Health & Fitness Journal
of Canada

Copyright © 2016 The Authors. Journal Compilation Copyright © 2016 Health & Fitness Society of BC

Volume 9 **May 30, 2016** **Number 2**

SYSTEMATIC REVIEW

Physical activity in the prevention and treatment of prostate cancer.

Roy J. Shephard[1]

Objectives: The objectives of this review were to examine the effectiveness of regular physical activity in the prevention of prostate cancer, to note the functional disturbances associated with the use of androgen deprivation therapy, and to assess the potential of exercise programmes in alleviating these side effects. *Methods:* The findings of previous reviews were supplemented by a search of the Ovid/Medline and PubMed data bases from 1996 to June 2016, looking for linkages between prostate cancer, the physical demands of occupation, reported leisure activity, involvement in sports, and attained levels of aerobic fitness. *Results:* At least 85 analyses have examined the influence of various forms of habitual activity upon the risk of prostate cancer, with about a quarter of reports showing a significantly lower risk in more active individuals, and a further quarter of studies a similar but non-significant trend. Findings are somewhat more consistent for occupational than for leisure activity, a risk reduction of 34% and 38% being associated with the 2 types of activity. The optimal age and pattern of preventive activity remains unclear, and possible underlying mechanisms have yet to be clarified. Androgen deprivation therapy following surgery or irradiation of a prostate tumour causes a loss of aerobic power, strength and bone density, with a reduced quality of life, and appropriately designed exercise programmes seem to have a role in countering such side-effects. *Conclusions:* Regular physical activity appears to reduce the risk of prostate cancer. More research is needed to prove this categorically, but the likely extent of benefit of around 35% is sufficient for this to be one further factor pointing the need for encouraging physical activity in the general population. Regular activity also seems of value in countering the side-effects of androgen-deprivation therapy. **Health & Fitness Journal of Canada 2016;9(2):56-107.**

Keywords: Aerobic fitness, Cancers, Leisure activity, Neoplasms, Occupational activity, Prevention, Sports participation

From [1]Faculty of Kinesiology & Physical Education, University of Toronto, Toronto, ON, Canada.
Email: royjshep@shaw.ca

Introduction

In Canadian men, prostate cancer is the most common type of malignant neoplasm, and it is the third most common source of cancer mortality. The Canadian Cancer Society estimated that in 2015 prostate tumours would be responsible for 24,000 new cases of cancer, and that 4100 men would die from this condition, accounting for 10% of all male cancer deaths (Canadian Cancer, 2015). In the U.S., the economic costs of prostate cancers were $9.86 billion dollars in 2006, with individual expenditures of $10,612 in the initial phase of the disease, $2134/year for continuing care, and a further $33,691 in the final year of life. In Canada, expenditure on hospital visits and drugs alone amounted to $103 Million in 1998 (Roehrborn and Black, 2011), with total expenditures accounting for some 5% of the total health care budget (Grover et al., 2000).

Despite the prevalence of this condition, little is known about prevention. Possible modifiable risk factors are thought to include the level of male hormones, diet, obesity, smoking, alcohol consumption, infection with sexually transmitted diseases, vasectomy and exposure to toxins such as cadmium and agricultural pesticides (Friedenreich and Thune, 2001). Several reviews (Liu et al., 2011; Torti and Matheson, 2004) have suggested that the risk of prostate cancer

is also reduced, possibly by 10-30%, in physically active individuals. Potential mechanisms of benefit could include the prevention of obesity (Lee et al., 2006), enhanced immuno-surveillance through an increased natural killer cell count (Shephard et al., 1994), a greater ability to counter oxidant stress (de Sousa et al., 2016), and a reduction in testosterone levels as seen in endurance competitors (Hackney et al., 1988).

Following diagnosis and immediate treatment by surgery or irradiation, it is common practice to discourage further proliferation of any remaining cancer cells by the prolonged administration of androgen suppressants. However, the many side-effects to such treatment mirror the changes seen with bed-rest or sedentary living. Unfortunately, few of those who have been treated for prostate cancer opt to engage in voluntary physical activity, although it seems likely that the functional deterioration could be countered by the institution of appropriate aerobic and strength training programmes soon after surgery or irradiation.

The present review has three main objectives:

- to weigh evidence that regular physical activity reduces the risk of prostate cancer.
- to identify adverse responses to the use of androgen deprivation therapy following the immediate treatment of prostate cancer,
- and to examine the potential value of exercise programming in countering the side-effects of androgen deprivation treatment.

Physical activity and the prevention of prostate cancer

Previous reviews. The review of Torti and Matheson, (2004) noted that early studies of physical activity and the prevention of prostate cancer were retrospective in design; 2 investigations had found an association of risk with a history of heavy occupational work, and a third had observed a greater risk among those who had been enrolled in university athletic teams during their youth. Between 1989 and 2001, 13 cohort studies had used the development of prostate cancer as their end-point, with 9 reporting some association between exercise and a decreased risk of prostate cancer. Five of 11 case-control studies from this same period had also reported an association between a high level of physical activity and a decreased risk of prostatic cancer. In all, 16 of 27 studies completed through to the year 2002 reported a trend to a lower risk in the most active men, with a statistically significant benefit of 10-30% in 9 of 16 analyses.

Liu and associates (2011) undertook a meta-analysis of findings from 19 cohort and 24 case-control studies. As in an analysis of exercise in the prevention of colon cancer (Shephard, 2016), Liu et al., (2011) found a larger effect for occupational than for leisure activity (respective relative risks and 95% confidence intervals for the active individuals of 0.81 [0.73-0.91] and 0.95 [0.89-0.97]), with benefit apparently limited to activity taken between the ages of 20 and 65 yr.

Many further investigations have now addressed the issue of the preventive value of regular physical activity in prostate cancer. In a few instances there have been repeat analyses of data sets, but in all there have been around 80

independent investigations based on the physical demands of occupation, reported leisure activity (sometimes in the same population sample as in an occupational study), sport involvement and/or attained levels of aerobic fitness.

Occupational activity. The physical demands of work have in some instances been inferred from occupational titles, and in other studies subjects have themselves categorized their employment, using semantic variables (heavy vs. light) or such markers as the fraction of the day spent sitting, standing, lifting or engaged in hard physical work. Occupational analyses of energy expenditures have some advantages over similar classifications of leisure activity. Typically, workers have maintained a relatively known level of physical activity for many years, including the period 10-30 yr prior to the clinical diagnosis of prostate cancer, when carcinogenic change is likely to have begun. The intensity of what is commonly classed as "heavy work" is less than in vigorous leisure pursuits (Bouchard and Shephard, 1992), but this level of activity is maintained for 4-5 hr per day, thus accumulating a substantial energy expenditure over the course of a typical working week.

However, occupation-based classifications also have some disadvantages. In particular, heavy physical employment has sometimes involved exposure to industrial toxins that could cause or predispose to prostate cancer. Moreover, there are usually large socio-economic differences between heavy industrial workers and sedentary office employees, influencing the individual's area of residence and potentially relevant risk factors such as diet, smoking habits and alcohol consumption, and unfortunately not all investigators have introduced appropriate co-variates into their analyses to allow for such confounding influences. Mechanization and automation are also progressively reducing the energy cost of what were once physically demanding occupations, limiting the possibility of future studies based upon the nature of an individual's employment.

Cross-sectional and cohort studies. At least 17 cross-sectional and cohort studies have related the risk of prostate cancer to occupation (Table 1). In many cases, the findings are nuanced, with differing responses distinguished *post-hoc* in sub-groups identified by such factors as age group or ethnicity; seven of these investigations have essentially shown no effect, five have identified a favourable trend, and five have demonstrated a significantly lower risk in the most active workers.

Among the seven neutral reports, Paffenbarger et al., (1987) followed a sample of 2665 U.S. longshoremen for 12 yr, during which time they developed 30 cases of prostate cancer. Despite the unpromisingly small total number of prostatic tumours, relative risks were classified in relation to 4 intensities of work (heavy, moderate, light-to-moderate, and light). Age-adjusted risk ratios for these 4 categories of energy expenditure showed no significant trend (1.0, 0.14, 1.41, 1.54). Hartman et al., (1998) observed a cohort of 29,133 male workers for up to 9 yr. There were 317 incident cases of prostate cancer over this time. The risk of prostate cancer was contrasted between those employed in sedentary occupations and those whose jobs required walking, combinations of walking and lifting, or heavy labour.

Table 1: Physical demands of occupation and the risk of prostate cancer.

Author	Sample	Activity measure	Findings	Comments
Cohort studies				
Albanes et al. (1989)*	95 cases of PC in 5141 men over 10 yr follow-up	Very active vs. quite inactive	RR 1.3 if quite inactive (ns)	Age adjusted
Clarke and Whittemore (2000)*	5377 men followed for 17-21 yr, 201 cases of PC	Very active vs. inactive	RR for inactive 1.75 (1.12-2.67), p = 0.05 for trend (effect greater in African-Americans)	Adjusted for age, education, ethnicity, and family history
Grotta et al. (2015)*	13,109 Swedish men followed for 13 yr, 904 cases of PC	Low vs. high level of occupational activity	HR 0.81 (0.61 - 1.07, ns)	Adjusted for age, education, smoking, BMI, alcohol consumption, diabetes mellitus
Hartman et al. (1998)*	29,133 men followed for up to 9 yr, 317 cases of PC	Sedentary vs. walkers vs. walkers/lifters vs. heavy labourers	RR 1.0, 0.6, 0.8, 1.2 (ns)	Adjusted for age, urban living, smoking, benign prostatic hyperplasia
Harvei & Kravdal (1997)	Follow-up of Norwegian men from age 50 yr, ~30,000 cases of PC	Fishing vs. agriculture vs. manufacturing vs. service	No impact of type of work on RI of PC; but increased by high vs. low education [RI 1.21 (1.13-1.29)]	Age, period and region included as co-variates; effect not due simply to greater detection, since applies to localized & metastasized tumours
Hrafnkelsdóttir et al. (2015)*	24-year follow-up of 8221 Icelandic men	Occupation involves mostly sitting vs. standing vs. on the move	HR 1.0, 0.97, 0.91 (0.79-1.06, ns)	Adjusted for age, height, BMI, diabetes, family history, education, medical check-ups
Hsing et al. (1994)	264 cases of PC, occupational title	Sitting time <2h/d vs. > 6h/d), intensity of physical activity (<8, >12 kJ/min)	SIR 0.94 vs. 1.23, p = 0.14; SIR 1.23 vs. 0.92, p = 0.06	Apparently no co-variates included in analyses
Johnsen et al. (2009)*	127,923 men followed for 8.5 yr; 2458 cases of PC	Sitting, standing or manual work; inactive, moderately inactive, moderately active, and active.	Occupational activity unrelated to PC	Adjusted for leisure activity, height, body mass, marital status & education
Lund Nielsen et al. (2000)*	22,895 Norwegian men followed for 9.3 yr, with 644 cases of PC	High vs. low level of occupational activity	No effect on PC	Multivariate adjusted
Norman et al. (2002)	3 cohorts of 43,836, 28,702 and 19,670 prostate cancers	Occupational titles (sedentary to very high level of activity)	RR for sedentary groups 1.11, 1.10 and 1.11 (p = 0.0001)	Adjusted for age, year of follow-up and area of residence
Orsini et al. (2009)*	45,887 men followed for 8 yr, 2735 incident cases of PC	4 categories of occupation (mostly sitting vs. heavy manual)	RR = 0.72 (0.57-0.90) p for trend 0.007; effects smaller for advanced & fatal cancers	Adjusted for leisure activity, age, smoking, alcohol consumption, education, diet, energy intake, waist/hip ratio, diabetes mellitus
Paffenbarger et al. (1987)	2665 longshoremen followed for 12 yr, 30 cases of PC	Heavy, moderate. light-to-moderate, light work	Inconsistent RR (1.0, 0.14, 1.41,1.54, ns);	Age adjusted, but small number of cases of PC.
Parent et al. (2011)	449 incident cases of PC	High vs. low lifetime occupational activity (METs)	OR 0.54 (0.31-0.95) favouring active work	

Table 1 Continued

Author	Sample	Activity measure	Findings	Comments
Putnam et al. (2000)*	101 cases of PC in 1572 initially cancer free men followed for 4 yr	Very active, moderately active or inactive at work	Risk of PC unrelated to occupational activity	Adjusted for age
Severson et al. (1989)*	8006 Japanese men on Oahu; 205 cases of PC	Self-estimate of job energy demands	Risk of PC unrelated to job activity	
Thune and Lund (1994)*	220 cases of PC in 53,242 Norwegians followed for 16.3 yr	4-level classification of work, sedentary to heavy manual	RR for heavy manual work 0.81 (0.50-1.30)	Age, BMI, geographic region of residence
Vena et al. (1987)	430,000 men in Washington State, 8116 deaths from PC	4-level classification of occupational activity	PMR low = 109, high = 93 (p = 0.05)	
Vidarsdottir et al. (2008)	60,194 men initially aged 20-64 yr followed 23 yr	Educational level (basic, medium, academic)	SIR basic = 0.92 (0.84-0.99) academic 1.17 (1.05-1.30)	Earlier and more complete diagnosis in academic group?
Zeegers et al. (2005)*	58,279 men aged 55-69 yr, 1386 cases of PC over 9.3 yr	Occupational activity (energy expenditure, sitting time)	Unrelated to PC	Adjusted for age, alcohol consumption, BMI, energy intake, family history, education
Case-control studies				
Bairati et al. (2000)	64 cases of PC, 5456 cases of benign prostate hyperplasia aged >45 yr	Ever had sedentary job or light work; 0, 1-49%, >50% of career spent in sedentary or light work	OR 2.0 (1.1-3.6); 1.0, 1.7, 2.8 (trend, p = 0.007)	Adjusted for age, education, total energy intake, smoking, use of vitamin supplements
Brownson, Chang, Davis, and Smith (1991)	Missouri cancer registry, 2878 cases of PC, controls are cancers at other body sites	High vs. moderate vs. low occupational activity	OR 1.0, 1.1, 1.5 (1.2-1.8), p <0.01	Adjusted for age, smoking
Doolan et al. (2014)	1436 cases of PC, 1349 matched controls	Finnish job matrix, physical work-rate tertiles	OR *highest* tertile 1.15 (0.95-1.40, ns)	Adjusted for age, family history, economic resources
Dosemeci et al. (1993)	27 cases PC, 2127 hospital controls	<8 kJ/min vs. > 12 kJ/min; active at work <2h/day vs. > 6h/day	OR 5.0 (1.1-31.7); OR 3.4 (1.1-10.6)	Adjusted for age & smoking; very small sample
Friedenreich et al. (2004)*	988 incident cases of PC, 1063 population controls	energy expenditure <74.2 vs. >161.9 MET-hr/wk	OR 0.90, 0.60-1.22(ns)	Adjusted for age, region, education, BMI, waist/hip ratio, energy intake, alcohol consumption, family & medical history
Hosseini et al. (2010)	137 cases of PC, 137 neighbourhood controls	Walking to work (<10 vs. >10 hr/wk), intensity of work (inactive/moderatel y active vs. highly active)	OR 0.7 (0.4-1.2) for longer walk (ns); OR = 6.7 (1.3-35.1) for highly active work (p = 0.02)	Multivariate adjusted
Ilić et al. (1996)	101 cases of incident PC, 202 hospital controls, mean age ~71 yr	Occupational activity in year preceding diagnosis	OR 3.87 (2.09-7.16)	Disease in controls may have limited industrial work; also differences in exposure to industrial toxins

Table 1 Continued

Author	Sample	Activity measure	Findings	Comments
Krishnadasan et al. (2008)	362 cases of PC, 1805 matched controls	Low vs. moderate vs. high occupational energy expenditure	OR 0.63 (0.40-1.00, p = 0.06 for trend)	Adjusted for matching variables, pay, trichlorethylene exposure
Lacey et al. (2001)*	258 cases of PC, 471 age-matched controls	Sedentary, moderate or high occupational energy expenditures at 20-29 yr, 40-49 yr or 12 yrs ago	RR 1.1 (0.7-1.7), 1.3 (0.8-1.9), 0.9 (0.5-1.8) favouring *sedentary* group	Adjusted for age, marital status, education, BMI, energy intake, waist/hip ratio
Lagiou et al. (2008)	320 histologically confirmed PC, 246 hospital controls	Low, medium, high level of occupational activity	OR 0.69 (0.40-1.22, ns) for physically demanding occupation	Adjusted for age and education
Le Marchand et al. (1991)	452 cases from Hawaii tumour registry, 899 population controls	Time spent in sedentary jobs (0 - >54%)	No effect if <70 yrs; if >70 yrs, OR 0.6 (0.4-1.0, p for trend = 0.07)	Adjusted for age and ethnicity
Pierotti et al. (2005)*	1294 incident cases of PC aged <75 yr & 1451 hospital controls	3-level categorization of occupational activity at ages 12, 15-19, 30-39 & 50-59 yr	OR age 12 = 0.84 (0.67-1.06), age 15-19 = 0.94 (0.75-1.17), age 30-39 = 0.78 (0.63-0.97), age 50-59 = 0.75 (0.61-0.93)	Adjusted for age, test centre, education, SES, BMI, total energy intake, smoking, alcohol consumption, family history
Sass-Kortak et al. (2007)	760 PC cases, 1632 telephone controls	Quartiles of lifetime occupational activity	OR 1.33 for active workers (1.02-1.74) p for trend = 0.18	Adjusted for age, family history, sunlight exposure
Strom et al. (2008)*	176 cases of PC in Mexican-Americans, 176 controls	None/low vs. moderate/high energy demands of work	Reduced risk in active (OR 0.46, 0.28-0.77, p = 0.003)	Adjusted for age, education, screening, exposure to agricultural chemicals
Villeneuve et al. (1999)*	1623 histologically confirmed cases of PC, 1623 controls	4-level classification of work (sitting to strenuous)	Significant benefit from activity in teens or early 20s, (OR 0.6, 0.4-0.9), ns 30s, 50s, or 2 yr before interview	Adjusted for age, area of residence, smoking, alcohol consumption, BMI, diet, income, family history
Wiklund et al. (2008)*	1449 incident cases of PC, 1118 population controls	MET-h/day of lifetime occupational activity, <11.8 to >19.8	OR 0.84 (0.61-1.15), ns; trend to benefit from active employment	Adjusted for age, region, education, BMI, alcohol consumption, family history, diabetes mellitus, energy intake

* same article also evaluated association of prostate cancer risk with leisure activity

ns = not significant. HR = hazard ratio. PC = prostate cancer. OR = odds ratio. PMR = proportionate mortality ratio. RR = relative risk or rate ratio. SIR = standardized incidence ratio.

After adjusting data for age, urban living, smoking, and a history of benign prostatic hyperplasia, the relative risk of prostate cancer showed no association with physical demands on the job (respective risk ratios 1.0, 0.6, 0.8 and 1.2). Johnsen et al., (2009) followed 127,923 men for an average of 8.5 yr, accumulating a larger sample of 2458 cases of prostate cancer. Data were controlled for leisure activity, height, body mass, marital status and educational attainment. The individual's level of occupational activity (whether classed as sitting, standing or manual work; or as inactive, moderately inactive, moderately active and active) bore no relationship to the risk of prostate cancer, although *advanced* prostate cancer was seen less frequently in those with a high level of occupational activity (p = 0.024);

one possible explanation of this finding is that those with advanced prostate cancer had already dropped out of heavy employment. Lund Nielsen et al., (2000) observed 22,895 Norwegian men for 9.3 yr, finding 644 incident cases of prostate cancer. The intensity of occupational activity was classed in binary fashion (high or low), and after co-variate adjustment, there was no association between this simple classification and the risk of prostate cancer. Putnam and associates (2000) found 101 cases of prostate cancer in a sample of 1572 initially cancer-free men who were followed for 4 yr. In this study, the type of employment was classified as very active, moderately active or inactive, but after controlling simply for age, the incidence of prostate cancer was unrelated to the energy demands of work. Severson et al. (1989) questioned 8006 Japanese men living on the island of Oahu, Hawaii; 205 of this group had developed prostate cancer. A self-estimate of the physical demands of employment for the study participants proved unrelated to the development of this condition. Zeegers and colleagues (2005) followed 58,279 Dutch men initially aged 55-69 yr over a period of 9.3 yr, encountering 1386 cases of prostate cancer. They classed occupational activity in terms of both estimated energy expenditures and sitting time, and after allowance for age, alcohol consumption, body mass index, total energy intake, family history and education, no association was found between either of these measures and the risk of prostate cancer. Of the six investigations pointing to a favourable trend in active individuals, Albanes et al. (1989) observed 95 cases of prostate cancer in 5141 men who had been followed for an average of 10 yr. Comparing those who very active with those who were quite inactive at work, the age-adjusted relative risk was 1.3, but given the small total number of cases, this ratio was not statistically significant. Grotta et al. (2015) followed 13,109 Swedish men for a total of 13 yr, finding 904 cases of prostate cancer. There was a weak trend to benefit from a high level of occupational activity after adjusting data for age, education, smoking, body mass index, alcohol consumption, and diabetes mellitus [a hazard ratio of 0.81 (0.61 - 1.07, not statistically significant)]. Harvei and Kravdal (1997) followed a large sample of Norwegian men over the age of 50 yr, finding upwards of 30,000 cases of prostate cancer. The type of occupation was classed as agriculture, manufacturing or service industry, and this rather coarse grouping proved unrelated to the relative incidence of prostate tumors; however, after adjusting data for the subject's age, period of observation and region of residence, there was an adverse effect of educational attainment. Comparing a high level of education relative to basic instruction, the relative incidence of prostate cancer was 1.21 (1.13-1.29); the authors of this report suggested the difference was unlikely to be a consequence of more frequent monitoring in the well-educated men, since it applied to both localized and metastasized tumours; possibly, education was serving as a surrogate marker of more sedentary employment. Hrafnkelsdóttir and associates (2015) carried out a 24-year follow-up of 822 Icelandic men. The pattern of occupational activity in this group was classed as mostly sitting, standing or moving. The hazard ratios, adjusted for age, height, body mass index, diabetes mellitus, family history, education, and medical check-ups showed a weak trend favouring those who were engaged in work that was physically more

demanding [respective values of 1.0, 0.97, and (for the most active group) of 0.91 (0.79-1.06, ns] (Hrafnkelsdóttir et al., 2015). Hsing et al. (1994) obtained occupational titles for 264 men with prostate cancer, calculating standardized incidence ratios (SIR) in relation to the anticipated sitting time and energy expenditures at work, apparently without using any co-variates. For sitting time, the SIR was 0.94 for those who were seated less than 2 hr per day, compared with 1.23 for those sitting longer than 6 hr per day ($p = 0.14$), and in terms of estimated energy costs the SIR was 1.23 for those with energy expenditures averaging <8 kJ/min, compared with 0.92 for those expending > 12 kJ/min ($p = 0.06$) (Hsing et al., 1994). Thune and Lund, (1994) examined 220 cases of prostate cancer in 53,242 Norwegians who had been followed for an average of 16.3 yr. After adjusting data for age, body mass index and geographic region of residence, a 4-level classification of the physical demands of occupation (which ranged from sedentary to heavy manual) found a trend to an advantageous risk ratio [0.81 (0.50-1.30)] in those who were engaged in heavy physical work (Thune and Lund, 1994).

