Physical activity and prostate cancer risk: a 24 year follow-up study among Icelandic men.

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Thesis for the degree of Master of Public Health Sciences
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HÁSKÓLI ÍSLANDS

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Tengsl hreyfingar og áhættu á krabbameini í blöðruhálskirtli: ferilrannsókn með 24 ára eftirfylgd meðal íslenskra karla

Soffía Margrét Hrafnkelsdóttir

Ritgerð til meistaragráðu í lýðheilsuvísindum
Umsjónarkennari: Jóhanna Eyrún Torfadóttir
Meistaranámsnefnd: Unnur Anna Valdimarsdóttir og Kristján Þór Magnússon

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Abstract

Background and aims: There are indications that physical activity may reduce prostate cancer risk. Few studies have assessed the role of physical activity across the lifespan, or combined recreational and occupational activity. Here, the aim was to explore the association of physical activity during adult years and the risk of prostate cancer.

Materials and methods: We undertook a prospective study using data from 9076 Icelandic men (born 1907 to 1935) who at enrollment, between 1967 and 1987, to the population-based Reykjavik study provided information on recreational physical activity since the age of 20 years and current occupational physical activity. Through linkage to cancer and mortality registers, the men were followed for prostate cancer diagnosis and mortality through 2009. We used Cox models to calculate risk of prostate cancer by level of physical activity. Models were adjusted for potential confounders.

Results: During a mean follow-up of 24.3 years, 1149 men were diagnosed with prostate cancer, of whom 387 had advanced disease. No significant association was observed for either recreational or occupational physical activity and total or localized prostate cancer. Recreational and occupational physical activity were neither independently associated with advanced prostate cancer. Among men who were physically active during working hours, men who participated in recreational physical activity had a decreased risk of advanced prostate cancer (hazard ratio =0.59; 95% confidence interval: 0.37 to 0.94) compared with men who did not. No association was found between recreational physical activity and advanced prostate cancer among men in sedentary jobs.

Conclusions: Our findings suggest that extensive amount of physical activity from early adulthood onwards may protect against advanced prostate cancer.

Ágrip

Inngangur: Sjúkdómsferli blöðruhálskirtilskrabbameins (BHKK) er ekki þekkt til hlítar, en rannsóknir benda til þess að umhverfis- og lífstílsþættir gegni mikilvægu hlutverki. Markmið þessarar rannsóknar var að skoða samband reglubundinnar hreyfingar á fullorðinsárum og áhættu þess að greinast með BHKK.

Efniviður og aðferðir: Upplýsingar um hreyfingu og aðra mögulega áhrifaþætti BHKK 9076 karlmanna voru fengnar úr Reykjavíkurrannsókn Hjartaverndar sem framkvæmd var á tímabilinu 1967-1987. Samkeyrsla við Krabbameinsskrá Íslands var notuð til að auðkenna þá þátttakendur sem greinst höfðu með eða látist úr BHKK frá fyrstu komu í Reykjavíkurrannsóknina til loka árs 2009. Hættuhlutfall (HR) fyrir BHKK með 95% öryggismörkum (CI) var reiknað með lifunargreiningu Cox. Einstaklingar sem stunduðu reglubundna hreyfingu í frítíma voru bornir saman við þá sem stunduðu enga líkamsrækt frá tvítugu, auk þess sem gerður var samanburður á þeim sem hreyfðu sig mikið í starfi samanborið við þá sem hreyfðu sig lítið á vinnutíma. Einnig var gerð greining m.t.t. heildarhreyfingar þar sem hreyfingu í frítíma var lagskipt eftir vinnutengdri líkamlegri áreynslu þátttakenda. Leiðrétt var fyrir mögulegum áhrifaþáttum.

Niðurstöður: Á eftirfylgdartímanum (meðaltal 24,3 ár) voru 1149 karlar greindir með BHKK, þar af 387 með langt gengið mein (dánarorsök eða stig III eða IV við greiningu).

Ekki fannst marktækt samband milli hreyfingar í frítíma eða í starfi, fyrir öll mein eða staðbundin mein. Ekki fannst heldur marktækt samband milli langt gengins BHKK og hreyfingar í frítíma annars vegar og á vinnutíma hins vegar. Borið saman við þá sem stunduðu enga líkamsrækt í frítíma en voru í líkamlega krefjandi starfi fannst marktæk minni áhætta á langtgengnu BHKK hjá þeim þátttakendum sem hreyfðu sig bæði í frítíma og við vinnu (HR = 0,59; 95% CI: 0,37-0,94). Ekki fannst samband milli hreyfingar í frítíma og langt gengins BHKK meðal þeirra sem voru í lítið líkamlega krefjandi starfi.

Ályktun: Niðurstöður gefa til kynna að mikil reglubundin hreyfing sem hefst snemma á fullorðinsárum geti minnkað áhættuna á að greinast með langt gengið BHKK síðar á ævinni.

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Finally, I would like to acknowledge the Icelandic Cancer Society for financial support.

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List of abbreviations

ASR (W), age-standardized rate (world)

BMI, body mass index

BPH, benign prostate hyperplasia

CI, confidence interval

DM2, diabetes mellitus type 2

et al., et alii

HR, hazard ratio

i.e., that is

IGF-1, insulin-like growth factor 1

IGFBP-1/3, insulin-like growth factor binding protein 1/3

IU, international unit

LCPUFAs, long-chain n-3 polyunsaturated fatty acids

LNCaP, lymph node carcinoma of the prostate

MET, metabolic equivalent

NEFA, non-esterified fatty acids

OPA, occupational physical activity

PCa, prostate cancer

PSA, prostate specific antigen

ROS, reactive oxygen species

RPA, recreational physical activity

SCID, severe combined immunodeficiency

SD, standard deviation

SEER = Surveillance Epidemiology and End Results

TPA, total physical activity

vs., versus

WHO, World Health Organization

List of tables and figures

Introduction

Article

1 Introduction

Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries, with estimated 12.7 million new cancer cases and 7.6 million cancer deaths in the world 2008 (1). Cancer was the cause of approximately 13% of all deaths worldwide in 2008 (2). Population aging and growth, as well as unhealthy lifestyle choices of smoking, westernized diet and lack of physical activity are leading to increased cancer burden, estimated to become 22 million new cases each year by 2030 (1). It has been suggested that between 9% and 19% of cancer cases in Europe in 2008 (165 000 to 330 000 cases) could be attributed to lack of physical activity (3). Many epidemiological, clinical and experimental studies have found an association between physical activity and reduced risk of several of the major types of cancer. The evidence is convincing for colon and breast cancers, probable for endometrial cancer and possible for lung and prostate cancers (4).

Prostate cancer is among the most serious health threats for men, especially in the developed countries, where it is the most frequently diagnosed and the third deadliest cancer in males (1). Among Icelandic men, it is the most frequently diagnosed cancer and the second leading cause of death from malignant disease (5). A few non-modifiable risk factors for prostate cancer have been identified, including age, ethnicity and family history of the disease but its etiology remains largely unclear (6-8). Ethnic variations and immigrant studies indicate that environmental and lifestyle factors may play an important role (7). Physical activity may be among the modifiable lifestyle factors that potentially could influence the pathogenesis of prostate cancer.

Prostate cancer is a disease of considerable heterogeneous etiology. A high proportion of males will develop an indolent form of the disease, without any symptoms. Serum measurements of prostate specific antigen (PSA) as a screening method for prostate cancer, has been in widespread use in many western countries since the late 1980s. This has resulted in a shift in the diagnosis pattern from advanced cancers to localized ones, including detection of indolent prostate cancer (8, 9). For identifying risk factors for the most clinically important form of prostate cancer, e.g. disease with the greatest potential of lethality, it is necessary to separate endpoints for clinical and indolent forms of the disease, when conducting epidemiological studies. It is also preferable to perform research in settings with more limited PSA testing (8).

When evaluating the effects of physical activity on prostate cancer risk, it is desirable to have information about lifetime total physical activity of study participants, as the most relevant time in life and/or length of exposure period needed to affect the risk is not known (3, 10). Few of the studies in this field have, however, used such comprehensive information about physical activity in their analysis (11). Data on physical activity in early life has especially been missing (10).

The focus of this thesis is the relationship between physical activity and prostate cancer risk, with emphasis on total physical activity (recreational activity since the age of 20 years and current occupational activity) and the risk of advanced prostate cancer later in life. Improved knowledge of the effects of physical activity on prostate cancer risk could be of great public health value, in terms of prevention and treatment of the disease.

1.1   Incidence and mortality of prostate cancer

Prostate cancer is the second-most frequently diagnosed malignant disease in males worldwide, accounting for 14% (903,500) of the total new cancer cases in males in 2008 (1). In the developed countries, it is the most frequently diagnosed malignancy in men, accounting for 20% of new cases of cancer in 2008 (2). There is, however, a profound global variation of the incidence of prostate cancer, with an estimated 25-fold difference (1), see figure 1. The rates are highest in the developed countries of Oceania, Europe, and North America and lowest in Asian countries (1). The Nordic countries of Finland, Sweden, Iceland and Norway have the highest incidence of prostate cancer in Europe (13, 14).

