

## Relation of Physical Activity to Risk of Testicular Cancer

Anil Srivastava<sup>1</sup> and Nancy Kreiger<sup>1,2</sup>

In North America and most Western European countries, testicular cancer is often cited as the most common cancer among young and middle-aged men, and yet few studies have examined the relation between modifiable factors and testicular cancer risk. Data collected between 1995 and 1996 in Ontario, Canada, as part of the Enhanced Cancer Surveillance Study were used to examine the relation between the frequency of recreational, and intensity of occupational, physical activity at various life periods, including cumulative and averaged lifetime activity and risk of testicular cancer. Analysis of 212 cases and 251 controls revealed that relatively high frequency of participation in moderate and strenuous recreational activity in the midteens may have an adverse effect on risk of testicular cancer (odds ratio = 2.36, 95% confidence interval: 1.20, 4.64 for moderate activity of greater than five times a week compared with three times or less a month and odds ratio = 2.58, 95% confidence interval: 1.14, 5.85 for strenuous activity of greater than five times a week compared with less than once a month). Moderate or strenuous occupational demands in one's 20s also increased risk of disease. *Am J Epidemiol* 2000;151:78–87.

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Testicular cancer is a rare disease; yet in North America and Western Europe, it is often cited as the most commonly occurring cancer among young and middle-aged men (1). Importantly, the incidence of testicular cancer has increased strikingly in many countries over the past couple of decades (1). Although a couple of medical risk factors for testicular cancer have been established, including inguinal hernia and cryptorchidism, the relation between lifestyle and testicular cancer risk is unclear. In particular, although a protective effect of physical activity has been demonstrated with a number of cancers, including those of the colon (2) and breast (3), the effect of physical activity on testicular cancer risk is not well known. Physical activity may exert a protective effect, among other possible mechanisms, through heightened immunity or modulation of hormonal levels; moderate exercise, for example, may result in an increase in number and/or activity of macrophages, natural killer cells, and other components of the immune system (4). Certainly,

the establishment of a modifiable risk factor such as physical activity is of great public health importance.

To date, few studies (5–10) have addressed the relation between physical activity and testicular cancer risk. While the results have been promising, thus far no study has assessed the separate and combined contributions of frequency and intensity of recreational activity and their association with testicular cancer risk. It is also important to establish the relevant period of exposure during which physical activity might influence cancer risk and to determine whether exposure over a lifetime is the relevant consideration. Finally, very few studies of physical activity and cancer, and none of testicular cancer, have accounted for any aspect of diet; failure to adjust for diet may result in spurious protective associations with physical activity.

### MATERIALS AND METHODS

Data were obtained from the Enhanced Cancer Surveillance Study, a Canadian case-control study of multiple cancer sites. Although the study was designed primarily to explore the relation between environmental factors and risk of cancer, information on lifestyle, including diet and physical activity, was also collected. Data were collected in all but two Canadian provinces, although only data from Ontario were used in this study because the physical activity questionnaire is distinct from that used in other provinces.

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Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; IGF-I, insulin-like growth factor 1.

<sup>1</sup> Department of Public Health Sciences, University of Toronto, Toronto, Ontario, Canada.

<sup>2</sup> Division of Preventive Oncology, Research Unit, Cancer Care Ontario, Toronto, Ontario, Canada.

Reprint requests to Dr. Nancy Kreiger, Division of Preventive Oncology, Cancer Care Ontario, 620 University Avenue, Toronto, Ontario M5G 2L7, Canada.

Cases were selected from a review of pathology reports received by the Ontario Cancer Registry; those with a new germ cell testicular cancer (*International Classification of Diseases*, Ninth Revision, code 186 (11) and *International Classification of Diseases for Oncology-M* code 906-9 (12)) diagnosed between January 1, 1995, and December 31, 1996, were included in the study. A self-administered, mailed questionnaire was sent to all eligible subjects between ages 20 and 74 years. Efforts, including telephone follow-up, were made to maximize both ascertainment and response. In total, 76 percent of the questionnaires were returned, a response rate that represented a total of 212 cases.

