.
21. Aakvaag A, Sand T, Opstad PK, Fonnum F. Hormonal changes in serum in young men during prolonged physical strain. Eur J Appl Physiol Occup Physiol 1978;39:283–91.
22. Hackney AC, Sinning WE, Bruot BC. Reproductive hormonal profiles of endurance-trained and untrained males. Med Sci Sports Exerc 1988; 20:60–5.
23. Heikkila R, Aho K, Heliovaara M, Hakama M, Marniemi J, Reunanen A, Knekt P. Serum testosterone and sex hormone-binding globulin concentrations and the risk of prostate carcinoma: a longitudinal study. Cancer 1999;86:312–15.
24. Hellenius ML, Brismar KE, Berglund BH, de Faire UH. Effects on glucose tolerance, insulin secretion, insulin-like growth factor 1 and its binding protein, IGFBP-1, in a randomized controlled diet and exercise study in healthy, middle-aged men. J Intern Med 1995;238: 121–30.
25. Ngo TH, Barnard RJ, Tymchuk CN, Cohen P, Aronson WJ. Effect of diet and exercise on serum insulin, IGF-I, and IGFBP-1 levels and growth of LNCaP cells in vitro (United States). Cancer Causes Control 2002;13:929–35.
26. Haffner SM. Sex hormones, obesity, fat distribution, type 2 diabetes and insulin resistance: epidemiological and clinical correlation. Int J Obes Relat Metab Disord 2000;24 (suppl. 2):S56–S58.
27. Li L, Yu H, Schumacher F, Casey G, Witte JS. Relation of serum insulin-like growth factor-I (IGF-I) and IGF binding protein-3 to risk of prostate cancer (United States). Cancer Causes Control 2003;14:721–6.
28. Woodson K, Tangrea JA, Pollak M, Copeland TD, Taylor PR, Virtamo J, Albanes D. Serum insulin-like growth factor I: tumor marker or etiologic factor? A prospective study of prostate cancer among Finnish men. Cancer Res 2003;63:3991–4.
29. Chen C, Lewis SK, Voigt L, Fitzpatrick A, Plymate SR, Weiss NS. Prostate carcinoma incidence in relation to prediagnostic circulating levels of insulin-like growth factor I, insulin-like growth factor binding protein 3, and insulin. Cancer 2005;103:76–84.
30. Stattin P, Rinaldi S, Biessy C, Stenman UH, Hallmans G, Kaaks R. High levels of circulating insulin-like growth factor-I increase prostate cancer risk: a prospective study in a population-based nonscreened cohort. J Clin Oncol 2004;22:3104–12.
31. Hong J, Zhang G, Dong F, Rechler M. Insulin-like growth factor (IGF)-binding protein-3 mutants that do not bind IGF-I or IGF-II stimulate apoptosis in human prostate cancer cells. J Biol Chem 2002; 277:10489–97.
32. Mettlin C, Jones GW, Murphy GP. Trends in prostate cancer care in the United States, 1974–1990: observations from the patient care evaluation studies of the American College of Surgeons Commission on Cancer. CA Cancer J Clin 1993;43:83–91.

論文名	Recreational physical activity and risk of prostate cancer: A prospective population-based study in Norway (the HUNT study)
著　者	Nilsen TI, Romundstad PR, Vatten LJ
雑誌名	Int J Cancer
巻・号・頁	119　　2943-2947
発行年	2006
PubMedリンク	http://www.ncbi.nlm.nih.gov/pubmed/17019717

対象の内訳	ヒト	動物	地　域	欧米	研究の種類	縦断研究
対象	一般健常者	空白		( )		コホート研究
性別	男性	( )		( )		( )
年齢	20歳以上			( )		前向き研究
対象数	10000以上			( )		( )

調査の方法	質問紙	( )				
アウトカム	予　防	なし	なし	ガン予防	なし	死亡	( )
	維持・改善	なし	なし	なし	なし	( )	( )

図　表

TABLE II - PHYSICAL ACTIVITY AND RELATIVE RISK (RR) OF INCIDENT PROSTATE CANCER, AND SPECIFICALLY ADVANCED PROSTATE CANCER, AMONG 29,110 NORWEGIAN MEN DURING 17 YEARS OF FOLLOW-UP