ASR (W) = age-standardized rate (world).
SEER = Surveillance Epidemiology and End Results.
*Average of rates for =4 yr in the time period 2000–2004.
Source: Cancer Incidence in Five Continents
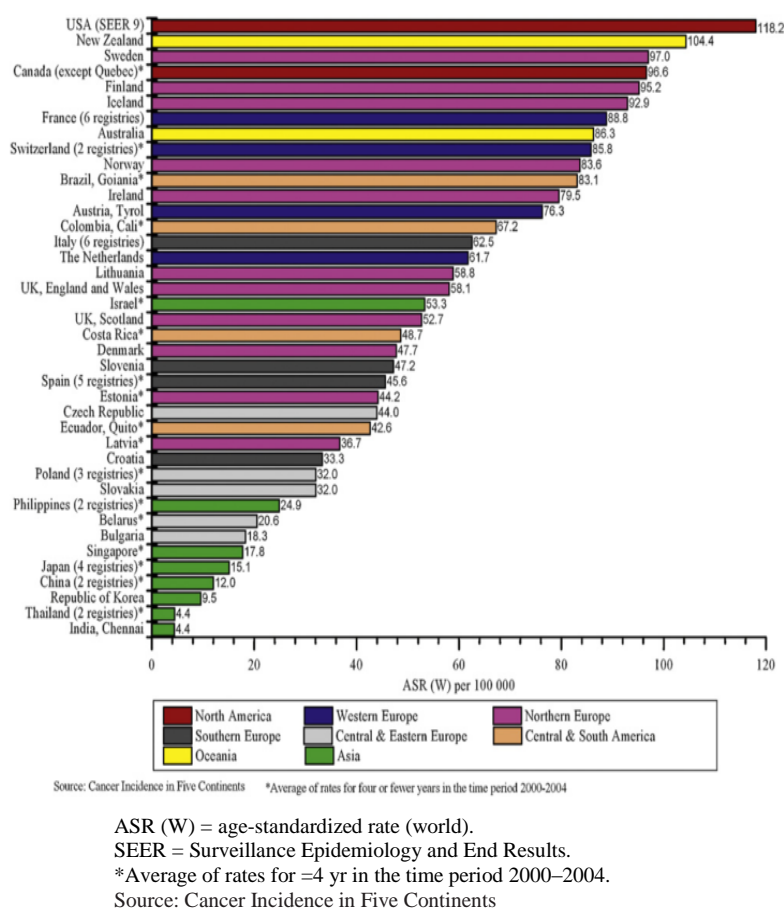
Figure 1 Prostate cancer incidence rates for select registries, 2000–2004 (12).

It is imperative to interpret prostate cancer incidence in the context of diagnostic intensity and screening behaviour. The incidence has been increasing over the last decades, on the order of about 3% per year. Likely explanations are increasing awareness of prostate-related symptoms, better access to health care, and the more frequent use of surgical treatment for benign prostate hyperplasia (BPH) (14). Beginning in the late 1980s, there has been a dramatic increase in areas employing routine screening of PSA, independent of symptoms from the prostate (2, 8). This was first observed in the USA (2, 14), where there was a twofold increase in rates of prostate cancer from 1986 to 1992 (14). In developed countries with more modest use of PSA testing, incidence rates have continued to increase at the slower rate of 3% per year (2). PSA testing has been more common in the USA than in Europe, up to 65% of men 50 years of age and older have been tested at least once in the USA as compared with 35% of men in this age group in European countries (15-17). Incidence rates are therefore not comparable between countries or time periods with different PSA screening intensity. In areas or periods with intense PSA screening the incidence rate reflects the sum of clinical and latent disease as compared with only clinical disease in the absence of PSA screening (8). In

the most recent years prostate cancer incidence has started to decrease somewhat, especially among high incidence countries, including all the Nordic countries except Denmark (5, 13). The incidence has, however, been increasing substantially in countries with traditionally low values, such as the republic of Korea (18). That is most likely due to changing diagnostic patterns (18). PSA screening has also affected the presentation of prostate cancer, with a shift from advanced cancers to earlier stages of the disease. It has resulted in increased detection of latent lesions and an estimated 23-66% overdiagnosis of the disease, depending on the population and age group being examined (9). Overdiagnosis in turn implies a considerable risk of overtreatment (9, 19).

Prostate cancer is the sixth-leading cause of death from cancer in males worldwide, accounting for 6% (258,400) of the total cancer deaths in males in 2008 (1). In developed countries prostate cancer ranks as the third most common cause of cancer death among men (1). In Europe, the highest prostate cancer mortality rates in 2006 were in the Baltic region (Estonia, Latvia and Lithuania) and in Denmark, Norway and Sweden (13). The lowest mortality rates for the disease are found among Asian countries, consistent with their low prostate cancer incidence (8). Males of African descent in the Caribbean region have the highest prostate cancer mortality rates in the world (1). In figure 2, prostate cancer age-standardized mortality rates (world standard) can be seen for various countries.
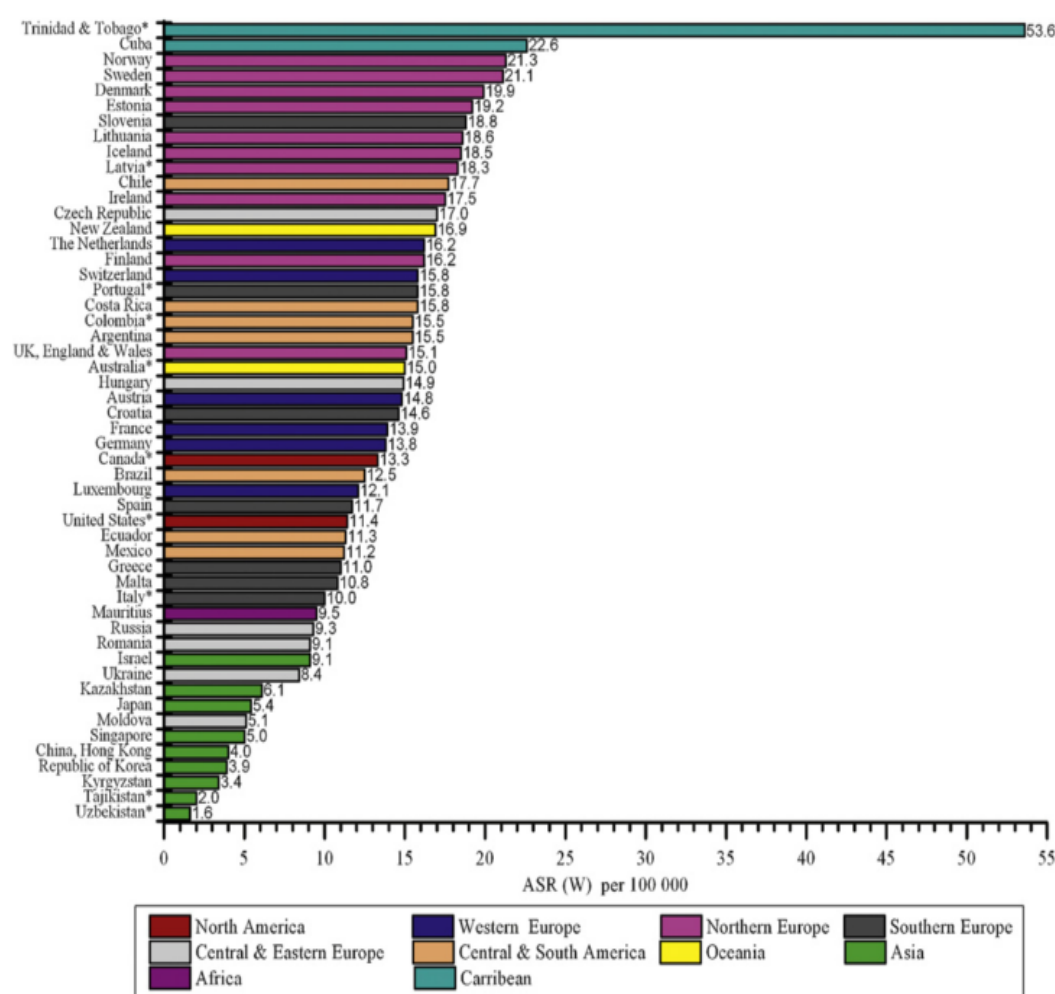
Source: WHO Mortality Database   *Average of rates for six or fewer years in the time period 2000-2006

*Average of rates for =6 yr in the time period 2000–2006.
Source: World Health Organization mortality database.
ASR (W) = age-standardized rate (world).

Figure 2 Prostate cancer mortality rates for select countries, 2000–2006 (12).