Among the 6 investigations observing a statistically significant lower risk of prostate cancer in those men who were more active at work, Clarke and Whittemore (2000) followed 5377 men for 17-21 yr, accumulating 201 incident cases of prostate cancer. Controlling data for age, educational attainment, ethnicity, and family history, the relative risk of sedentary versus active employment was 1.75 (1.12-2.67, $p = 0.05$ for a trend), apparently with an even greater effect in the small African-American subset of their sample (Clarke and Whittemore, 2000). Norman et al. (2002) examined data for 3 cohorts of 43,836, 28,702 and 19,670 patients with prostate cancer. The physical demands of the various occupational titles were categorized from sedentary to very high, and with adjustment of data for age, year of follow-up and area of residence, a small but highly significant increase of relative risk was seen in sedentary individuals [respective risks for the 3 cohorts of sedentary individuals, 1.11, 1.10 and 1.11 ($p = 0.0001$)] (Norman et al., 2002). Orsini et al. (2009) followed 45,887 men for 8 yr, accumulating 2735 incident cases of prostate cancer. Four categories of employment were recognized (ranging from mostly sedentary jobs to heavy manual work). After allowing for leisure activity, age, smoking, alcohol consumption, educational attainment, diet, energy intake, waist/hip ratio and diabetes mellitus, the risk ratio favoured active workers [0.72 (0.57-0.90), p for trend = 0.007]; however, the advantage was smaller for individuals with advanced or fatal cancers (Orsini et al., 2009). Parent et al. (2011) questioned 449 incident cases of prostate cancer on the level of their lifetime occupational energy expenditures (high vs. low, METs); the odds ratio for this sample strongly favoured those in active employment [0.54 (0.31-0.95)]. Vena et al., (1987) obtained data on 430,000 men in Washington State, including 8116 men who had died from prostate cancer. A 4-level classification of occupational activity was made, and although the findings were not altogether consistent from decade to decade and did not show clear trends, a comparison of the overall proportional mortality between those with low (109) and high (93) occupational demands showed a clear advantage to the heavy workers ($p < 0.05$) (Vena et al., 1987). Vidarsdottir et al. (2008) followed a

group of men ranging broadly in age from 20 to 64 yr for a total of 23 yr. As in the study of (Harvei and Kravdal, 1997), the main focus was on the level of education (basic, medium or academic), and the academic group showed a significant disadvantage relative to those receiving only a basic education [a standardized incidence ratio of 1.17 (1.05-1.30)]. Here, academic education again possibly served as a surrogate measure of a sedentary career, although no check was made for the possibility that the better-educated group also had more frequent medical examinations and thus a more complete diagnosis of small tumors.

Case-control studies. Of 16 case-control studies, 6 found either no effect or a trend to a higher risk of prostate cancer in individuals who had been engaged in heavy employment, 3 observed a positive trend, and in 7 there was significant benefit from heavy work.

Of the neutral findings, Ilić et al. (1996) compared 101 cases of incident prostate cancer with 202 hospital controls, asking about occupational activity in the year immediately preceding the diagnosis. There was a substantial adverse odds ratio among those engaged in heavy work during this period [3.87 (2.09-7.16)], but the authors of this report recognized 2 important weaknesses in their analysis. As in several other investigations, the controls were drawn from hospital patients, and some of these individuals had serious diseases that may have restricted their participation in heavy industrial work. Moreover, a number of those with prostate cancer had been exposed to potentially carcinogenic industrial toxins (Ilić et al., 1996). Doolan et al., (2014) compared 1436 cases of prostate cancer with 1349 matched controls, using the Finnish job matrix to classify the physical workload into tertiles of energy expenditure. After adjusting their data for age, family history, and economic resources, the odds ratio for developing prostate cancer tended to be higher in those individuals with the highest workload [odds ratio 1.15 (0.95-1.40)] (Doolan et al., 2014). Hosseini et al., (2010) related 137 cases of prostate cancer to 137 neighbourhood controls. Although a binary classification of walking to work (<10 vs. >10 hr/wk) tended to show a reduce risk for those taking a longer walk [odds ratio 0.7 (0.4-1.2)(ns)], a comparison between those with inactive or moderately active employment and those with highly active work yielded a large multivariate adjusted odds ratio favouring those with the less demanding work [6.7 (1.3-35.1)(p = 0.02)] (Hosseini et al., 2010). Lacey et al. (2001) compared 258 cases of prostate cancer with 471 age-matched controls. The type of occupation (classed as sedentary, moderate or highly active) yielded similar findings whether examined at ages 20-29, 40-49, or 12 yr prior to the report; after adjusting data for age, marital status, educational attainment, body mass index, energy intake and waist/hip ratio, risk ratios 1.1 (0.7-1.7), 1.3 (0.8-1.9), 0.9 (0.5-1.8) tended to favour the sedentary over the highly active group (Lacey et al., 2001). Sass-Kortak et al., (2007) compared 760 prostate cancer cases with 1632 controls gleaned from telephone listings. Quartiles of lifetime occupational activity adjusted for age, family history and sunlight exposure showed an adverse effect in the most active workers [odds ratio 1.33 (1.02-1.74), p for trend 0.18] (Sass-Kortak et al.,2007). Friedenreich and associates (2004) found no effect of occupation upon the risk of prostate cancer; they compared data for 988 incident cases

with 1063 population controls in terms of the estimated energy expenditures at work (<74.2 vs. >161.9 MET-hr/wk). After controlling for age, region, educational attainment, body mass index, waist/hip ratio, energy intake, alcohol consumption, family and medical history, there was no association between prostate cancer and the physical demands of work (Friedenreich et al., 2004).

In three reports, there was a trend to lower risk among those who had been engaged in heavy work. Lagiou et al. (2008) assigned each of 320 histologically confirmed cases of prostate cancer and 246 hospital controls between 3 categories of occupational energy expenditure (low, medium or high). Following data adjustment for age and educational attainment, there was a non-significant trend [odds ratio 0.69 (0.40-1.22] suggesting a lower risk among those with physically demanding work (Lagiou et al., 2008). Le Marchand et al. (1991) found 452 cases of prostate cancer in the Hawaii tumour registry. The portion of the lifespan spent in sedentary jobs (0 - >54%) was compared with that seen in 899 controls from the same population. In those under the age of 70 yr, after adjustment of data for age and ethnicity, the risk of developing prostate cancer was unaffected by sedentary employment; however, in older individuals there was a trend for a decreased risk in those with more active jobs [odds ratio 0.6 (0.4-1.0, p = 0.07 for trend] (Le Marchand et al., 1991). Wiklund et al. (2008) compared 1449 incident cases of prostate cancer with 1118 population controls; the average intensity of lifetime occupational activity was classed over a range from <11.8 to >19.8 MET-h/day, and there was a weak trend to lower risk among those with the most demanding occupations [odds ratio 0.84 (0.61-1.15), ns] after controlling data for age, region, educational attainment, body mass index, alcohol consumption, family history, diabetes mellitus and total energy intake (Wiklund et al., 2008).

Seven case-control studies found an association between physically active employment and a significantly lower risk of prostate cancer. Bairati and colleagues (2000) compared 64 cases of prostate cancer with 5456 cases of benign prostate hyperplasia, all aged >45 yr. After adjusting for age, educational attainment, total energy intake, smoking, and the use of vitamin supplements, the odds ratio associated with ever having held a sedentary job or light work was 2.0 (1.1-3.6), and on the basis of spending 0%, 1-49%, or >50% of one's career in sedentary or light work, the respective odds favouring the heavy workers were 1.0, 1.7, and 2.8 (trend, p = 0.007). The advantage was even greater for those whose longest-held job had involved high or very high rates of energy expenditure [odds ratio 0.2 (0.1-0.7)] (Bairati et al. 2000). Brownson et al. (1991) drew 2878 cases of prostate cancer from the Missouri cancer registry, comparing the level of occupational activity (high vs. moderate vs. low physical demand) with controls registered as having developed other types of cancer. Odds ratios for the 3 categories of work, after controlling for age and smoking, were 1.0, 1.1, and 1.5 (1.2-1.8), with a statistically significant trend favouring the heavy workers (p <0.01) (Brownson et al., 1991). Darlington et al. (2007) drew a comparison between the experience of 752 cases of prostate cancer selected from the Ontario cancer registry, and telephone listing controls. Subjects were asked about undertaking strenuous occupational activity in their mid-teens, early 30s, and early 50s. After adjusting

data for age, educational attainment, body mass index, family history, and occupation, strenuous physical activity by men in their 50s was associated with a reduced the risk of prostate cancer [odds ratio 0.8 (0.6-0.9)], but the effect was not statistically significant if the heavy work had been performed only during the other 2 age periods (Darlington et al., 2007). Dosemeci and associates (1993) contrasted occupations between 27 cases of prostate cancer and 2127 hospital controls; after adjusting for age and smoking habits, significant adverse odds were found for men having a low energy expenditure at work (<8 kJ/min vs. > 12 kJ/min) and for those spending a low proportion of their working day in physical activity (<2 hr versus 6 hr) with respective odds ratios of 5.0 (1.1-31.7) and 3.4 (1.1-10.6); however, these findings should probably be discounted because of the very small sample size. In a nested case-control study, Krishnadasan et al. (2008) rated the intensity of occupational energy expenditures as low, moderate or high in 362 cases of prostate cancer and 1805 matched controls. Adjusted data for matching variables, salary, and trichloroethylene exposure, there was a strong trend for reduced risk in the more active workers [odds ratio 0.63 (0.40-1.00, p = 0.06 for trend]. This was statistically significant for aerospace workers, but not for radiation workers, although the reason for the discordant effect between the 2 types of work was not elucidated (Krishnadasan et al., 2008). Pierotti et al. (2005) compared 1294 incident cases of prostate cancer with 1451 hospital controls, making a 3-level categorization of occupational demands at 12, 15-19, 30-39, and 50-59 yr of age. After adjusting findings for age, test centre, education, socio-economic status, body mass index, total energy intake, smoking, alcohol consumption and family history, the risk of prostate cancer was lower in heavy than in sedentary workers, with respective odds ratios of 0.84 (0.67-1.06) at age 12, 0.94 (0.75-1.17) at age 15-19, 0.78 (0.63-0.97) at age 30-39, and 0.75 (0.61-0.93) at age 50-59 yr (Pierotti et al., 2005). Strom et al. (2008) compared 176 cases of prostate cancer found in Mexican-Americans, with data for 176 matched controls. Occupational activity was rated as none/low vs. moderate/high, and after allowing for the effects of age, educational attainment, cancer screening and exposure to agricultural chemicals, a reduced risk was seen in those with active occupations [odds ratio 0.46, 0.28-0.77, p = 0.003] (Strom et al. 2008). Villeneuve et al. (1999) compared 1623 histologically confirmed cases of prostate cancer with 1623 controls. After adjusting data for age, area of residence, smoking, alcohol consumption, body mass index, diet, income and family history, a 4-level classification of occupational energy demands (ranging from sitting to strenuous work) found significant benefit was associated with heavy physical activity in the teens or early 20s, [odds ratio 0.6 (0.4-0.9)], with parallel but non-significant trends in the 30s, 50s, and during the 2 yr before being interviewed (Villeneuve et al., 1999).

Leisure activities. Patterns of recent leisure activity could theoretically be ascertained by interview, by the use of a personal monitor such as a pedometer or accelerometer, or by inference from surrogate measures such as maximal oxygen intake, but because of the large number of subjects involved in many epidemiological studies, recourse has usually been to physical activity questionnaires. Not only do these

instruments have limited reliability and validity (Shephard, 2003), but also they usually examine current or recent activity, rather than an individual's behaviour 10 to 30 yr previously, when carcinogenesis likely began. Attempts to determine lifelong activity patterns face inevitable problems when dealing with elderly individuals who have fading memories of their lifestyle as young adults.

Retrospective and prospective cohort studies. Of 28 retrospective and prospective cohort studies (Table 2), one found a strong (but not statistically significant) adverse trend, and 11 others found no clear association between physical activity and the risk of prostate cancer; 12 further analyses noted trends suggesting a lower risk those among with an active lifestyle, and 4 reports presented statistical evidence of a favorable outcome for those individuals within their sample who were active during their leisure time (Cerhan et al., 1997).

Cerhan and colleagues (1997) found a strong trend to an adverse effect of exercise among a population in rural Iowa, observing a relative risk of 2.7 (0.87-9.9) among those who reported engaging in vigorous physical activity. In interpreting this data, note should be taken of a small sample size (there were only 71 cases of prostate cancer, divided between 5 categories of leisure activity). Moreover, the measure of physical activity used in this study was relatively crude, and although data were adjusted for age, body mass index and smoking, no information was obtained on occupation and thus possible exposure to agricultural toxins (Cerhan et al., 1997).

Among the 11 investigations with neutral findings, Crespo et al. (2008) followed a group of 9824 men initially aged 35-79 yr until their death. Data were adjusted for age, educational attainment, urban residence, smoking, and body mass index, but no relationship was found between the likelihood of death from prostate cancer and physical activity as assessed by the Framingham index (Crespo et al., 2008). Giovannucci et al., (1998) observed 47,452 health professionals for 8 yr, finding 1362 incident cases of prostate cancer. Individual leisure energy expenditures, graded from 1 to 46.8 MET-hr/wk, were adjusted for age, vasectomy, diabetes mellitus, smoking, energy intake, and diet. No significant relationship to prostate cancer was seen, except for a suggestion of less metastatic activity among the more active individuals (Giovannucci et al., 1998). Grotta and associates (2015) followed 13,109 Swedish men for 13 yr, during which time 904 cases of prostate cancer developed. After co-varying data for age, educational attainment, smoking, body mass index, alcohol consumption and diabetes mellitus, the hazard ratio [0.93 (0.76 - 1.14, ns)] showed little tendency to a lower risk among those who engaged in greater leisure activity (Grotta et al., 2015). Johnsen et al. (2009) followed 127,923 men for 8.5 yr, accumulating 2458 cases of prostate cancer. With adjustment of their data for occupational activity, height, body mass, marital status and education, no association was seen between quartiles of leisure energy expenditure (<25 to >71 MET-hr/wk) and the risk of prostate cancer. Moreover, unlike their occupational data, no significance was seen when the analysis focused simply on the risk of advanced tumors (Johnsen et al., 2009). Lee and colleagues (2001) made one of several examinations of their data on the leisure activity of Harvard

alumni, using a questionnaire to estimate weekly active energy expenditures at entry to the study. Data were placed into quartiles (<4.2 >12.6 MJ). After allowing for age, body mass index, smoking, alcohol consumption, and family history, prostate cancer was found to be unrelated to either the total weekly active energy expenditure or the volume of *vigorous* physical activity (Lee et al., 2001). Littman et al. (2006) studied 34,757 men who were initially aged 50-76 yr, finding 583 incident cases of prostate cancer. An exhaustive study of each individual's leisure behaviour looked at the total MET-hr/wk of physical activity, typical walking pace, the number of stairs climbed, the amount of high intensity activity, and physical activity performed at earlier points in the lifespan. Controlling for family history, body mass index and income, none of these analyses found any association with the risk of prostate cancer, except in a sub-group aged >65 yr who had maintained a normal body mass; in contrast, active older subjects who were overweight had an increased risk of prostate cancer (Littman et al., 2006). Liu and associates (2000) found 982 cases of prostate cancer when they followed 22,071 physicians over a period of 11 yr. The frequency of taking a sufficient amount of exercise to work up a sweat ranged from less than once a week to more than 5 times per week; with adjustment for smoking, alcohol consumption, height, diabetes mellitus, high cholesterol, hypertension and the use of multi-vitamins, the frequency of vigorous activity showed no association with the risk of prostate cancer (Liu et al., 2000). Parent et al. (2011) questioned 449 incident cases of prostate cancer on their involvement in recreational activities; no significant association with the risk of prostate tumors was seen. Platz et al. (2003) examined 46,786 health professionals; over 14 yr, they found 2896 incident cases of prostate cancer in this sample. Noting all periods when subjects were exercising at an intensity >6 METS, a binary classification of the volume of *vigorous* leisure activity was made (<3, >3 MET-hr/wk). Adjusting for age, family history, body mass index, diabetes mellitus, smoking, and diet, there was no difference in the incidence of prostate cancer between the 2 halves of the sample. However, an increase of risk was seen in individuals reporting a high energy intake, suggesting the possibility that some people may have used an excess energy intake for the growth of tumor tissue rather than for fat formation (Platz et al., 2003). Putnam et al. (2000) found 101 cases of prostate cancer in 1572 initially cancer-free men who were followed for 4 yr. A 3-level classification of leisure activity (very active, moderately active, and inactive) proved unrelated to the risk of prostate cancer after adjusting data for the total energy intake. Thune and Lund (1994) observed 220 cases of prostate cancer in 53,242 Norwegians who were followed for 16.3 yr. A three-level classification of leisure behaviour (sedentary to undertaking regular training) was made, but they found no association between this classification and the risk of prostate cancer after adjustments for age, body mass index and geographic region of residence (Putnam et al., 2000). A similar number of investigations found suggestive but non-significant trends favouring active individuals. Clarke and Whittemore (2000) followed 5377 men for 17-21 yr, accumulating 201 cases of prostate cancer. Data were adjusted for age, educational attainment, ethnicity, and family history, and a cross-sectional comparison was then made between

Table 2: Leisure-time physical activity and the risk of prostate cancer.

Author	Sample	Activity measure	Findings	Comments
Cohort studies				
Albanes et al. (1989)*	95 cases of PC in 5141 men over 10 yr follow-up	Much vs. little or no recreational exercise	RR for inactive 1.8 (1.1-3.3).p = 0.02 for trend	Age-adjusted
Cerhan et al. (1997)	20-yr follow-up of 1050 men initially aged 73.5 yr and cancer free, 71 cases of PC	5-question assessment of physical activity (vigorous, moderately active or inactive)	Risk relative to non-cases: Inactive RR = 1.0, Moderate = 1.9 (0.5-6.5) Vigorous = 2.7 (0.7-9.9)	Adjusted for age, BMI, smoking; no information on occupational activity or agricultural chemicals
Chen, Chiang, and Lin (2005)	237 cases of PC, 481 controls aged >50 yr	Primarily a dietary study- 4 level categorization of physical activity	Adverse effect of high vs. moderate exercise: OR 1.84 (1.01-3.34)	Multivariate analysis (age, BMI, income, marriage & dietary variables
Clarke and Whittemore (2000)*	5377 men followed for 17-21 yr, 201 cases of PC	Much vs. little or none	RR for inactive 1.17 (ns)	Adjusted for age, education, ethnicity, and family history
Crespo et al. (2008)	9824 men initially aged 35-79 yr followed for mortality	Framingham index (quartiles)	No relationship between physical activity & prostate deaths	Adjusted for age, education, urban residence, smoking, BMI
Giovannucci et al. (1998)* **	47,452 health professionals followed for 8 yr, 1362 incident cases of PC	Leisure activity, 1 vs. 46.8 MET-hr/wk	No significant relationship except suggestion of less metastatic activity with vigorous intensity exercise	Adjusted for age, vasectomy, diabetes mellitus, smoking, energy intake, diet
Giovannucci et al. (2005)	47,620 health professionals, 14 yr follow-up, 2892 incident cases of PC (482 advanced, 280 fatal)	Vigorous physical activity, 0 vs >29 MET-hr/wk	No relationship for all subjects; if > 65yr, OR for advanced cancer 0.33 (0.17-0.62)	Age, BMI, smoking, height, family history, diabetes mellitus, ethnicity, non-vigorous activity, energy intake & diet
Grotta et al. (2015)*	13,109 Swedish men followed for 13 yr, 904 cases of PC	Low vs. high leisure activity	HR 0.93 (0.76 - 1.14, ns)	Adjusted for age, education, smoking, BMI, alcohol consumption, diabetes mellitus
Hartman et al. (1998)*	29,133 men followed for up to 9 yr, 317 cases of PC	Sedentary vs, moderate/heavy leisure activity in working men	RR 0.7 (0.46-0.94) favouring active leisure	Adjusted for age, urban living, smoking, benign hyperplasia
Hrafnkelsdóttir et al. (2015)*	24-year follow-up of 822 Icelandic men	Regular physical activity from age of 20 yr vs. sedentary	HR 0.93 (0.83-1.07) for active individuals	Adjusted for age, height, BMI, diabetes, family history, education, medical check-ups
Johnsen et al. (2009)*	127,923 men followed for 8.5 yr; 2458 cases of PC	Quartiles of leisure activity (<25 to >71 MET-hr/wk)	Leisure activity unrelated to PC	Adjusted for occup. activity, height, body mass, marital status & education
Lee et al. (1992)**	17, 719 Harvard alumni, 419 cases of PC	Activity questionnaire completed on 2 occasions	OR if weekly expenditure >16 MJ 0.12 (0.02-0.89) (only 1 case of PG)	Adjusted for age
Lee et al. (2001)	8922 Harvard alumni, 439 developed PC	Physical activity questionnaire completed twice, weekly energy expenditure quartiles (<4.2 MJ - > 12.6 MJ)	PC unrelated to total activity or weekly volume of vigorous physical activity	Adjusted for age, BMI, smoking, alcohol consumption, family history