Physical activity	No. of person-years	All incident prostate cancers				Advanced[1] prostate cancer			
		No. of cases	RR[2]	RR[2] (95% CI)	p-trend[4]	No. of cases	RR[2]	RR[2] (95% CI)	p-trend[4]
No activity (reference)	53,081	127	1.00	1.00 (Reference)		47	1.00	1.00 (Reference)	
Frequency per week									
<1	130,221	206	1.08	1.05 (0.84–1.32)		61	0.87	0.83 (0.57–1.22)	
1	102,073	226	1.15	1.11 (0.89–1.39)		53	0.73	0.68 (0.46–1.02)	
2–3	99,146	192	0.99	0.94 (0.75–1.18)		35	0.72	0.72 (0.48–1.07)	
≥4	51,961	206	1.04	1.01 (0.81–1.27)	0.64	59	0.69	0.66 (0.44–0.99)	0.04
Duration per episode of exercise (minutes)									
<15	25,331	87	1.13	1.12 (0.85–1.47)		25	0.89	0.88 (0.54–1.42)	
15–30	85,589	242	1.15	1.13 (0.90–1.39)		65	0.84	0.80 (0.55–1.17)	
31–60	121,982	237	1.03	0.99 (0.79–1.23)		60	0.71	0.66 (0.45–0.98)	
>60	75,983	148	0.97	0.93 (0.73–1.19)	0.38	39	0.69	0.65 (0.42–1.00)	0.02
Intensity									
Low	131,248	477	1.05	1.01 (0.85–1.26)		122	0.73	0.70 (0.50–0.98)	
Moderate/high	171,089	246	1.13	1.07 (0.85–1.33)	0.56	68	0.86	0.80 (0.54–1.18)	0.39
Summary score[5]									
Low	130,221	206	1.08	1.05 (0.84–1.32)		61	0.87	0.83 (0.57–1.22)	
Medium	133,036	389	1.17	1.12 (0.92–1.38)		95	0.77	0.73 (0.51–1.04)	
High	117,129	201	0.90	0.86 (0.68–1.07)	0.20	56	0.68	0.64 (0.43–0.95)	0.02

CI denotes confidence interval.
[1]Advanced prostate cancer is defined as those who presented with regional or distant metastases at diagnosis. [2,3]Adjusted for age in 5-year categories (<40, 40–44, . . . , 75–79, ≥80 years). [3]Adjusted for age in 5-year categories (<40, 40–44, . . . , 75–79, ≥ 80 years), body mass index (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m²), marital status (married, unmarried, widower, divorced/separated), education (<10, 10–12, ≥13 years), alcohol consumption (frequency last 2 weeks) and smoking status (never, former, current). [4]p-value from linear trend test when exposure categories were treated as an ordinal variable in the Cox model. [5]Summary score combining information on frequency, duration and intensity for men who exercised once a week or more; classified into medium an high activity by the median score value, and low activity includes men with a frequency of <1 week.

TABLE III - PHYSICAL ACTIVITY AND RELATIVE RISK (RR) OF DEATH FROM PROSTATE CANCER AMONG 29,110 NORWEGIAN MEN DURING 17 YEARS OF FOLLOW-UP

Physical activity	No. of person-years	No. of cases	RR[2]	RR[2] (95% CI)	p-trend[3]
No activity (reference)	57,712	64	1.00	1.00 (Reference)	
Frequency per week					
<1	133,324	62	0.70	0.71 (0.50–1.01)	
1	110,038	68	0.72	0.74 (0.52–1.04)	
2–3	101,736	64	0.65	0.67 (0.47–0.95)	
≥4	54,127	96	0.84	0.85 (0.62–1.17)	0.49
Duration per episode of exercise (minutes)					
<15	26,289	32	0.76	0.79 (0.52–1.21)	
15–30	88,323	89	0.81	0.83 (0.60–1.14)	
31–60	125,237	82	0.73	0.75 (0.55–1.05)	
>60	78,003	55	0.68	0.68 (0.47–0.98)	0.04
Intensity					
Low	136,660	183	0.74	0.75 (0.56–1.00)	
Moderate/high	174,664	78	0.79	0.81 (0.57–1.14)	0.28
Summary score[4]					
Low	133,324	62	0.71	0.71 (0.50–1.02)	
Medium	137,483	137	0.79	0.81 (0.60–1.10)	
High	120,079	77	0.66	0.67 (0.48–0.94)	0.07

CI denotes confidence interval.
[1]Adjusted for age in 5-year categories (<40, 40–44, . . . , 75–79, ≥80 years). [2]Adjusted for age in 5-year categories (<40, 40–44, . . . , 75–79, ≥80 years), body mass index (<18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m²), marital status (married, unmarried, widower, divorced/separated), education (<10, 10–12, ≥13 years), alcohol consumption (frequency last 2 weeks) and smoking status (never, former, current). [3]p-value from linear trend test when exposure categories were treated as an ordinal variable in the Cox model. [4]Summary score combining information on frequency, duration and intensity for men who exercised once a week or more; classified into medium an high activity by the median score value, and low activity includes men with a frequency of <1 week.