Controls were randomly sampled from the Ontario Ministry of Finance Property Assessment database within age and sex strata; 904 male controls (approximately 64 percent of those sampled) returned the mailed questionnaire. Because controls were selected for a number of cancer sites, the age distribution was highly skewed to older ages relative to testicular cancer cases; it was therefore necessary to further frequency match within appropriate age strata in an approximate 1:1 ratio to cases, yielding a total of 251 male controls.

### Assessment of physical activity (appendix 1)

Questions on recreational physical activity asked subjects to identify the frequency of exercise at "moderate" and "strenuous" levels in different life periods (teens, early 30s, early 50s, and at the reference age of 2 years previously). Moderate and strenuous levels were not explicitly defined, but examples of activities, such as "gardening" or "brisk walking" for moderate activity, were provided; for strenuous activity, a minimum period of 20 minutes was specified. The five closed frequency categories ranged from "less than once per month" to "more than five times per week." Intensity of occupational activity was also assessed by asking subjects to identify the type of activity (from "sitting" to "strenuous physical activity") that was most representative of job duties, again by life period (early 20s, early 30s, and at the reference age of 2 years previously). Examples of activities or jobs were provided for each of the four categories. Because of insufficient numbers, neither recreational nor occupational activity for "in your early 50s" was analyzed independently.

Within the appropriate life period, two indices were created for frequency of both moderate and strenuous activity combined. In the first index, equivalency of moderate and strenuous activity was assumed; original categorical designations were thus standardized to times per week by using the mean value of the range (e.g., "1-3 times per month" = 2 times per month =

0.5 time per week) and summed across moderate and strenuous categories within a given life period. This total was categorized into quartiles based on the distribution among the controls. The second index accounted for intensity of activity as follows: a weighting of 2.0 was applied to frequency (times/week) of strenuous activity, based on tables of metabolic equivalency threshold values published by Ainsworth et al. (13), where 2.0 represents the approximate difference in metabolic equivalency threshold values between strenuous and moderate activity (14). The weighted values of strenuous activity were then added to frequencies (times/week) of moderate activity, as in the unweighted index, again within the life period.

Lifetime recreational physical activity, examined for both moderate and strenuous activity separately and in combination, was assessed by summation of the ordinal category scores across appropriate life periods. Two indices were then examined: averaged lifetime activity and cumulative exposure. For averaged lifetime activity, the initial index score was divided by the number of categories summed; cumulative exposure was calculated without division by categories. The index totals for averaged and cumulative moderate and strenuous activity were then divided into quartiles according to the respective control distributions. Lifetime occupational activity was assessed similarly.

### Assessment of other variables

Diet was assessed using a semiquantitative food questionnaire. Subjects were asked about their dietary habits 2 years previously for representative foods within categories such as fruits and vegetables; closed frequency categories ranged from "never or less than once per month" to "six or more per day," although these were ultimately converted to servings per week. Approximate serving sizes were provided as a reference. For our study, only information on fruits and vegetables was used. Information was obtained on a variety of lifestyle and demographic characteristics. Among these, subjects were asked about their marital status, years of schooling, household income, and smoking habits. Anthropometric measures, namely, weight and height, were also self-reported. Potential confounders included age, fruit and vegetable consumption, body mass index (BMI) (weight (kg)/height (m<sup>2</sup>)), pack-years of smoking, and education. Age, which was adjusted for in all analyses, was categorized into 5-year age groups. Other variables, including fruit and vegetable consumption expressed as servings per week and BMI, were created as quartiles based on their distribution among the controls. Pack-years of smoking (in which 1 pack-year was taken to be 7,305 cigarettes, or 20 cigarettes in a package) for both ciga-

rette and pipe smokers (in which one pipe was deemed equivalent to five cigarettes (15)) was formed into quartiles after excluding nonsmokers; pack-years were adjusted for years since quitting, modeled as a continuous variable. Degree of social support was gauged by assessing marital status: Subjects were dichotomized into married (including, "common-law," "other") and not married ("single," "divorced," "widowed," "separated"). Because of a large number of missing values for income and because of the young age of our subjects, years of education was used as an indicator of socioeconomic status.