Mortality rates for prostate cancer have increased over the past several decades, predominantly among men over the age of 65 years. In recent years mortality rates have been increasing in countries with traditionally low prostate cancer incidence, like the republic of Korea, most likely due to changes in lifestyle (18). In contrast, mortality rates have started to decline in countries with high incidence of prostate cancer (8). This decrease of about 1-3% per year was first observed in the United States and more recently in several European countries, mostly in the more affluent countries in Western Europe (13). It may be due to improved treatment and/or early detection of prostate cancer as a result of PSA screening (13). The benefit of PSA screening with respect to mortality has, though, been questioned as

the decline in mortality has not been dramatic in areas employing PSA screening (8). The European Randomized Study of Screening for Prostate Cancer (ERSPC) showed that PSA-screening lowered the mortality rate of prostate cancer by 21%, after a median follow-up of nine years, yet it was associated with a high risk of overdiagnosis (20). Another randomized trial on the efficacy of PSA testing in reducing mortality from prostate cancer, conducted in the USA, found no benefit (1). Furthermore, despite quite high mortality rates among the Nordic countries, there has been little correlation over time between incidence and mortality (21), see figures 3 and 4. This indicates that increases in incidence are likely due to overdiagnosis of non-lethal disease as a result of increased use of PSA screening (21). The understanding of which tumors, detected in PSA-screening, will progress to become lethal is still very limited. Gleason grade may perhaps be the best predictor of tumor progression, according to a recent mRNA expression study (22).
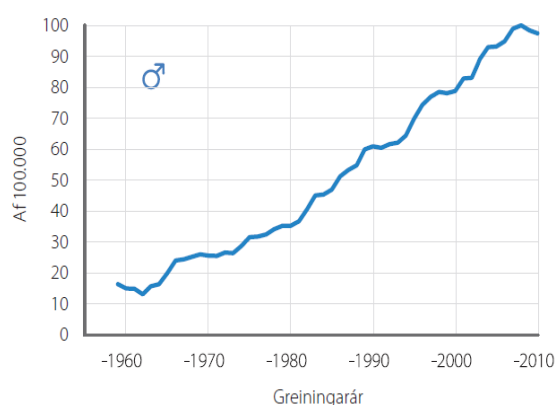
Fig 3a. Age-standardized prostate cancer incidence rate (per 100 000) in Iceland
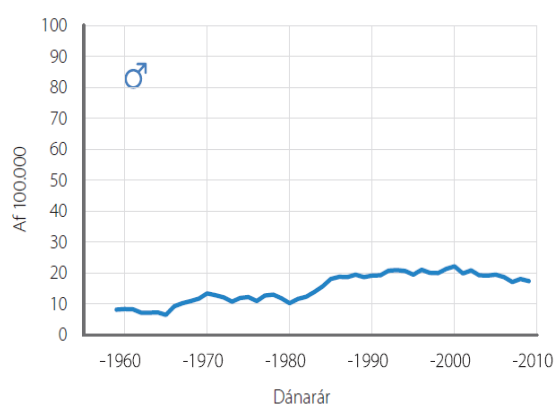
Fig. 3b Age-standardized prostate cancer mortality rate (per 100 000) in Iceland

Figure 3. Prostate cancer incidence rate (fig. 3a) and mortality rate (fig. 3b) in Iceland, per 100 000, age-standardized (world) (5).
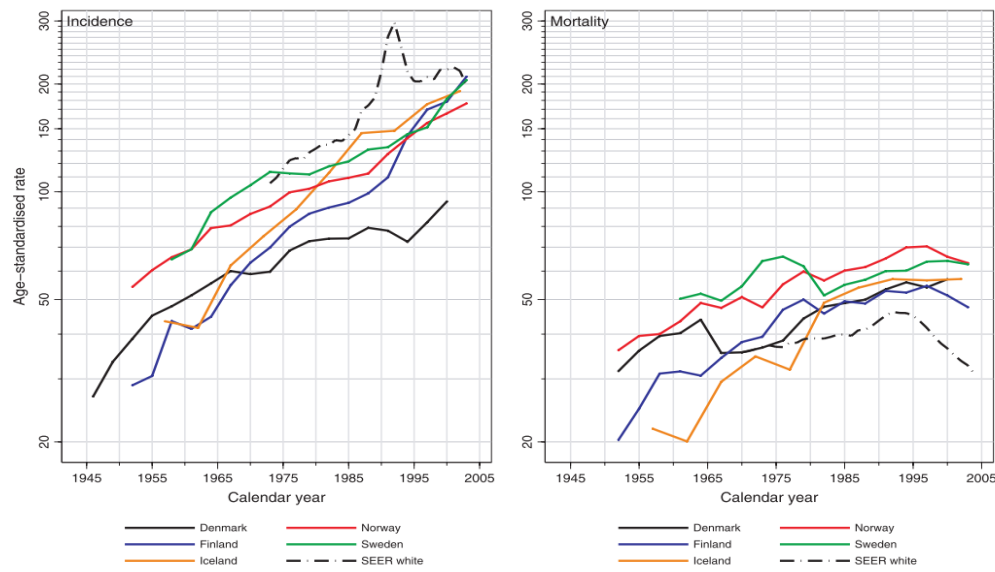
Figure 4. Observed age-standardized rates (Nordic standard 2000) of prostate cancer incidence and mortality in the Nordic countries and the United States (all ages) (14).

1.2 Ascertainment of prostate cancer outcome

Outcome ascertainment is complex regarding prostate cancer. The heterogeneous nature of prostate tumors, having very different progression rates, makes association studies complex and emphasizes the need for well-defined endpoints for this disease. Furthermore, tumors in the prostate that previously might not have been detected and possibly never would have reached a critical state are being discovered with PSA screening. Over-diagnosis of indolent tumors is in that way confounding the relationship between the exposure in question and prostate cancer, as well as complicating comparison between pre-PSA and PSA-era studies and across different geographic areas. In addition, much fewer advanced tumors are being diagnosed in the PSA-era and the spectrum has changed with tumors in their early stages being more prominent than before (8).

Advanced or fatal prostate cancer may be more relevant endpoints for this disease than incidence. Therefore, epidemiological studies should preferably divide cases into sub-groups with regard to endpoints when performing statistical analysis in order to minimize outcome misclassification bias (23). In addition, there may be a potential problem concerning the comparison groups in the cohorts, i.e. "healthy" men (23). Undetected subclinical prostate cancer is quite prevalent among elderly men, up to 30% of men over the age of 50 (8) and more than 50% of males 70 years or older (13) will have indolent prostatic adenocarcinoma upon autopsy. This may give rise to misclassification of outcome among the comparison group and differential misclassification bias resulting in weaker associations being observed

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(23). Still another problem with prostate cancer outcome ascertainment arises when the exposure in question is physical activity. Physically active men tend to be more health conscious and go more regularly for health checkups than sedentary men, increasing their likelihood of being diagnosed with prostate cancer via screening (6). Being able to adjust for this and other potential confounders, when performing statistical analysis on the association between physical activity and prostate cancer risk is therefore important. Taken together, the undetected cases among controls and overestimated incidence among physically active men may diminish an inverse relationship between physical activity and prostate cancer risk in epidemiological studies.

1.3   Established Risk factors

Knowledge of the etiology of prostate cancer is still very limited. Family history, age, and ethnicity are the only risk factors that have been established to date (8, 24). Incidence of prostate cancer increases with advancing age and is higher among men having first-degree relatives with the disease (8, 24). Ethnic factors are believed to explain much of the observed global variation in prostate cancer risk (8, 24).

1.3.1   Age

Age is the best established risk factor for prostate cancer. The disease seldom occurs in men younger than 50 years but the incidence rises exponentially after the age of 50-55 years, with the steepest age-dependent incline of any cancer in western countries (8, 24). Age-specific incidence rates of prostate cancer in Iceland are shown in figure 5; the mean age at diagnosis was 70 years for the time-period 2007-2011 (5). PSA screening has resulted in a shift in age-specific incidence curves to a younger age in populations with widespread use of PSA screening (8).
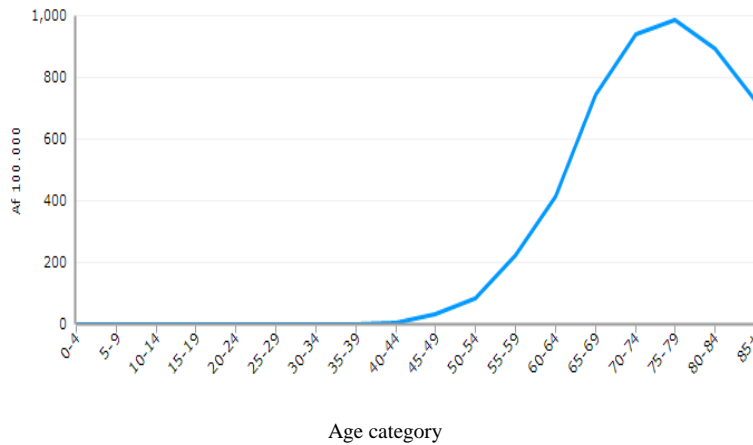
Figure 5. Age-specific incidence rates per 100 000 for prostate cancer in the period 2007-2011 (5).

1.3.2 Family history

It has been estimated, based on data from twin studies, that 30%-40% of prostate cancer risk may be explained by genetic factors (25, 26). Epidemiological studies likewise support a heritable component (8). Mucci and coworkers (8) have summarized the main observations regarding family history and prostate cancer risk, as follows: 1) Men with a first-degree relative with prostate cancer, especially a brother, have a 2-4 fold increased risk of being diagnosed with this disease, 2) Family history seems to be a stronger risk factor in early onset cases (usually defined as diagnosis before the age of 70 years), 3) Having a male relative with early onset prostate cancer, increases the risk of being diagnosed with the disease, 4) The larger number of affected first-degree relatives, the higher the prostate cancer risk.

It is believed that common, but low penetrant genes are associated with modest increase of prostate cancer risk and that it is unlikely that highly penetrant genes are responsible for the majority of cases (8). That makes genetic studies challenging, as sample sizes need to be large for making detection of effect possible. Genes encoding for androgen receptor, vitamin D receptor, IGF-1 and molecules involved in inflammation response of the immune system are among the ones that have been suggested to play a role in the etiology of prostate cancer (8, 27). The pathogenesis of prostate cancer likely involves complex interactions between genetic factors and environmental and/or lifestyle factors (24).