図表掲載箇所	P2945, Table2, Table3
概　要 (800字まで)	本研究は、ノルウェーのThe HUNT Studyに参加した男性29,110名を対象に平均17.5年間の追跡調査を行い、余暇時間身体活動と進行性前立腺がん発症/死亡リスクとの関連を検討したものである。質問紙により余暇時間身体活動の週当たりの平均実施頻度、平均実施時間、身体活動の強度を尋ね、頻度は1回/週未満、1回、2-3回、4回/週以上の4群に、時間は15分未満、15-30分、31-60分、60分以上の4群に、強度は低強度、中・高強度の2群に分類した。また、それらを数値化し、総身体活動スコアを順に低、中、高の3群に分類した。進行性前立腺がん発症リスクに関して、余暇時間身体活動を全くしないと回答した集団と比較すると、週当たり4回以上行う集団で0.66(95%信頼区間:0.44-0.99)と有意な減少がみられ、31-60分間行う集団で0.66(0.45-0.98)、60分以上行う集団で0.65(0.42-1.00)のリスク減少がみられた。強度では低強度で行った集団で0.70(0.50-0.98)と減少し、総身体活動スコアが高の集団で0.64(0.43-0.95)と有意な減少がみられた。前立腺がんによる死亡リスクに関して、余暇時間身体活動を全くしないと回答した集団と比較すると、週当たり2-3回行う集団で0.67(0.47-0.95)、60分以上行う集団で0.68(0.47-0.98)、総身体活動スコアが高の集団で0.67(0.48-
結　論 (200字まで)	余暇時間身体活動を行うことで、進行性前立腺がん発症リスクを低下させ、さらには前立腺がんによる死亡リスクに対する保護効果も示唆された。
エキスパートによるコメント (200字まで)	身体活動基準の策定に用いられた研究の1つである。余暇時間身体活動を行うことで、進行性前立腺がん発症リスクを低下させることを示した。強度、時間、量の違いに基づいた詳細な検討を行った点に意義がある。

担当者　久保絵里子・村上晴香・宮地元彦

The association between cardiorespiratory fitness and prostate cancer

SUSAN A. OLIVERIA, HAROLD W. KOHL III,
DIMITRIOS TRICHOPOULOS, and STEVEN N. BLAIR

Strang Cancer Prevention Center,
New York, NY;
Department of Epidemiology,
Harvard School of Public Health,
Boston, MA; and
Cooper Institute for Aerobics Research,
Dallas, TX

ABSTRACT

SUSAN A. OLIVERIA, HAROLD W. KOHL III, DIMITRIOS TRICHOPOULOS, and STEVEN N. BLAIR. The association between cardiorespiratory fitness and prostate cancer. *Med. Sci. Sports Exerc.*, Vol. 28, No. 1, pp. 97–104, 1996. We conducted a prospective study to assess the association between cardiorespiratory fitness and prostate cancer. The subjects were men, aged 20–80 yr, who received a preventive medical exam at the Cooper Clinic in Dallas, TX, during 1970–1989 and provided information on cardiorespiratory fitness and prostate cancer (N = 12,975). Cardiorespiratory fitness was assessed at a baseline examination between 1971 and 1989 using a maximal exercise treadmill test. Questionnaires were mailed to the men in 1982 and 1990 to ascertain incident cases of prostate cancer. Ninety-four cases of incident prostate cancer were identified. Higher cardiorespiratory fitness levels were inversely associated with the probability of development of incident prostate cancer after controlling for age, body mass index, and smoking habits; adjusted estimates of the incidence rate ratio declined from 1.1 (95% CI 0.63–1.77) to 0.73 (95% CI 0.41–1.29) to 0.26 (95% CI 0.10–0.63) across increasing quartiles of fitness (P for trend <0.004). This protective effect was limited to participants <60 yr old. Also, an inverse association was observed between physical activity and prostate cancer. Compared with expending <1000 kcal·wk^{-1}, participants who expended 1000-<2000, 2000–<3000, or ≥3000 kcal·wk^{-1} had adjusted incidence rate ratios of 0.37 (95% CI 0.17–0.79), 0.62 (95% CI 0.27–1.41), and 0.37 (95% CI 0.14–0.98), respectively. The results suggest that cardiorespiratory fitness and physical activity levels may protect against the development of incident prostate cancer.

EXERCISE, MAXIMAL EXERCISE TREADMILL TEST, MEN, NEOPLASMS, PHYSICAL ACTIVITY, PROSPECTIVE STUDY

Prostate cancer is the second leading cause of death from cancer among men in the U.S.; during 1993, prostate cancer accounted for 13% of all male cancer deaths (14). An estimated 165,000 cases are being diagnosed in the U.S. each year, making prostate cancer the most frequently diagnosed cancer among men (14). Blacks in the U.S. have the highest incidence rates of prostate cancer, followed by whites from North America (53). The etiology of prostate cancer is unknown. Studies have been conducted examining potential risk factors such as diet, venereal diseases, sexual habits, smoking, occupational exposures, and physical activity; however, the results have been inconsistent (21,53).