### Statistical analysis

Unconditional logistic regression, adjusted only for age (and in the case of pack-years, years since quitting), was performed for all variables defined above. Log odds were cursorily examined for possible parametric patterns to determine the appropriate scale of the variable in multivariate modeling. On this basis, BMI was modeled as a categorical variable with the assumption of different slopes. Pack-years of smoking, education, and age were modeled as categorical variables with the assumption of a common slope. Fruit and vegetable consumption was modeled continuously.

Combined frequency of strenuous and moderate recreational physical activity at "2 years ago," unweighted, was used for all models to assess potential confounding, as judged by a change of 10 percent in any one of the primary exposure odds ratios, from the fully adjusted model to that without the potential confounder.

Results based on this primary model were then generalized to others. BMI and age were tested as possible multiplicative interaction terms in the primary model and in other models, as deemed appropriate. An interaction term between occupational and recreational activity was also included when appropriate. A global test for interactions was performed, such that in the case of models with multiple interaction terms, each individual term was successively tested only if the log-likelihood difference between the models with and those without the terms was significant (16).

### RESULTS

The frequency distribution of cases and controls for age and other characteristics is presented in table 1. Cases appeared to be more educated and more likely to smoke than were controls. Education and smoking (pack-years, adjusted for years since quitting) were significantly and positively associated with disease risk in a multivariate model (data not shown). Results of the confounding analysis revealed that no variable,

**TABLE 1. Frequency distribution of cases and controls by age and other characteristics, Ontario, Canada, 1995–1996**

Variable	Cases		Controls	
	No.	%	No.	%
Age group (years)				
20–24	23	10.8	26	10.3
25–29	28	13.2	38	15.1
30–34	47	22.2	46	18.3
35–39	45	21.2	45	17.9
40–44	29	13.6	41	16.3
45–49	19	9.0	26	10.4
50–54	9	4.2	11	4.4
≥55	12	5.7	18	7.2
BMI*,†				
<22.7	44	20.8	63	25.3
22.7–24.9	50	23.6	66	26.5
25.0–27.5	63	29.7	61	24.5
≥27.6	55	25.9	59	23.7
Marital status				
Not married	142	67.0	171	68.0
Married	70	33.0	80	32.0
Education				
Grade 11 or less	38	18.1	51	20.7
More than grade 11, no postsecondary	39	18.6	52	21.1
More than grade 11, some postsecondary	133	63.3	143	58.1
Smoking‡ (pack-years)				
0 (nonsmoker)	77	36.7	114	45.6
0.1–5.0	34	16.2	34	13.7
5.1–12.0	33	15.7	35	14.1
12.1–24.0	34	16.2	32	12.9
≥24.1	32	15.2	33	13.3
Vegetable consumption†,‡ (servings/week)				
<11	54	28.4	59	24.9
11–14.9	52	27.4	58	24.5
15–21.4	47	24.7	58	24.7
≥21.5	37	19.5	62	26.2
Fruit consumption†,§ (servings/week)				
<3.5	58	28.4	61	25.4
3.5–6.9	47	23.0	61	25.4
7–12.9	58	28.4	59	24.6
≥13	41	29.1	59	24.6

\* BMI, body mass index.

† Quartiles based on the control distribution; for pack-years, quartiles formed after excluding nonsmokers.

‡ Tomatoes, carrots, broccoli, cabbage, cauliflower, Brussels sprouts; spinach or other greens; yellow (winter) squash; any other vegetable, including green beans, corn, and peas; and soups with vegetables.

§ Apples or pears; oranges; bananas; cantaloupe; and other fresh or canned fruit.

including diet, was influential; because of the large number of missing values, dietary information was

ultimately dropped from the overall model. All other variables were retained.

Results of modeling for moderate physical activity, classified by life period, are presented in table 2. In comparison with the referent category, relatively high frequency of moderate activity in the teens appeared to be harmful; activity greater than five times a week was observed to have a statistically significant adverse effect (odds ratio (OR) = 2.36, 95 percent confidence interval (CI): 1.20, 4.64). No other life period, including either index of lifetime activity, showed a similarly noteworthy association. No statistically significant interactions were observed for BMI, age, or occupational activity.