Table 2 Continued

Author	Sample	Activity measure	Findings	Comments
Paffenbarger et al. (1987)**	16,936 male Harvard graduates followed 12-16 yr, with 36 deaths from PC	Questionnaire-based physical activity index (<2 MJ/wk vs >8 MJ/wk)(	Mortality rate 2.7 vs. 1.5/10,000 man-yr (ns)	Adjusted for age, smoking, BMI
Littman et al. (2006)	34,757 men initially aged 50-76 yr, 583 cases of PC	MET-hr/wk, walking pace, stair climbing, high intensity activity, activity at earlier ages	No association with PC except in sub-group aged >65 yr with normal body mass	Adjusted for family history, BMI, income
Liu et al. (2000)	982 cases of PC in 22,071 physicians over 11 yr	Exercise sufficient to cause a sweat <1/wk. vs. >5/wk	No relationship to PC	Adjusted for smoking, alcohol consumption, height, diabetes mellitus, high cholesterol, hypertension, use of multi-vitamins
Lund Nielsen et al. (2000)*	22,895 Norwegian men followed for 9.3 yr, with 644 cases of PC	High vs. low leisure activity	RR 0.80 (0.62-1.03)	Multivariate adjusted
Moore et al. (2008)	293,902 men initially aged 50-71 yr followed for up to 8.2 yr, 17,872 cases PC	Exercise at baseline and in adolescence (never/rarely to >5 times/wk)	RR 0.97 (0.91 - 1.03) p for trend favouring activity during adolescence = 0.03. But no relationships to exercise habits at baseline.	Adjusted for age, marital status, education, smoking, medical history, BMI, waist circumference, family history, diet & supplements
Nilsen et al. (2006)	29,110 Norwegian men followed for 7 yr, 957 incident cases PC	Score based on frequency, intensity & duration of activity (low vs. high)	Relationship for total cancer ns (RR = 0.86), but for advanced cancer RR = 0.64 (0.43-0.95), inverse trend p = 0.02	Adjusted for age, marital status, education, BMI, smoking, alcohol consumption
Orsini et al. (2009)*	45,887 men followed for 8 yr, 2735 incident PC	Walking or cycling, 5 categories (hardly ever to > 60 min/day)	RR = 0.86 (0.76-0.98) p for trend 0.028; effects greater for advanced (RR = 0.74) & fatal (RR = 0.72) cancers	Adjusted for occupational activity, age, smoking, alcohol consumption, education, diet, energy intake, waist/hip ratio, diabetes mellitus
Parent et al. (2011)	449 incident cases of PC	Involvement in sports & outdoor activities	No significant effect on PC	
Patel et al. (2005)	72,174 men, 5503 incident cases of PC over 9 yr	MET-hr/wk (<0.7-35) at age 40 & in 1992(Patel et al., 2005)	No significant effect (but active have fewer aggressive tumours, RR 0.69, 0.52-0.92, p for trend = 0.06)	Adjusted for age, ethnicity, BMI, weight change, energy intake, diet & vitamin use, diabetes mellitus, family & medical history
Platz et al. (2003)**	46,786 health professionals, 2896 incident cases PC over 14 yr	Vigorous leisure activity <3, >3 MET-hr/wk	No relationship to PC	Adjusted for age, family history, BMI, diabetes mellitus, smoking, diet
Putnam et al. (2000)*	101 cases of PC in 1572 initially cancer free men followed for 4 yr	Very active, moderately active, inactive	Risk of PC unrelated to leisure activity	Adjusted for total energy intake

Table 2 Continued

Author	Sample	Activity measure	Findings	Comments
.Severson et al. (1989)*	8006 Japanese men on Oahu; 205 cases of PC	Framingham index, resting heart rate, self-estimate of moderate or heavy leisure activity	Risk of PC un related to Framingham index or resting heart rate; suggestion of benefit from self-assessment (OR 0.77, 0.58-1.01)	Adjusted for age, BMI
Steenland et al. (1995)	156 cases of PC in NHANES I survey follow-up	Physical activity- little vs. lots.	Suggestion of benefit from activity, OR 1.31 (0.76-2.26, ns)	Adjusted for age, BMI, smoking, alcohol consumption, income
Thune and Lund (1994)*	220 cases of PC in 53,242 Norwegians followed for 16.3 yr	3-level classification, sedentary to regular training	No effect of leisure activity	Adjusted for age, BMI, geographic region
Wannamethee et al. (2001)***	Prospective study of 7588 men with 120 incident cases of PC	6-level classification of leisure activity from none to vigorous	Benefit from vigorous activity, OR 0.25 (0.06-0.99, p for trend = 0.06)	Adjusted for age, smoking, alcohol consumption, BMI, social class
Zeegers et al. (2005)*	58,279 men aged 55-69 yr, 1386 cases of PC over 9.3 yr	Biking/walking (min/day), gardening (hr/wk)	Gardening unrelated to PC; biking/walking <10 vs. > 60 min/d, RR 0.85 (0.69-1.05, ns)	Adjusted for age, alcohol consumption, BMI, energy intake, family history, gardening, sport involvement
Case/control studies				
Andersson et al. (1995)	252 cases of PC, 243 controls	Pubertal activity relative to peers, lower, same or higher	OR = 1.3, 1.0, 0.7 (p for trend 0.13)	Adjusted for age, urbanization, adult farming
Darlington et al. (2007)	752 cases from Ontario cancer registry aged 50-84 yr, telephone listing controls	Strenuous activity mid-teens, early 30s, early 50s	Strenuous activity by men in 50s reduced risk (OR 0.8, 0.6-0.9). Other age groups ns	Adjusted for age, education, BMI, family history, occupation
Friedenreich et al. (2004)*	988 incident cases of PC, 1063 population controls	<78.5 vs. >25.1 MET-hr/wk	OR 1.00, 0.80 (0.61-1.04) (p = 0.06 for trend)	Adjusted for age, region, education, BMI, waist/hip ratio, energy intake, alcohol consumption, family & medical history
Jian et al. (2005)	130 histologically confirmed PC, 274 controls	Reported MET-h of moderate & total activity (<40 vs >120; <44 vs. >135)	OR 0.20 (0.07-0.62, p = 0.015), 0.39 (0.15-0.99, p = 0.50 for trend)	Adjusted for age, area of residence, education, income, marital status, number of children, years in work force, family history, BMI, energy intake
Lacey et al. (2001)*	258 cases of PC, 471 age-matched controls	Tertiles of moderate/vigorous or all physical activity at 20-29, 40-49 and 12 yrs ago	No relationship to PC	Adjusted for age, marital status, education, BMI, energy intake, waist/hip ratio
Pierotti et al. (2005)*	1294 incident cases of PC aged <75 yr & 1451 hospital controls	3-level categorization of physical activity at ages 12, 15-19, 30-39 & 50-59 yr	No effect on risk of PC at any age	Adjusted for age, test centre, education, SES, BMI, total energy intake, smoking, alcohol consumption, family history

Table 2 Continued

Author	Sample	Activity measure	Findings	Comments
Sanderson et al. (2004)	416 incident cases of PC, 429 Medicare beneficiary controls aghed 65-79 yr	Tertiles of strenuous and of moderate physical activity (hr/wk)	No relationship to PC in either African American or Caucasian men	Adjusted for age, geographic region & family history
Strom et al. (2008)*	176 cases of PC in Mexican-Americans, 176 controls	Leisure activity <1/wk vs. >1/wk	No effect on risk of PC	
Sung et al. (1999)	90 cases of PC, 180 controls	Exercise (yes vs. no) 5-10 yr before diagnosis	*Adverse* effect of exercise [OR 2.16, 1.18-3.96, p = 0.01]	Multivariate adjusted
West et al. (1991)	358 cases of PC, 679 controls	Activity questionnaire	No relationship between activity and PC	
Whittemore et al. (1995)	1655 cases of PC, 1645 population controls	Activity questionnaire	No relationship between activity and PC	
Wiklund et al. (2008)	1449 incident cases of PC, 1118 population controls	MET-h/day lifetime recreational activity, <7.4 to >13.5	OR 1.56 (1.16-2.10), p= 0.006, adverse effect of active leisure	Adjusted for age, region, education, BMI, alcohol consumption, family history, diabetes mellitus, energy intake
Yu et al. (1988)	1162 cases of PC, 3124 matched hospital controls	Leisure activity (active, moderate or seldom)	Risk higher in sedentary (OR 1.3, 1.0-1.6 p = 0.03)	Adjusted for age

* The same report also presented data on occupational activity and prostate cancer risk. ** Duplicate analyses of same data set. *** The same report also presented data on the frequency of sports participation
ns = non-significant. BMI = body mass index. HR = hazard ratio. MET = metabolic equivalent. OR = odds ratio. PC = prostate cancer. RR = relative risk.

those taking much versus those engaging in little or no recreational activity. The relative risk for the inactive men was 1.17 (not statistically significant); a much higher apparent risk was found in the relatively small African-American segment of the total sample (relative risk 3.17, 0.96-10.46, p = 0.08) (Clarke and Whittemore, 2000).

Giovannucci et al. (2005) analyzed data for U.S. health professionals over a 14-year follow-up. Data were analyzed in terms of the amount of vigorous physical activity undertaken. No relationship was found for younger adults, but in those over the age of 65 yr, *vigorous* physical activity was associated with a decreased risk of advanced cancers and a lower tumour aggressivity as assessed by the Gleason score (odds ratio 0.33, 0.17-0.62) (Giovannucci et al., 2005). Hrafnkelsdóttir and colleagues (2015) completed a 24-year follow-up of 822 Icelandic men. They tested the benefit of engaging in regular physical activity from the age of 20 yr, finding that the hazard ratio for development of prostate cancer was 0.93 (0.83-1.07) for the active group after adjusting data for age, height, body mass index diabetes, family history, educational attainment and the frequency of medical check-ups (Hrafnkelsdóttir et al., 2015). Paffenbarger et al. (1987) followed 16,936 male Harvard graduates for 12-16 yr. There were only 36 deaths from prostate cancer during this period. Nevertheless, the prostate cancer mortality rate was related to a questionnaire-based physical activity index; respective values adjusted for age, smoking and body mass index were 2.7 versus 1.5/10,000 person-yr (ns) in those

with weekly energy expenditures of <2 MJ and >8 MJ (Paffenbarger et al., 1987). Lee and associates (1992) made a further examination of data for this same population, applying a physical activity questionnaire on 2 occasions to 17, 719 Harvard alumni, including 419 men who had developed prostate cancer. The age-adjusted odds ratio for the risk of prostate cancer in those who had maintained a very high energy expenditure at both assessments (>16 MJ/wk) was 0.12 (0.02-0.89), but this figure must be regarded as an outlier, since it was based on only a single case of prostate cancer in the most active group (Lee et al., 1992). Benefit was not seen when the cut-point for a high energy expenditure in the same population was reduced from 16 to 10 MJ/wk (Lee and Paffenbarger, 1994). Lund Nielsen et al., (2000) followed 22,895 Norwegian men for 9.3 yr, encountering 644 incident cases of prostate cancer. Multivariate adjustment of a simple binary classification of leisure activity found a trend for an association between a high level of physical activity and a reduced risk of prostate cancer [relative risk 0.80 (0.62-1.03)] (Lund Nielsen et al., 2000). Moore et al. (2008) examined a very large sample of 293,902 men initially aged 50-71 yr. During an 8.2-year follow-up, there were 17,872 cases of prostate cancer, 1942 of which were advanced and 513 of which were fatal. After adjusting findings for age, marital status, educational attainment, smoking, medical history, body mass index, waist circumference, family history, diet and the use of nutritional supplements, vigorous exercise during adolescence was linked to a small reduction in relative risk [odds ratio 0.97 (0.91 - 1.03), p for a trend favouring physical activity during adolescence = 0.03], but exercise at entry to the study was unrelated to the number of tumours, advanced lesions or fatal cases (Moore et al., 2008). Nilsen and associates (2006) studied 29,110 Norwegian men for 7 yr, finding 957 incident cases of prostate cancer. Physical activity was scored based on the frequency, intensity and duration of physical activity (rated as low, medium or high). With statistical allowance for effects of age, marital status, educational attainment, body mass index, smoking, and alcohol consumption, physical activity bore no significant relationship to the risk of all prostate cancers (risk ratio = 0.86), but there was a significant inverse trend to a decreased risk of advanced tumours [relative risk = 0.64 (0.43-0.95), trend p = 0.02] (Nilsen et al., 2006). Patel et al. (2005) followed a sample of 72,174 men, accruing 5503 incident cases of prostate cancer over 9 yr. Individual leisure energy expenditures were classified in MET-hr/wk (ranging from <0.7 to > 35). Following adjustments for age, ethnicity, body mass index, changes in body mass, energy intake, diet and vitamin use, diabetes mellitus, and family and medical history, there was no significant association between energy expenditures and the incidence of prostate cancer, but a sub-category of tumours with a high Gleason score for aggressiveness tended to be less prevalent among active individuals [risk ratio 0.69 (0.52-0.92), p for trend = 0.06] (Patel et al., 2005). Severson and associates (1989) found 205 cases of prostate cancer among 8006 Japanese men living on the island of Oahu, in Hawaii. Leisure activity was assessed by 3 measures (the Framingham index, the resting heart rate, and a self-estimate of involvement in moderate or heavy leisure activity), all adjusted for age and body mass index; the first 2 of these indices were unrelated to the risk of prostate

cancer, although there was a suggestion of benefit associated with a subjective report of engagement in moderate or heavy leisure activity (OR 0.77, 0.58-1.01) (Severson et al., 1989). Steenland et al. (1995) found 156 cases of prostate cancer in a follow-up of participants in the NHANES I survey. Contrasting those who had reported taking little physical activity with those who said that they were taking "lots," there was a weak trend to a lower risk of prostate cancer in the more active individuals [odds ratio 1.31 (0.76-2.26, ns)] after adjustment of the data for age, body mass index, smoking, alcohol consumption and income (Steenland et al., 1995). Zeegers et al. (2005) followed 58,279 men who were initially aged 55-69 yr for an average of 9.3 yr, accumulating 1386 cases of prostate cancer. Leisure activity was assessed in terms of the time individuals allocated to bicycling, walking, and gardening. Gardening was unrelated to the risk of prostate cancer, but after controlling for age, alcohol consumption, body mass index, energy intake, family history, gardening and sport involvement, there was a weak trend to benefit from walking and cycling; compared with those who were active <10 min/day, the odds ratio for those allocating >60 minutes per day to walking and cycling was 0.85 (0.69-1.05, ns) (Zeegers et al., 2005).

Among the 4 investigators who reported statistically significant findings, Albanes and colleagues (1989) found 95 cases of prostate cancer in a sample of 5141 men during a 10-year follow-up of participants in the NHANES I survey. Comparing those who took much versus those who engaged in little or no recreational exercise, the age-adjusted relative risk was 1.8 (1.1-3.3), with a statistically significant trend favouring those individuals who were more active ($p = 0.02$) (Albanes et al., 1989). Hartman et al. (1998) followed 29,133 men for up to 9 yr, finding 317 incident cases of prostate cancer. After adjusting for age, urban living, smoking, and a history of benign prostatic hyperplasia, a comparison of those reporting a sedentary lifestyle versus those engaging in moderate or heavy leisure activity found a relative risk of 0.7 (0.46-0.94) favouring the more active group (Hartman et al., 1998). Orsini et al. (2009) followed 45,887 men for 8 yr, accumulating 2735 cases of prostate cancer. The time allocated to walking and cycling was sorted into 5 categories, ranging from hardly ever to more than 60 minutes per day. After adjusting for a substantial range of co-variates (age, smoking, alcohol consumption, educational attainment, diet, energy intake, waist/hip ratio, and diabetes mellitus), the relative risk of prostate cancer in the most active category was 0.86 (0.76-0.98); risk decreased by some 8% for each 30 minutes of daily walking or cycling over the range 30-120 minutes/day. Effects of an active lifestyle were even greater for advanced (relative risk = 0.74) and fatal (relative risk = 0.72) tumours (Orsini et al., 2009). Wannamethee and associates (2001) carried out a prospective study of 7588 men, finding 120 incident cases of prostate cancer. A 6-level classification of leisure activity ranged from none to vigorous. After adjusting for age, smoking, alcohol consumption, body mass index, and social class, there was a substantial reduction in the risk of prostate cancer associated with participation in vigorous activity [odds ratio 0.25 (0.06-0.99, p for trend = 0.06] (Wannamethee et al., 2001).

Case-control studies. Of 15 case-control studies, three found an adverse effect of

physical activity, seven found no clear effect, two a suggestive positive trend, and three noted a statistically significant reduction of risk.

Among the adverse findings, Chen et al. (2005) compared 237 cases of prostate cancer with 481 controls, all over the age of 50 yr. The primary focus of the investigation was dietary, but a 4-level classification of leisure activity was also made. In a multivariate analysis with adjustments of data for age, body mass index, income, marriage and dietary variables, a comparison between a high and a moderate level of physical activity yielded an odds ratio of 1.84 (1.01-3.34) (Chen et al., 2005). Sung and colleagues (1999) related the findings in 90 cases of prostate cancer to data for 180 controls, noting exercise participation (yes vs. no) 5-10 yr prior to the diagnosis. In a multivariate analysis, they observed that exercise was associated with a significant *increase* in the risk of prostate cancer [odds ratio 2.16, 1.18-3.96, p = 0.01] (Sung et al., 1999). Wiklund et al. (2008) compared 1449 incident cases of prostate cancer with 1118 population controls. After adjusting for age, region of residence, educational attainment, body mass index, alcohol consumption, family history, diabetes mellitus and energy intake, a classification of lifetime recreational activity (MET-h/day <7.4 to >13.5) showed a significant increase of risk in those with a history of active leisure [odds ratio 1.56 (1.16-2.10), p= 0.006] (Wiklund et al., 2008).

Seven investigations reported little effect of leisure activity upon the risk of prostate cancer. In a sample of 258 cases of prostate cancer and 471 age-matched controls, Lacey et al. (2001) asked for information about moderate/vigorous and all physical activity at 3 points in the life cycle (12, 20-29, 40-49 yr of age). Adjusting data for age, marital status, educational attainment, body mass index, energy intake and waist/hip ratio, leisure activity was unrelated to the risk of prostate cancer. Pierotti et al. (2005) compared 1294 incident cases of prostate cancer under the age of 75 yr with 1451 hospital controls. A 3-level categorization of physical activity was made for ages 12, 15-19, 30-39 & 50-59 yr. After adjustment of data for age, test centre, educational attainment, socio-economic status, body mass intake, total energy intake, smoking, alcohol consumption, and family history, vigorous physical activity showed no association with prostate cancer at any of the 4 points in the individual's life (Pierotti et al., 2005). Sanderson and associates (2004) examined 416 incident cases of prostate cancer, drawing 429 controls from Medicare beneficiaries. After adjusting for age, geographic region of residence and family history, tertiles of strenuous and of moderate physical activity (expressed in hr/wk) proved unrelated to prostate cancer in either African American or Caucasian men (Sanderson et al., 2004). Strom et al. (2008) compared a binary classification of the duration of leisure activity (<1/wk vs. >1/wk) between 176 cases of prostate cancer in Mexican-Americans and 176 matched controls; the risk of prostate cancer in this sample was unaffected by the frequency of leisure activity. Villeneuve and colleagues (1999) related data on 1623 histologically confirmed cases of prostate cancer to findings in 1623 controls. A 5-level classification of the frequency of leisure activity (<1/month to > 5/wk) showed no clear relationship to prostate cancer, after control of the data for age, area of residence, smoking, alcohol consumption, body mass index, diet, income, and family history (Villeneuve et al., 1999). West et

al. (1991) compared 358 cases of prostate cancer with 679 controls; subjects were questioned on physical activity in a survey that focused primarily on diet, and no relationship was seen between leisure activity and tumour development. In another study where physical activity was not the main emphasis, Whittemore et al. (1995) studied 1655 cases of prostate cancer and 1645 population controls; they, also, found no relationship between leisure activity and prostate cancer.

The data from 2 studies showed trends suggesting a lower risk in those with an active leisure. Andersson and associates (1995) compared 252 cases of prostate cancer with 243 controls. The pubertal physical activity of these subjects was rated relative to that of their peers, as lower, the same or higher, and the respective odds ratios for subsequent development of a prostate tumour (adjusted for age, urbanization and adult farming) were 1.3, 1.0 and 0.7 ($p = 0.13$ for a trend favouring those who were active as adolescents). An association of prostate cancer with life in a densely populated area was also seen, possibly indicating that crowded living quarters had an indirect effect by limiting the individual's physical activity as a youth (Andersson et al., 1995). Friedenreich et al., (2004) examined 988 incident cases of prostate cancer and 1063 population controls. Multiple co-variates included age, region, educational attainment, body mass index, waist/hip ratio, energy intake, alcohol consumption, and the family and medical history. This data set showed a trend towards a favourable odds ratio [0.80 (0.61-1.04) $p = 0.06$ for trend)] when those with the greatest leisure activity (>25.1 MET-hr/wk) were compared with the least active individuals (< 8.5 MET-hr/wk) (Friedenreich et al., 2004).

Only 3 case-control studies showed a statistically significant effect favouring active individuals. Darlington et al. (2007) enquired regarding strenuous activity in the mid-teens, early 30s, and early 50s in a sample of 752 cases drawn from the Ontario cancer registry. Findings were related to comparable data for telephone-list controls. After adjusting data for age, educational attainment, body mass index, family history, and occupation, the risk of prostate cancer was lower in those undertaking strenuous activity in their 50s, but benefit was not statistically significant for the other 2 age groups (Darlington et al., 2007). Jian et al. (2005) compared 130 histologically confirmed cases of prostate cancer with 274 controls. After adjusting data for age, area of residence, educational attainment, income, marital status, number of children, years in the work force, family history, body mass index and energy intake, tumours were more closely related to a low volume of moderate activity (<40 vs >120 MET-hr/wk) than to a low total volume of physical activity (<44 vs. >135 MET-hr/wk, with strongly favourable respective odds ratios for the more active individuals of 0.20 (0.07-0.62, $p = 0.015$) and 0.39 (0.15-0.99, $p = 0.50$ for trend) (Jian et al., 2005). Yu and colleagues (1988) compared 1162 cases of prostate cancer with 3124 matched hospital controls. Leisure activity, adjusted for age, was classed as active, moderate, or seldom, with a higher odds ratio [1.3 (1.0-1.6), $p = 0.03$] for the sedentary group (Yu et al., 1988).