It has been suggested that physical activity may protect against the development of prostate cancer through reduction of levels of endogenous testosterone (24,44). Male athletes have been shown to have lower levels of circulating testosterone than nonathletes, and men who exercise have reduced testosterone levels immediately after an exercise session (1,20,26,27,37,49,51). The physical activity-prostate cancer hypothesis is compatible with the fact that the standard treatment for prostate cancer is antitestosterone therapy in which the circulating androgen, testosterone, is essentially reduced to levels observed after castration (24). Furthermore, some studies have shown that men with prostate cancer have higher levels of endogenous testosterone compared with nondiseased men, and cancerous tissue has been reported to have higher levels of testosterone compared with normal tissue (2,22,25,28,31).

Despite these hypothesized mechanisms, previous studies have provided inconclusive findings on the relationship between physical activity and prostate cancer (4,17,33,34,40,42,47,50,52). An inverse association between physical activity and prostate cancer was found in six studies (4,17,33,47,50,52), while three studies (34, 40,42) revealed a positive association. No data exist on the relationship between cardiorespiratory fitness and prostate cancer. Fitness level is likely to represent the end result of physical activity and may be considered a good

0195-9131/96/2801-0009$3.00/0
MEDICINE AND SCIENCE IN SPORTS AND EXERCISE®

Submitted for publication August 1994.
Accepted for publication June 1995.

indicator of long-term physical activity participation (6). No gold standard exists for the measurement of physical activity; however, cardiorespiratory fitness can be measured validly using a maximal exercise treadmill test to provide estimates of maximal oxygen uptake (10,13).

The purpose of this paper is to report our prospective observations of the association between cardiorespiratory fitness and incident prostate cancer.

METHODS

Study Population

The total population at the Cooper Clinic is composed of 28,072 subjects. The population for analysis was composed of 12,975 primarily white (>99%), married, college-educated men, aged 20–80 yr, with no history of prostate cancer, who received a voluntary, preventive medical examination at the Cooper Clinic in Dallas, TX, during 1971–1989 and who provided information on cardiorespiratory fitness and prostate cancer. Fifty percent of the men in this cohort were over the age of 42 yr, with 25% over the age of 50. This baseline examination included a physical examination: a questionnaire on demographic characteristics, physical activity, and health habits; a personal and family health history; anthropometric measures; resting and exercise electrocardiography; blood chemistry tests; blood pressure measurements; and a maximal exercise treadmill test to determine cardiorespiratory fitness. Written informed consent was obtained from the participants. Examination methods and procedures followed a standard manual of operations and have been previously described (10,11,13).

Fitness Measurement

Cardiorespiratory fitness was assessed at the baseline examination with a maximal exercise treadmill test using the Balke protocol (7). The treadmill speed was 88 $m \cdot min^{-1}$ for the first 25 min. During this time the grade was 0% for the first minute, 2% the second minute, and increased 1% each minute until 25 min had elapsed. After 25 min, the grade remained constant while the speed increased 5.4 $m \cdot min^{-1}$ each minute until test termination (10). The outcome of interest was total treadmill time in minutes. The duration of the maximal exercise treadmill test is highly correlated with measured maximal oxygen uptake in men ($r = 0.92$), an accepted measure of cardiorespiratory fitness (43). Fitness levels were created by categorizing total treadmill time in minutes by quartiles.

Prostate Cancer Measurement

Questionnaires were mailed to the men in 1982 and 1990 for the purposes of periodic health status updates and monitoring. A series of case finding questions were included on each questionnaire. Cases of incident prostate cancer were ascertained by asking each individual whether he had ever been diagnosed with prostate cancer. If the answer was affirmative, the year of diagnosis was also obtained. Fatal cases of prostate cancer were ascertained by mortality surveillance using Social Security Administration files, Departments of Motor Vehicles, nationwide credit bureau network, National Death Index, and local area telephone directories. Further details of this mortality surveillance have been described elsewhere (10,13). Vital status through 1989 is 93% complete. However, only six prostate cancer cases were fatal due to the limited duration of follow-up. Therefore, all analyses included only the incident prostate cancer cases. All participants with existing prostate cancer at their first visit were eliminated. The remaining participants were followed from their baseline examination to the outcome of interest, newly diagnosed prostatic cancer, death from other causes, loss to follow-up due to administrative difficulties or operational limitations, or until the end of the study period. Vigorous attempts to reach all participants could not be implemented before the undertaking of the present analysis; therefore, we did not have the ability to separate true nonresponders from those who never received the mail survey and thus did not have the opportunity to respond. Information was obtained on cancer occurrence from 47% ($N = 12,975$) of the participants.