Results similar to those seen for moderate activity were observed for strenuous recreational physical activity (table 3), namely, both of the upper two cate-

gories of frequency of activity in the teens exhibited an adverse association with testicular cancer risk relative to the referent category. The magnitude of the effect was somewhat larger than that observed for moderate activity. Again, no other life period, including lifetime activity, exhibited an association with risk.

Combining moderate and strenuous activity resulted in associations similar to those in the separate models (data not shown): Frequent exercise in one's teens resulted in an increased risk of testicular cancer in both unweighted (for the upper two quartiles, OR = 1.66, 95 percent CI: 0.94–3.03 and 0.91–3.01 relative to the referent) and weighted models (upper two quartiles, OR = 1.74, 95 percent CI: 0.97–3.12 and OR = 1.77, 95 percent CI: 0.98–3.21 relative to the referent), although the magnitude of the observed associations was smaller than that for either moderate or strenuous

**TABLE 2. Frequency distribution\* of cases and controls, multivariate adjusted odds ratio estimates and 95% confidence intervals for recent, past, and lifetime† frequency of moderate physical activity, Ontario, Canada, 1995–1996**

Life period	No. of cases	%	No. of controls	%	OR‡,§	95% CI‡
<b>2 years previous</b>						
Less than once/month	18	9.5	23	11.0	1.00	
1–3 times/month	30	15.8	30	14.4	1.68	0.70, 4.04
1–2 times/week	48	25.3	62	29.7	1.06	0.48, 2.34
3–5 times/week	51	26.9	52	24.9	1.42	0.64, 3.17
More than 5 times/week	43	22.6	42	20.1	1.41	0.61, 3.29
<b>Teens</b>						
3 or fewer times/month	18	8.6	35	14.6	1.00	
1–2 times/week	31	14.9	53	22.2	1.15	0.54, 2.44
3–5 times/week	65	31.3	72	30.1	1.77	0.88, 3.53
More than 5 times/week	94	45.2	79	33.1	2.36	1.20, 4.64
<b>Early 30's</b>						
Less than once/month	13	8.4	20	11.2	1.00	
1–3 times/month	23	14.9	30	16.8	1.13	0.44, 2.89
1–2 times/week	41	26.6	50	27.9	1.22	0.51, 2.91
3–5 times/week	41	26.6	50	27.9	1.34	0.56, 3.22
More than 5 times/week	36	23.4	29	16.2	1.74	0.68, 4.42
<b>Cumulative lifetime</b>						
1	51	26.7	49	23.1	1.00	
2	60	31.4	69	32.5	0.79	0.53, 1.74
3	50	26.2	47	22.2	1.16	0.60, 2.27
4	30	15.7	47	22.2	0.97	0.38, 1.74
<b>Averaged lifetime</b>						
1	53	29.8	55	28.8	1.00	
2	50	28.1	45	23.6	1.03	0.53, 1.98
3	44	24.7	51	26.7	1.36	0.71, 2.60
4	31	17.4	40	20.9	1.08	0.56, 2.06

\* Numbers are for regression models with missing values on covariates deleted.

† Approximate quartiles; includes exercise in early 50s, when applicable.

‡ OR, odds ratio; CI, confidence interval.

§ Odds ratios adjusted for age, body mass index, education, smoking (pack-years, years since quitting), and marital status; odds ratios for 2 years previous, early 30s, and lifetime activity were also adjusted for occupational activity.

**TABLE 3.** Frequency distribution\* of cases and controls, multivariate adjusted odds ratio estimates, and 95% confidence intervals for recent, past, and lifetime† frequency of strenuous physical activity, Ontario, Canada, 1995–1996