1.3.3 Ethnicity

A consistently observed but poorly understood risk factor for prostate cancer risk is ethnicity (24). There is a striking global variation of the incidence of prostate cancer, as previously mentioned (see section 1.1, figure 1), with more than 25-fold difference between the highest

and the lowest values. African-Americans in the Caribbean region have the highest incidence rates in the world while men in Shanghai, China have the lowest rates (1, 24). In Europe, a fivefold difference was observed in the time period 2001–2005, with Finland and Sweden having the highest values and the Russian Federation the lowest (13). This difference cannot be completely explained by differences in the use of PSA-testing, as data from the pre-PSA era show a geographic variation in prostate cancer incidence similar to the current standings (8). In addition, migrant studies have demonstrated that both incidence and mortality rises among men migrating from low-risk to high-risk countries, lending further support to the existence of environmental and/or lifestyle causes (8). Ethnicity reflects genetic profile, lifestyle and environmental factors that may affect prostate cancer risk and explain much of the variance in risk between high- and low-risk populations (24).

1.4 Potential risk factors

Various factors, in addition to the established risk factors, have been implicated in prostate cancer risk. These include hormones and growth factors, as well as metabolic and anthropometric factors (8, 27, 28). Modifiable lifestyle factors, such as diet and physical activity, are also believed to have a potential role in determining prostate cancer risk. They may affect the hormonal milieu and metabolic activity in the body and have effects on the immune system and antioxidant mechanisms (3, 28-30) (see also section 1.7.2).

1.4.1 Hormones and growth factors

Androgens, in particular testosterone and dihydrotestosterone, are essential endogenous hormones needed for normal growth and functioning of the prostate (8, 24). Levels of androgens increases sharply at puberty (31) and may also be elevated for males adhering to diet rich in animal fat (32). Physical activity, on the other hand, has been found to lower testosterone levels (33) (see further section 1.7.2). Testosterone diffuses into cells of the prostate, where 90% is irreversibly converted into the more active intracellular dihydrotestosterone by 5-alpha-reductase. Both of these hormones form a complex with a cytoplasmic androgen receptor which binds to specific DNA-sites, upregulating transcriptional activity and cell division (8). Increased levels of these androgens might therefore be involved in the development of malignant transformation in the prostate (28), as observed in experimental animal studies (8, 24). Epidemiological studies have, however, shown inconsistent results with regard to the role of endogenous androgen levels in prostate cancer development (8, 24, 27). A quantitative review of prospective studies did not find levels of circulating androgens to be any different for prostate cancer patients than for men

free of the disease (34). A meta-analysis from 2008 confirmed these findings (35). And paradoxically, serum testosterone levels are declining in men at the age of peak cancer incidence (28).

Insulin-like growth factor-1 (IGF-1) is a peptide hormone with a major growth-regulating role. It is produced mainly in the liver but also in several other tissues, including the prostate, in response to growth hormone. There is a high concentration of IGF-1 in circulation, which can have systemic or local effects on cell behavior. Most of the circulating IGF-1 is bound to its binding protein-3 (IGFBP-3). Free IGF-1 binds to IGF-1 receptors, expressed on the surface of prostate cells, resulting in induction of cellular proliferation. IGF-1 has been implicated in cancer initiation and progression and epidemiological and experimental evidence strongly suggest that it may be a key risk factor for prostate cancer (8, 24, 27). Some studies have found IGF-1 to be more related to advanced rather than localized prostate cancer (36, 37) but others have reported IGF-1 to be more positively associated with low-grade rather than high-grade disease (38). The bioavailability of IGF-1 is modulated by IGFBP-3, which has been implicated as potential mediator of prostate cancer risk (8, 24). IGF binding protein-1 (IGFBP-1), which shuttles IGF across blood vessel membranes, has also been speculated to be associated with the disease, but studies exploring the association between these binding proteins and prostate cancer risk have reported inconsistent findings (8). Elevated IGF-1 levels may be the result of diets high in fat and simple carbohydrates, due to increased levels of insulin and growth hormone (27, 30). Decreased insulin levels in people with diabetes tend to upregulate the levels of IGFBP-1, resulting in lower concentration of free IGF-1 and possibly reduced prostate cancer risk (38).

1.4.2 Diabetes Mellitus, type 2.

Patients with diabetes mellitus type 2 (DM2) initially experience hyperglycemia and hyperinsulinemia. These conditions may increase IGF-1 bioactivity and stimulate growth promotion and increase cancer risk (*39*). Although not entirely consistent, evidence suggest an association between elevated levels of fasting plasma insulin and fasting plasma glucose and increased prostate cancer risk (*40-42*). In the development of DM2, insulin levels are at first elevated as compensation for reduced insulin sensitivity but later fall as a result of β-cell depletion and reduced pancreatic production of insulin (*39*). Various epidemiological studies have found reduced risk of prostate cancer among diabetics, which might be explained by reduced levels of IGF-1 and testosterone accompanying advanced DM2 (*27*, *39*). The

relationship between diabetes and prostate cancer risk is thus complex and likely dependent on the disease stage.

1.4.3 Anthropometric measures

Body mass index (BMI) and/or body composition can influence endogenous levels of sex hormones, as well as many other biomarkers, spurring interest on the association between BMI and prostate cancer risk (8). The results of epidemiological studies on this subject have been inconsistent (39). Some evidence suggests decreased risk for localized prostate cancer but increased risk for advanced and fatal disease (43). As BMI does not distinguish well between adiposity and lean muscle mass, it might be more appropriate to use other measures of adiposity, such as waist-to-hip ratio for abdominal adiposity (27). This ratio has been positively associated with prostate cancer risk (44). Obesity is a major risk factor for insulin resistance and is also associated with increased levels of leptin, conditions which are believed to increase the risk of aggressive prostate cancer (39). Alternatively, obesity is associated with reduced production of testosterone and an increase in aromatization of testosterone to estradiol, which is thought to decrease the risk of non-aggressive prostate cancer (39). Epidemiological data suggest that weight change in late adult life may be a critical factor with regard to prostate cancer risk (8).

Data on the relationship of adult **height** and prostate cancer risk are conflicting. Several studies have observed no association while others have reported 15% to 100% increased risk for taller men (8). The levels of circulating growth factors and other hormones during puberty is one determinant for male adult height (45). Testosterone stimulates the production of IGF-1, which has been positively associated with adult height (46). Tall height might also be a marker for large prostate size, with larger number of cells at risk (8).

1.4.4 Diet

Despite extensive research, no definite findings have emerged for the relationship between diet and prostate cancer risk (8). That may partly be due to difficulties in measuring exposure when exploring diet-disease associations in epidemiological studies (47). Although conclusive evidence is limited, the current data indicate that avoiding high energy intake and excessive consumption of meat, dairy products and calcium, and consuming a diet low in fat but high in vegetables and fruits, is possibly effective in preventing prostate cancer (30).

Antioxidants may be important in terms of reducing prostate cancer risk, although results from epidemiological studies have been equivocal (48). There is a fairly strong

indication of the benefits of lycopene intake (an antioxidant found in tomatoes). Lycopene has been proposed to limit oxidative damage to cellular macromolecules and in vitro studies have found lycopene to impact on IGF-1 signaling (8, 27, 30, 48). Moderate vitamin E intake (not exceeding 400 IU per day) may also be beneficial, especially for smokers and those with low serum levels of vitamin E (8, 30). This vitamin may aid in cancer prevention due to its role as an intracellular antioxidant and antiprostaglandin (30). Dietary selenium intake might reduce prostate cancer risk, especially among individuals with low serum levels of this trace element (8, 24, 27, 30, 49). Selenium prevents clonal expansion of tumors by causing cell cycle arrest, promoting apoptosis, and modulating p53 dependent DNA-repair mechanisms, according to molecular data (24, 49). Vitamin D intake and fatty fish consumption are plausible candidates for beneficial effects on prostate cancer risk (8, 30). A metabolite of vitamin D, 1,25-dihydroxy-vitamin D has antiproliferative and antidifferentiative effects and is believed to be an inhibitor of prostate carcinogenesis (28, 50). Long-chain n-3 polyunsaturated fatty acids (LCPUFA) found in oily fish may affect prostate inflammation and carcinogenesis (51). Isoflavonoids found in soybeans have been shown to inhibit the growth of both benign and malignant prostatic epithelial cells in vitro (8, 27, 30). Polyphenolic compounds present in green tea have been found to induce apoptosis and cell growth inhibition and a large prospective cohort study in Japan found consumption of green tea to be associated with a dose-dependent decrease in the risk of advanced prostate cancer (30). High-fiber diet may be beneficial, as it is associated with lower levels of circulating androgens (24). Cruciferous vegetables such as broccoli, cabbage, cauliflower and Brussels sprouts, and allium vegetables such as onion, garlic and chives, have also been implicated in prostate cancer risk reduction (24). Isothiocyanates, sulfophorane and other phytochemicals found in these vegetables can inhibit tumorigenesis and may be the reason for this potential beneficial effect (24, 30). The epidemiological data have, however, been inconsistent and possible risk reduction may be limited to younger men (30).