Sport involvement and attained fitness. Studies based on an individual's involvement in organized sport are often based simply on the behaviour reported during a person's youth or when attending university. This may be a

relevant period in terms of carcinogenesis, but there is also the important disadvantage that by middle-age, former university athletes are often less active and more obese than those who were not recognized as athletes when they were attending university (Montoye et al., 1957). Comparisons with non-athletes are further complicated in that athletes are selected for many categories of sport in part on the basis of their body build (Eisenmann and Malina, 2000). A final difficulty is that a substantial proportion of athletes have been involved in the abuse of androgenic steroids, and this may in itself increase the risk of prostate cancer (Klap et al., 2015; Noble, 1984).

An alternative option is to look at the attained level of aerobic fitness among those who have been involved in aerobic fitness programmes, considering this as an objective and quantifiable surrogate of habitual physical activity. Some indeed have considered this as a preferable alternative to reliance upon a physical activity questionnaire (Blair et al., 2001), although it must be recognized that if the individual's maximal oxygen intake is expressed in mL/[kg·min], then the accumulation of body fat has an important negative effect upon this index.

Retrospective and prospective cohort studies. Four cross-sectional and cohort studies of sport and fitness have been published (Table 3). Two of these reports found no benefit from sport involvement, but the third associated a lower risk of prostate cancer with a high-attained level of aerobic fitness, and in the fourth there was a dose-related benefit from an increased frequency of sport participation.

Merrill et al. (2002) evaluated the prostate serum antigen (PSA) levels of 536 participants in seniors' games. The age-adjusted PSA (a measure of prostate cancer of limited validity) was unrelated to the number of years that subjects had been physically active more than 3 times per week (Merrill et al., 2002). Zeegers and associates (2005) also found no association of benefit with a simple binary classification of community sport involvement ("never" vs. "ever") when 58,279 men initially aged 55-69 yr were followed for an average of 9.3 yr, with the accumulation of 1386 cases of prostate cancer.

Oliveira et al. (1996) obtained data on 12,975 men who were attending the Cooper Fitness Clinic in Dallas, Texas. Quartile scores on a simple treadmill test of aerobic fitness (the maximal exercise time) were inversely related to the individual's risk of prostate cancer. After allowing for the effects of age, body mass index and smoking, effects were non-linear, with a large reduction of risk in the fittest group [respective incidence rates for increasing quartiles of fitness 1.1, 0.73, ns; 0.26 (0.10-0.63) (Oliveira et al., 1996).

Case-control studies. Three case-control studies of involvement in sport all reported a substantial *increase* of risk in the athletes. Hållmarker and colleagues (2015) completed a case-control study of 185,412 participants in the Vasaloppet, a Swedish long-distance cross-country ski contest; 184,617 non-participants were matched with the skiers for age, sex, and county of residence. The 2 groups included 1827 and 1435 cases of prostate cancer, respectively, and thus a hazard ratio of 1.22 (1.13-1.30) favoured non-participants in the event (Hållmarker et al., 2015).

Table 3: Sports involvement, attained aerobic fitness and risk of prostate cancer.

Author	Sample	Activity measure	Findings	Comments
Cohort studies				
Merrill et al. (2002)	PSA levels of 536 participants in seniors' games aged >50 yr	Years active > 3 times/wk	Physical activity unrelated to PSA levels	Adjusted for age
Oliveira et al. (1996)*	12,975 men attending Cooper Fitness Clinic	Quartile scores on maximal exercise treadmill test	Incidence rate inversely related to aerobic fitness [1.1, 0.73, ns; 0.26 (0.10-0.63)]	Adjusted for age, BMI, smoking
Wannamethee et al. (2001)***	Prospective study of 7588 men aged 40-59 yr, with 120 incident cases of PC	Sporting activity (none, >1/month, >1/wk, >2/wk)	RR 1.00, 0.98, 0.63,0.53 (p = 0.05)	Age, smoking, alcohol, BMI, SES,
Zeegers et al. (2005)	58,279 men aged 55-69 yr, 1386 cases of PC over 9.3 yr	Sport participation (never/ever; frequency; duration, yr)	Sport participation unrelated to PC	Adjusted for age, alcohol consumption, BMI, energy intake, family history, education
Case/control studies				
Hållmarker et al. (2015)	185,412 participants in Vasaloppet ski contest and 184,617 non-participants	1827 vs. 1435 cases PC	HR 1.22 (1.13-1.30) favouring non-participants	Non-participants matched for age, sex, and county of residence
Paffenbarger et al. (1987)	56,683 university alumni followed >28 yr, 104 PC cases vs. controls	Playing university sport > 5hr/wk	RR 1.20 favouring non-athletes (p = 0.028)	Data adjusted for age, sex & birth year of classmate controls
Polednak (1976)	8393 university graduates, 124 PC deaths	Athletes vs. minor athletes vs. non-athletes	Age of PC death 70.9, 74.2, 74.8 (p < 0.05)	

*** The same report also presented data on leisure physical activity.
ns = non-significant. BMI = body mass index/ PC = prostate cancer. PSA = prostate serum antigen. RR = relative risk.

Paffenbarger et al. (1987) followed 56,683 university alumni for 28 or more years, accumulating 104 cases of prostate cancer; participants in university sports teams were compared with classmate controls, matched for age and birth year. Involvement in university sport for longer than 5 hr per week was associated with a significant adverse effect, showing a relative risk of 1.20 (p = 0.028) relative to non-participants (Paffenbarger et al., 1987). Polednak (1976) explored data for 8393 university graduates, comparing the experience of "major" athletes, "minor" athletes, and non-athletes. In his study, there was a statistically significant trend for the "major" athletes to die of prostate cancer at a younger age than that found for the other 2 categories of alumni (70.9, 74.2 and 74.8 yr, respectively, p < 0.05) (Polednak, 1976).

Possible mechanisms. The demonstration of likely mechanisms whereby exercise modifies the process of carcinogenesis could reinforce the tentative epidemiological evidence of benefit from regular physical activity. In

addition to such general protective actions of exercise such as a reduction of obesity and oxidant stress and a modulation of immune responses, prolonged endurance exercise may reduce circulating levels of testosterone and insulin-like growth factors (Heitkamp and Jelas, 2012; Klap et al., 2015), thus reducing the tendency to growth and proliferation of neoplasms. Barnard et al. (2007) collected serum from men who were undertaking aerobic exercise 5 times per week and from sedentary controls. When this serum was applied to lymph nodes that had been infiltrated with prostate cancer cells, samples from the exercisers decreased levels of insulin-like growth factor, increased insulin-like growth factor binding protein and increased the extent of apoptosis among the tumour cells. However, it is less certain that the average exerciser in the epidemiological studies discussed above reached the intensity and duration of activity where such hormonal responses might be anticipated (Barnard et al., 2007).

Conclusions from epidemiological research. Despite a considerable volume of research, we still lack incontrovertible proof that those who live a physically active lifestyle have a reduced risk of prostate cancer (Table 4). Moreover, although some studies have shown a clear dose-response relationship, otherwise there is as yet little evidence to confirm the view that any association is causal in nature. Clear conclusions, are hampered by the fact that many investigators have drawn conflicting inferences from *post-hoc* analyses based upon small sub-groups within their overall populations. Further, in terms of occupational activity, relatively few investigators have co-varied their findings for exposure to toxic chemicals, and often there has been an incomplete allowance for socio-economic and dietary differences between those engaged in sedentary and physically demanding work.

In all, there have been at least 85 analyses of this issue, 35 based on differences of occupational activity, 43 on differences in leisure behaviour, six on involvement in sport, and one on differences in levels of attained aerobic fitness. However, 18 of these reports have examined both occupational and leisure activity, one has covered both sport participation and other forms of active leisure, and in a few instances there have been repeated analyses of the same data set. Summarizing across the various measures of physical activity, 22 of the 85 analyses (26%) found significant benefit in one or more of their analyses, and a further 25 (29%) found a non-significant trend favouring the more active individuals, but against this must be set 31 (36%) analyses finding no effect and at least 7 analyses (8%, including 3 of the 6 studies of involvement in sport) that found an adverse effect associated with an active lifestyle. It is also apparent from Table 4 that the reduction of risk is shown more consistently for occupational than for leisure studies, although it is unclear whether this is because a man's occupational title provides a more accurate categorization of his activity patterns, or whether the prolonged moderate energy expenditures demanded by "heavy" work provide a more effective antidote to carcinogenic change. The overall evidence is to date far from conclusive, although it generally supports earlier contentions that the risk of prostate cancer is reduced among individuals who engage in regular physical activity.

Looking specifically at analyses that have yielded statistically significant results (Table 5), the benefit seems of practical clinical importance. In 12 occupational studies, the effect ranged broadly from 9 to 57%, with an average of 34%, and a similar average effect was seen in the 7 leisure studies (range 20-75%, with an average of 38%). The inconsistency of trial outcomes reflects in part the well-recognized limitations in questionnaire assessment of physical activity, and in part issues in the diagnosis of prostatic cancer (such as a diagnostic reliance upon increased levels of prostate-specific antigens or on prostate cancer-related death rather than on histological confirmation of the development of clinically important disease). A further potential difficulty complicating occupational analyses is that a sedentary occupation tends to be associated with a higher socio-economic status, a greater frequency of medical examinations, and thus the likelihood of an early diagnosis of prostate cancer (Morote et al., 2014).

The research to date provides little guidance as to the optimum frequency, intensity and volume of preventive programmes. Often, it is difficult to discern dose-response (Table 5). Magnitude of reduction in risk associated with an active lifestyle, based on analyses with statistically significant findings, and relationships, because categorization of the intensity or volume of activity has been semantic rather than numeric. Again focusing upon the studies where a significant association was established, 2 investigations found the largest effect at the second of 3 levels of physical activity, (Clarke and Whittemore, 2000; Parent et al., 2011) but the majority of reports have shown a progressive decrease of risk over 3 or 4 gradations of activity (Andersson et al., 1995; Bairati et al., 2000; Brownson et al., 1991; Giovannucci et al., 2005; Norman et al., 2002; Orsini et al., 2009; Vena et al., 1987; Villeneuve et al., 1999; Wannamethee et al., 2001; Yu et al., 1988), with 3 series showing little effect except at the highest level of effort (Giovannucci et al., 2005; Krishnadasan et al., 2008; Wannamethee et al., 2001). Orsini et al. (2009) noted specifically that the relative risk of prostate cancer decreased by some 8% for each additional

Table 4. Summary of epidemiological evidence on the association between habitual physical activity and a reduced risk of prostate cancer.

Type of study	Adverse effect	No effect	Positive trend	Positive effect
Occupational activity				
Cross-sectional & cohort (19)		7	6	6 (32%)
Case-control (16)		6	3	7 (44%)
Total (35)		13	9	13 (37%)
Leisure activity				
Cross-sectional & cohort (28)	1	11	12	4 (14%)
Case-control (15)	3	7	2	3 (20%)
Total (43)	4	18	14	7 (16%)
Sports & attained fitness				
Cross-sectional & cohort(4)			2	2 (50%)
Case-control (3)	3			(0%)
Total (7)	3		2	2 (29%)
Overall total (85)	7 (8%)	31 (36%)	25 (29%)	22 (26%)

30 minutes of walking or cycling taken over the range 30-120 min/day.

The optimal age to engage in preventive activity also remains unclear. Several reports have suggested that the risk of prostate cancer is linked most closely linked to physical activity undertaken during puberty and/or young adulthood (Andersson et al., 1995; Moore et al., 2008; Villeneuve et al., 1999). However, others have found greater benefit from activity taken at a later stage in life. Darlington et al. (2007) saw no significant benefit if activity was taken in the mid-teens, or the early 30s, but there was an effect if taken in the 50s. Likewise, Pierotti et al. (2005) pointed to the largest reduction of risk when heavy occupational work had been performed between 50 and 59 yr of age. Finally, Lacey and associates (2001) found no significant relationship between occupational activity and the risk of prostate cancer at any time point in the careers of their subjects.

The benefits of occupational activity seem to vary with age-cohort. Thus, Giovannucci and colleagues (2005) found a relationship only in subjects who were over the age of 65 yr, where vigorous physical activity was associated with a decreased risk of advanced cancer and a lower Gleason score for aggressively of the tumour (odds ratio 0.33, 0.17-0.62). Likewise, Le Marchand et al. (1991) reported a trend to benefit from heavy work, but this was only seen among men over the age of 70 yr. Possibly, this may reflect the fact that older individuals in any given occupation faced heavier physical demands than the younger cohorts.

It is unclear how far these uncertainties will be resolved by further research. Criteria for the incidence of a prostate cancer could certainly be clarified in future investigations, and a better measure of leisure activity could possibly be obtained by the use of objective monitors such as accelerometers. More use could also be made of surrogates of habitual physical activity, such as careful measurements of the attained level of aerobic fitness. Possibly, prospective trials could also be instituted, with monitoring for prostatic cancer among individuals assigned to exercise programmes of clearly defined intensity, frequency and duration. Finally, further research on causal mechanisms such as an altered hormonal milieu may provide some clues as to the pattern of activity most likely to reduce the likelihood of carcinogenic change.

Despite these uncertainties, regular physical activity appears likely to make a substantial contribution to a decrease in the risk of developing prostate cancer, and given the many other general health benefits of an active lifestyle, it should be recommended to older men as a potentially important component of preventive programmes.

The side-effects of androgen deprivation therapy

The immediate treatment of prostate cancer by irradiation or surgery is followed in about a half of patients, by 2-3 yr of continuous or intermittent androgen deprivation therapy (ADT). This treatment probably reduces the risk of tumour recurrence, but it also has a number of major physical side-effects that mimic the response to bed-rest or sedentary living (Table 6), including a persistent decrease in maximal aerobic power (Alibhai et al., 2015) and muscle strength 2008; Galvao et al., 2010; Levy et al., 2008; Stone et al., 2000; van Londen et al., 2008), a 3-5% loss of bone mineral density and osteoporosis with an

Table 5: Magnitude of reduction in risk associated with an active lifestyle, based on analyses with statistically significant findings.

Author	Occupational activity	Leisure activity	Sports participation/attained Fitness
Albanes et al. (1989)		44%	
Bairati et al. (2000)	50, 64% = 57%		
Brownson et al. (1991)	33%		
Clarke & Whittemore (2000)	43%		
Darlington et al. (2007)		20% (activity aged 50-59 yr)	
Hartman et al. (1998)		30%	
Jian et al. (2005)		61% (total activity)	
Krishnadasan et al. (2008)	37%		
Norman et al. (2002)	9%		
Oliveira et al. (1996)			74%
Orsini et al. (2009)	28%	14%	
Parent et al. (2011)	46%		
Pierotti et al. (2005)	25% (ages 50-59 yr)		
Strom et al. (2008)	54%		
Vena et al,(1987)	15%		
Vidarsdottir et al. (2008)	21%		
Villeneuve et al. (1999)	44%		
(Wannamethee et al. (2001)		75%	47%
Yu et al. (1988)		23%	

Omitting Dosemeci et al. (1993)(Dosemeci et al., 1993) (a small sample, yielding outlying values)

increased risk of fractures (Basaria et al., 2002; Berrutti et al., 2002; Chen et al., 2002; Daniell, 1997; Daniell, 2001; Galvao et al., 2008; Greenspan et al., 2005; Hatano et al., 2000; Kiratli et al., 2001; Maillefert et al., 1999; Malcolm et al., 2007; Morote et al., 2006; Oefelein et al., 2001; Preston et al., 2002; Ross and Small, 2002; Shahinian et al., 2005; Smith et al., 2005; Stoch et al., 2001; Townsend et al., 1997) and a decrease in the overall quality of life. There may also be an increased risk of cardiovascular disease and acute renal injury, possibly due to the breakdown of atherosclerotic plaques (Crawford and Moul, 2015).

Aerobic performance. Alibhai and colleagues (2015) compared 87 cases of prostate cancer receiving ADT for 36 months with 86 cases who were not receiving ADT and 86 matched controls. In those who were receiving ADT, they found a poorer performance on one simple measure of aerobic function (the 6 minute walking distance).

Muscle strength. Consistent responses to ADT have included a decrease in lean body mass and an increase in body fat (Berrutti et al., 2002; Dacal et al., 2006). Thus, a comparison between 30 cases of prostate cancer who were receiving ADT for 6 months and 25 healthy men without cancer demonstrated a decrease of skeletal muscle mass and lean tissue in the limbs of the affected individuals, with an associated increase of body fa content (Boxer et al., 2005). Galvao et al. (2008) reported that after 36 weeks of ADT, the loss of lean tissue in 72 cases of prostate cancer was distributed across all body sites (with respective decreases of 5.6, 3.7, 1.4 and 2.4% in the upper and lower limbs, trunk, and total body). van Londen et al. (2008) presented data for 43 men

Table 6: Side-effects associated with the androgen-deprivation treatment of prostate cancer.

Author	Sample	Findings	Comments
Aerobic performance			
Alibhai et al. (2015)	87 cases of non-metastatic PC receiving ADT for 36 months, 86 matched cases not receiving ADT	6 min walk distance poorer if receiving ADT	Side-effects seen at 12 months persisted at 36 months. No specific rehabilitation programme adopted
Muscular performance			
Alibhai et al. (2015)	87 cases of non-metastatic PC receiving ADT, 86 matched cases not receiving ADT for 36 months	Grip strength & timed get-up & go poorer if receiving ADT	Side-effects seen at 12 months persisted at 36 months. No specific rehabilitation programme adopted
Basaria et al. (2002)	20 cases of PC treated by ADT, 18 treated cases of PC awaiting ADT, 20 age-matched healthy controls	Reduced upper body strength with ADT	
Muscular performance			
Berrutti et al. (2002)	36 cases of PC with 12 months ADT	Decrease of LBM	Increase of body fat
Boxer et al. (2005)	30 cases of PC with 6 months ADT vs. 25 healthy controls	Decrease of muscle mass and lean tissue in limbs with ADT	Associated increase of body fat
Bylow et al. (2008)	50 men aged >70 yr treated with ADT	24% had impaired ADL, deterioration of balance, walking and chair stand times	22% had falls within 3 months
Stone et al. (2000)	62 men receiving ADT as primary treatment of PC	Loss of muscle bulk & reduction in voluntary muscle function (grip, grip fatigue)	
van Londen et al. (2008)	43 men on ADT <6 months, 67 cases on chronic ADT, 81 not on ADT, 53 age-matched controls	Losses of lean mass 0.93 kg at 12 months, 1.79 kg after 24 months in acute ADT, smaller loss in chronic ADT group at 24 months	Associated increases of fat mass
Bone strength			
Basaria et al. (2002)	20 cases of PC treated by ADT, 18 treated cases of PC awaiting ADT, 20 age-matched healthy controls	BMD lower, increased urinary N-telopeptide with ADT	
Berrutti et al. (2002)	36 cases of PC with 12 months ADT	Decreased BMD at hip & lumbar spine relative to baseline	
Chen et al. (2002)	62 cases of PC, 1-5 yr of ADT, 47 healthy controls	Low BMD (total, trochanter, inter-trochanter & hip sites)	Associated higher percent body fat
Daniell (1997)	26 cases of PC with ADT or orchidectomy followed 6-42 months	2.4% and 7.6% decrease of BMD in femoral neck after 1 and 2 yr respectively	Further 1.4-2.6%/yr loss of BMD over yr 3-8
Galvao et al. (2008)	72 men treated by ADT for 36 wks	Decreases of BMD at hip, spine, upper limb, whole body 1.5, 3.9, 1.3 2.4% respectively, but no change in lower limbs	Associated decrease of lean mass
Greenspan et al. (2005)	30 with acute ADT <6 months, 50 with chronic ADT > 6 months, 72 no ADT, 43 healthy controls	5 to 10-fold increase in loss of bone mineral relative to no ADT or healthy controls	Bone loss maximal in first year of ADT

Table 6 Continued

Hatano et al. (2000)	218 cases of PC treated with ADT for >6 months	6% of cases had bone fractures unrelated to metastasis	Low bone density and increased N-telopeptides in those developing fractures
Kiratli et al. (2001)	36 patients with PC, age matched controls; ADT or surgical castration for up to 10 yr	Bone mineral loss continues relative to controls for 10 yr	Effect greater with surgical than with chemical castration
Maillefert et al. (1999)	12 cases of PC receiving ADT for 6, 12 & 18 months	BMD decreased 2.7, 3.9 and 6.6% over 18 months	Increased serum osteocalcin
Malcolm et al. (2007)	395 cases of PC receiving ADT followed for average of 66 months	23% developed osteoporosis, 7% developed non-pathological fractures	Osteoporosis related to duration of treatment
Morote et al. (2006)	31 cases on ADT, 31 controls not on ADT	Bone mass loss of 2.3-5.6% at 12 months, less severe further loss at 24 months	Major bone loss in Ward's triangle

who had been receiving ADT for less than 6 months, 67 cases on chronic ADT, 81 who were not receiving ADT and 53 age-matched controls. The acute ADT group showed lean mass losses of 0.93 kg at 12 months, and 1.79 kg after 24 months, although the losses at 24 months were smaller in the chronic ADT group. As in the other studies, there were associated increases of fat mass (van Londen et al., 2008). Stone and colleagues (2000) followed 62 men who were receiving ADT as a primary treatment of prostate cancer; they observed not only a progressive loss of muscle bulk, but also a reduction in voluntary muscle function (a decrease of grip strength and a faster fatigue of grip strength). Basaria et al., (2002) also found a reduction of upper body strength when 20 cases of prostate cancer that had been treated with ADT were compared with 18 cases that were awaiting such treatment.