Life period	Cases		Controls		OR‡,§	95% CI‡
	No.	%	No.	%		
2 years previous						
Less than once/month	41	22.2	57	27.4	1.00	
1–3 times/month	40	21.6	35	16.8	1.50	0.77, 2.90
1–2 times/week	46	24.9	50	24.0	1.19	0.64, 2.23
3–5 times/week	37	20.0	43	20.7	1.09	0.57, 2.09
More than 5 times/week	21	11.35	23	11.1	1.18	0.52, 2.65
Teens						
Less than once/month	11	5.4	26	10.7	1.00	
1–3 times/month	12	5.9	17	7.0	1.94	0.66, 5.74
1–2 times/week	30	14.7	36	14.8	2.04	0.83, 5.04
3–5 times/week	69	33.8	83	34.2	2.07	0.91, 4.72
More than 5 times/week	82	40.2	81	33.3	2.58	1.14, 5.85
Early 30s						
Less than once/month	29	19.3	43	24.0	1.00	
1–3 times/month	34	22.7	35	19.6	1.37	0.67, 2.79
1–2 times/week	42	28.0	49	27.4	1.20	0.60, 2.37
3–5 times/week	28	18.7	33	18.4	1.21	0.58, 2.53
More than 5 times/week	17	11.3	19	10.6	1.27	0.52, 3.10
Cumulative lifetime						
1	54	32.0	52	27.2	1.00	
2	43	25.4	52	27.2	0.92	0.49, 1.71
3	37	21.9	49	25.7	0.93	0.48, 1.83
4	35	20.7	38	19.9	1.21	0.58, 2.53
Averaged lifetime						
1	55	32.2	52	27.2	1.00	
2	36	21.1	39	20.4	0.87	0.45, 1.67
3	50	29.2	64	33.5	0.89	0.44, 1.83
4	30	17.5	36	18.8	0.98	0.50, 1.94

\* Numbers are for regression models with missing values on covariates deleted.

† Approximate quartiles; includes exercise in the early 50s, when applicable.

‡ OR, odds ratio; CI, confidence interval.

§ Odds ratios adjusted for age, body mass index, education, smoking (pack-years, years since quitting), and marital status; odds ratios for 2 years previous, early 30s, and lifetime activity were also adjusted for occupational activity.

activity separately. Overall, little difference was seen between weighted and unweighted analyses. No interaction terms were found to be statistically significant.

Table 4 illustrates, by life period, the results of modeling occupational intensity. Those who worked in their early 20s in occupations that required a moderate or strenuous level of activity had approximately a 70–85 percent increased risk of testicular cancer (strenuous, OR = 1.67, 95 percent CI: 0.92–3.00; moderate, OR = 1.85, 95 percent CI: 1.05–3.26) relative to those engaged in occupations with sitting as the primary activity. Neither averaged nor cumulative lifetime occupational intensity exhibited a revealing association with disease risk. No interaction terms were found to be statistically significant.

## DISCUSSION

Our study found evidence that a relatively high frequency of participation in moderate and strenuous recreational activity in one's midteens may have an adverse effect on risk of testicular cancer. Moderate or strenuous occupational demands in one's 20s also increased risk of disease. No protective associations were observed for either recreational or occupational activity in any life period, including lifetime activity. Little difference was seen in the magnitude or significance of the odds ratios between analyses of moderate and strenuous activity separately. Analyses of total recreational activity, in which equivalency of moderate and strenuous activity was assumed, and those in which

**TABLE 4.** Frequency distribution\* of cases and controls, multivariate adjusted odds ratio estimates, and 95% confidence intervals for recent, past, and lifetime† intensity of occupational activity, Ontario, Canada, 1995–1996

Life period	Cases		Controls		OR‡,§	95% CI‡
	No.	%	No.	%		
2 years previous						
Sitting	59	31.7	66	32.2	1.00	
Light	48	25.8	42	20.5	1.32	0.73, 2.37
Moderate	48	25.8	60	29.3	0.98	0.55, 1.75
Strenuous	31	16.7	37	18.1	0.94	0.46, 1.90
Early 20s						
Sitting	39	18.9	59	24.4	1.00	
Light	41	19.9	50	20.7	1.30	0.71, 2.39
Moderate	65	31.6	63	26.0	1.85	1.05, 3.26
Strenuous	61	29.6	70	28.9	1.67	0.92, 3.00
Early 30s						
Sitting	42	28.0	54	29.7	1.00	
Light	29	19.3	38	20.9	0.99	0.51, 1.94
Moderate	49	32.7	49	26.9	1.46	0.77, 2.78
Strenuous	30	20.0	41	22.5	1.30	0.60, 2.78
Cumulative lifetime						
1	41	24.1	46	24.0	1.00	
2	43	25.3	45	23.4	1.10	0.57, 2.14
3	54	31.8	57	29.7	0.97	0.50, 1.89
4	32	18.8	44	22.9	0.75	0.33, 1.67
Averaged lifetime						
1	40	23.7	42	22.5	1.00	
2	37	21.9	39	20.9	0.93	0.51, 1.69
3	43	25.4	50	26.7	1.22	0.63, 2.35
4	49	29.0	56	29.9	1.36	0.68, 2.72