Consumption of meat especially processed or charcoaled meat containing substances that have been shown to induce prostate cancer in rats, may increase prostate cancer risk (24, 30, 52). High milk consumption may increase plasma IGF-1 levels and thus potentially increase the risk of prostate cancer (53). An Icelandic study found frequent milk intake in early life to be associated with three-fold increased risk of advanced prostate cancer (54). Dietary calcium, a major nutrient in milk and milk products, may increase the risk of prostate cancer (8, 27, 30, 52), by reducing circulating 1,25-dihydroxy-vitamin D (55). Animal fat intake is also a possible risk factor (8, 30), although the consumption of red meat or dairy

products per se rather than fat itself may be conferring increased risk (8). In addition, excessive energy intake and obesity, independent of dietary fat consumption, may increase the risk of prostate cancer (8, 30).

1.4.5 Physical activity

As previously noted, modifiable lifestyle factors may have a potential role in the etiology of prostate cancer. Physical activity might be one of the most important lifestyle determinants in that respect. As this lifestyle factor and its relationship with prostate cancer risk is the main focus of this thesis, it will be discussed in more detail in the following sections (see sections 1.5, 1.6 and 1.7).

1.5 Definitions and guidelines of physical activity

Physical activity has been defined as the work done by skeletal muscles that increases the energy used by a person from the energy needed at rest (56, 57). Parameters used to describe physical activity are the following: type, duration, frequency and intensity (56, 57). Metabolic equivalent (MET) is the unit defined to describe energy use, 1 MET being the energy required at rest or 3.5-7 kcal/min (56, 57). Moderate physical activity has been defined as the activity requiring 3-6 METs, e.g. brisk walking, gardening, domestic cleaning and moderate exercise such as easy cycling, swimming, jogging and weightlifting (56, 57). Vigorous activity is the physical exertion that requires more than 6 METs, such as brisk uphill walking, strenuous gardening, running and most competitive sports (56, 57). The health benefits of physical activity are most likely on a continuum, i.e. all activity is good but more benefits are to be had with increasing physical activity (56, 57). The rate of gain is highest when going from being sedentary to moderately active. Increasing activity gives further health benefits but at a decreasing rate, as the upper limit of the fitness capacity of an individual is approached (57). Increased activity can be in the form of increased amount (longer duration of each session or increased frequency) or increased intensity. Public health guidelines generally call for a minimum of 30–60 minutes of moderate to vigorous intensity physical activity done at least 5 days per week (56, 57). For cancer prevention, the activity should be at the upper limits of this range (3, 57).

1.6 Assessment of physical activity exposure

Physical activity is a complex exposure, making it difficult to be evaluated. Type and parameters (frequency, intensity, duration) of the activity and time periods in life when physical activity was performed, need to be integrated when estimating the exposure. The

reporting of activities by study participants should be as accurate and unbiased as possible. As the most relevant time periods for maximum benefit of physical activity with regard to prostate cancer risk are not known, it would be most beneficial to gather information of physical activity from across the lifespan of the participants (lifetime data). In addition, it should preferably be assessed at multiple time points during the follow-up period in cohort studies, to monitor the consistency of the exposure. Furthermore, the activity should be estimated in both recreational and occupational settings, for obtaining information of the total physical activity of the individuals. Experimental study design (randomized controlled trial) for assessing the effect of physical activity on disease risk would be ideal, but difficulties with compliance and monitoring of large number of participants over extended periods of time make such studies both challenging and expensive. Ethical considerations may also question the appropriateness of using trial study design (3, 10, 23, 58).

The assessment of physical activity has been far away from the ideal in most observational epidemiological studies. Setting, period of life examined and parameters of activity have varied substantially across studies, making comparison of their results difficult. Most studies have used data on recent physical activity only and few studies have evaluated total physical activity. None of the cohort studies have used validated instruments, such as accelerometers, for monitoring the activity. Most of the studies have relied on self-report (via questionnaires) for exposure assessment, which could give rise to misclassification errors when reporting physical activity performed decades prior to baseline. Still, despite limited reliability and validity of using questionnaires for historical recall of physical activity, especially at the individual level, it is most often the only way to assess past activity and is believed to be useful as an activity-ranking instrument for large study populations (59, 60). Recall bias may be a problem in case-control studies, where case subjects may recall their physical activity differently from control subjects, based on their knowledge of disease status. The need for standard definitions of physical activity is urgent to facilitate epidemiological research and harmonization between studies. Furthermore, effect modification by tumor type and population sub-groups likely exists for prostate cancer and needs to be taken into account in study design and evaluation of findings, as well as when comparing results across studies (3, 10, 23, 59).

1.7 Physical activity and prostate cancer

1.7.1 Literature review

Previous cohort studies exploring the association between physical activity and prostate cancer risk have reported inconsistent results (3, 6, 7, 10, 11, 27, 57, 61-81). Many of the studies have concluded that physical activity reduces the risk of prostate cancer (61-65, 69, 71, 73, 75-78, 80, 81), although some have observed no association (66, 67, 70, 72, 74, 79) and one study found an increased risk of prostate cancer for physically active men (68). Some of the studies have analyzed both total and advanced prostate cancer (11, 62-65, 70, 71, 77, 79-81), others have explored total disease only (61, 66-69, 72-76, 78). Majority of the cohort studies have focused on recreational physical activity (RPA) (61-73), while others have explored both RPA and occupational physical activity (OPA) (74-80) or OPA only (81). Among the studies looking at both RPA and OPA (11, 74-80), OPA has more often given stronger inverse association with prostate cancer risk than RPA (11, 75, 76, 80) when association has been observed (11, 75-78, 80).

Very few cohort studies reported to date have analyzed total physical activity (TPA), e.g. combined RPA and OPA (11, 75, 78). One of the few to do so, and among the most detailed studies, is the one by Orsini et al. (11). They explored the risk of total, localized and advanced prostate cancer of Swedish men aged 45-79 years with regard to lifetime average RPA, OPA and TPA. Physical activity was assessed with a detailed validated questionnaire at baseline, including information on duration and intensity of activities. The cohort (n = 45 887) was followed for up to 10 years. Multivariate Cox regression analysis was used to calculate risk of prostate cancer by level of physical activity, adjusting for the following potential confounders: baseline age, waist-to-hip ratio, height, diabetes, alcohol consumption, smoking status, education, total energy intake, consumption of dairy product and red meat and parental history of prostate cancer. When TPA was analyzed, a 16% risk reduction was found for total prostate cancer and 25% for advanced disease, comparing the most active men (top quartile) with the least active ones (bottom quartile). They also observed a decreased risk of prostate cancer in separate analysis for OPA and RPA. For men sitting half of the time during working hours as compared with those sitting most of the time, a decreased risk of 20% was observed for total prostate cancer and 26% for advanced disease. The rate ratio linearly decreased by 7% for total, 8% for localized and 12% for advanced prostate cancer for every 30 minutes per day increase of lifetime walking or bicycling in the range of 30-120 minutes per day.

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In two other cohort studies exploring TPA, one by Hartman et al. (78) and the other by Clarke and Whittemore (75), the lowest risk was seen for the most active men. The endpoint analyzed in these studies was, however, total prostate cancer but not advanced disease. Hartman et al. asked participants (n=29 133, age= 50-69 years), at study entry, to describe their physical activity in work and leisure within the past year. The authors followed the men for up to nine years and found a borderline significantly reduced risk of total prostate cancer for men in the OPA category „walking" compared with sedentary men (RR=0.6, 95% CI: 0.4-1.0). Those active in their leisure time had a significantly reduced risk compared with sedentary participants (RR=0.7, 95% CI: 0.5-0.9). The risk was lowest for men belonging to the „walking at work/active in leisure time "category (RR=0.4, 95% CI: 0.2-0.9). Multivariate Cox regression models used in the analysis were adjusted for intervention group, benign prostatic hyperplasia, age, smoking and urban residence.

Clarke and Whittemore (75) based their analysis on self-reported current physical activity at baseline, with a follow-up period of up to 21 years (n = 5377). Multivariate Cox models were adjusted for age, education, family history and race. Inactive men, as compared with the most active men, were found to have increased risk of being diagnosed with prostate cancer. When the analysis was stratified according to race, this effect was strong among African-American participants (14% of the cohort, contributing 23.4% of cases) but was not significant among Caucasian men. This indicates that there may be etiological differences between ethnic subgroups. The increase was most profound in the case of TPA, somewhat less for non-RPA but the smaller increase for RPA was not statistically significant.

The results of case-control studies on the association between physical activity and prostate cancer risk have also been inconsistent. When analyzing TPA and prostate cancer risk, some studies have reported reduced risk for the most active men (82, 83), while others have found borderline association (84) or no association (85, 86). For OPA, a reduced risk for the most occupationally active men has been found in several studies (84, 87-89) but not all (85, 86). Results for RPA have been less convincing. One study found a reduced risk for strenuous recent RPA (90), but others have found no association (84, 86, 89) or increased risk for men participating in vigorous RPA (85).

