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Physical activity and prostate cancer in the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study (Finland)

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The association between physical activity and prostate cancer was evaluated in the trial-based cohort of the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study (*n* = 29,133). During up to nine years of follow-up, 317 men developed incident prostate cancer. The relationship between occupational, leisure, and combined activity and prostate cancer was assessed in multivariate Cox regression models that adjusted for intervention group, benign prostatic hyperplasia, age, smoking, and urban residence. Compared with sedentary workers, relative risks (RR) and 95 percent confidence intervals (CI) for occupational walkers, walker/lifters, and heavy laborers were 0.6 (CI = 0.4-1.0), 0.8 (CI = 0.5-1.3), and 1.2 (CI = 0.7-2.0), respectively. Among working men, leisure activity (active *cf* sedentary) was associated inversely with risk (RR = 0.7, CI = 0.5-0.9). This inverse association for leisure activity was observed, with the exception of heavy laborers, for all occupational activity levels, and was strongest among walkers compared with men sedentary at work and leisure, and to a lesser degree among walker/lifters. These results are consistent with a protective effect of physical activity on prostate cancer. *Cancer Causes and Control* 1998, **9**, 11-18

Key words: Exercise, Finland, men, physical activity, prostate cancer.

Introduction

Despite the evidence that prostate cancer incidence rates are declining,[1] prostate cancer remains the most common cancer among American males.[2] Physical inactivity is associated with increased morbidity and mortality from several disease states including cardiovascular disease, diabetes mellitus, and possibly some cancers.[3,4] Prostate cancer is a hormonally mediated disease,[5] and it has been suggested that physical fitness may protect against the development of prostate cancer by favorable effects on hormone profiles.[6] Previous reports of physical activity and prostate cancer risk have been inconsistent.[7] This prompted us to evaluate the effect of both occupational and leisure-time physical activity on prostate cancer within the Alpha-Tocopherol Beta-Carotene (ATBC)

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Cancer Prevention Study, a large randomized, double-blind, placebo-controlled, primary prevention trial conducted in Finland.

Materials and methods

Sample population

The ATBC Study was conducted in Finland as a joint project between Finland's National Public Health Institute (NPHI) and the United States National Cancer Institute (NCI). Details concerning the study rationale, methods, participant characteristics, and compliance have been described.[8] Briefly, the ATBC Study was conducted to determine whether daily supplementation with α-tocopherol, β-carotene, or both, would reduce the incidence of lung or other cancers. Male smokers between the ages of 50 and 69 were recruited from southwestern Finland between April 1985 and June 1988. A total of 29,133 men were randomly assigned to one of four intervention groups: 50 mg/day α-tocopherol (as *dl*-α-tocopheryl acetate); 20 mg/day β-carotene; both α-tocopherol and β-carotene; or placebo. They were followed for five to eight years during the trial, until death, or 30 April 1993 when intervention was stopped (median follow-up, 6.1 years). Follow-up for endpoints was continued post-intervention. This report includes follow-up through the end of April 1994. Men who were alcoholics, who had cirrhosis of the liver, severe angina with exertion, chronic renal insufficiency, were receiving anticoagulant therapy, or who had been diagnosed previously with cancer were excluded prior to randomization. Those taking supplements of vitamins E or A or β-carotene in excess of defined amounts also were not eligible to participate.[8]

Case identification

Incident cases of prostate cancer (ICD-9[9] code 185) diagnosed between May 1985 and April 1994 ($n = 317$) were included in this analysis. These cancers were identified primarily through the Finnish Cancer Registry and the Register of Causes of Death. Medical records were reviewed centrally by study physicians, including oncologists, to confirm diagnoses. Cases with histology or cytology available (98 percent) also were reviewed by pathologists.