\* Numbers are for regression models with missing values on covariates deleted.

† Approximate quartiles; includes occupational activity in the early 50s, when applicable.

‡ OR, odds ratio; CI, confidence interval.

§ Odds ratios adjusted for age, body mass index, education, smoking (pack-years, years since quitting), and marital status; odds ratios for 2 years previous, early 30s, and lifetime activity were also adjusted for combined moderate and strenuous recreational activity.

weights were based broadly on metabolic equivalency threshold equivalents yielded similar results. It would appear, then, that frequency of activity in adolescence is the relevant measure. The finding of a harmful effect of physical activity is contrary to that of our original hypothesis; the limitation of the adverse association of activity and testicular cancer risk to adolescence, however, and its consistency across various measures of activity support its interpretation as a true effect.

Adolescence has been purported to be influential in subsequent risk of testicular cancer; a secular trend toward earlier age at puberty, for example, has been suggested to be at least partly responsible for the observed increase in testicular cancer incidence, and indeed, earlier age at puberty among cases has been observed by some investigators (17, 18). Recreational physical activity may, however, delay onset of puberty among males (19), although perhaps because the onset

of puberty in males is ill defined, studies are few. It is possible that altered modulation of androgen levels in adolescence is responsible for the observed adverse association between physical activity and testicular cancer risk.

Although the peak incidence of testicular cancer is observed in young men with high levels of androgens and gonadotrophins, the relation between sex hormones and testicular cancer is not well defined. One study (20), for example, noted a statistically insignificant relation between baldness, a possible indicator of high androgen levels, and testicular cancer. Another (21) noted a lower incidence of severe acne at puberty among those with subsequent testicular cancer; acne may be caused by increased levels of testosterone. Rajpert-De Meyts and Skakkebaek (22) observed that 40–45 percent of their patients expressed androgen receptors in neoplastic cells. The role of gonadotrophins, which stimulate the

production of androgens, may also be an important consideration: Subfertile patients have developed germ cell tumors after the administration of gonadotrophins (23). Several proteins participating in the regulation of gonadotrophins are also thought to exert paracrine effects in the testis and may be involved in germ cell differentiation (22).

In males, acute increases in androgens, primarily testosterone, have been demonstrated after exercise (24–28), although moderate activity is rarely investigated; Sutton et al. (25), for example, examined exercise among cyclists and Olympic level rowers and swimmers. One study that investigated aerobic and anaerobic exercise found statistically significant elevated levels of testosterone postexercise in both groups, but no difference between the groups relative to sedentary controls (28). These increases in testosterone are thought to be the result of a decreased metabolic clearance of the hormone and not of an increase in hormone production (25). It is believed that these increases are transient; a return to baseline levels is observed 1–2 hours after exercise (28). It may be that repeated surges in testosterone lead to partial androgen sensitivity; patients with such partial insensitivity have an especially high incidence of carcinoma in situ (29). With respect to gonadotrophins, most studies have found no effect of acute exercise on levels of either luteinizing (25, 27, 28) or follicle-stimulating (27, 28) hormone.

Basal, rather than acute, hormonal levels may be more relevant; among endurance athletes, some studies have found that chronic training has a depressive effect on serum testosterone (30, 31), while others (27, 32), including one by Lucia et al. (32) among professional cyclists, elite triathletes, recreational marathon runners, and sedentary subjects, found no effect of endurance training on androgen levels. Studies that have examined gonadotrophin levels among endurance athletes relative to controls are similarly equivocal, with some observing lower levels or less frequent pulses of luteinizing hormone (24, 27), higher levels of luteinizing hormone (31), or no differences in levels of either luteinizing hormone or follicle-stimulating hormone (30). To our knowledge, no study has directly examined frequency of activity and its effect on hormonal levels, nor has any study compared hormonal profiles of men according to intensity of occupational activity.