In a recent meta-analysis by Liu et al. (6) data from 19 cohort studies and 24 case-control studies were pooled together with a total of 2 123 844 participants, including 88 294 cases. Significantly reduced risk of total prostate cancer was found with regard to OPA (19%) and TPA (10%) and a borderline significant risk for RPA (5%), for men 20-65 years of

age. When the TPA-analysis was stratified according to stage of disease, the relative risk was 0.94 (95% CI: 0.80-1.10) for advanced prostate cancer and 0.96 (95% CI: 0.87-1.05) for localized disease, e.g. the risk reduction was found to be non-significant. When the cohort studies were stratified according to the length of follow-up, risk reduction was only observed for studies with follow-up period of 10 years or more. This highlights the importance of the length of the follow-up and suggests that the effects of physical activity may be accumulative over time and/or need to be continuous during the induction time of prostate cancer, which tends to be long (3, 6). Stratification with regard to PSA-screening (in the 3 years period prior to baseline) and BMI did not result in substantial difference of risk between strata. When cohort studies and case-control studies were analyzed separately, risk reduction was typically less for the higher quality cohort studies than the lower scoring case-control studies. Liu et al. could not assess dose-response relationship (see figure 6) or estimate threshold value of physical activity required for prostate cancer prevention, due to differences in physical activity measurements and classification methods across the evaluated studies.
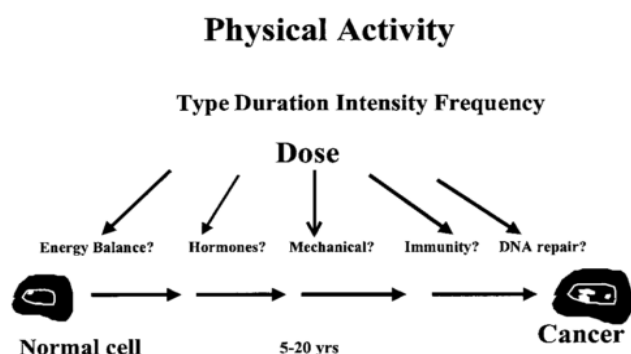
Figure 6 Hypothesis of the influence of dose of physical activity (type, duration, intensity, frequency) on possible biological mechanisms operating on cancer development (91).

The results of previous studies point to the importance of physical activity during working hours rather than in leisure time for reducing prostate cancer risk. Liu et al. speculate that the weaker effects of RPA than OPA on prostate cancer risk may be attributed to the inconsistency in the definition and assessment of RPA across studies, lack of regularity, more lifetime variability and possibly greater recall error. OPA is most likely undertaken more consistently and with longer duration than RPA (6, 10). The total activity, TPA, may still be the most relevant factor regarding risk reduction. Being active not only at work but in leisure time as well seems to give the best protection against prostate cancer (23, 75, 78).

Intensity of the physical activity might also be an important factor with regard to prostate cancer risk. More vigorous activity has, in general, tended to give more beneficial effect (10). In some studies, decreased prostate cancer risk has been found for vigorous activity only (7, 8).

Physical activity may give the best protection against advanced prostate cancer (3). Among seven cohort studies analyzing endpoints for both total and advanced prostate cancer and reporting an inverse association (11, 63-65, 71, 80, 81), four did so for physical activity and advanced disease only but not for total prostate cancer (63, 65, 71, 80). Orsini et al. (11) found an inverse association between physical activity and all stages of prostate cancer, but it was strongest for advanced disease. One study observed protective effect of physical activity for total disease but not for fatal prostate cancer (81) and another one found a reduced risk of non-aggressive disease for physically active men older than 65 years (64).

The time-period in life when performing physical activity may be of importance with respect to prostate cancer risk. The prostate may be more susceptible to environmental and lifestyle factors at certain time in its development, such as around puberty (23). Some of the previous cohort studies have analyzed separately the effects of physical activity for different life periods (61, 62, 64-66, 69, 70), but few have included early life activity (43, 61, 62, 64). One study (62) found a weak protective effect for RPA during adolescence but not for current RPA. Another (61) found prostate cancer risk to be somewhat reduced for non-OPA during young adulthood (at ages 19-29 and 35-39 years), for African-American men. In the meta-analysis by Liu et al. physical activity before age 20 and after age 65 did not reduce prostate cancer risk. Liu et al. speculate that difficulties with recall of physical activity in the distant past may obscure the effect of physical activity before the age of 20 years. The lesser effect of physical activity among older men might be explained both by increased incidence of prostate cancer and decreased participating in physical activity (6). In contrast, men 65 years or older engaging in at least 3 hours per week of vigorous physical activity had a markedly lower risk of being diagnosed with high-grade, advanced, or fatal prostate cancer in a study by Giovannucci et al. (7). In a study by Littman et al. (64), physical activity was associated with a decreased risk of non-aggressive prostate cancer among men 65 years or older at diagnosis. Both Giovannucci et al. and Littman et al. speculate that the etiology of prostate cancer may differ for early and late onset disease, with genetic factors being more important in the early onset cases.

Physical activity might affect ethnic groups differently. Ethnicity has been identified as a risk factor for prostate cancer, with African-American men having the highest risk (10). Two studies enrolling both Caucasian and African-American men (61, 75) observed protective effect of physical activity for African-American men, but not for Caucasian men.

In summary, evidence from the literature suggests that physical activity has a modest protective effect against prostate cancer risk. This may especially be the case for advanced/aggressive disease and vigorous and/or occupational activity conducted over extended period of time. The effects may depend on ethnicity and time-period of life when engaged in the activity. Study results have though been inconsistent, most likely due to methodological problems and heterogeneous nature of prostate cancer.

1.7.2 Biological mechanisms

Understanding of the biological mechanisms involved in the relationship between physical activity and prostate cancer risk is important with regard to preventive strategies and public health recommendations. The exact biological pathways through which physical activity might reduce prostate cancer risk remain unclear, but several mechanisms have been suggested. Physical activity may lower the levels of some of the endogenous growth factors and hormones that have been implicated in prostate cancer risk, aid in weight control and prevention of obesity, improve immune function, prevent chronic low-grade inflammation and augment antioxidant defense mechanisms (3, 6, 23, 29) (see figure 7 for schematic overview).
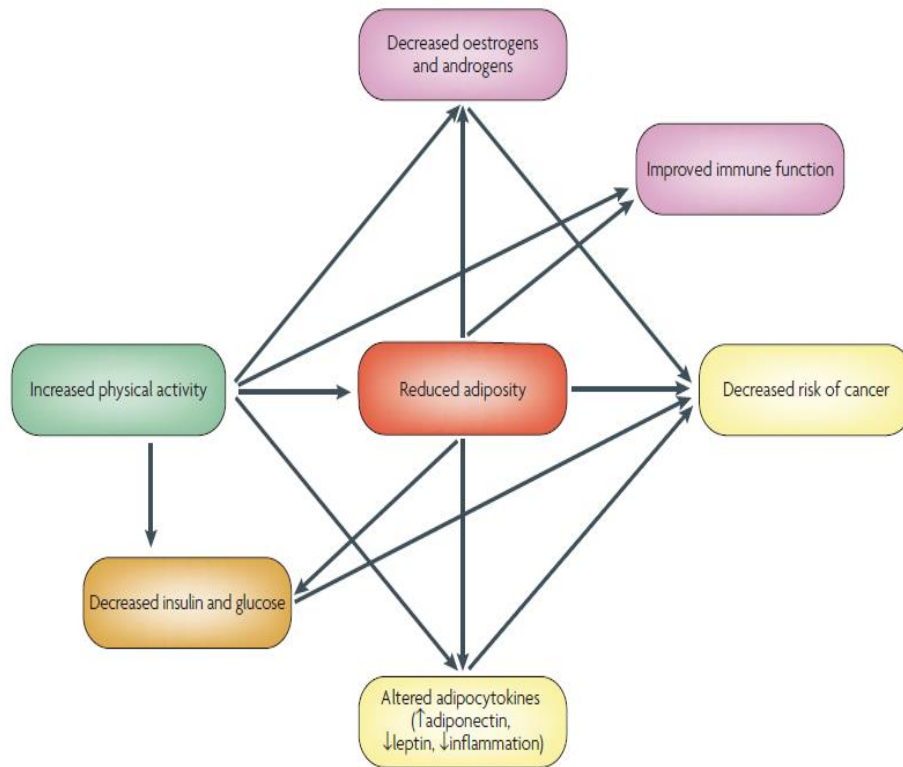
Figure 7. Hypothesized mechanisms linking physical activity to cancer risk or prognosis.

Physical activity might work through reducing the amount of adipose tissue, which lowers production of sex hormones, insulin, leptin and inflammatory markers, thereby decreasing the exposure to these potentially carcinogenic hormones and peptides and reducing cancer risk (29).

Hormones and growth factors: Physical activity may lower the levels of some of the endogenous growth factors and hormones that have been implicated in prostate cancer risk (see sections 1.4.1 and 1.4.2), such as testosterone (23, 29, 33), serum insulin (92, 98) and IGF-1 (93-97).

Testosterone: Physical activity may lead to decreased concentration of testosterone by a disruption in the HPT axis at the central (hypothalamus or pituitary) and/or peripheral levels (testicular function). It is believed that there is a "breakdown" in the negative feedback loop that regulates testosterone production (33). Physical activity also increases production of sex hormone-binding globulin, leading to lower levels of free testosterone (23, 29). In addition, physical activity may influence the level of endogenous androgens through its influence on height and weight, such as around puberty (23).