Data collection

At baseline, study subjects completed a general medical history questionnaire, a food-use (history) questionnaire, and provided a blood sample. Occupational and leisure-time physical activity was assessed based on two questions. The first asked the respondent to describe activity in their work, within the past year as: (i) mainly sitting; (ii) walking quite a lot, but not lifting or carrying; (iii) walking and lifting; or (iv) heavy physical work (*e.g.,* lifting heavy things, digging, shoveling). In addition, there was a category for those who were not working. The second question asked participants to describe their activity during leisure time during the past year as: (i) sedentary (*e.g.,* reading, watching television); (ii) moderate (walking, fishing, hunting, gardening); or (iii) heavy (running, jogging, skiing, swimming, *etc.* fairly regularly).

Statistical analysis

Statistical analyses were performed using Statistical Analysis Systems (SAS) software.[10,11] Cox regression methods were used to estimate the associations between leisure and work-related physical activity and incidence of prostate cancer.[12] These analyses used follow-up time as the underlying time metric and adjusted for age at randomization as a continuous variable. Intervention status was coded as three indicator variables for α-tocopherol, β-carotene, or both α-tocopherol and β-carotene supplementation, with the placebo group serving as the referent. For analyses, physical activity variables were entered into models as four indicator variables for work-related physical activity, with sedentary work as the referent. These variables designate occupational physical activity within the past year as 'walking,' 'walking and lifting,' or 'heavy labor.' 'Non-working' designates those who were not employed. For leisure activity, few individuals responded that they ran, jogged, swam, or engaged in other heavy exercise regularly; therefore, individuals were coded as regularly participating in 'sedentary' or 'moderate or heavy' physical activity during the past year. To evaluate the effect of total physical activity on prostate cancer risk, individuals were coded according to their combined levels of occupational and recreational activity (*e.g.,* the reference group is sedentary at work and during leisure).

Variables included in the multivariate models were those that produced significant changes in log likelihoods or produced a material (greater than 10 percent) change in the coefficient for another covariate. The intervention group was included in the models because of the significant protective effect of α-tocopherol supplementation on prostate cancer incidence observed during the trial;[13] however, intervention status was distributed uniformly across levels of both occupational and leisure-time physical activity. The association between physical activity and prostate cancer incidence was evaluated in a multivariate model which also included intervention group, age at randomization, smoking, prior history of benign prostatic disease (BPH) (self-reported; yes/no), and urban residence (yes/no). Body mass index (BMI) (wt/ht^2) and other dietary factors were not important predictors for prostate cancer or significant confounders in these analyses, and are not included in the models.

Results are reported as adjusted relative risks (RR) of prostate cancer incidence with 95 percent confidence intervals (CI). Effect modification was assessed by including factors and their cross-product terms in the model and through stratified analysis by splitting factors at the median into low and high categories. We checked the validity of the proportional hazards assumption by examining the cross-product terms of follow-up time and the covariates of interest. There were no departures from proportional hazards assumptions for any covariate included in the final models. The results were unchanged when persons with cancers diagnosed during the first two years of follow-up were excluded from the analysis.

Results

This report includes 317 incident cases of prostate cancer documented over approximately nine years of follow-up (median follow-up time of 7.0 years). Mean age of cases at the time of diagnosis was 65.4 years. Table 1 includes selected baseline characteristics of the study population including physical activity levels. Those who developed prostate cancer were, on average, 3.7 years older (60.9 *cf* 57.2 years) than non-cases; were more likely to have a history of BPH (8.8 *cf* 3.9 percent); were more likely to be nonworking (61.5 *cf* 42.1 percent); and were more likely to live in an urban area (51.1 *cf* 42.3 percent). The distribution of occupational activity also differed between cases and non-cases, and prostate cancer cases had a lower total energy intake than non-cases. BMI, educational attainment, family history of prostate cancer (available on 72 percent of the cohort), marital status, and physical activity during leisure time did not differ significantly between the two groups. Staging information is available for the 246 cases which were diagnosed during the ATBC trial. In this subset of cases, there was no striking association between stage and follow-up time or stage and level of either occupational or leisure-time physical activity (data not presented).