Several authors have found functional consequences from this loss of muscle tissue. Alibhai and associates (2015) not only found a reduction of handgrip strength in those receiving ADT, but also a deterioration in their times for a "get up and go" test, with the poor performance persisting throughout the 36 months of treatment. Bylow et al., (2008) also found an adverse effect upon performance of the activities of daily living in a quarter of 50 men aged >70 yr who were treated by ADT, with a deterioration in balance, walking and chair-stand times. Levy et al. (2008) reviewed data for 23 men who had received ADT for less than 6 months, and 12 men who had received ADT for a longer period relative to 13 who were not receiving ADT. The lean tissue mass decreased with the duration of ADT, and 4 metre walk velocities were also slower for those receiving ADT (Levy et al., 2008).

Bone mineral density. Many investigations have associated androgen deprivation therapy with a progressive decrease in bone mineral density and an increased vulnerability to fractures. Thus, Berrutti and colleagues (2002) followed 36 cases of prostate cancer over a 12-month course of ADT; lumbar spine and hip bone mineral density were decreased relative to baseline over the 12 months of observation. Chen et al. (2002) compared 62 cases of prostate cancer treated with ADT for 1-5 yr and 47 healthy controls; a lower bone mineral density was seen in the trochanter, inter-trochanter, hip and total scores. Daniell (1997) noted that in 26 cases treated by ADT or orchidectomy, the decrease of bone mineral density in the femoral neck continued unremittingly, with 2.4% and 7.6% decrease in years 1

and 2, and a further 1.4-2.6%/yr bone loss over years 3-8.

The extent of bone loss seems to vary from one site to another. Preston et al. (2002) compared 23 men who had been receiving ADT for 24 months with 30 controls. There was less bone loss in controls at all sites except in the lumbar spine. The site most affected was the distal forearm, where respective losses over 2 yr were -9.4% and -4.4% (Preston et al., 2002). Galvao and associates (2008) found decreases of bone mineral density of 1.5, 3.9, 1.3 and 2.4% respectively for the hip, spine, upper limb, and whole body in a group of 72 men who were treated by ADT for 36 weeks; however, possibly because of some protection from ambulation, these cases showed no changes of bone density in the lower limbs. Greenspan et al. (2005) measured changes of bone mineral density in 30 men who received ADT for less than 6 months, 50 men who received a longer period of treatment, 72 who did not receive ADT and 43 healthy controls. The rate of loss of bone mineral with ADT was increased 5 to 10-fold relative to that seen in patients not receiving ADT or in controls, with the maximal rate of bone loss occurring during the first year of such treatment (Greenspan et al., 2005). Morote and associates (2006) compared 31 cases of prostate cancer on ADT with 31 patients who were not receiving ADT. Those receiving androgen suppression experienced a 2.3-5.6% loss of bone mass at 12 months, and as in the previous study, a less severe loss continued to 24 months (Morote et al., 2006). Kiratli et al. (2001) compared 36 patients with prostate cancer who received ADT or surgical castration with age-matched controls. Bone mineral loss continued relative to the controls for 10 yr, and interestingly the effect was greater following surgical treatment than after chemical castration (Kiratli et al., 2001).

Some investigations have demonstrated a substantial increase in markers of bone turnover. Thus, Maillefert et al. (1999) evaluated 12 cases of prostate cancer who were receiving ADT at 6, 12 and 18 months. There was a progressive decrease of bone mineral density (2.7, 3.9 and 6.6% at successive assessments) and increased serum osteocalcin levels supported the idea that there was an increased bone turnover (Maillefert et al., 1999). Basaria and colleagues (2002) found that bone mineral density (BMD) was lower in 20 cases of prostate cancer that had been treated with ADT than in 18 men who were awaiting such treatment; moreover, the ADT group showed an increase of urinary N-telopeptide, another marker of bone turnover. Stoch et al. (2001) examined 60 men with prostate cancer, including 19 who were receiving ADT. The ADT group showed a lower BMD than the other cases at various bone sites, and they also high levels of 2 markers of bone turnover (N-telopeptides and bone-specific alkaline phosphatases) (Stoch et al., 2001). Likewise, Hatano and associates (2000) reported that 6% of 218 cases of prostate cancer who were treated with ADT for longer than 6 months developed fractures that were unrelated to tumour metastasis; a low bone mineral density and high N-telopeptide concentrations were found in those developing fractures.

A greater propensity to fractures is an inevitable consequence of bone mineral loss. Malcolm et al. (2007) followed 395 cases of prostate cancer who had received ADT for an average of 66 months; 23% showed signs of osteoporosis, and 7% developed non-pathological fractures, with the risk of osteoporosis being related

to the duration of ADT. In their studies of bone-loss, the primary end-point for Oefelein and colleagues (2001) was again the development of an osteoporotic fracture. In 181 cases of prostate cancer who were receiving ADT, 4% had sustained a fracture after 5 yr, and 20% after 10 yr, this risk being lower in those who had conserved their body mass by maintaining an adequate level of physical activity (Oefelein et al., 2001). Shahinian and associates (2005) examined data for 50,613 cases of prostate cancer. In those who had survived for 5 yr or more, the risk of fracture with ADT was 19.6%, compared with 12.6% in those who did not receive such treatment; moreover, in this series the risk of fracture was correlated with the dose of ADT that had been administered (Shahinian et al., 2005). Smith et al. (2005) evaluated medical claims from 5% of welfare beneficiaries under their care; this approach provided a sample of 3887 non-metastatic cases of prostate cancer. The overall clinical fracture rate was 7.88 per 100 person-yr in those receiving ADT, compared with 6.51 per 100 person-yr in matched controls, and this difference was confirmed by specific data on the risk of hip and vertebral fractures (Smith et al., 2005). Townsend and colleagues (1997) studied 224 cases of prostate cancer who were treated with ADT; 9% of this group sustained 1 or more fractures within an average of 22 months of beginning treatment. Some of the fractures were due to severe trauma, but more than a half of these were due to osteoporosis (Townsend et al., 1997).

Quality of life. Not surprisingly, the loss of aerobic function, muscle strength and bone density associated with ADT is accompanied by a significant deterioration in the individual's quality of life, as indicated by changes in the score for such items "physical health" and "physical function" on the short form medical health outcomes questionnaire (SF-36). Dacal et al. (2006) used the SF-36 questionnaire to demonstrate significant deterioration in physical function, general health and physical health in men who were receiving ADT relative to those who did not, although in this study changes did not appear to be related to the duration of ADT; they were associated with low levels of testosterone and free testosterone. Fowler et al., (2002) conducted a large scale survey of men following radical prostatectomy; 298 of this group who received ADT were compared with 2240 who did not, and ADT was shown to be associated with lower scores on all 7 measures of the health-related quality of life. Potosky and associates (2001) evaluated 431 cases of prostate cancer who had been treated simply by ADT or orchidectomy. In this study, fewer of the orchidectomy patients rated their health as only fair or poor as compared with those who were receiving a chemical suppression of androgen levels (Potosky et al., 2001). Sadetsky et al. (2011) examined 2922 cases of prostate cancer; in their sample, the 24-month self-reported quality of life was poorer in those who had been receiving androgen suppressants, and they noted that the adverse effect was most marked if androgen deprivation was the primary form of treatment.

At least a part of the low scores recorded on the SF-36 questionnaire seems related to a reduction of sexual function by ADT. Thus, Basaria et al., (2002) reported not only a low score for the physical function and physical health scales of the SF-36 questionnaire, but also specific decreases in measures of sexual function that included decreases in desire,

arousal and erections, and a reduced score on Watt's scale of overall sexual function. Green et al. (2002) compared 65 cases of prostate cancer receiving ADT for 6 months and 16 community controls; in this study, the main adverse effects of ADT were a decreased sexual function, and a decrease in SF-36 scores for social and role functioning. Spry and colleagues (2006) followed 250 men who received ADT for 9 months or longer. There was a decrease of global health-related quality of life and reduced SF-36 scores on most function and symptom scales during treatment; recovery commonly occurred within 3 months of halting ADT, but was slower in older men (Spry et al., 2006). Stone et al. (2000) followed 62 men who were receiving ADT as the primary treatment of prostate cancer. A significant increase of fatigue severity was seen over 3 months of treatment; 28% of this was explained by psychological distress, but there were also effects from a loss of virility and potency (Stone et al., 2000).

Countering the side-effects of androgen deprivation therapy and prostate surgery.

Urinary incontinence is a frequent sequel to either radical prostate surgery or irradiation of the pelvic region. Many of the side-effects of subsequent androgen deprivation mirror what might be anticipated from an excessively sedentary lifestyle, and an early countering of the resulting loss of physical function is particularly important in what is typically an elderly population. A reversal of these side effects will likely contribute not only to general well-being and independence, but also to survival. Reviewers have found at least 25 controlled trials of various exercise programmes undertaken during the medical treatment (radiation or prostatectomy, androgen deprivation) of prostate cancer, and several studies have looked at exercise responses during the period of after-care (Baumann et al., 2012; Champ et al., 2016; Gardner et al., 2014); these analyses have generally pointed to improvements of aerobic and muscular fitness, a reduction of fatigue, less bone demineralization, an enhanced quality of life, and a lower risk of urinary incontinence among the adherents to exercise programmes.

We will look here at issues of spontaneously chosen levels of habitual physical activity, and specific programmes of aerobic and resistance exercise, emphasizing the often overlooked need to adapt these programmes in the light of specific complications of prostatic surgery and irradiation such as urinary incontinence and exercise-induced diarrhea.

Habitual physical activity. Often, patients who are undergoing treatment for prostate cancer choose a level of habitual physical activity that falls far below minimum levels recommended for population health (Table 7). Chipperfield et al. (2013) evaluated the reported habitual physical activity of 356 men with prostate cancer; activity levels were lower in those receiving ADT than in those treated only by irradiation. Only 42% of the group as a whole met the national physical activity guidelines, a low level of physical activity being associated with depression, anxiety, and the presence of co-morbid conditions (Chipperfield et al., 2013). Keogh et al. (2010) studied 84 cases of prostate cancer that were receiving ADT. In terms of questionnaire responses, they also found that less than a half of the sample reported that they were physically active, although those who were active had a higher quality of life score. The

individual's attitude towards physical activity was the dominant predictor of his intention to be active, and perceived behavioural control was the dominant predictor of actual behavior (Keogh et al., 2010).

Livingston and associates (2015) assigned 54 cases of prostate cancer who were receiving ADT to an exercise programme (2 supervised sessions/wk for 12 weeks), and 93 others served as usual care controls The 12-week programme increased the volume of self-reported vigorous activity and cognitive function, and reduced depression, with the investigators suggesting that the main unresolved issue was how long the stimulation of physical activity persisted after completion of the immediate intervention.

Several reports have underlined the association between an adequate level of physical activity and health outcomes, although given the cross-sectional nature of the observations, this could imply either benefit from the greater volume of exercise or less severe disease in those who maintained a good level of physical activity. Mennen-Winchell et al. (2014) used Canada Fitness Survey data to estimate the aerobic activity of 96 men who had been treated with ADT for longer than 9 months. The reported absolute level of energy expenditure averaged 4.6 MET-hr/wk, and the bone mineral density of the hip and spine were significantly correlated with the reported volume of activity, whether expressed in minutes per week or MET-hr/wk Self-reported participation in endurance exercise was also associated with greater density of the hip bones as assessed by dual energy x-ray absorptiometry (Mennen-Winchell et al., 2014).

Others have commented on an association of habitual physical activity with muscular fitness, physical functioning and quality of life in prostate cancer survivors (Galvao et al., 2010; Gardner et al., 2014; Thorsen et al., 2008). Thus, a survey of questionnaire respondents (137 of 348 men treated for prostate cancer) made a cross-sectional comparison between those who maintained an adequate level of habitual physical activity and those who did not; it found greater social participation, a better quality of life on the WHO scale and lower prostate serum antigen levels in the more active individuals (Boisen et al., 2016).

Both a lower overall and lower prostate-specific mortality have been seen in the more active individuals. Bonn et al. (2014) followed 4623 men with localized prostate cancer for 10-15 yr. A questionnaire assessed the volume of physical activity (MET-hr/day) that was invested in walking/cycling, household work and exercise. There were 194 deaths from prostate cancer during the follow-up, with a lower risk lower among those walking and/or cycling for more than 20 min/day or exercising for longer than 1 hour per week (Bonn et al., 2014). A similar study by Kenfield et al. (2011) looked at 548 deaths in 2705 cases of prostate cancer who were followed for 18 yr; survival was compared between those taking more than 3 hr vigorous activity per week and those spending less than 1 hour per week. Those taking a greater amount of vigorous activity had a 61% lower risk of dying from prostate cancer (hazard ratio 0.39, 0.18-0.84) (Kenfield et al., 2011). The same group of investigators Richman et al. (2011) followed 1455 cases of localized prostate cancer for an average of around 2 yr. Over the period of follow-up, there were a total of 117 events (a local recurrence of the cancer, a need for secondary treatment, the detection of metastases, or

Table 7. Habitual physical activity and response to rehabilitation during and following the treatment of prostate cancer.

Author	Sample	Type of physical activity	Findings	Comments
Habitual physical activity				
Boisen et al. (2016)	137 cases of PC	Self-selected	Active individuals had better quality of life on WHO scale and lower PSA levels	Cross-sectional comparison
Bonn et al. (2014)	4623 men with localized PC followed for 10-15 yr	MET-h/day of walking/cycling, household work & exercise	194 deaths from PC, risk lower if walking/cycling > 20 min/d or exercising > 1 hr/wk	Cross-sectional comparison
Chipperfield et al. (2013)	356 men with PC	Adherence to national physical activity guidelines	42% of sample met guidelines; low activity was associated with depression, anxiety, & co-morbid conditions	ADT patients less active than those given only irradiation
Kenfield et al. (2011)	548 deaths in 2705 cases of PC followed 18 yr	Vigorous activity >3 hr /wk vs. <1 hr/wk	61% lower risk of PC death (HR 0.39, 0.18-0.84) in active	
Keogh et al. (2010)	84 cases of PC on ADT	"Active" on questionnaire response	Less than half reported they were active; active individuals had higher QOL	Attitude & perceived behavioural control main determinants of physical activity
Livingston et al. (2015)	147 cases of PC on ADT, 54 exercised, 93 usual care	Self-reported activity, QOL, anxiety & depression	Exercise programme increased vigorous exercise, cognitive functioning, reduced depression	Duration of study only 12 weeks
Mennen-Winchell et al. (2014)	96 men treated with ADT >9 months	Canadian Fitness Survey measure of habitual physical activity	BMD of hip and spine correlated with reported endurance activity (min/wk or MET-hr/wk)	Self-reported endurance exercise 4.6 MET-hr/wk, Resistance exercise 0.7 MET-hr/wk
Richman et al. (2011)	1455 cases of localized PC followed ~ 2 yr	Activity, walking duration & pace	117 events (local recurrence, secondary treatments, metastases, deaths) inversely associated with brisk walking	Few engaged in vigorous physical activity
Wolin et al. (2010)	589 men undergoing radical prostatectomy for PC	Activity, obesity	Men active >1 hr/wk and not obese less likely to be urinary incontinent (RR 0.74, 0.52-1.06)	
Aerobic and/or Resistance Exercise				
Buffart et al. (2015)	100 cases of PC aged 71.7 yr	6 months supervised aerobic & resistance exercise (2 times/wk), pedometer, exercise prescription, 6 months home programme vs. printed advice	Exercise programme had significant benefits for global QOL, physical function & social function at 6 months	Gains of physical function sustained at 12 months
Cormie et al. (2015)	63 cases of PC within 10 days of commencing ADT	3 months supervised aerobic & resistance exercise (32) vs. usual treatment (31)	Exercise preserved lean mass, avoided fat accumulation, greater aerobic power & muscle strength, lower body function, sexual function, less fatigue & psychological distress	

Table 7 Continued

Author	Sample	Type of physical activity	Findings	Comments
Culos-Reid et al. (2010)	100 cases of PC receiving ADT > 6 months; 53 in intervention group vs. 47 controls	16 week programme (supervised once/wk, 4 home sessions/wk)	Significant increases in physical activity, changes in girth & blood pressure, trends to less depression & fatigue in exercise group	Conclusions limited by drop-outs (11/53 in intervention, 23/47 in controls)
Galvao et al. (2006)	10 men with localized PC on ADT	20 wk resistance training at 6-12 RM	Muscle strength & endurance increased, gains of forward & backward walking, chair rise time, stair climbing, 400 m walk & balance	
Galvao et al, (2010)	57 cases of PC with ADT	12 weeks resistance & aerobic exercise vs. usual care	Increase of lean mass & muscle strength, faster forward & backward walk, less c reactive protein, less fatigue & enhanced QOL in exercised group	No adverse events among exercisers
Hansen et al. (2009)	10 cases of PC, 5 receiving ADT	Recumbent, high force eccentric cycle ergometer exercise 3 times/wk for 12-15 min	Both groups showed enhanced strength & functional mobility (6 min walk distance)	Strength training response not impaired by ADT
Hanson et al. (2013)	17 African Americans with PC, on ADT	12 weeks of strength training	Increase of muscle mass (2.7%), strength (28%), QOL (7%), decreased perceived fatigue (38%)	Muscle hypertrophy occurs in absence of testosterone. No control group.
Jones et al. (2014)	50 cases of PC treated by radical prostatectomy	5 walking sessions/wk at 55-100% of peak oxygen intake vs. usual care	Similar reduction of erectile dysfunction in intervention & control group (20, 24%)	
Kvorning et al. (2006)	22 healthy but untrained men, 11 treated with ADT for 12 wk	8 wk strength training at 6-10 RM	No change of isometric knee extension in ADT group, untreated men show 10% increase	ADT reduced testosterone level 22.6 to 2.0 nmol/L
Monga et al. (2007)	21 cases of PC treated by radiation alone; 11 aerobic exercise, 10 controls	Aerobic exercise 3 times/wk for 8 weeks	Exercised group showed gains in aerobic fitness, strength, flexibility, QOL, physical & social well-being, less fatigue	
Nilsen et al. (2015)	58 cases of PC on ADT	28 followed 16 wk high-load strength training, 30 usual care controls	Gains of LBM in upper & lower limbs, but not total LBM; gains of 1-RM strength, sit-to-stand, stair climbing & shuttle walk in exercisers	No change in fat mass in exercisers
Norris et al. (2015)	30 cases of PC not receiving ADT	12 weeks of resistance exercise 3 or 2 times/wk	Gains of lower body strength, chair stand time, sit-and-reach and 6 min walk distance greater for 3/wk than for 2/wk group	2/wk more favourable for mental component of QOL

Table 7 Continued

Author	Sample	Type of physical activity	Findings	Comments
Park et al. (2012)	49 cases of PC	Resistance, flexibility & Kegel exercises 2/wk for 12 weeks vs. Kegel exercises alone	Exercise group fared better on strength (except grip), continence (71% vs. 44%) & QOL	
Segal et al. (2003)	155 cases of PC on ADT	Resistance exercise 3/wk for 12 wks (n = 82) vs. wait-list controls (n = 73)	Increased levels of upper & lower body fitness, less fatigue, increased QOL in exercisers	No changes in BMI or body fat in exercisers
Segal et al. (2009)	121 cases of PC, some receiving ADT	Aerobic exercise vs. resistance exercise vs. usual care	Both aerobic & resistance exercise reduced fatigue; resistance exercise also yielded gains of strength & QOL,	Resistance exercise reduced triglycerides and body fat
Windsor et al. (2004)	66 cases of localized PC	Aerobic exercise (home-based walking 30 min 3/wk) vs. controls	Improvement of shuttle-run score with no significant increase in fatigue in exercisers	
Special programmes				
Bourke et al. (2011)	25 patients with advanced PC on ADT, vs. 25 standard treatment	12-week lifestyle programme (aerobic & resistance exercise, dietary advice)	Improved exercise behaviour, diet, energy intake, aerobic tolerance, muscle strength, less fatigue in exercisers	Attrition of exercisers 44% at 6 months, no effect on clinical disease
Bruun et al. (2014); Uth et al. (2013)	Men receiving ADT > 6 months, 21 soccer group, 20 controls, 32-wk follow-up	Community-based recreational football (45-60 min, 2-3/wk) vs. standard care	Soccer gave significant advantages in bone density, jump height, & stair climbing	2 fibula fractures & 3 muscle or tendon injuries in soccer group
Craike et al. (2016)	52 men treated for PC	3 month supervised exercise programme	Adherence 80%; role functioning & hormonal symptoms predicted adherence	Positive perceptions of ability increased adherence
Demark-Wahnefried et al. (2007)	543 prostate and breast cancer survivors	Tailored diet & exercise print intervention vs. non-tailored materials	Tailored programme increased exercise (59 vs. 39 min/wk), BMI -0.3 vs. +0.1 kg/m^2	95.6% completed 1-yr intervention
Sajid et al. (2016)	19 cases of PC on ADT	Home-based walking/resistance exercise 5 days/wk vs. technology-mediated home programme vs. usual care for 6 wks	Best response is to home-based programme (increase of 2720 steps/day)	
Santa Mina et al. (2012)	10 cases of PC on ADT	60 min group exercise or personal trainer, 3/wk for 8 wk	Suggestion of better response with personal trainer	
Skinner et al. (2016)	51 cases of PC	4 sessions of supervised exercise over 4 wk	Gains of strength, 400 m walk, chair stands, walking speed, sit-and-reach, well-being	Uncontrolled study
Uth et al. (2014; 2016)	57 men receiving ADT >6 months	32 weeks of recreational football 2-3 times/wk vs. standard care	Football gave significant gains in BMD, LBM, muscle strength, maximal oxygen intake, jump height, & stair climbing	

ADT = androgen deprivation therapy. BMD = b one mineral density. HR = hazard ratio. LBM = lean body mass. MET = metabolic equivalent. PC = prostate cancer. PSA = prostate serum antigen. QOL = quality of life. RM = repetition maximum. RR = relative risk.

death). Relatively few of the samples had engaged in vigorous physical activity following diagnosis. Nevertheless, disease progression was less likely in those men who had walked briskly for 3 or more hr per week, or who had engaged in vigorous physical activity for longer than 3 hr per week [hazard ratio = 0.63 (0.32-1.23, p for trend = 0.17] (Richman et al., 2011).