Physical Activity Measurement

Physical activity was assessed in a subsample of the total Cooper Clinic population ($N = 28,072$) at baseline and in the 1982 mail survey by inquiring about participation in various sports and activities. The subsample available for analysis consisted of men who provided information on physical activity, prostate cancer, age, body mass index, and smoking status ($N = 7570$). A self-administered questionnaire, which included a checklist of aerobic activities (Appendix) was provided to the subject during the baseline examination and in the 1982 mail survey. Each person was asked "For the last 3 months which of the following activities have you performed regularly?" Individuals provided information about participation, frequency per week, the intensity level, and duration per workout for the sports and activities on the checklist. This information was then used to create a physical activity index to estimate the total energy in kilocalories (kcal) expended in sport or activity each week, by multiplying the MET score (3,5) by the duration of the workout, body weight in kilograms, and frequency per week engaged in the sport or activity. Total weekly energy expenditure was calculated by summing $kcal \cdot wk^{-1}$ expended for each sport or activity. Physical activity levels were created by categorizing total weekly energy expenditure as follows: <1000, 1000–<2000, 2000–<3000, and ≥3000 $kcal \cdot wk^{-1}$. The cutpoints were defined *a priori* based upon published work (33).

ata Analysis

Descriptive analyses were performed to characterize e study population. Subsequently, the association be-een cardiorespiratory fitness and incident prostate can-r was assessed using proportional hazards regression 8,19). This technique allows estimation of the inci-nce rate ratio while controlling for available potential nfounding variables. Baseline values of age, body mass dex, and smoking status were potential confounding ariables adjusted in the multivariate analyses. The Sta-stical Analysis System (SAS) was used for all analyses 46).

The duration of the maximal exercise treadmill test in inutes was used to define quartiles of baseline cardio-espiratory fitness, <13.7, 13.7-<17.0, 17.0-<21.0, and ≥21.0 min on treadmill test. These categories were en-ered into the multivariate model as indicator variables, with the lowest level representing the referent category. Person-time was assigned to the appropriate fitness cat-gories according to the baseline fitness level.

We also evaluated physical activity as a risk factor for ncident prostate cancer, although information on physi-al activity was available for only a subsample of the tudy cohort, men who provided fitness and prostate ancer information. The two physical activity measures assessed at baseline and 1982 survey) were used to reate an average physical activity variable with four levels of energy expenditure (N = 12,098). If an indi-vidual only provided one measure of physical activity at the initial visit or in the 1982 survey, then the single measure was used as the average measure. For those participants whose single 1982 physical activity measure was used as the average measure, we eliminated them if there was any prior evidence of prostate cancer. Fol-low-up information on prostate cancer was available for 63% (N = 7,570) of the participants who had at least one measure of physical activity.

To assess confounding, we included each potential confounder in the model and compared its effect on the incidence rate ratio with that of the model without the potential confounder. The final model was selected based on the change in the estimate of effect produced by including the potential confounder in the model and the *a priori* biological importance of the potential con-founder (45). A 10% change was the minimum criterion deemed necessary for confounding variable inclusion. The potential confounders were categorized and entered into the model as indicator variables. We examined age categorized in groups: 60–64, 65–69, and 70–80 yr old. Because prostate cancer rarely occurs in younger men, the age group composed of 20- to 59-yr-olds was the referent category. The effect of age was also examined by stratifying young (<60 yr old) versus old (≥60 yr old) and assessing the association between fitness and cancer. Body mass index was dichotomized at the median, and we compared those above the median to those below the median. To control for smoking status, we classified participants as current, past, or never smokers based upon responses to questions asked at the baseline examination. The category composed of never smokers was the referent group.

Follow-up studies of clinical diseases with potentially long latency periods must account for the frequently uncertain temporality between the exposure and the outcome of interest. Latent or subclinical disease could be responsible for a level of the hypothesized exposure. To address the concern of bias that could be due to latent disease, we analyzed the data with 1, 3, and 5 yr of person-time follow-up removed after the time of the initial questionnaire.

The results of all the regression analyses are presented in the form of mutually adjusted incidence rate ratios and 95% confidence intervals.

RESULTS

Demographic and anthropometric data of the study population (N = 12,975) by fitness level are detailed in Table 1. Age, weight, and body mass index were lower in men with higher levels of fitness. Men with higher levels of fitness were more likely to have never smoked compared with those men with a low level of fitness, who were more likely to be current smokers.

There were 14,849 participants lost to follow-up from the initial cohort of 28,072. We examined loss to follow-up by levels of fitness and found virtually no difference between the groups. Subjects lost to follow-up had similar baseline characteristics compared with subjects with follow-up information (Table 2). Of the subjects successfully followed, 24% included in the analysis for fitness were followed for the entire study period and there were 4,719 (36%) followed from baseline through 1982.

Because the results comparing the estimates among analyses with 1, 3, or 5 yr of person-time removed were similar, we excluded only 1 yr of person-time from the final analyses to maximize the amount of person-time available. Exclusion of first year cases is done to avoid confusion by subtle changes of exposure variables in response to incipient disease (33). In addition to the baseline exclusions, subjects with less than 1 yr of follow-up were excluded from the analyses (N = 248).

The data in Table 3 show results on cardiorespiratory fitness. Higher cardiorespiratory fitness levels were inversely associated with the probability of development of prostate cancer. Relative to the least fit group, crude incidence rate ratios changed from 0.76 to 0.52 to 0.18 across levels of fitness (P for trend = 0.0001). The adjusted point estimates changed from about 1 in the first two categories to 0.73 and 0.26 in the categories of the more fit individuals (P for trend = 0.0036). When the data were stratified by young (<60 yr old) versus old

TABLE 1. Characteristics of study participants by cardiorespiratory fitness level* at baseline examination; Aerobics Center Longitudinal Study, 1971–1989.