Table 2 shows the RR of prostate cancer by level of occupational or leisure-time physical activity. For occupational activity, we observed nonsignificant reductions in the RR both for workers who walked (RR = 0.6, CI = 0.4-1.0) and those who did lifting and walking (RR = 0.8, CI = 0.5-1.3). Workers engaged in heavy manual labor had a nonsignificant increase in RR compared with sedentary workers (RR = 1.2, CI = 0.7-2.0). Nonworking men had an RR of prostate cancer similar to that of sedentary workers (RR = 0.9, CI = 0.6-1.4). The results for the relationship between prostate cancer and leisure activity were more complex. For the group as a whole, and among the subgroup of nonworking men, leisure activity had little association with prostate cancer risk. Among working men, however, there was a tendency for increased leisure activity to protect against prostate cancer (RR = 0.7, CI = 0.5-0.9).

The results of the combined physical activity analyses are presented in Table 3. Compared with the reference

Table 1. Selected baseline characteristics for prostate cancer cases and non-cases;[a] ATBC Study

Characteristic	Prostate cancer (*n* = 317)	No prostate cancer (*n* = 28,816)
Age (yrs)	60.9 ± 5.1	57.2 ± 5.1
Body mass index (kg/m^2)	26.4 ± 3.6	26.3 ± 3.8
Smoking (cigarettes/day)	18.8 ± 5.0	20.4 ± 8.8
Total energy intake (kcal/day)	2,737 ± 824	2,816 ± 787
Marital status (% married)	77.9	80.2
Living in urban area (% yes)	51.1	42.3
Education (% > elementary)	23.0	21.0
Family history[b] (% positive)	18.0	14.2
Benign prostatic disease (% with)	8.8	3.9
Nonworking (%)	61.5	42.1
Occupational activity[c] (%)		
Sedentary	28.7	23.8
Walking	23.8	31.6
Lifting/walking	24.6	28.6
Heavy manual	23.0	15.9
Leisure activity (%)		
Sedentary	42.9	41.8
Moderate/heavy	57.1	58.2

[a] Mean ± standard deviation; some percentages may not add to 100 due to rounding error.
[b] Available for only 72% of the cohort, collected during follow-up, not at baseline.
[c] Among working men only.

Table 2. Relative risk (RR) and 95% confidence interval (CI) of prostate cancer associated with occupational and leisure time physical activity,[a] ATBC Study

Physical activity	Cancer cases (n = 317)	RR	(CI)
Occupational			
Sedentary	35	1.0	Reference
Walking	29	0.6	(0.39-1.05)
Lifting/walking	30	0.8	(0.48-1.26)
Heavy manual	28	1.2	(0.74-2.03)
Non-working	195	1.0	(0.65-1.40)
Leisure			
Sedentary	136	1.0	Reference
Moderate/heavy	181	0.9	(0.73-1.14)
Leisure (workers)[b]			
Sedentary	64	1.0	Reference
Moderate/heavy	58	0.7	(0.46-0.94)
Leisure (nonworkers)[c]			
Sedentary	72	1.0	Reference
Moderate/heavy	123	1.1	(0.83-1.49)

[a] Models adjusted for age, living in an urban area, smoking, history of benign prostatic disease, and intervention.
[b] Model limited to employed persons only (excludes nonworkers).
[c] Model limited to nonworkers only.