Urinary incontinence is often a major handicap following radical prostatectomy. Wolin and associates (2010) demonstrated that in 589 men who had undergone such treatment; there was a trend to a lower risk of incontinence in men who were active for longer than 1 hour per week [relative risk 0.74, 0.52-1.06)]. However, it is difficult to be sure whether this finding was cause or effect!

Aerobic and resistance exercise programmes. Many investigators have followed the types of programme currently recommended to prostate cancer patients by consensus groups; such initiatives include aerobic, resistance, impact and flexibility exercises. However, some studies have focused uniquely on aerobic or resistance training.

Some combined aerobic and resistance exercise programmes have continued for as long as a year. Galvao et al., (2014) compared the response to 6 months of supervised exercise followed by a 6 months home exercise programme with the effects of simply providing educational material in 100 cases of prostate cancer who were receiving ADT. The direct exercise intervention enhanced aerobic performance, muscle mass, strength and self-reported physical functioning compared to the educational group; benefits were apparent at 6 months, and were maintained at 12 months, following the period of reliance upon the home exercise programme (Galvao et al., 2014). In another report from the same laboratory, Buffart et al. (2015) followed 100 cases of prostate cancer, initially aged an average of 71.7 yr, for 12 months. A half of the group received 6 months of supervised aerobic and resistance exercise twice per week, followed by a 6-month home exercise programme based upon a pedometer and a detailed exercise prescription, and the remaining subjects received standard treatment plus some printed advice. At 6 months, the exercise group showed significant benefit relative to the comparison group in terms of the global quality of life, physical function and social function, and the gains of physical function were maintained at 12 months (Buffart et al., 2015).

Culos-Reid et al. (2010) assigned 53 of 100 cases of prostate cancer who had been receiving ADT for longer than 6 months to a 16 week programme of once weekly supervised exercise, supplemented by up to 4 home sessions per week. Relative to 47 controls, they showed significant increases in physical activity, with decreases in abdominal girth and blood pressure, and trends to less depression and fatigue, although the statistical significance of their conclusions was limited by a substantial number of drop-outs (11 in the intervention group and 23 among the controls) (Culos-Reid et al., 2010).

The benefits of increased exercise can be realized relatively quickly. Thus, Galvao and colleagues (2010) examined 57 cases of prostate cancer who were receiving ADT 12 weeks after they had been assigned to either a bi-weekly aerobic and resistance exercise programme or to usual care. The 3-month exercise intervention was sufficient to induce a wide range of beneficial

responses, including increases of lean mass and muscle strength, faster forward and backward walking speeds, a decrease of c-reactive protein concentrations, less fatigue and an enhanced quality of life. Moreover, there were no adverse consequences from what was a quite vigorous exercise programme (Galvao et al., 2010). Cormie and associates (2015) examined the benefits of early initiation of an aerobic and resistance exercise programme. Cases of prostate cancer were contacted within 10 days of beginning ADT; 32 patients followed a 3-month aerobic and resistance exercise programme (twice weekly, supplemented by home exercise), and the remaining 31 patients served as controls. The exercise programme conserved lean mass and reduced the accumulation of body fat relative to the controls. The exercisers also showed a greater aerobic power and muscular strength, with better lower body function and sexual function, less fatigue and less psychological distress (Cormie et al., 2015).

Segal et al. (2009) compared aerobic exercise with resistance exercise or usual treatment controls in 121 cases of prostate cancer, some of whom were receiving ADT. Both aerobic and resistance exercise increased aerobic fitness and reduced fatigue relative to usual treatment, but the resistance exercise group also demonstrated gains of strength and quality of life, with a reduction of triglycerides and body fat (Segal et al., 2009).

Among interventions limited to aerobic training, some have found a good response, but in others the benefit has been disappointing. Monga and colleagues (2007) investigated 21 patients with localized prostate cancer who were treated by irradiation alone. Eleven of the group undertook 8 weeks of aerobic exercise (3 times/wk), and despite the short duration of their programme, they showed substantial response relative to the 10 controls (gains in aerobic fitness, strength, flexibility, quality of life, physical and social well-being, and less fatigue) (Monga et al., 2007). Windsor et al. (2004) examined 66 cases of localized prostate cancer. A half of the group was assigned to a modest home-based aerobic walking programme (30 minutes, 3 times /wk). All of the exercisers maintained at least this minimum programme over the 4 weeks of radiotherapy. Despite the very brief duration of the intervention, the exercised group again showed improvements in their score on the shuttle run test, with no significant increase of fatigue (Windsor et al., 2004). In contrast, Jones et al. (2014) studied 50 cases of prostate cancer who had undergone radical prostatectomy, but apparently were not receiving ADT. In this group, a 6-month aerobics programme (5 walking sessions/wk at 55-100% of peak oxygen intake) led to no greater reduction of erectile dysfunction than that seen in the usual care group (Jones et al., 2014).

Of programmes that focussed specifically on resistance training, some have shown substantial gains of muscle strength despite androgen suppression. Galvao and associates (2006) enrolled 10 men with localized prostate cancer who were receiving ADT in a 20-week resistance training programme at a 6-12 repetition maximum intensity. This induced gains in muscle strength and endurance, forward and backward walking times, chair-stand speed, stair-climbing, 400-m walk and balance scores (Galvao et al., 2006). Hansen et al. (2009) looked at the effects of eccentric training in 10 cases of prostate cancer, five of who were receiving ADT. The programme

involved recumbent, high force eccentric cycle ergometer exercise performed for 12-15 minutes, 3 times per week. This regimen enhanced isometric strength and functional mobility, whether or not the subject was receiving ADT (Hansen et al., 2009). Hanson and colleagues (2013) made similar observations on 17 African Americans with prostate cancer who were receiving ADT; 12weeks of strength training led to an increase of muscle mass (2.7%), strength (28%), and quality of life (7%), and a decreased perception of fatigue (38%), despite the demonstrated suppression of testosterone levels. Nilsen et al. (2015) studied 58 cases of prostate cancer on ADT; 28 of the group followed a 16-week high-load strength training programme, and the other 30 men served as usual care controls. Relative to the controls, the strength-training group showed a number of advantages, including gains of lean body mass in the upper and lower limbs (although not in the total lean mass); gains of 1-RM strength, sit-to-stand times, stair climbing performance and shuttle-walk scores (Nilsen et al., 2015). Segal and colleagues (2003) evaluated 155 cases of prostate cancer on ADT; 82 were assigned to resistance exercise 3 times per week for 12 weeks, and 73 remained in a wait-list control group. Despite the ADT, the exercised group again showed increased levels of upper and lower body fitness, less fatigue, and an increased quality of life (Segal et al., 2003).

In contrast to the gains of muscle function observed in the prostate cancer cases given ADT, Kvorning et al. (2006) carried out a study on 22 healthy but untrained men, administering ADT to 11 of the group for 12 weeks. In this population, a programme of strength training (8 weeks at 6-10 RM) increased the isometric knee extension of the controls by 10%, but there was no change of strength in those receiving the ADT (where testosterone levels had dropped from 22.6 to 2.0 nmol/L) (Kvorning et al., 2006). Possibly, the gains of muscle strength seen in those receiving ADR in the treatment of prostate cancer may reflect better neuromuscular coordination rather than muscle hypertrophy, since in general such individuals have been no changes of body mass index or body fat in response to the resistance training.

How often should resistance exercise be performed? Norris and associates (2015) assigned 30 cases of prostate cancer who were not receiving ADT to 12 weeks of resistance exercise, performed 2 or 3 times per week. The thrice weekly group fared better than the twice weekly group on the physical components of response, including gains of lower body strength, chair-stand times, sit-and-reach distances and the 6 minute walk distance, but the twice per week group fared better on the mental component of quality of life, including scores for mental health, vitality, emotional role, anxiety, happiness, and perceived stress (Norris et al., 2015).

The loss of bone mineral is a major concern during ADT. Winters-Stone et al. (2014) thus compared one year of combined high impact plus resistance exercise (2 one-hour supervised and one home session/wk) with a placebo programme of light stretching exercises in a group of 51 cases of prostate cancer who were receiving ADT. The resistance exercise group showed a 1-year adherence of 84%, without injuries, and a substantial reduction of the decrease in bone mineral density relative to those assigned to the stretching programme (an average loss of only -0.4%, versus -3.1%

in the controls) (Winters-Stone et al., 2014).

Park and colleagues (2012) evaluated a combination of resistance, flexibility and Kegel (pelvic floor muscle) exercises vs. Kegel exercises alone in a 12-week biweekly intervention. The exercise group fared better on most measures of strength (except grip strength), urinary continence (71% vs. 44%, with respective 24-hour urine-pad weights of 12 vs. 46 g)), quality of life and depression (Park et al., 2012).

Special considerations in programme design. Unfortunately, vigorous physical activity seems necessary to ensure enhanced functional outcomes during ADT (Livingston et al., 2015). Relatively few prostate cancer survivors spontaneously engage in levels of physical activity that are adequate to ensure benefit (Chipperfield et al., 2013). This may be in part because most cases are relatively elderly, and discouraging symptoms are associated with androgen-suppression (Craike et al., 2016), but another issue not always considered is the need to adapt programmes in the light of specific complications of prostate surgery and irradiation such as urinary incontinence and exercise-induced diarrhoea. Some investigators have found good sustained compliance with what seem fairly standard exercise programmes, albeit with some individual tailoring, but others have suggested that motivation can be boosted by novel approaches such as recruitment to a recreational soccer programme (Uth et al., 2013) or the use of a personal trainer (Santa Mina et al., 2012).

Craike et al. (2016) examined factors influencing adherence to a 3-month exercise programme (2 supervised sessions, 1 unsupervised session/wk) in 52 men who were undergoing treatment for prostate cancer. Adherence, which averaged 80%, was influenced by role functioning and the extent of hormone-related symptoms, with perceptions of functional ability increases the likelihood of adherence (Craike et al., 2016).

Bourke and colleagues (2011) compared the response to a 12-week lifestyle programme with standard treatment in 2 groups of 25 men with advanced prostate cancer who were each receiving ADT. The 12-week lifestyle programme comprised of aerobic and resistance exercise (twice weekly for 6 weeks, once weekly for a further 6 weeks, plus self-directed exercise and dietary advice). This programme improved exercise behaviour, diet, energy intake, aerobic tolerance, muscle strength, and reduced fatigue in participants relative to controls, but there was no effect on clinical disease, and the attrition rate had risen to 44% by 6 months (Bourke et al., 2011).

Demark-Wahnefried et al. (2007) explored the value of individually tailored mailed recommendations for diet and exercise vs. non-tailored guidelines in a mixed sample of 543 breast and prostate cancer survivors. The personally tailored information led to a larger increase in weekly exercise than that seen with the non-tailored recommendations (59 vs. 39 min), and there was also a favourable change of body mass index in the experimental group (-0.3 vs. +0.1 kg/m^2). Moreover, the compliance for the 1-year intervention was high (95.6%) (Demark-Wahnefried et al., 2007). Another comparison of a supervised programme of aerobic and resistance exercise with general printed physical activity recommendations found that the former gave greater improvements in the global quality of life as well as in physical and social functioning, all mediated by

improved lower body functioning (Buffart et al., 2015; Galvao et al., 2014; Livingston et al., 2015). Sajid et al. (2016) divided 19 cases of prostate cancer on ADT between a home-based walking and resistance exercise programme, a technology mediated programme and usual care. The sample was rather small for clear conclusions, but the home programme appeared to yield the best results, with an increase in step count of 2720 steps/day over the course of the trial (Sajid et al., 2016).

Skinner and colleagues (2016) examined the effects of a minimal exercise intervention (4 sessions of supervised exercise over 4 weeks) in an uncontrolled study of 51 cases of prostate cancer. They reported gains of muscle strength, 400-m walk times, chair-stand times, walking speed, sit-and-reach and well-being with this very limited intervention (Skinner et al., 2016).

Bruun et al. (2014) and Uth et al. (2013) argued for the motivational value of participating in community-based recreational soccer. Men with prostate cancer who had been receiving ADT for longer than 6 months were divided into a soccer group (n=21) and a usual treatment group (n=20) over a 32-week follow-up. The soccer participants gained significant advantages in terms of bone density, jump-height, and stair-climbing relative to those receiving standard care, but on the other hand the soccer players sustained 2 fractures of the fibula and 3 muscle or tendon injuries over the period of observation (Bruun et al., 2014; Uth et al., 2013). Uth et al. (2016) and Uth et al. (2014) further evaluated the motivational and therapeutic value of participation in recreational soccer (2-3 games/wk for 32 weeks) in 57 men who were receiving ADT. Relative to usual-care controls, the soccer players again showed substantial gains in bone mineral density, along with increases of lean body mass, muscle strength, maximal oxygen intake, jump-height and stair-climbing ability (Uth et al., 2016; Uth et al., 2014).

Santa Mina et al. (2012) compared the response to 60 minutes of group exercise, 3 times per week to benefits from the services of a personal trainer in a small 8-week pilot trial of 10 cases of prostate cancer receiving ADT. Despite the limited number of subjects, there was a trend suggesting that the personal trainer was somewhat more effective than the group exercise programme (Santa Mina et al., 2012).

Areas for future research

The value of regular physical activity as a means of reducing the risk of prostate cancer is still far from certain. One obstacle to obtaining more conclusive data is that even when a very large population is followed for a long period, the number of cases of prostate cancer remains quite small. Given the number of studies that have already been carried out, meta-analysis may provide some resolution to this question, although there are major challenges to such an approach, including differences between samples, differing criteria used to identify physically active individuals, and the incidence of prostate cancer, and variations in the age at which activity has been evaluated. Possibly, as mechanisms of carcinogenesis are clarified, it may be possible to determine which types of physical activity are best suited to modulate the causal agents. It also seems worth following up on suggestions from *post-hoc* analyses that susceptibility to exercise may be modified by the subject's age or by the aggressivity of the tumour.

The spontaneously chosen level of physical activity amongst those

undergoing ADT following surgical treatment or pelvic irradiation is typically below levels recommended for population health, and there is a need for research on tactics that will induce a sustained increase of physical activity, correcting deficits of aerobic function, muscle strength and bone density and enhancing the quality of life in this population. The gains of strength observed with resistance training in patients who are receiving ADT are intriguing, since blood levels of androgenic hormones are very low, and studies are needed to examine how far the observed changes represent true muscle hypertrophy, and how far they are simply a reflection of test learning and greater neuromuscular coordination.

Practical Applications and conclusions

There is little evidence suggesting that regular moderate exercise has any adverse impact upon the prostate gland, a possible favourable impact upon the risk of prostate cancer is yet one more reason to recommend that older men maintain a habit of regular moderate exercise. A combination of aerobic and muscle strengthening exercise can also play a useful role in countering such side-effects of ADT as a loss of aerobic power, muscle strength and bone mineral, with an increase in many components of the quality of life.

Acknowledgements

The author acknowledges no funding relationships or conflicts of interest.

Author's qualifications

The author's qualifications are as follows: Roy J. Shephard, C.M.; Ph.D., M.B.B.S., M.D. [Lond.], D.P.E., LL.D., D.Sc., FACSM, FFIMS.

References

Albanes, D., Blair, A., & Taylor, P.R. (1989). Physical activity and the risk of cancer in the NHANES I population. *Am. J. Publ. Health, 79:* 744-750. doi: 10.2105/AJPH.79.6.744.

Alibhai, S.M.H , Breunis, H., Timilshina, N., Naglie, G., Tannock, I., Krahn, M., Warde, P., Fleshner, N.E., Canning, S.D., and Tomilinson, G. (2015). Long-term impact of androgen-deprivation therapy on physical function and quality of life. *Cancer, 121(14)*: 2350-2357. doi.org/10.1002/cncr.29355.

Andersson, S-O., Baron, J., Wolk, A., Lindgren, C., Bergström, R., and Adami, H.O.(1995). Early life risk factors for prostate cancer: A population-based case-control study in Sweden. *Cancer Epidemiol. Biomarkers Prev, 4*: 187-192. URL: http://www.ncbi.nlm.nih.gov/pubmed/7606192

Bairati, I., Larouche, R., Meyer, F., Moore, L., and Fradet, Y. (2000). Lifetime occupational physical activity and incidental prostate cancer (Canada). *Cancer Causes Control, 11*: 759-764. doi.org/10.1023/A:1008936826337.

Barnard, R.J., Leung, P.S., Aronson, W.J., Cohen, P., and Golding, L.A. (2007). A mechanism to explain how regular exercise reduces the risk for prostate cancer. *Eur. J. Cancer Prev. 16*: 415-421. doi.org/10.1097/01.cej.0000243851.66985.e4

Basaria, S., Lieb, J., Tang, A.M., DeWeese, T., Carducci, M., Eisenberger, M., and Dibs, A.S. (2002). Long-term effects of androgen deprivation therapy in prostate cancer patients. *Clin. Endocrinol. 56:* 779-786. doi.org/10.1046/j.1365-2265.2002.01551.x

Baumann, F.T., Zopf, E.M., and Bloch, EW. (2012). Clinical exercise interventions in prostate cancer patients- a systematic review of randomized controlled trials. *Suppoirt Care Cancer, 20:* 221-233. doi.org/10.1007/s00520-011-1271-0.

Berrutti, A., Dogliotti, L., Terrone, C., Cerutti, S., Isala, G., Tarabuzzi, R., Reimondo, G., Mari, M., Ardissone, P., De Luca, S., Fasolis, G., Fontana, D., Rossetti, S.R., and Angeli, A; Gruppo Onco Urologico Piemontese (G.O.U.P), Rete Oncologica Piemontese

(2002). Changes in bone mineral density, lean body mass and fat content as measured by dual energy in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. *J. Urol. 167*: 2361-2367. doi.org/10.1016/S0022-5347(05)64985-3.

Blair, S.N., Cheng, Y., and Holder, J.S. (2001). Is physical activity or physical fitness more important in defining health benefits? *Med. Sci. Sports Exerc. 33 (6 Suppl)*: S379-S399. doi.org/10.1097/00005768-200106001-00007.

Boisen, S., Krägeloh, C., Shepherd, D., Ryan, C., Masters, J., Osborne, S., Macleod, R.D., Gray, M., and Keogh, J.W. (2016). A cross-sectional comparison of quality of life between physically active and under-active older men with prostate cancer. *J. Aging Phys. Act. In press*. doi.org/10.1123/japa.2015-0195.

Bonn, S.E., Sjölander, A., Lageross, Y.T., Wiklund, F, Stattin, P., Holmberg, E., Grönberg, H., and Bälter, K. (2014). Physical activity and survival among men diagnosed with prostate cancer *Cancer Epidemiol. Biomarkers Prev. 24(1):* 57-64. doi.org/10.1158/1055-9965.EPI-14-0707.

Bouchard, C., and Shephard, R.J. (1992). Physical activity, fitness and health. The model and key conceptsl. In: C. Bouchard, R.J. Shephard, and T. Stephens (Eds.), *Physical activity, fitness and health*. Champaign, IL: Human Kinetics, pp. 77-88.

Bourke, L., Doll, H., Crank, H., Dasley, A., Rosario, D., and Saxton, J.M. (2011). Lifestyle intervention in men with advanced prostate cancer receiving androgen suppression therapy: A feasibility study. *Cancer Epidemiol. Biomarkers Prev. 20(4):* 647-657. doi.org/10.1158/1055-9965.EPI-10-1143.

Boxer, R.S., Kenny, A.M., Dowsett, R., and Taxel, P. (2005). The effect of 6 months of androgen deprivation therapy on muscle and fat mass in older men with localized prostate cancer. *Aging Male, 8(3/4)*: 207-212. doi.org/10.1080/13685530500361226.

Brownson, R.C., Chang, J.C., Davis, J.R., and Smith, C.A. (1991). Physical activity on the job and cancer in Missouri. *Am. J. Publ. Health, 81(5)*: 639-642. doi.org/10.2105/AJPH.81.5.639.

Bruun, D.M., Bjerre, E., Krustrup, P., Brasso, K., Johansen, C., Rørth, M., and Midtgaard, J. (2014). Community-based recreational football: A novel approach to promote physical activity and quality of life in prostate cancer survivors. *Int. J. Environ. Res. Public Health, 11*: 5567-5585. doi.org/10.3390/ijerph110605567.

Buffart, L.M., Newton, R.U., Chinapaw, M.J., Taaffe, D.R., Spry, N.A., Denham, J.W., Joseph, D.J., Lamb, D.S., Brug, J., and Galvão, D.A. (2015). The effect, moderators, and mediators of resistance and aerobic exercise on health-related quality of life in older long-term survivors of prostate cancer. *Cancer Cases Control, 121*: 2821-2830. doi.org/10.1002/cncr.29406.

Bylow, K., Dale, W., Mustian, K., Stadler, W.M., Rodin, M., Hall, W., Lachs, M., and Mohile, S.G. (2008). Falls and physical performance deficits in older patienrs with prostate cancer undergoing androgen deprivation therapy. *Urology, 72*: 422-427. doi.org/10.1016/j.urology.2008.03.032.

Canadian Cancer Society. (2015). Prostate Cancer. URL: http://www.cancer.ca/en/cancer-information/cancer-type/prostate/statistics/?region=bc. Accessed June 26th, 2016.

Cerhan, J.R., Torner, J.C., Lynch, C.F., Rubenstein, L.M., Lemke, J.H., Cohen, M.B., Lubaroff, D.M., and Wallace, R.B. (1997). Association of smoking, body mass and physical activity with risk of prostate cancer in the Iowa 65+ rural health study (United States). *Cancer Causes Control, 8*: 229-238.doi.org/10.1023/A:1018428531619.

Champ, C.E., Francis, L., Klement, R.J., Dickerman, R., and Smith, R.P. (2016). Fortifying the treatment of prostate cancer with physical activity. *Prostate Cancer, Article ID 9462975*. doi.org/10.1155/2016/9462975.

Chen, Y.C., Chiang, C.I., Lin, R.S., Pu, Y.S., Lei, M.K., and Sung, F.C. (2005). Diet, vegetarian food and prostate carcinoma among men in Taiwan. *Br. J. Cancer, 93:* 1057-1061. doi.org/10.1038/sj.bjc.6602809.