IGF-1: Physical activity has been found to reduce IGF-1 levels (93, 94). It may lower the bioavailability of IGF-1 by increasing levels of IGFBP-1(94-96). In a study exploring the effects of acute exercise on prostate cancer cell growth, serum collected from menpost exercise had a growth inhibitory effect on cells from the established prostate cancer cell line

LNCaP, by inhibiting their proliferation (96). In addition to these in vitro findings, there was also in vivo evidence of inhibition of tumorigenesis. A delay in tumor formation was observed in SCID mice receiving subcutaneous injection of LNCaP cells that had been pretreated with exercise serum (96). Studies looking at the effects of long-term endurance training similarly found it to exert an inhibitory effect on LNCaP growth, attributed to low - 1levels of IGF-1 and high levels of IGFBP-1 (95-97). Furthermore, addition of IGFBP to the control serum reduced tumor cell growth to the same extent as the exercise serum.

Insulin: Physical activity may improve glycemic control by lowering serum insulin and decreasing insulin resistance (92). Possible underlying mechanisms include upregulation of the rate-limiting enzymes of glycolysis and proteins in the insulin-signaling cascade, lowering of triacylglycerol and non-esterified fatty acids (NEFA), stimulated endothelial release of nitric oxide and modulation of appetite via the leptin pathway (92). In addition, muscle contraction allocates glucose transporter-4 to the cell membrane, resulting in increased transport of glucose from plasma into the cell (92, 98). Moderate to vigorous activities may be more beneficial than light intensity activities for decreasing fasting insulin levels (92).

Adiposity and weight control: Being physically active is a key element in weight control and the prevention of obesity, which has been associated with advanced prostate cancer risk (43). Physical activity increases total energy expenditure, reduces fat mass and maintains/increases lean body mass and basal metabolic rate (99). Importantly, it may reduce visceral adipose tissue and thus improve metabolic health and hinder adipose-induced inflammation (99).

Immune function: Physical activity may have beneficial effects on immune functioning (100). Moderate physical activity has been shown to increase resting levels of natural killer cells of the immune system. Levels of cytotoxic T-lymphocytes are also increased following exercise and the monocyte-macrophage system stimulated. These cells are all part of the immune system response towards killing cancer cells (100).

Inflammation: Epidemiologic, genetic and molecular pathological data indicates a role of chronic inflammation in the pathogenesis and progression of prostate cancer (8). Chronic inflammation induces cellular damage and compensatory cellular proliferation and clinical prostatitis has been associated with risk and progression of prostate cancer. Infectious agents are thought to be involved in the initiation and aggravation of chronic inflammation (8).

Physical activity is believed to act against inflammation, by activating cytokines that decrease the inflammation response of the immune system (101). It is also thought to act indirectly by controlling weight, thus hampering adipose-induced activation of pro-inflammatory cytokines (102-104).

Oxidative stress: Physical activity increases oxygen uptake, generating reactive oxygen species (ROS). ROS are formed continuously in normal biochemical processes in the body, as well as when environmental stressors are encountered. Endogenous antioxidant defense mechanisms take care of removing ROS molecules (4). A decline in ROS detoxification enzyme activities occurs in most tissues with aging (28). Moderate physical activity creates mild oxidative stress, activating cellular stress response signaling and augmenting antioxidant defense capacity. Exhaustive exercise may, however, result in accumulation of ROS, which may lead to DNA damage, mutations or promotion of tumorigenesis by activating proinflammatory signaling (4, 23).

Several of the proposed mechanisms are interrelated (see figure 7), and the effects of physical activity via these pathways may be additive, opposing and even synergistic. This makes research of single mechanisms very challenging and complex. It is possible that one key mechanism is at work, underlying and driving several other related pathways. Identifying this mechanism may be crucial to aid in the formulation of physical activity recommendations for cancer prevention (3). In vitro studies using cancer cells derived from prostate cancer patients and measuring their growth in serum from individuals participating in randomized intervention trials may help in prevention research. One such intervention study examining the effects of exercise and diet reported eight-fold more growth inhibition when the cells where grown in serum from men in the intervention group as compared with serum from the control group (105). The problem with the study was, however, that changes in both exercise and diet were made simultaneously, so the effects on cell growth may have been related to changes in either physical activity or diet or both (10). This mimics the complexity of real life situations, where physical activity and diet may interact to affect metabolism. Furthermore, individuals who exercise regularly tend to have healthier diet and better control of weight. Perhaps it would, indeed, be better to study clusters of health behaviours rather than single components, to encompass the real life complexities of health (10).

1.8 Study motivation.

It is very relevant to conduct epidemiological research on prostate cancer in Iceland. The incidence is among the highest in the world (96.4 per 100 000 in 2006-2010 (5)) and it is the most frequently diagnosed cancer and the second leading cause of death from malignant disease among Icelandic men (5). Few risk factors are known for prostate cancer and there is a great need to gain more information about the etiology of the disease and identify factors that might reduce the disease risk. Environmental and lifestyle factors are thought to be important, based on immigrant studies and ethnic variations in incidence rates (7, 8). Physical activity might be one of the modifiable lifestyle factors that could be of value for preventive purposes.

Valuable data sources for undertaking epidemiological studies exist in Iceland. The Icelandic Heart Association initiated a large population-based prospective cohort study in 1967, the Reykjavik Study (106). All men and women born in the period 1907-1935 and living in the capital area in December 1966 were identified and a randomly selected subset was invited to participate in the study. At entry to the Reykjavik study participants underwent a detailed medical examination and serum measurements were performed, yielding data on anthropometric factors and potential covariates. Participants also completed a questionnaire regarding health and lifestyle factors, which included questions on physical activity in leisure time and during working hours. Linking data on physical activity and potential confounders obtained from the Reykjavik study with the diagnosis information from the Icelandic cancer registry made it possible to explore whether regular physical activity from early adulthood onwards was associated with the risk of prostate cancer. The long and complete follow-up (through year 2009) and extensive covariate data available for this population-based cohort makes this study opportunity very valuable.

This will be the first study on the association between physical activity and prostate cancer in Iceland, enriching the studies on lifestyle factors (diet, sleep) and prostate cancer conducted at the Center of public health research at the University of Iceland.

2 Aims

The overall aim of this study was to explore whether there is an association between physical activity and the risk of prostate cancer. As few studies have assessed the role of early life activity, or combined recreational and occupational activity, our focus was on lifetime total physical activity and the risk of advanced prostate cancer (the clinically important form of the disease) later in life.

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Physical activity and prostate cancer risk: a 24 year follow-up study among Icelandic men.

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Abstract

Background: Physical activity may reduce prostate cancer risk. Few studies have assessed the role of early life physical activity, or combined recreational and occupational physical activity on prostate cancer risk and mortality.

Methods: We undertook a prospective study using data from 9076 Icelandic men (born 1907 to 1935) who at enrollment, between 1967 and 1987, to the population-based Reykjavik study provided information on recreational physical activity since the age of 20 years and current occupational activity. Through linkage to cancer and mortality registers, the men were followed for prostate cancer diagnosis and mortality through 2009. We used Cox models to calculate risk of prostate cancer by level of physical activity.

Results: During a mean follow-up of 24.3 years, 1149 men were diagnosed with prostate cancer, of whom 387 had advanced disease. No significant association was observed for either recreational or occupational physical activity and total or localized prostate cancer. Recreational and occupational physical activity were neither independently associated with advanced prostate cancer. Among men who were physically active during working hours, those who participated in recreational physical activity had a decreased risk of advanced prostate cancer (hazard ratio =0.59; 95% confidence interval: 0.37 to 0.94) compared with men who did not. No association was found between recreational physical activity and advanced prostate cancer among men in sedentary jobs.

Conclusions: Our data suggests that extensive physical activity from early adulthood onwards may reduce the risk of advanced prostate cancer.

Introduction

Prostate cancer is the second most common cancer among men worldwide, but with a striking international variation in incidence rates (1). Widespread prostate specific antigen (PSA) testing has in many Westernized countries led to a rise in the detection of indolent tumors from the large but silent reservoir of latent prostate cancer (2). For identifying risk factors for aggressive prostate cancer, which is the third deadliest cancer among men in developed countries (3), it is important to separate endpoints (aggressive vs. indolent) of the disease.

Age, family history and ethnicity are the main established risk factors for prostate cancer (4-6), all being non-modifiable. Despite a great need for preventive strategies, few modifiable risk factors have to date been detected. Yet, increasing body of evidence, including the findings of a recent meta-analysis (7), suggests that physical activity and fitness may play a preventive role in prostate cancer development and progression (4, 7-9). Results have though been equivocal, likely due to several inherent methodological differences across studies. These include substantial heterogeneity in disentangling lethal from indolent prostate cancers and variation in follow-up times and methods for ascertainment of physical activity. Importantly, as few studies have total lifetime information on physical activity it is not known whether persistent activity or physical activity during any specific period of the life course affects prostate cancer risk (8, 9). Moreover, few studies have assessed the role of early life activity, or combined recreational and occupational activity.

Leveraging the population-based Reykjavik cohort (10) with more than 24 years of follow-up and the nationwide Icelandic Cancer Registry (11), we conducted a prospective analysis on regular recreational physical activity (RPA) in adulthood and occupational physical activity (OPA) at entry and risk of prostate cancer. We hypothesized that the combined effect of physical activity in leisure time and during working hours would be associated with decreased risk of prostate cancer, particularly for advanced disease.