Table 3. Relative risk (RR) and 95% confidence interval (CI) of prostate cancer and combined occupational and leisure time physical activity,[a] ATBC Study

Physical activity		Cases	RR	(CI)	Trend P[b]
Occupational	Leisure				
Sedentary	Sedentary	19	1.0	Reference	
Sedentary	Moderate/heavy	16	0.7	(0.4-1.4)	—
Walking	Sedentary	15	0.7	(0.4-1.4)	
Walking	Moderate/heavy	14	0.4	(0.2-0.9)	0.007
Lifting/walking	Sedentary	15	0.8	(0.4-1.5)	
Lifting/walking	Moderate/heavy	15	0.6	(0.3-1.1)	0.11
Heavy manual	Sedentary	15	1.0	(0.5-2.1)	
Heavy manual	Moderate/heavy	13	1.0	(0.5-2.0)	0.80
Nonworking	Sedentary	72	0.8	(0.5-1.3)	
Nonworking	Moderate/heavy	123	0.8	(0.5-1.4)	0.85

[a] Models adjusted for age, living in an urban area, smoking, history of benign prostatic disease, and intervention.
[b] The reference category for all of the trend tests is men who are sedentary at work and during leisure.

group of sedentary workers who reported sedentary activity in their leisure time, occupational walking or walking and lifting was protective. Within these two occupational categories, higher leisure-time physical activity further reduced the RR of prostate cancer, with a significant trend observed for men walking at work. Heavy manual labor at work did not lower risk for prostate cancer, regardless of leisure-time activity. Nonworkers had a nonsignificant reduction in risk; however, in this group, the effect was essentially flat across level of leisure-time activity. We observed no significant effect modification by age, weight, total energy intake, total fat intake, place of residence, history of BPH, intervention group, or length of follow-up time for any of the physical activity variables.

Because working status seemed to be an important modifier for the relationship between physical activity and prostate cancer, we looked at selected characteristics of workers and nonworkers. As a group, the nonworking men were older than working men (mean 60.3 *cf* 55.0 years, $P < 0.001$), and as a result had smoked longer (mean 39.3 *cf* 33.4 years, $P < 0.001$), even though the age when they began smoking was younger for working men (19.7 *cf* 19.2 years, $P < 0.001$). Current smoking, as well as

current alcohol consumption was higher among workers compared with nonworkers (21.4 *cf* 19.0 cigarettes/day, $P < 0.001$ and 19.2 *cf* 16.3 grams/day, $P < 0.001$, respectively. Nonworking men also were more likely than workers to have had BPH (5.7 *cf* 2.6 percent, $P = 0.001$) and to be unmarried (24 *cf* 17 percent, $P = 0.001$). In contrast, BMI was not significantly different between workers and nonworkers (26.2 *cf* 26.3 kg/m^2, $P = 0.10$). We controlled for age, smoking, and BPH in our analyses; alcohol consumption and marital status were not important predictors of prostate cancer incidence and were not significant confounders. Overall, the RR of prostate cancer for nonworkers compared with workers after controlling for other covariates was 1.1 (CI = 0.9-1.5).

Discussion

This study suggests that physical activity, both work-related and recreational, may reduce prostate cancer risk. When occupational and leisure-time physical activity were considered jointly, occupational walking or walking and lifting was predictive of reduced risk of prostate cancer at all levels of leisure-time activity. Further, greater leisure-time physical activity lowered prostate cancer risk within occupational physical activity subgroups with the exception of heavy manual laborers. Among men walking during occupational hours, a significant trend with increasing level of leisure-time physical activity was observed in compared with men who were sedentary at work and during leisure.

Our findings are in agreement with those of several other studies. Thune *et al*[14] observed a similar pattern of results in their cohort of 53,000 Norwegian men. In particular, these investigators also found a protective effect for walking during occupational hours and the lack of an association for heavy manual labor. They suggested that heavy manual labor may be a more 'static' activity which may not influence prostate cancer risk in the same way that 'dynamic' activities might. Several other studies of occupational physical activity have observed a protective effect of work-related activity for prostate cancer. Hsing and co-authors[15] showed a moderate (28 percent) increase in the standard incidence ratio of prostate cancer risk for sedentary Chinese workers. A Missouri-based (US) case-control study found an increased risk of prostate cancer among men with low levels of occupational activity (RR = 1.5).[16] In Washington State, there was a tendency for higher proportional mortality ratios for men with low occupational activity,[17] and among San Francisco longshoremen, light job-related activity was associated with an elevated risk (RR = 1.5) of prostate cancer mortality compared with heavier activity.[18] A multicenter, hospital-based, case-control study[19] used job titles to assess occupational physical activity and found that, compared with active workers, there was a nonsignificant increase in risk of prostate cancer mortality for moderately active (RR = 3.0) or sedentary workers (RR = 3.6), after adjusting for confounders.