Chen, Z., Maricic, M., Nguyen, P., Ahmann, F.R., Bruhn, R., and Dalkin, B.L. (2002). Low bone density and high percentage body fat among men who were treated with androgen deprivation therapy for

prostate cancer. *Cancer, 95(10)*: 2136-2144. doi.org/10.1002/cncr.10967.

Chipperfield, K., Fletcher, J., Millar, J. , Brooker, J., Smith, R.P., Frydenberg, M., Oh, T., and Burney, S. (2013). Factors associated with adherence to physical activity guidelines in patients with prostate cancer. *Psychooncology, 22:* 2478–2486. doi.org/10.1002/pon.3310.

Clarke, G.,and Whittemore, A.S. (2000). Prostate cancer risk in relationship to anthropometry and physical activity: The National Health and Nutrition Examination Survey I epidemiological follow-up study. *Cancer Epidemiol. Biomarkers Prev, 9:* 875-881. URL: http://www.ncbi.nlm.nih.gov/pubmed/11008903.

Cormie, P., Galvão, D.A., Spry, N., Joseph, D., Chee, R., Taaffe, D.R., Chambers, S.K., and Newton R.U. (2015). Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. *BJU Int. 115:* 256-266. doi.org/10.1111/bju.12646.

Craike, M., Gaskin, C.J., Courneya, K.S., Fraser, S.F., Salmon, J., Owen, P.J., Broadbent, S., and Livingston, P.M. (2016). Predictors of adherence to a 12-week exercise program among men treated for prostate cancer: ENGAGE study. *Cancer Med. Feb 12. doi: 10.1002/cam4.639. [Epub ahead of print]*. doi.org/10.1002/cam4.639.

Crawford, E.D., and Moul, J.W. (2015). ADT risks and side-effects in advanced prostate cancer: cardiovascular and renal injury. *Oncology, 29(1)*: 55-58, 65-66. URL: http://www.ncbi.nlm.nih.gov/pubmed/19164825.

Crespo, C.J. , Garcia-Palmieri, M.R. , Smit, E.,, Lee, I.-M., McGee, D., Muti, P., Figueroa Valle, N.R., Ramierez-Marrero, F.A., Freudenheim, J.L., and Sorlie, P. (2008). Physical activity and prostate cancer mortality in Puerto Rican men. *J. Phys. Activ. Health, 5(6)*: 918-929. URL:

Culos-Reid, S.N., Robinson, J.W., Lau, H., Stephenson, L., Keats, M., Norris, S., Kline, G., and Faris, P. (2010). Physical activity for men receiving androgen deprivation therapy for prostate cancer; benefits from a 16-week intervention. *Support Care Cancer, 18*: 591-599. doi.org/10.1007/s00520-009-0694-3.

Dacal, K., Sereika, S.M., and Greenspan, S .L. (2006). Quality of life in prostate cancer patients taking androgen deprivation therapy. *J. Am. Geriatr. Soc. 54:* 85-90. doi.org/10.1111/j.1532-5415.2005.00567.x.

Daniell, H.W. (1997). Osteoporosis after orchidectomy for prostate cancer. *J. Urol, 157:* 439-444. URL: http://www.ncbi.nlm.nih.gov/pubmed/8996327.

Daniell, H.W. (2001). Osteoporosis due to androgen deprivation therapy in men with prostate cancer. *Urology, 58(Suppl. 2A)*: 101-107. doi.org/10.1016/S0090-4295(01)01251-1.

Darlington, G.A., Kreiger, N., Lightfoot, N., Purdham, J., and Sass-Kortak, A. (2007). Prostate cancer risk and diet, recreational physical activity and cigarette smoking. *Chron. Dis. Canada, 27(4)*: 145-153. URL: http://www.ncbi.nlm.nih.gov/pubmed/17623560.

de Sousa, C.V., Sales, M.M., Rosa, T.S., Lewis, J.E., de SAndrade, R.V., and Simões, H.G. (2016). The antioxidant effect of exercise: A systematic review and meta-analysis. *Sports Med. June 3rd, e-pub ahead of print*. doi.org/10.1007/s40279-016-0566-1.

Demark-Wahnefried, W., Clipp, E.C., Lipkjus, I.M., Lobach, D., Snyder, D.C., Sloane, R. Peterson, B., Marcri, J.M., Rock, C.L., McBride, C.M., and Kraus, W.E. (2007). Main outcomes of the FRESH START trial: A sequentially tailored, diet and exercise mailed print intervention among breast and prostate cancer survivors. *J. Clin. Oncol. 25(109):* 2709-2718. doi.org/10.1200/JCO.2007.10.7094.

Doolan, G.W., Benke, G., Giles, G.G., Severi, G., and Kauppinen, T. (2014). A case control study investigating the effects of levels of physical activity at work as a risk factor for prostate cancer. *Environ. Health, 13:64*. doi.org/10.1186/1476-069X-13-64.

Dosemeci, M., Hayes, R.B., Vetter, R., Hoover, R.N., Tucker, M., Engin, K., Unsal, M., and Blair, A. (1993). Occupationakl physical activity, socioeconomic status, and risks of 15 cancer sites in Turkey. *Cancer Causes Control, 4*: 313-321. doi.org/10.1007/BF00051333.

Eisenmann, J.C., and Malina, R.M. (2000). Body size and endurance performance. In: R.J. Shephard & P-O. Åstrand (Eds.),

Endurance in sport, 2nd ed., Oxford, U.K.: Blackwell Scientific, pp. 37-51. doi.org/10.1002/9780470694930.ch4.

Fowler, F.J., Collins, McN., Corkery, E.W., Elliott, D.B., and Barry, M.J. (2002). The impact of androgen deprivation on quality of life after radical prostatectomy for prostate cancer. *Cancer, 95*: 287-295. doi.org/10.1002/cncr.10656.

Friedenreich, C.M., McGregor, S.E., Courneya, K.S., Angyalfi, S.J., and Elliot, F.G. (2004). Case-control study of lifetime physical activity and prostate cancer. *Am. J. Epidemiol. 159(8)*: 740-749. doi.org/10.1093/aje/kwh106.

Friedenreich, C.M., and Thune, I. (2001). A review of physical activity and prostate cancer risk. *Cancer Cases Control, 12*: 461-475. doi.org/10.1023/A:1011210121901.

Galvão, D.A., Nosaka, K., Taaffe, D.R., Spry, N., Kristjanson, L.J., McGuigan, M.R. Suzuki, K., Yamava, K., and Newton, R.U. (2006). Resistance training and reduction side effects in prostate cancer patients treatment. *Med. Sci. Sports Exerc. 38(12)*: 2045-2052. doi.org/10.1249/01.mss.0000233803.48691.8b

Galvão, D.A., Spry, N., Denham, J., Taaffe, D.R., Chambers, S.K., and Newton, R.U. (2014). A multicentre year-long randomised controlled trial of exercise training targeting physical functioning in men with prostate cancer previously treated with androgen suppression and radiation from TROG 03.04 RADAR. *Eur. Urol. 65*: 856-864. doi.org/10.1016/j.eururo.2013.09.041.

Galvão, D.A., Spry, N.A., Taaffe, D.R., Newton, R.U., Stanley, J., Shannon, T., Rowling, C., and Prince, R. (2008). Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. *BJU Int, 102:*, 44-47. doi.org/10.1111/j.1464-410X.2008.07539.x.

Galvão, D.A., Taaffe, D.R., Spry, N., Joseph, D., and Newton, R.U. (2010). Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. *J. Clin. Oncol. 28:* 340-347. doi.org/10.1200/JCO.2009.23.2488.

Gardner, J.R., Livingston, P.M., and Fraser, S.F. (2014). Effects of exercise on treatment related adverse effects for patients with prostate cancer receiving androgen-deprivation therapy: a systematic review. *J. Clin. Oncol. 32*: 335-346. doi.org/10.1200/JCO.2013.49.5523.

Giovannucci, E. , Liu, Y., Leitzman, M.F., Stampfer, M.J., and Willett, W.C. (2005). A prospective study of physical activity and incident and fatal prostate cancer. *Arch. Intern. Med, 165*: 1005-1010. doi.org/10.1001/archinte.165.9.1005.

Giovannucci, E., Leitzmann, E., Spiegelman, D., Rimm, E.B., Colditz, G.A., Stampfer, M.J., and Willett, W.C. (1998). A prospective study of physical activity and prostate cancer in male health professionals. *Cancer Res, 58:* 5117-5122. URL: http://www.ncbi.nlm.nih.gov/pubmed/9823321.

Green, H.J., Pakenham, K.I., Headley, R.C., and Gardiner, R.A. (2002). Coping and health-related quality of life in men with prostate cancer randomly assigned to hormonal medication or close monitoring. *Psychooncology, 11:* 401-414. doi.org/10.1002/pon.599.

Greenspan, S.L. , Coates, P., Sereiuka, S.M., Nelson, J.B., Trump, D.L., and Resnick, N.M. (2005). Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. *J. Clin. Endocrinol. Metab. 90(12)*: 6410-6417. doi.org/10.1210/jc.2005-0183.

Grotta, A., Bottai, M., Adami, H-O., Adams, S.A., Akre, O., Blair, S.N., Mariosa, D., Nyrén, O., Ye, W., Stattin, P., Bellocco, R., and Trolle Lagerros, Y. (2015). Physical activtiy and body mass index as predictors of prostate cancer. *World J. Urol. 33*: 1495-1502. doi.org/10.1007/s00345-014-1464-5.

Grover, S.A., Coupal, L., Zowall, H., Rajkan, R., Trachtenberg, J., Elhilali, M., Chetner, M., and Goldenberg, L. (2000). The economic burden of prostate cancer in Canada: forecasts from the Montreal prostate cancer model. *Can. Med. Assoc. J. 162(7)*: 987-992. URL:http://www.ncbi.nlm.nih.gov/pubmed/10763396.

Hackney, A.C., Sinning, W.E., and Bruot, B.C. (1988). Reproductive hormonal profiles of endurance trained and untrained males. *Med. Sci. Sports Exerc. 20*: 60-65.

.doi.org/10.1249/00005768-198802000-00009.

Hållmarker, U., James, S., Michaëlsson, K., Amlöv, J., Sandin, F., and Holmberg, L. (2015). Cancer incidence in participants in a long-distance ski race (Vasaloppet, Sweden) compared to the background population. *Eur. J. Cancer, 51(4)*: 558-568. doi.org/10.1016/j.ejca.2014.12.009.

Hansen, P.A., Dechet, C.B., Porucznik, C.A., and LaStayo, P.C. (2009). Comparing eccentric resistance exercise in prostate cancer survivors on and off hormone therapy: A pilot study. *PM R, 1(11):* 1019-1024. doi.org/10.1016/j.pmrj.2009.09.016.

Hanson, E.D., Sheaff, E.K., Sood, S., Ma, L., Francis, J.D., Goldberg, A.P., and Hurley, B.F. (2013). Strength training induces muscle hypertrophy and functional gains in black cancer prostate cancer patients despite androgen deprivation therapy. *J. Gerontol. A Biol. Med. Sci, 68(4)*: 490-498. URL: http://www.ncbi.nlm.nih.gov/pubmed/23089339.

Hartman, T.J., Albanes, D., Rautalahti, M., Tangrea, J.A., Virtamo, J., Stolzenberg, R., and Taylor, P.R. (1998). Physical activity and prostate cancer in the alpha-tocopherol, beta carotene (ATBC) cancer prevention study (Finland). *Cancer Causes Control, 9*: 11-18. doi.org/10.1023/A:1008889001519.

Harvei, S. and Kravdal, Ø. (1997).The importance of marital and socioeconomic status in incidence and survival of prtostate cancer. An analysis of complete Norwegian bith cohorts. *Prev. Med, 26*: 623-632. doi.org/10.1006/pmed.1997.0153.

Hatano, T., Oishi, Y., Furuta, A., Iwamuro, S., and Tashiro, K. (2000). Incidence of bone fracture in patients receiving luteinizing hormone releasing hormone agonists for prostate cancer. *BJU International, 86*: 449-452. doi.org/10.1046/j.1464-410X.2000.00774.x.

Heitkamp, H.C., and Jelas, I. (2012). Korperlich Activitat zur Primarpravention des Prostata karzinoms. Mogliche Mechanismen. [Physical activity in the prevention of prostate carcinoma. Possible mechanisms]. *Urologe, 51*: 527-532. doi.org/10.1007/s00120-011-2799-9.

Hosseini, M., Alinaghi, S.A.S., Mahmoudi, M., and McFarland, W. (2010). A case-control study of risk factors for prostate cancer in Iran. *Acad. Med. Iran, 48(1)*: 61-66. URL: http://www.ncbi.nlm.nih.gov/pubmed/21137672.

Hrafnkelsdóttir, S, M., Torfadóttir, J., Aspelund, T., Magnusson, K.T., Tryggvadóttir, L., Gudnason, V., Mucci, L.A., Stampfer, M., and Valdimarsdottir, U.A. (2015). Physical activity from early adulthood and risk of prostate cancer: A 24-year follow-up study among Icelandic men. *Cancer Prev. Res. Published Online July 7, 2015;* doi: 10.1158/1940-6207.CAPR-15-0035.

Hsing, A.W., McLaughlin, J.K., Zheng, W., Gao, Y-T., and Blot, W.J. (1994). Occupation, physical activity, and risk of prostate cancer in Shanghai, People's Republic of China. *Cancer Causes Control, 5*: 136-140. doi.org/10.1007/BF01830259.

Ilić, M., Vlajinac, H., and Marinković, J. (1996). Case-control study of risk factors for prostate cancer. *Br. J. Cancer, 74*: 1682-1686. doi.org/10.1038/bjc.1996.610.

Jian, L., Shen, Z.J., Lee, A.H., and Binns, C.W. (2005). Moderate physical activity and prostate cancer risk: A case-control study in China. *Eur. J. Epidemiol. 20*: 155-160. doi.org/10.1007/s10654-004-3007-7.

Johnsen, N.F., Tjønneland, A., Thomsen, B.L.R., Christensen, J., Loft, S., Friedenreich, C., Key, T.J., Allen, N.E., Lahmann, P.H., Mejlvg, L., Overvad, K., Kaaks, R., Rohmann, S., Boing, H., Misirli, G., Trichopoulou, A., Zylis, D., Tumino, R., Pala, V., Bueno-de-Mesquita, H.B., Kiemeney, L.A., Suarez, L.R., Gonzalez, C.A., Sánchez, M.J. Huerta, J.M., Gurrea, A.B., Manjer, J., Wirfält, E., Khaw, K.T., Wareham, N., Boffetta, P., Egevad, L., Rinaldi, S., and Riboli, E. (2009). Physical activity and risk of prostate cancer in the European prospective investigation into cancer and nutrition (EPIC)cohort. *Int. J. Cancer, 125*: 902-908. doi.org/10.1002/ijc.24326.

Jones, L.W., Hornsby, W.E., Freedland, S.J., Lane, A., West, M.J., Moul, J.W., Ferrandino, M.N., Allen, J.D., Kenjale, A.A., Thomas, S.M., Herndon II, J.E., Koontz, B.F., Chan, J.M., Khouri, M.G., Douglas, P.S., and Eves, N.D. (2014). Effects of nonlinear aerobic training on erectile dysfunction and cardiovascular function following radical prostatectomy for clinically localized

prostate cancer. *Eur, Urol. 65:* 852-855. doi.org/10.1016/j.eururo.2013.11.009.

Kenfield, S.A., Stampfer, M.J.., Giovannucci, E., and Chan, J.M. (2011). Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. *J. Clin. Oncol. 29*: 726-732. doi.org/10.1200/JCO.2010.31.5226.

Keogh, J.W.L., Shepherd, D., Krägeloh, C.U., Ryan, C., Masters, J., Shepherd, G., and Macleod, R. (2010). Predictors of physical activity and quality of life in New Zealand prostate cancer survivors undergoing androgen-deprivation therapy. *NZ. Med. J. 123(1325)*: 20-28. URL: http://www.ncbi.nlm.nih.gov/pubmed/?term=Predictors+of+physical+activity+and+quality+of+life+in+New+Zealand+prostate+cancer+survivors+undergoing+androgen-deprivation+therapy.

Kiratli, B.J., Srinivas, S., Perkash, I., and Terris, M.K. (2001). Progressive decrease in bone density over 10 years of androgen deprivation therapy in patients with prostate cancer. *Urology 57*: 127-132. doi.org/10.1016/S0090-4295(00)00895-5.

Klap, J., Schmid, M., and Loughlin, K.R. (2015). The relationship between total testosterone levels and prostate cancer: A review of the continuing controversy. *J. Urol. 193*: 404-415. doi.org/10.1016/j.juro.2014.07.123.

Krishnadasan, A ., Kennedy, N., Zhao, Y., Morgenstern, H., and Roitz, B. (2008). Nested case-control study of occupational physical activity and prostate cancer among workers using a job exposure matreix. *Cancer Causes Control, 19*: 107-114. doi.org/10.1007/s10552-007-9076-7.

Kvorning, T., Andersen, M. , Brixen, K., and Madsen, K. (2006). Suppression of endogenous testosterone production attenuates the response to strength training: a randomized, placebo controlled, and blinded intervention study. *Am. J. Physiol. 291*: E1325-E1332. doi.org/10.1152/ajpendo.00143.2006.

Lacey, J.V., Deng, J., Dosemeci, M., Gao, Y.T., Mostofi, F.K., Sesterhenn, I.A., Xie, T., and Hsing, A.W. (2001). Prostate cancer, benign prostate hyperplasia and physical activity in Shanghai, China. *Int. J. Epidemiol. 30*: 341-349. doi.org/10.1093/ije/30.2.341.

Lagiou, A., Samoli, E., Georgila, C., Minaki, P., Barbouni, A., Tzonou, A., Trichopoulos, D., and Lagiou, P. (2008). Occupational physical activity in relation with prostate cancer and benign prostate hyperplasia. *Eur. J, Cancer Prev. 17*: 336-339. doi.org/10.1097/CEJ.0b013e3282f5221e.

Le Marchand, L. , Kolonel, L.N., and Yoshizawa, C.N. (1991). Lifetime occupational phyical activity and prostate cancer. *Am. J. Epidemiol. 133(2)*: 103-111. URL: http://www.ncbi.nlm.nih.gov/pubmed/1985441.

Lee, I-M., and Paffenbarger, R.S. (1994). Physical activity and its relation to cancer risk: a prospective study of college alumni. *Med. Sci. Sports Exerc, 26(7)*: 831-837. doi.org/10.1249/00005768-199407000-00004.

Lee, I-M., Paffenbarger, R.S., and Hsieh, C-C. (1992). Physical activity and risk of prostatic cancer among College alumni. *Am. J. Epidemiol. 135(2)*: 169-179. URL: http://www.ncbi.nlm.nih.gov/pubmed/7934755.

Lee, I-M., Sesso, H.D., and Paffenbarger, R.S. (2001). A prospective cohort study of physical activity and body size in relation to prostate cancer risk (United States). *Cancer Causes Control, 12*: 187-193. doi.org/10.1023/A:1008952528771.

Lee, S., Min, H.G., Choi, S.H. , Kim, Y.J., Oh, S.W. , Kim, Y.J., Oh, S.W., Kim, Y.J., Park, Y., and Kim, S.S. (2006). Central obesity as a risk factor for prostatic hyperplasia. *Obesity, 14:* 172-179. doi.org/10.1038/oby.2006.21.

Levy, M.E., Perera, S., van Londen, G.J., Nelson, J.B., Clay, C.A., and Greenspan, S.L. (2008). Physical function changes in prostate cancer patients on androgen deprivation therapy: A 2-year prospective study. *Urology, 71*: 735-739. doi.org/10.1016/j.urology.2007.09.018.

Littman, A.J., Kristal, A.R., and White, E. (2006). Recreational physical activity and prostate cancer risk (United States). *Cancer Causes Control, 17*: 831-841. doi.org/10.1007/s10552-006-0024-8.

Liu, S., Lee, I-M., Linson, P., Ajani, U., Buring, J.E., and Hennekens, C.H. (2000). A prospective study of physical activity and risk of prostate cancer in US physicians.

Int. J. Epidemiol. 29: 29-35. doi.org/10.1093/ije/29.1.29.

Liu, Y.P., Hu, F.L. , Li, D.D. , Wang, F., Zhu, L. , Chen, W.Y., Ge, J., An, R., and Zhao, Y. (2011). Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis. *Eur. Urol. 60*: 1029-1044. doi.org/10.1016/j.eururo.2011.07.007.

Livingston, P.M., Craike, M., Salmon, J., Courneya, K.S., Gaskin, C.J., Fraser, S.F., Mohebbi, M., Broadbent, S., Botti, M., and Kent, B.; ENGAGE Uro-Oncology Clinicians' Group. (2015). Effects of clinician referral and exercise program for men who have completed active treatment for prostate cancer: A multicenter cluster randomized controlled trial (ENGAGE). *Cancer Causes Control, 121(15)*: 2646-2654. doi.org/10.1002/cncr.29385.

Lund Nielsen, T.I., Johnsen, R., and Vatten, L.J. (2000). Socio-economic and lifestyle factors associated with the risk of prostate cancer. *Br. J. Cancer, 82(7)*: 1358-1363. URL: http://www.ncbi.nlm.nih.gov/pubmed/10755415.

Maillefert, J.F., Sibilia, J., Michel, F., Saussine, C., Javier, R.M., and Tavernier, C. (1999). Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. *J. Urol. 161(4)*: 1219-1222. doi.org/10.1016/S0022-5347(01)61639-2

Malcolm, J.B., Derweesh, I.H., Kincade, M.C., DiBlasio, C.J., Lamar, K.D., Wake, R.W., and Patterson, A.L. (2007). Osteoporosis and fractures after androgen deprivation initiation for prostate cancer. *Can. J. Urol. 14(3)*: 3551-3559. URL: http://www.ncbi.nlm.nih.gov/pubmed/17594745.

Mennen-Winchell, L.J., Groigoriev, V., Alpert, P., Dos Santos, H., and Tonstad, S. (2014). Self-reported exercise and bone mineral density in prostate cancer patients receiving androgen deprivation therapy. *J. Am. Assoc. Nurse Pract. 26*: 40-48. doi.org/10.1002/2327-6924.12066.