Fitness Level	<13.7 (*N* = 3026)	13.7–<17.0 (*N* = 2828)	17.0–<21.0 (*N* = 3546)	≥21.0 (*N* = 3575)
Age (mean ± SD) (yr)	50.0 (10.0) (*N* = 3015)	44.9 (9.4) (*N* = 2815)	42.5 (8.9) (*N* = 3525)	40.2 (8.6) (*N* = 3516)
Weight (mean ± SD) (kg)	87.0 (14.1) (*N* = 2991)	84.0 (11.1) (*N* = 2821)	81.4 (10.3) (*N* = 3540)	77.5 (9.0) (*N* = 3556)
Height (mean ± SD) (m)	1.77 (0.06) (*N* = 3024)	1.78 (0.06) (*N* = 2828)	1.79 (0.06) (*N* = 3541)	1.79 (0.06) (*N* = 3571)
Body Mass Index† (mean ± SD)	27.6 (3.9) (*N* = 2990)	26.3 (2.9) (*N* = 2821)	25.3 (2.6) (*N* = 3536)	24.1 (2.3) (*N* = 3555)
Energy expenditure per week (mean ± SD) (kcal)	1476.5 (1287.3) (*N* = 1090)	1611.0 (1305.9) (*N* = 1311)	1793.9 (1390.0) (*N* = 2228)	2542.4 (1716.0) (*N* = 2945)
Smoking status				
% current	39.0	34.1	25.8	14.7
% past	58.2	58.7	66.1	70.4
% never	2.8	7.2	8.0	14.9

* Fitness level expressed in treadmill time (min).
† Quetelet Index = wt(kg) · ht^{-2}(m).
Within each category of fitness the total number of subjects for each variable may not equal the total for the category due to missing data.

TABLE 2. Characteristics of study participants by lost to follow-up status*; Aerobics Center Longitudinal Study, 1971–1989.

	Successfully Followed (*N* = 13,223)	Lost to Follow-up (*N* = 14,849)
Age (mean ± SD) (yr)	44.2 (9.9) (*N* = 13,118)	42.1 (9.8) (*N* = 14,628)
Weight (mean ± SD) (kg)	82.2 (11.7) (*N* = 13,156)	84.3 (12.8) (*N* = 14,707)
Height (mean ± SD) (m)	1.79 (0.06) (*N* = 13,212)	1.79 (0.07) (*N* = 14,822)
Body Mass Index* (mean ± SD)	25.7 (3.2) (*N* = 13,150)	26.4 (3.6) (*N* = 14,702)
Treadmill time (mean ± SD) (min)	17.6 (5.2) (*N* = 13,223)	17.1 (5.5) (*N* = 14,849)
Energy expenditure per week (mean ± SD) (kcal)	2007.2 (1561.7) (*N* = 7746)	1670.7 (1356.6) (*N* = 4528)
Smoking status		
% current	16.9	22.2
% past	38.0	34.8
% never	5.6	5.5

* Quetelet Index = wt(kg)/height^2 (m).
The total number of subjects for each variable may not equal the total lost to follow-up due to missing data.

(≥60 yr old), the protective effect of fitness on prostate cancer was limited to the younger group. The adjusted estimates ranged from 0.75 to 0.11 for increasing levels of fitness in the group <60 yr of age. These results should be interpreted with caution due to the small number of cases in the older group, $N = 33$. There were no significant interactions for body mass index or smoking status.

Incidence rate ratios for prostate cancer and activity level in the subcohort with information on physical activity and prostate cancer are presented in Table 4. Crude and adjusted estimates show an inverse association between physical activity and prostate cancer, comparing increased levels of physical activity to the referent. The data do not support a linear trend; however, the results are based on a small number of cases that may lead to imprecise estimates. The results in Table 4 were not altered when the cutpoints for the physical activity levels were changed to <1000, 1000–<2500, 2500–<3000, and ≥3000 kcal·wk^{-1}.

The validity of the physical activity measure and the consistency of fitness and activity levels over time were assessed by comparing total weekly energy expenditure in sports or activities to the results of the maximal treadmill exercise test. Participants who have high levels of total energy expenditure are expected to have better fitness. A significant correlation between self-reported physical activity levels and maximal exercise treadmill time was observed. The correlation coefficient was r = 0.41 for baseline physical activity level and maximal exercise treadmill time and for the correlation between 1982 activity level and treadmill time, r = 0.32. The correlation between baseline physical activity and 1982 physical activity levels was r = 0.35. In other analyses we found that the incidence of prostate cancer was similar in individuals who did not provide physical activity information as in those who did. We also established that the basic assumption of the proportional hazards model (e.g., hazards are proportional over time) was appropriate for our data.