Investigators also have reported protective effects of recreational activity or overall fitness with respect to prostate cancer. Gann *et al*[20] measured resting heart rate, which is correlated inversely with fitness, in the Chicago Heart Association cohort and found that the RR of prostate cancer increased 26 percent for every 10 beat/minute increase in heart rate. Oliveria and colleagues[21] assessed cardiorespiratory fitness using a maximal exercise treadmill test and found higher fitness levels were associated inversely with development of incident prostate cancer after adjusting for age, BMI, and smoking. In the US NHANES I population, Albanes *et al*[22] observed a significant inverse association between recreational exercise and prostate cancer (RR = 0.6 for much exercise *cf* little or no exercise, trend $P = 0.02$), but no effect was seen for non-recreational activity. In the Harvard Alumni Study, Lee[23] found that alumni who expended more than 4,000 kcal/week on post-college activity had a reduced risk of prostate cancer. Yu and co-authors,[24] in a large case-control study with hospital controls, found a weak, but significant inverse association (RR = 1.3 for < 1 times/wk *cf* > 3 times/wk) between aerobic exercise and risk of prostate cancer.

In contrast to the above studies, Whittemore and co-authors[25] observed no association between 24-hour physical activity patterns and prostate cancer. Le Marchand and associates[26] found a positive association between lifetime occupational physical activity and prostate cancer based on cases identified from the Hawaii Tumor Registry. These results, however, were limited to men over age 70; no association was found in younger men. In a large population-based, case-control study in Utah, West and co-authors[27] found a nonsignificant increase in risk for 'aggressive' tumors among active compared with inactive males. Among the Harvard alumni, individuals who participated in five or more hours/week of sports as college students had an increased death rate from prostate cancer (RR = 1.7) after over 25 years of follow-up.[28] Lastly, Severson,[29] among Japanese-Hawaiian men, found that men with decreased muscle mass had a lower risk of prostate cancer. This group found no association between increased activity at work and prostate cancer (RR = 1.0), but moderate or heavy activity at home was inversely, but not significantly associated with prostate cancer risk (RR = 0.8).

The amount of exercise required, the optimal age at which to begin exercise, and the duration and intensity required to afford protection have not been established for any of the cancer sites.[4] In this study, we do not have good information on long-term physical activity; how-

ever, others have demonstrated that lifetime activity and activity at a single time during adult life are generally highly correlated.[30]

There are possible biological mechanisms which may explain the observed protective association between physical activity and risk for prostate cancer. In general, immune system functions are enhanced by physical activity. Natural killer-cell activity, which is enhanced by exercise, has been associated with preventing of the development and progression of cancer.[31] Frequent, exhaustive exercise, however, may depress natural killer-cell activity.[32] Monocytes and macrophages are also important immune-system factors which may act to prevent the development and spread of malignancies. Moderate physical exercise is thought to have positive effects, while severe exhaustive exercise is thought to have negative effects on monocyte and macrophage activity.[32]

It has been hypothesized that male hormones are associated with risk of prostate cancer. Studies of hormone levels have produced equivocal results with respect to prostate cancer risk.[33] For the most part, these studies have been case-control studies with blood samples taken from cases after diagnosis. A recent nested case-control study conducted within the Physicians' Health Study[34] found that high levels of circulating testosterone and low levels of sex hormone-binding globulin were associated with increased risk of prostate cancer. A non-linear inverse association was found for serum estradiol and prostate cancer. These results are supported by tissue culture studies of human prostate cancer cells which show increased proliferation following androgen administration and inhibition of proliferation by estradiol administration.[35,36]