Another theory contends that body composition is key: Relatively high muscularity may be positively associated with serum androgens (26). If degree of muscularity is indeed at issue, it is possible that men with higher muscle mass were likely to participate in recreational activity or to engage in more physically demanding occupations, or even that higher muscle mass had resulted as a consequence of these activities.

Prostate cancer risk has also been suggested to be modified by androgen levels (33). The relation between physical activity and prostate cancer is unclear (34), although, interestingly, of the three studies that have examined similar life periods for which we noted effects (6, 35, 36), the two to report significant results (6, 36) noted adverse associations. Paffenbarger et al. (6) found that those who participated in college athletics for at least 5 hours a week were 1.66 times more likely to develop prostate cancer than were those who participated less than 5 hours a week ( $p = 0.028$ ), while another study (36) found that those college athletes who had attained one or more letters in varsity sports had increased mortality from prostate cancer relative to those who had not ( $p < 0.05$ ).

Because adolescence is a period during which reproductive hormonal influences are likely to be most influential, adverse modulation of these hormones seems to be a plausible hypothesis for our findings. Although it is less clear how such processes would be more important in adolescence, other biologic mechanisms may be explored. Physical activity modulates a number of hormones other than reproductive, including insulin-like growth factor I (IGF-I). High levels of IGF-I have been implicated in a number of cancers, including cancer of the prostate (37, 38). Some studies have found that IGF-I increases after acute exercise (39–41), while others have observed decreased levels resulting from chronic exercise (42). Free radical production, which renders the body more vulnerable to cell and tissue damage as a result of oxidation and peroxidation of lipids, proteins, and DNA, increases with exercise (43). Immunosuppression among exercisers has also been demonstrated, although, as with free radical production (44), this is thought to be a concern largely with strenuous activity (45). The observation of a similar effect for moderate and strenuous recreational activity and a stronger association with moderate than strenuous occupational levels would appear not to support these latter hypotheses.

It has been suggested by some that testicular trauma may be responsible for a harmful effect of physical activity, such as that observed by Coldman et al. (5) for cycling and horseback riding. The relation between trauma to the testis sufficient to cause injury and testicular cancer has been investigated by some (5, 9); although it is possible that such injury may result in increased mitotic activity (46), we note that it is more likely that any observed associations can be attributed to recall bias on the part of cases. The UK Testicular Cancer Group (47), for example, noted that proportionally more of the cases than of the controls reported injuries to the testis that were not medically confirmed or that, upon checking other sources, were not actually

to the testis. It is also possible that in some cases the injury may have led to the detection of the tumor. Furthermore, the relation between physical activity and resultant injury to the testis, including the proportion so affected among those exercising, is not known; trauma sufficient to cause only subclinical injury might still affect cancer risk, but such effects are difficult to measure directly.

Whatever the underlying mechanism, if, in fact, participation in even moderate activity contributes to an increase in testicular cancer risk, then our findings may be reconciled with the observed Canadian increase of testicular cancer: Over the period 1981–1988, 26 percent of Canadians changed from being sedentary to being moderately active, and 6 percent decreased from being highly to being moderately active (48). Worldwide, in Canada, Finland, Scotland, and the United States, moderate levels of exercise became more common during the 1980s (49). Although it is likely that occupational demands have decreased over the years, it is also true that in modern industrialized societies, occupational activity typically does not add much to total energy expenditure. Further, one study found that office workers and manual laborers were about equally likely to exercise in their spare time (48). Despite our consistent and plausible findings, a number of limitations must be considered.