DISCUSSION

These results provide support for the hypothesis that cardiorespiratory fitness is inversely associated with risk of incident prostate cancer. The upper two quartiles of fitness levels were associated with reduced risks of prostate cancer compared with the lowest quartile of fitness. An age interaction was evident with the protective effect limited to the young age group. Energy expenditure ≥1000 kcal·wk^{-1}, was consistently associated with reduced risks of prostate cancer compared with energy expenditure levels less than 1000 kcal·wk^{-1}. Adjustment for available potential confounders did not substantially alter this association. The point estimates for the 2000 <3000 kcal·wk^{-1} category were higher than the adjusted estimates for the other activity categories. This is likely due to chance because of the small number of cases

3. Estimates of the association between fitness level* at baseline and prostate cancer; Aerobics Center Longitudinal Study, 1971–1989.

Fitness Level	<13.7 (*N* = 3026)	13.7–<17.0 (*N* = 2828)	17.0–<21.0 (*N* = 3546)	≥21.0 (*N* = 3575)	
of cases	40	27	21	6	
son-years of follow-up	30,160	26,738	31,144	26,260	
de incidence rate ratio (95% CI)	1.00†	0.76 (0.46–1.23)	0.52 (0.30–0.87)	0.18 (0.08–0.43)	*P* trend = 0.0001
isted incidence rate ratio‡ (95% CI)	1.00†	1.1 (0.63–1.77)	0.73 (0.41–1.29)	0.26 (0.10–0.63)	*P* trend = 0.0036

s level expressed in treadmill time (min).
ent category.
ted for age, body mass index, and smoking status.
onfidence interval.

4. Estimates of the association between activity level* and prostate cancer, physical activity measured as an average of the baseline and 1982 measures; Aerobics Center dinal Study, 1971–1989.

Activity Level	<1000 (*N* = 2070)	1000–<2000 (*N* = 2600)	2000–<3000 (*N* = 1407)	≥3000 (*N* = 1493)	
. of cases	21	10	8	5	
rson-years of follow-up	17,367	22,364	12,418	13,295	
ide incidence rate ratio (95% CI)	1.00†	0.36 (0.17–0.76)	0.52 (0.23–1.16)	0.29 (0.11–0.76)	*P* trend = 0.7946
justed incidence rate ratio‡ (95% CI)	1.00‡	0.37 (0.17–0.79)	0.62 (0.27–1.41)	0.37 (0.14–0.98)	*P* trend = 0.8263

ty level expressed in energy (kcal) expenditure per week.
ent category.
sted for age, body mass index, and smoking status.
onfidence interval.

his is the first study reporting on fitness level and risk rostate cancer. Fitness is clearly correlated with ha- al physical activity and represents a characteristic that be relevant to the occurrence of chronic disease, pared with short-term physical activity that may vary nding on transient motivation and opportunity or curate reporting. These data on fitness concern the lity of the population enrolled in the study, and al- gh 53% of the subjects eventually did not provide rmation on prostate cancer outcome, there was no lence in these data to suggest that nonresponse was *ly* associated with fitness and prostate cancer (a condition for bias). This is further supported by the ilarity of the proportion of subjects with prostate cer information in those who have only fitness data l in those with both fitness and physical activity data l by the similar incidence of prostate cancer among se with and those without physical activity informa- n. Furthermore, the data on physical activity are es- ntially compatible with the fitness results and they pear to be in agreement with the weight of the existing idence.

Observational studies of this nature have the potential r bias. The maximal exercise treadmill test, used to ess fitness, is an accepted and validated measure of diorespiratory fitness (43). Any misclassification of is exposure would be random since prostate cancer tcome was not known at the time of treadmill testing. ur results are not subject to recall bias because of the spective nature of the study.

Cases of prostate cancer were identified using self- ported data. No validation of self-reported prostate ncer has been accomplished; however, self-report of other diseases such as myocardial infarction, stroke, and hypertension were validated in this population (13). Self-reported hypertension had a sensitivity of 98% and a specificity of 99% in a study conducted in this population by Blair et al. (13). In a study conducted by Giovannucci et al. (23), in a different population, self-reported prostate cancer was validated by review of medical and pathology records and a diagnosis of adenocarcinoma was confirmed in 99.4% of the men.

There is potential for bias in this study if there was differential diagnosis of prostate cancer between fitness levels. However, subjects who are fit are *more* health conscious. There is a body of literature indicating that physically active subjects are more likely to have contact with physicians and the health care system than subjects who are not physically active (8,9,32,35,48). This difference would create an increased likelihood of diagnosis of prostate cancer in those men with increased levels of fitness and thus would reduce the strength of an inverse association between fitness and prostate cancer. Therefore, if diagnostic bias occurred in this study, the observed estimates are likely to be an underestimate of the true strength of the association between fitness and prostate cancer. It would be important to have information on the stage of diagnosis of the tumor to predict what implications fitness may have on the future progression of the tumor, but such data are not available.