Physical activity is thought to alter hormonal patterns. Although trained athletes[37,38] and physically active young men[39] have lower serum testosterone levels at rest, a relationship between physical activity and testosterone level has not been confirmed in older men[40] and the effects of moderate and light regular exercise on hormonal status have not been evaluated. More work is needed in this area to help clarify any association among physical activity, hormone levels, and prostate cancer.

There are probably other differences between physically active and sedentary individuals which also may be of importance. In addition to differences in immune factors or hormonal patterns, persons who exercise may have better overall lifestyles than sedentary individuals, they may have lower body fat, and their antioxidant enzyme systems may be enhanced, all of which might contribute to decreasing prostate cancer risk.[41]

The lack of a protective effect of physical activity in workers engaged in heavy manual labor in our study and others[14] deserves further exploration. One explanation is that any protective effect of physical activity in this group may be overcome by the influence of other occupational exposures on prostate cancer risk in this group. For example, a higher incidence of prostate cancer has been reported in men working in various occupations which might involve heavy labor, including plumbers, mechanics, farmers, and rubber factory workers.[42] An additional consideration is that while regular aerobic exercise generally has been associated with enhanced immune function, Pederson *et al*[43] demonstrated that in the same group of subjects, 60 minutes of bicycling increased natural killer-cell activity, but 60 minutes of back-muscle training had no effect. This suggests that qualitatively different types of activities may not have similar effects on immune factors. In addition, the duration, intensity, and type (static *cf* dynamic) of activity may influence hormonal status, and the physiological significance of these responses is unclear. With prolonged exercise, hormone concentrations return relatively slowly towards basal values.[37] In contrast, after short-term, heavy exercise, normalization of hormone levels appears to occur quickly, and there may be a rebound effect for some hormones.[44] Three groups of investigators have found that hormone responses to anaerobic or static exercise differ from those to aerobic or dynamic exercise,[45–47] and although exercise generally lowers resting plasma levels of testosterone, participation in a strength training program appears to have no effect.[48,49]

Some limitations of this study, and of the etiologic studies of physical activity in general, need to be considered when interpreting our study results. Although physical activity is likely to be recalled with reasonable accuracy, misclassification with respect to activity level may still exist. The physical activity data pertain only to activity in the 12 months prior to collection of the baseline data; no information is available for activity prior to this. Also, no additional assessment of physical activity was made during the follow-up period, and some cohort members may have changed their activity habits during this time. With regard to occupational physical activity, this is not likely to play a major role in this study. According to Statistics of Finland, for Finnish men over 50 years of age, the frequency of changing jobs in recent years has been only one to three percent annually. Random errors like these likely will attenuate the true association between physical activity and prostate cancer. Another limitation of this study is the small number of men who reported being very active in their leisure time, making it impossible for us to look at heavy leisure activity as a separate category. There is also the possibility that active men are at lower risk for prostate cancer for other reasons; however, our analyses adjusted for all relevant measured confounders, and our results are biologically plausible. Lastly, the generalizability of these results may be somewhat limited because the study was restricted to

older male smokers who participated in a clinical trial.

Regarding occupational activity specifically, these analyses also point out that nonworking men are probably not a homogeneous group and additional information regarding past employment and reasons for not working would have been helpful for interpretation of these results. This group is likely comprised of men who reached the age of retirement and quit working, men who were able to retire early because of financial security, and also men who were forced to quit working for health reasons.

In summary, our results are consistent with a protective association between both occupational and leisure-time physical activity and prostate cancer incidence. Further investigation into the mechanisms by which physical activity and different types of activities can influence prostate cancer risk are needed.

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