Merrill, R.M., Perego, U.A.M., and Heiner, S.W. (2002). Age, lifestyle, health risk indicators and prostate specific antigen scores in men participating in the world senior games. *Urol. Oncol. 7*: 105-109. doi.org/10.1016/S1078-1439(01)00176-4.

Monga, U. , Garber, S .L., Thornby, J., Vallbona, C., Kerrigan, A.J., Momnga, T.N., and Zimmerman, K.P. (2007). Exercise prevents fatigue and improves quality of life in prostate cancer patients undergoing radiotherapy. *Arch. Phys. Med. Rehabil. 88*: 1416-1422. doi.org/10.1016/j.apmr.2007.08.110.

Montoye, H.J., Van Huss, W.D., Olson, H., Pierson, W.R., and Hudec, A.J. (1957). *The longevity asd morbiditty of college athletes*. East Lansing, MI: Phi Epsiklon Kappa Fraternity, Michigan State University.

Moore, S.C., Peters, T.M., Ahn, J., Park, Y., Schatzkin, A., Albanes, D. Ballard-Barbash, R., Hollenbeck, A., and Leitzmann, M.F. (2008). Physical activity in relation to total, advanced and fatal prostate cancer. *Cancer Epidemiol. Biomarkers Prev. 17(9)*: 2458-2466. doi.org/10.1158/1055-9965.EPI-08-0403.

Morote, J., Celma, A. , Planas, J., Placer, J., Konstantinidis, C., Iztueta, I., de Torres, I.M., Oliván, M., Reventós, J., and Doll, A. (2014). Sedentarismo y sobrepeso como factores de riesgo en la detección del cáncer de prostáta y su agresividad [Sedentarism and overweight as risk factors in the detection and aggressivity of prostate cancer]. *Actas Urol Esp. 38(4)*, 232-237. doi.org/10.1016/j.acuro.2013.09.001.

Morote, J., Orsola, A., Abascal, J.M., Planas, J., Trilla, E., Raventos, C.X., Cecchini, L., Encabo, G., and Reventos, J. (2006). Bone mineral density changes in patients with prostate cancer during the first 2 years of androgen suppression. *J. Urol. 175*: 1679-1683. doi.org/10.1016/S0022-5347(05)00999-7.

Nilsen, T.I.L., Romundstad, P.R., and Vatten, L.J. (2006). Recreational physical activity and risk of prostate cancer; A prospective population-based study in Norway (the HUNT study). *Int. J. Cancer, 119*: 2943-2947. doi.org/10.1002/ijc.22184.

Nilsen, T.S., Raastad, T., Skovlund, E., Courneya, K.S., Langberg, C.W., Lilleby, W., Fosså, S.D., and Thorsen, L. (2015). Effects of strength training on body composition, physical functioning, and quality of life in prostate cancer patients during androgen deprivation therapy. *Acta Oncol. 54*: 1805-

1813. doi.org/10.3109/0284186X.2015.1037008.

Noble, R;L. (1984). Androgen use by athletes: a possible cancer risk. *Can. Med. Assoc. J. 130*: 549-550. URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1875750/.

Norman, A. , Moradi, T., Gridley, G. , Dosemeci, M., Rydh, B., Nyrén, O., and Wolk, A. (2002). Occupational physical activity and risk for prostate cancer in a nationwide cohort study in Sweden. *Brt J Cancer, 86*, 70-75. doi.org/10.1038/sj.bjc.6600023.

Norris, M.K., Bell, G.J., North, S., and Courneya, K.S. (2015). Effects of resistance training frequency on physical functioning and quality of life in prostate cancer survivors: a pilot randomized controlled trial. *Prostate Cancer Prostate Dis. 18*: 281-287. doi.org/10.1038/pcan.2015.28.

Oefelein, M.G., Ricchuiti, V., Conrad, W., Seftel, A., Bodner, D., Goldman, H., and Resnick, M. (2001). Skeletal fracture associated with androgen suppression induced osteoporosis: The clinical incidence and risk factors for patients with prostate cancer. *J. Uro.l 166*: 1724-1728. doi.org/10.1097/00005392-200111000-00024

Oliveira, S.N., Kohl, H.W., Trichopoulos, T., and Blair, S.N. (1996). The association between cardiorespiratory fitness and prostate cancer. *Med. Sci. Sports Exerc. 28(1)*: 97-104. doi.org/10.1097/00005768-199601000-00020.

Orsini, N. , Bellocco, R. , Botti, M. , Pagano, M., Andersson, S-O., Johansson, J-E., Giovannucci, E., and Wolk, A. (2009). A prospective study of lifetime physical activity and prostate cancer incidence and mortality. *Br. J. Cancer, 101*: 1932-1938. doi.org/10.1038/sj.bjc.6605404.

Paffenbarger, R.S., Hyde, R.T., and Wing, A.L. (1987). Physical activity and incidence of cancer in diverse populations: a preliminary report. *Am. J. Clin. Nutr. 45 (1 Suppl)*: 712-717. URL: http://www.ncbi.nlm.nih.gov/pubmed/3799521.

Parent, M.E., Rousseau, M.C., El Zein, M., Latreille, B., Désy, M., and Siemiatycki, J. (2011). Occupational and recreational physical activity during adult life and the risk of cancer among men. *Cancer Epidemiol. 35(2)*: 151-159. doi.org/10.1016/j.canep.2010.09.004.

Park, S.W., Kim, T.N., Nam, J.K., Ha, H.K., Shin, D.G., Lee, W., Kim, M.S., and Chung, M.K. (2012). Recovery of overall exercise ability, quality of life, and continence after 12-week combined exercise intervention in elderly patients who underwent radical prostatectomy. *Urology, 80:* 299-305. doi.org/10.1016/j.urology.2011.12.060.

Patel, A.V., Rodriguez, C., Jacobs, E.J., Solo0mon, L., Thun, M.J., and Calle, E.E. (2005). Recreational physical activity and risk of prostate cancer in a large cohort of U.S. men. *Cancer Epidemiol. Biomarkers Prev. 14(1)*: 275-279. URL: http://www.ncbi.nlm.nih.gov/pubmed/?term=Recreational+physical+activity+and+risk+of+prostate+cancer+in+a+large+cohort+of+U.S.+men.

Pierotti, B. , Altieri, A., Talamini, R., Montella, M., Tavani, A., Negri, E., Franceschi, S., and La Vecchia, C. (2005). Lifetime physical activity and prostate cancer risk. *Int. J. Cancer, 114:* 639-642. doi.org/10.1002/ijc.20783.

Platz, E., Leitzmann, M.F., Michaud, D.S., Willett, W.C., and Giovannucci, E. (2003). Interrelation of energy intake, body size and physical activity with prostate cancer in a large prospective cohort study. *Cancer Res.. 63*: 8542-8548. URL: http://www.ncbi.nlm.nih.gov/pubmed/?term=Interrelation+of+energy+intake%2C+body+size+and+physical+activity+with+prostate+cancer+in+a+large+prospective+cohort+study.

Polednak, A.P. (1976). College athletics, body size and cancer mortality. *Cancer, 38*: 382-387. doi.org/10.1002/1097-0142(197607)38:1<382::AID-CNCR2820380155>3.0.CO;2-V.

Potosky, L. , Kropf, K. , Clegg, L.X., Albertsen, P.C., Stanford, J.L., Hamilton, A.S., Gilliland, F.D., Eley, J.W., Stephenson, R.A., and Hoffman R.M. (2001). Quality of life outcomes after primary androgen deprivation therapy: results from the prostate cancer outcomes study. *J. Clin. Oncol. 19*: 3750-3757. URL: http://www.ncbi.nlm.nih.gov/pubmed/11533098.

Preston, D.M., Torréns, J.I., Harding, P., Howard, R.S., Duncan, W.E., and McLeod, D.G.

(2002). Androgen deprivation in men with prostate cancer is associated with an increased rate of bone loss. *Prostate Cancer Prostate Dis. 5*: 304-310. doi.org/10.1038/sj.pcan.4500599.

Putnam, S.D., Cerhan, J.R., Parker, A.S., Bianchi, G.D., Wallace, R.B., Cantor, K.P., and Lynch, C.F. (2000). Lifestyle and anthropometric risk factors for prostate cancer in a cohort of Iowa men. *Am. J. Epidemiol. 10*: 361-369. doi.org/10.1016/s1047-2797(00)00057-0.

Richman, E.L., Kenfield, S.A., Stampfer, M.J., Paciorek, A., Carroll, P.R., and Chan, J.M. (2011). Physical activity after diagnosis and risk of prostate cancer progression: data from the cancer of the prostate strategic urologic research endeavor. *Cancer Res. 71:* 3889-3895. doi.org/10.1158/0008-5472.CAN-10-3932.

Roehrborn, C.G., and Black, L.K. (2011). The economic burden of prostate cancer. *BJU Int, 108(6)*: 806-813. doi.org/10.1111/j.1464-410X.2011.10365.x.

Ross, R.W. , and Small, E.J. (2002). Osteoporosis in men treated with androgen deprivation therapy for prostate cancer *J. Urol. 167*: 1952-1956. doi.org/10.1016/S0022-5347(05)65060-4.

Sadetsky, N. , Greene, K. , Cooperberg, Hubbard, SA., Carroll, P.R., and Satariano, W. (2011). Impact of androgen deprivation on physical well-being in patients with prostate cancer. *Cancer, 117(19)*: 4406-4413. doi.org/10.1002/cncr.26064.

Sajid, S. , Dale, W. , Mustian, K. , Kotwal, A., Heckler, C., & Porto, M. Fung, C., and Mohile, S.G. (2016). Novel physical activity interventions for older patients with prostate cancer on hormone therapy: A pilot randomized study. *J. Geriatr. Oncol. 7*: 71-80. doi.org/10.1016/j.jgo.2016.02.002.

Sanderson, M., Coker, A.L., Logan, P., Zheng, W., and Fadden, M.K. (2004). Lifestyle and prostate cancer among older African-American and Caucasian men in South Carolina. *Cancer Causes Control, 15*: 647-655. doi.org/10.1023/B:CACO.0000036172.63845.d4.

Santa Mina, D.F, Ritvo, P., Matthew, A.G. , Rampersad, A., Stein, H., Cheung, A.M. Trachtenberg, J., and Alibhai, S.M.H. (2012). Group exercise versus personal training for prostate cancer patients: a pilot randomized trial. *J. Cancer Ther. 3*: 146-156. doi.org/10.4236/jct.2012.32020.

Sass-Kortak, A.M., Purdham, J.T., Kreiger, N., Darlington, G.A., and Lightfoot, N.E. (2007). Occupational risk factors for prostate cancer. *Am. J. Industr. Med. 50*: 568-576. doi.org/10.1002/ajim.20495.

Segal, R.J., Reid, R.D., Courneya, K.S., Malone, S.C., Parliament, M.B., Soctt, C.G. Venner, P.M., Quinney, H.A., Jones, L.W., D'Angelo, M.E., and Wells, G.A. (2003). Resistance exercise in men receiving androgen deprivation therapy for prostate cancer *J. Clin. Oncol. 21*: 1653-1659. doi.org/10.1200/JCO.2003.09.534.

Segal, R.J., Reid, R.D., Courneya, K.S., Sigal, R.J., Kenny, G.P., Prud'homme, D.G., Malone, S.C., Wells, G.A., Scott, C.G., Slovinec, and D'Angelo, M.E. (2009). Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J. Clin. Oncol. 27:* 344-351. doi.org/10.1200/JCO.2007.15.4963.

Severson, R.K., Nomura, A.M.Y., Grove, J.S., and Stemmerman, G.N. (1989). A prospective analysis of physical activity and cancer. *Am. J. Epidemiol. 130(3)*: 522-529. URL: http://www.ncbi.nlm.nih.gov/pubmed/?term=A+prospective+analysis+of+physical+activity+and+cancer++Severson.

Shahinian, V.B., Kuo, Y-F., Freeman, J.L., and Goodwin, J.S. (2005). Risk of fracture after androgen deprivation for prostate cancer. *N. Engl. J. Med. 352(2)*: 154-164. doi.org/10.1056/NEJMoa041943

Shephard, R.J. (2003). Limits to the measurement of habitual physical activity by questionnaires. *Br. J. Sports Med, 37*: 197-206. doi.org/10.1136/bjsm.37.3.197.

Shephard, R.J. (2016). Exercise in the prevention and treatment of colorectal neoplasms. *Health Fitness J, Canada*, In press.

Shephard, R.J., Rhind, S., and Shek, P.N. (1994). Exercise and the immune system. Natural killer cells, interleukins and related responses. *Sports Med. 18(5)*: 340-369. doi.org/10.2165/00007256-199418050-00006.

Skinner, T.L., Peeters, G., Croci, I., Bell, K.R., Burton, N.W., Chambers, S.K., and Bolam, K.A. (2016). Impact of a brief exercise program on the physical and psychosocial health of prostate cancer survivors: A pilot study. *Asia-Pacific J. Clin. Oncol. doi: 10.1111/ajco.12474. [Epub ahead of print]*.

Smith, M.R., Lee, W.C., Brandman, J., Wang, Q., Botteman, M., and Pashos, C.L. (2005). Gonadotrophin-releasing hormone agonists and fracture risk: A claims-based cohort study of men with nonmetastatic prostate cancer. *J. Clin. Oncol. 23(31)*: 7897-7903. doi.org/10.1200/JCO.2004.00.6908.

Spry, N.A., Kristjanson, L., Hooton, B., Hatyden, L., Neerhut, G., Gurney, H., Corica, T., Korbel, E., Weinstein, S., and McCaul, K. (2006). Adverse effects of life arising from treatment can recover with intermittent androgen suppression in men with prostate cancer. *Eur. J. Cancer, 42*: 1083-1092. doi.org/10.1016/j.ejca.2006.01.029.

Steenland, K., Nowlin, S., and Palu, S. (1995). Cancer incidence in the National Health and Nutirtion Survey I follow-up data: Diabetes, cholesterol and physical activity. *Cancer Epidemiol. Biomarkers Prev. 4*: 807-811. URL: http://www.ncbi.nlm.nih.gov/pubmed/8634649.

Stoch, S.A., Parker, R.A., Chen, L., Bubley, G., Ko, Y.J., Vincelette, A., and Greenspan, S.L. (2001). Bone loss in men with prostate cancer treatred with gonadotropin-releasing hormone agonists. *J. Clin. Endocrinol. Metab. 86:* 2787-2791. URL: http://www.ncbi.nlm.nih.gov/pubmed/11397888.

Stone, P., Hardy, J., Huddart, R., A'Hern, R., and Richards, M. (2000). Fatigue in patients with prostate cancer receiving hormone therapy. *Eur. J. Cancer, 36:* 1134-1141. doi.org/10.1016/S0959-8049(00)00084-8.

Strom, S.S., Yamamura, Y., Flores-Sandoval, F.N., Pettaway, C.A., and Lopez, D.S. (2008). Prostate cancer in Mexican-Americans: Identification of risk factors. *Prostate, 68:* 563-570. doi.org/10.1002/pros.20713.

Sung, J.F., Lin, R.S., Pu, Y.S,, Chen, Y.C., Chang, H.C., and Lai, M.K. (1999). Risk factors for prostate carcinoma in Taiwan: a case-control study in a Chinese population. *Cancer, 86(3)*: 484-491. doi.org/10.1002/(SICI)1097-0142(19990801)86:3<484::AID-CNCR17>3.0.CO;2-P.

Thorsen, L., Courneya, K.S., Stevinson C., and Fosså, D. (2008). A systematic review of physical activity in prostate cancer survivors: outcomes, prevalence, and determinants. *Support Care Cancer, 16:* 987-997. doi.org/10.1007/s00520-008-0411-7.

Thune, I., and Lund, E. (1994). Physical activity and the risk of prostate and testicular cancer: a cohort study of 53,000 Norwegian men. *Cancer Causes Control, 5*: 549-556. doi.org/10.1007/BF01831383.

Torti, D., and Matheson, G.O. (2004). Exercise and prostate cancer. *Sports Med. 34(6)*: 363-369. doi.org/10.2165/00007256-200434060-00003.

Townsend, M.F., Sanders, W.H., Northway, R.O., and Graham, S.D. (1997). Bone fractures associated with luteinizing hormone-releasing hormone agonists used in the treatment of prostate carcinoma. *Cancer, 79(3)*: 545-550. doi.org/10.1002/(SICI)1097-0142(19970201)79:3<545:AID-CNCR17>3.0.CO;2-3.

Uth, J. , Schmidt, J.F., Christensen, J.F. Hornstrup, T., Andersen, L.J., Hansen, P.R., Christensen, K.B., Andersen, L.L., Helge, E.W., Brasso, K., Rørth, M., Krustrup, P., and Midtgaard, J. (2013). Effects of recreational soccer in men with prostate cancer undergoing androgen deprivation therapy: Study protocol for the "FC Prostate" randomized controlled trial. *BMC Cancer, 13,* doi:10.1186/1471-2407-13-595.

Uth, J., Hornstrup, T., Christensen, J.F., Christensen, K.B., Jørgensen, K.R., Schmidt, J.F., Brasso, K., Jakobsen, M.D., Sundstrup, E., Andersen, L.L., Rørth, M., Midtgaard, J., Krustrup, P. and Helge, E.W. (2016). Efficacy of recreational football on bone health, body composition and physical functioning in men with prostate cancer undergoing androgen deprivation therapy: 32 week follow up of the FC prostate randomized controlled trial. *Osteoporosis Int. 27:* 1507-1518. doi.org/10.1007/s00198-015-3399-0.

Uth, J., Hornstrup, T. , Schmidt, J.F., Christensen, J.F., Frandsen, C., Christensen, K.B., Helge,

E.W., Brasso, K., Rørth, M., Midtgaard, J., and Krustrup, P. (2014). Football training imrpoves lean body mass in men with prostate cancer undergoing androgen deprivation therapy. *Scand. J. Med. Sci. Sports, 24(Suppl. 1)*: 105-112. doi.org/10.1111/sms.12260.

van Londen, G.J., Levy, M.E., Perera, S., Nelson, J.B., and Greenspan, S.L. (2008). Body composition changes during androgen deprivation therapy for prostate cancer: a 2-year prospective study. *Crit. Rev. Oncol. Hematol. 68(2):* 172-177. doi.org/10.1016/j.critrevonc.2008.06.00.

Vena, J.E., Graham, S., Zielezny, M., Brasure, J., and Swanson, M.K. (1987). Occupational exercise and risk of cancer. *Am. J. Clin. Nutr. 45 (1 Suppl. 1)*: 318-327. URL: http://www.ncbi.nlm.nih.gov/pubmed/3799522.

Vidarsdottir, H., Gunnarsdottir, H.K., Olafsdottir, E.J. , Olafsdottir, G.H., Pukkala, E., and Tryggvadottir, L. (2008). Cancer risk by education in Iceland; a census-based cohort study. *Acta Oncol. 47:* 385-390. doi.org/10.1080/02841860801888773.

Villeneuve, P.J., Johnson, K.C., Kreiger, N., Mao, Y., and Canadian Cancer Registries Epidemiology Research Group. (1999). Risk factors for prostate cancer: results from the Canadian national enhanced cancer surveillance system. *Cancer Causes Control, 10:* 355-367. doi.org/10.1023/A:1008958103865.

Wannamethee, S.G., Shaper, A.G., and Walker, M. (2001). Physical activity and risk of cancer in middle-aged men. *Br. J. Cancer, 85(9)*: 1311-1316. doi.org/10.1054/bjoc.2001.2096.

West, D.W., Slattery, M.L., Robison, L.M., French, T.K., and Mahoney, A.W. (1991). Adult dietary intake and prostate cancer risk in Utah: a case-control study with special emphasis on aggressive tumours. *Cancer Causes Control, 2*: 85-94. doi.org/10.1007/BF00053126.

Whittemore, A.S., Kolonel, L.N., Wu, A.H., John, E.M., Gallagher, R.P., Howe, G.R. Burch, J.D., Hankin, J., Dreon, D.M., West, D.W. , Teh, C.Z, and Paffenbarger R.S. (1995). Prostate cancer in relation to diet, physical activity, and body size in blacks, whites, and Asians in the United States and Canada. *J. Natl. Cancer Inst. 87*: 652-661. doi.org/10.1093/jnci/87.9.652.

Wiklund, F. , Lageros, Y.T., Chang, E. , Bätter, K., Johansson, J.E., Adami, H-O., and Grönberg, H. (2008). Lifetime total physical activity and prostate cancer in a population-based case-control study in Sweden. *Eur. J. Epidemiol. 23*: 739-746. doi.org/10.1007/s10654-008-9294-7.

Windsor, P.M., Nicol, K.F., and Potter, J. (2004). A randomized controlled trial of aerobic exercise for treatment-related fatigue in men receiving radical external beam radiotherapy for localized prostate carcinoma. *Cancer, 101*: 550-557. doi.org/10.1002/cncr.20378.

Winters-Stone, K.M., Dobek, J.C., Bennett, J.A. , Maddalozzo, G.F., Ryan, C.W., and Beer, T.M. (2014). Skeletal response to resistance and impact training in prostate cancer survivors. *Med. Sci. Sports Exerc. 46(8)*: 1482-1488. doi.org/10.1249/MSS.0000000000000265.

Wolin, K.Y., Luly, J., Sutcliffe, S. , Andriole, G.L., and Kibel, A.S. (2010). Risk of urinary incontinence following prstatectomy: The role of physical activity and obesity. *J. Urol. 183(2)*: 629-633. doi.org/10.1016/j.juro.2009.09.082.

Yu, H., Harris, R.E., and Wynder, E.L. (1988). Case-control study of prostate cancer and socio-economic factors. *Prostate, 13*: 317-325. doi.org/10.1002/pros.2990130407.

Zeegers, M.P.A. , Dirx, M.J.M., and van den Brandt, P.A. (2005). Physical activity and the risk of prostate cancer in the Netherlands cohort study, results after 9.3 years follow-up. *Cancer Epidemiol. Biomarkers Prev. 14(6)*: 1490-1495. doi.org/10.1158/1055-9965.EPI-04-0771.