Our questionnaire was not validated to any degree. Indeed, although self-reported physical activity assessment is commonly used in large-scale epidemiologic studies, mainly because of its economy and ease of administration, extensive validation of self-reported physical activity questionnaires has not been undertaken, in part because of the difficulty in obtaining acceptable criterion measures. For example, some investigators have attempted to validate their questionnaires through comparison of results with measures of cardiovascular fitness, such as maximal oxygen uptake (50). Such measures of validation assume that cardiovascular fitness is the main area of interest; the relation between exercise and effect is probably more complex. We believe that our lack of correspondence with objective physiologic parameters is not, in and of itself, reason to suspect validity of our assessment. We also note that such validation could be conducted only for current physical activity levels.

It is perhaps more informative to examine our questionnaire with respect to the comprehensiveness of physical activity assessment. Although frequency and intensity of activity were assessed, we note that additional information on duration of exercise may be revealing, particularly if episodic testosterone surges are the relevant insult; for example, peak levels of

androgens may be attained 20–40 minutes after exercise (25, 27). Information on the specific type of activity, such as resistance exercise versus aerobic activity, may yield additionally meaningful information, even given the implausibility of testicular trauma as an intermediary between physical activity and testicular cancer.

Differential misclassification (in particular, recall bias) is unlikely to be a concern because we believe that it is improbable that an association between physical activity and testicular cancer is likely to be known by the general public. Further, for a positive association to be spurious, cases would have had to overreport their exposure relative to controls, a phenomenon that seems unlikely. Nondifferential misclassification may be a more relevant issue, particularly given that subjects were asked to recall participation in activity that occurred, in some cases, more than 4 decades earlier. For example, when attitudes toward physical activity have changed over time, individuals may assume a correspondence between these new attitudes and their earlier behavior and can falsely infer that they have already engaged in actions consistent with their new attitudes (51). We might surmise that the observation of similar odds ratios for both moderate and strenuous activity, even for the teen years (when we might expect greatest misclassification), suggests that the contribution of misclassification was not large, since moderate activity is most poorly recalled relative to strenuous activity (52). There is no reason to suggest that such misclassification was greater in our study than in others that have examined physical activity.

Our study had no information on the two established risk factors for testicular cancer, namely, cryptorchidism and inguinal hernia. This is unlikely to have been a limitation, however: Because there is almost certainly no relation between these and other lifestyle factors, the potential for confounding is minimal. Certainly, it is often true that adjustment for these risk factors does not alter odds ratios much (5, 9, 10).

In summary, our results are specific to a particular age group and are consistent within this group; furthermore, the observed positive effect of physical activity is supported by a plausible biologic hypothesis. In addition to further examination of the period of adolescence, future studies of physical activity and testicular cancer risk should incorporate some measure of duration of exercise, along with the components of frequency and intensity. Important insights might also be gained from further investigation of the relation between hormone levels and physical activity, particularly with respect to frequency of exercise.



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APPENDIX TABLE 1. Physical activity questionnaire

How often did you usually do *strenuous physical activity or sports* during the following time periods? (Some examples: racquet sports, hockey, basketball, soccer, jogging, aerobics, cycling, swimming, skiing, or skating)

	In your midteens	In your early 30s	In your early 50s	About 2 years ago
Less than once/month	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
1–3 times/month	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
1–2 times/week	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3–5 times/week	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
More than 5 times/week	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Not applicable	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

How often did you usually do *moderate physical activity or exercise* for at least 20 minutes during the following time periods? (Some examples: brisk walking, gardening, yard work, golf, bowling, curling, social dancing, softball, volleyball)

	In your midteens	In your early 30s	In your early 50s	About 2 years ago
Less than once/month	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
1–3 times/month	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
1–2 times/week	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
3–5 times/week	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
More than 5 times/week	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Not applicable	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

What was your usual *type of activity* in your daily work, job, or occupation (include homemaker, student, volunteer, etc.) during the following time periods? Please select the single best category for each age period

	In your midteens	In your early 30s	In your early 50s	About 2 years ago
Sitting activity (e.g., desk job, telephone operator)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Light activity (e.g., driving, standing jobs)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Moderate physical activity (e.g., lifting and carrying light loads, heavy cleaning, carpentry)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Strenuous physical activity (e.g., carrying moderate-to-heavy loads, heavy construction or manual labor)	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Not applicable	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>