Loss to follow-up was defined as a nonresponse to both the 1982 and 1990 questionnaires. Loss to follow-up could have generated biased results only if nonresponse was correlated with both fitness level and prostate cancer. However, a substantial amount of bias would need to exist to explain the strong inverse associations observed

in these data. We examined loss to follow-up by levels of fitness and found virtually no difference between the groups. Subjects lost to follow-up had similar baseline characteristics compared with subjects with follow-up information. We believe the high percentage of loss to follow-up was due in part to the mobility of the population, and our inability to maintain current addresses on some of the men. Thus, many nonresponders did not have the opportunity to answer the mail survey because they did not receive it.

We were unable to control for the potential confounding effects of diet in our analyses. A positive association between fat intake and prostate cancer has been observed in some case-control and cohort studies (39,41). For diet to be confounding the observed association between fitness and prostate cancer, active men would have to consume a diet composed of less fat. There are no data available on the association between diet and fitness levels, and no association has been observed between physical activity level and dietary composition (9,12,15, 36). The results of Lee et al. (33) showed increased caloric intake in highly active men compared with those who were less active, but the proportion of calories from fat consumed was the same across inactive, moderately active, and highly active groups.

Also, we were unable to control for some other potential risk factors: venereal disease, sexual habits, and occupational exposures. The results of previous studies examining these factors have been inconsistent (21,39, 53). It is unlikely that one or more of these factors is strongly associated with both fitness and prostate cancer incidence, and could cause substantial confounding.

Varying amounts of person-time after completion of the baseline questionnaire were eliminated to assess the effect of latent disease, which may have affected fitness levels in diseased individuals. If participants with existing disease had altered fitness results, then the association between fitness and prostate cancer could be spurious. Eliminating 1, 3, or 5 yr of person-time follow-up, however, did not substantially alter the results.

The mechanism behind the protective effect of fitness on prostate cancer may be related to the sex hormone testosterone. The prostate is a secondary sex gland that is affected by hormonal stimulation. The growth and development of the organ relies on the presence of sex hormones. Testosterone was singled out as a possible cause of prostate cancer as early as 1941 when androgen deprivation was used as therapy in advanced prostatic cancer (30). Currently, metastatic prostate cancer is treated with antitestosterone therapy or adrenal androgen blockage (24). Animal studies have shown that prostate cancer can be induced in rats by the administration of exogenous testosterone (16,29,38). In studies involving humans, prostate cancer cases appear to have higher levels of endogenous testosterone compared with nondiseased men (2,22,31). This evidence seems to implicate thermore, athletes have been shown to have lower levels of testosterone, and individuals who exercise may have a temporary decrease in post-exercise levels of testosterone (1,20,26,27,37,49,51). If fit individuals have lower levels of endogenous testosterone and lower levels of testosterone are associated with decreased incidence of prostate cancer, it should be expected that men who are more physically fit or active would be at a lower risk of developing prostate cancer compared with men who are inactive.

It should be noted highly trained athletes have been observed to have lower basal circulating testosterone, whereas men who exercise experience a more acute and temporary drop in testosterone levels. It would seem that a continued decrease of testosterone levels would be more important in influencing a decreased prostate cancer risk compared with a transient change due to an exercise session. We observed a protective effect on prostate cancer across all levels of increased fitness and physical activity.

There are no previously reported data concerning cardiorespiratory fitness and prostate cancer. Epidemiological studies on the association between prostate cancer and physical activity are not entirely consistent. Increased exercise in the form of occupational activity, recreational exercise, or household work has been observed to be protective for prostate cancer in six studies (4,17,33,47,50,52). Conversely, three studies have shown an increased risk of prostate cancer with increasing levels of physical activity (34,40,42). In two of the studies, participation in college athletics was the exposure of interest (40,42). In the third study, an inverse association was found between risk of prostate cancer and the proportion of life spent in occupations involving only sedentary or light work (34). It may be that college athletic participation is too remote in time to be etiologically relevant for prostate cancer or may not be related to lifetime fitness and that the proportion of time spent in sedentary occupation is a poor indicator of overall fitness.

These results suggest that moderate to high levels of cardiorespiratory fitness may protect against the incidence of prostate cancer. This study supports the physical activity-prostate cancer hypothesis and provides evidence that cardiorespiratory fitness may be a better predictor of prostate cancer risk than physical activity.

Appreciation is expressed to Ms. Beth Barlow, M.S., for her continued assistance with data preparation and Ms. Marianne Uhickas, M.P.H., for her invaluable comments and guidance during manuscript preparation. We acknowledge the Cooper Clinic physicians for assistance with data collection and especially thank the participants of the study for their ongoing participation.

This research was supported in part by U.S. Public Health Service research grant AG06945 from the National Institute on Aging, Bethesda, MD.

Address for correspondence: Susan A. Oliveria, Sc.D., M.P.H.,