Methods

Study population

Participants came from the Reykjavik Study, a population-based prospective cohort study initiated in 1967 by the Icelandic Heart Association (10). All men born in the period 1907-1935 and living in the capital area in December 1966 were identified (n = 14 923), of whom 12 842 were randomly selected and invited to participate in the study. The response rate was

71% (n = 9115). At entry, participants underwent a detailed medical examination and serum measurements were performed, yielding data on anthropometric factors and potential covariates. Participants also completed a questionnaire regarding health and lifestyle factors, including questions on physical activity in leisure time and during working hours. For the present study, men with diagnosed prostate cancer at baseline (n = 19) and those with incomplete follow-up (n = 20) were excluded, leaving 9076 men in our cohort (see figure 1).

Assessment of physical activity

For obtaining information about physical activity in leisure time, participants were asked whether they had regularly participated in sports or recreational exercise since the age of 20 years. Those who answered "yes" to this question were then asked how much they exercised during winter and summer, given two categories to choose from: 5 hours or less or more than 5 hours per week. Hours of exercise in winter and summer were used to calculate the overall hours spent on RPA per week. Additional information on age of participation (4 categories: 20-29, 30-39, 40-49 and 50-59 years) was collected in the Reykjavik Study, but was not used in our analysis as the age at enrollment varied (the 20-29 years category was the only one that applied to all participants, 63% reported participation in RPA in this age period) and to reserve the power of the analysis. To avoid misclassification, those who categorized themselves as being physically active, but did not answer the question on how much they exercised were excluded from the analysis (n = 292). For meaningful analysis, as few participants exercised for more than 5 hours per week (n = 475), men were considered exposed if they did any exercising in their leisure time (n = 2277). Participants that reported no exercise at all were placed in a non-RPA group (n = 6507).

For evaluating physical activity at work, participants were asked whether they were mostly sitting, mostly standing or mostly on the move during working hours. Based on the responses, two additional categories were defined for the present study: low-OPA (mostly sitting or mostly standing at work) and high-OPA (mostly on the move during working hours). To study the combined effect of physical activity in leisure time and during working hours, participants were categorized into four different total physical activity (TPA) groups: 1) non-RPA/low-OPA, 2) RPA/low-OPA, 3) non-RPA/high-OPA and 4) RPA/high-OPA.

Follow-up and ascertainment of prostate cancer

Data on prostate cancer diagnoses until the end of 2009 were obtained via record linkage to the Icelandic Cancer Registry (11). Information on prostate cancer as the underlying cause of death was retrieved from Statistics Iceland (12). Classification of stage of disease at diagnosis was based on medical records using the TNM stage classification: stage I (incidental finding), including T1a, NX/0, and MX/0; stage II (tumor confined to prostate gland), including T1b/1c/1/2, NX/0, and MX/0; stage III (tumor extending through prostatic capsule), including T3, NX/0, and MX/0; or stage IV (locally advanced or metastatic disease), including T4, NX/0, MX/0 or any T, N1 and/or M1. Stage information was available for approximately 60% of cases. Men were classified as having advanced prostate cancer if they died from the disease or were diagnosed with a stage III or IV tumor. Other cases were classified as localized. Participants were followed from study entry (between 1967 and 1987) until diagnosis of prostate cancer, death or the end of the study period (December 31, 2009). Follow-up was virtually complete.

Reykjavik Study – initiated in 1967

14923 men born 1907-1935, with residency in the capital area in december 1966, identified

Random set of 12842 invited to participate, in 5 phases, between 1967 and 1987

71% response rate, leaving 9115 participants in cohort

Exclusion of 39 participants*, leaving 9076 in study cohort

*prior diagnosis of prostate cancer (n=19) incomplete follow-up (n=20)

Icelandic Cancer Registry

1149 men diagnosed with prostate cancer by the end of 2009
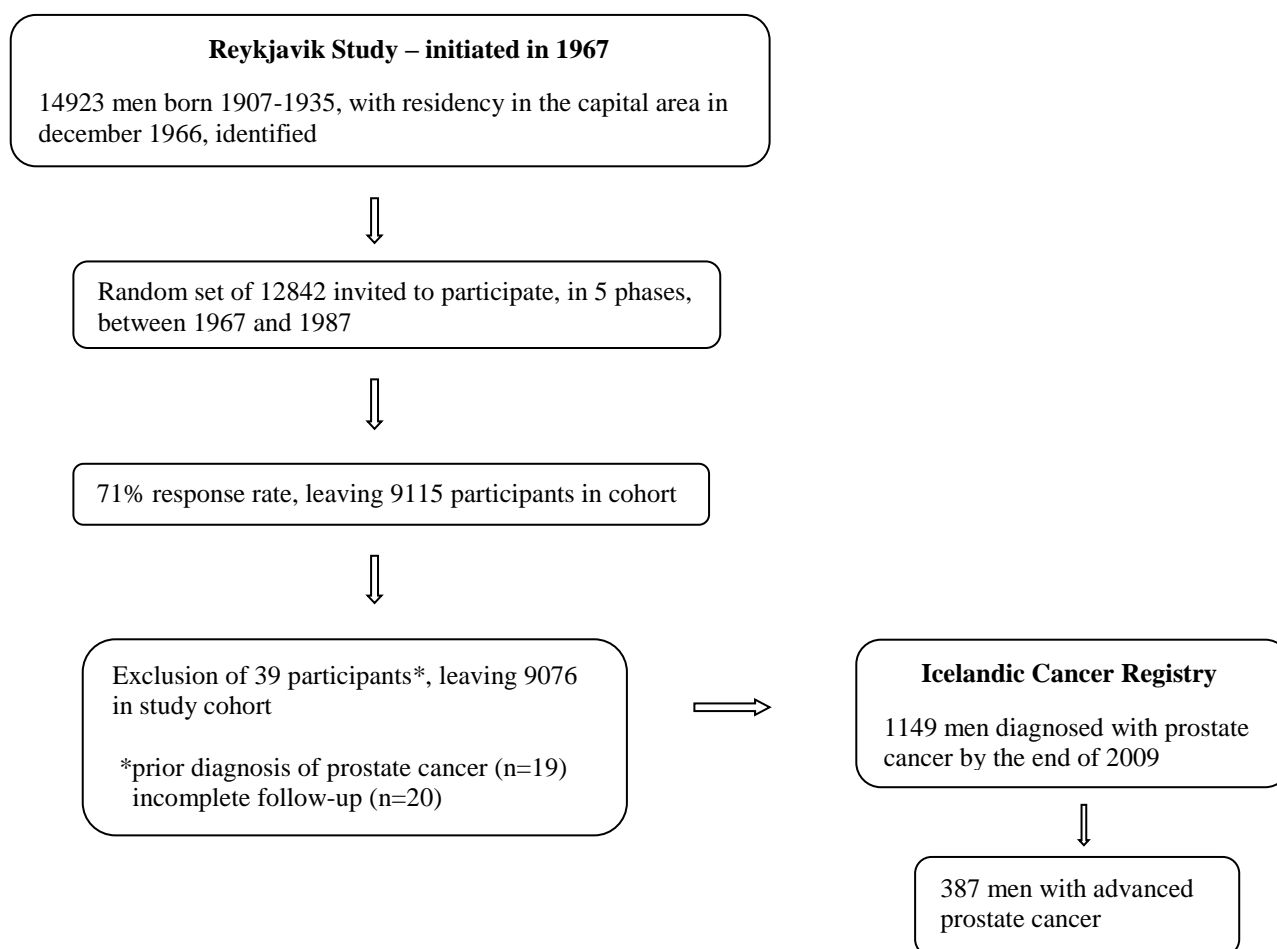
387 men with advanced prostate cancer

F**igure 1** Number of men entering the study and developing prostate cancer.

Statistical analysis

We used two sample t-test for continuous variables and χ^2 test for categorical variables (95% confidence level) to compare baseline demographic and health characteristics for the four different PA groups.

Cox proportional hazards modeling was used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for localized, advanced and total prostate cancer according to different levels of RPA and OPA. Associations were explored for RPA and OPA separately as well as combined (TPA), and also for RPA within strata of OPA (two levels: high and low). The reference in the RPA analysis/stratified RPA analysis was the group reporting no RPA and in the OPA-analysis the low-OPA group. In the analysis for TPA the reference was the non-RPA/low-OPA group. Multivariate models were used for simultaneously controlling for the following covariates (values at baseline): birth-year (continuous), age (continuous), height (continuous), body mass index (continuous), type 2 diabetes (yes/no), smoking (never/former/current), family history of prostate disease (yes/no), having a health check-up regularly (yes/no), educational attainment (elementary/secondary school, college education or university education) and residency in early life (Reykjavik, seaside village, rural area or combination of seaside village and rural area (13)). We tested for interaction between RPA and OPA.

Of the 9076 subjects, information on RPA was incomplete for 292 men, reducing the cohort to 8784 men during RPA analysis. Data for OPA were missing for 587 subjects, resulting in cohort of 8489 men for the OPA analysis. In the OPA-stratified RPA analysis, data on physical activity were missing or incomplete for 855 men, leaving 8221 men in the analytic cohort.

A sensitivity analysis was performed to address the potential effect of an existing undiagnosed prostate cancer on physical activity, where participants diagnosed with the disease within the first 3 years from entry to the study were excluded. We used SAS software, version 9.2 (SAS Institute Inc., Cary, NC; www.sas.com) for all statistical analysis. The study protocol was approved by the Icelandic Ethical Review Board (VSNb2007120014/03-7) and the Icelandic Data Protection Authority.

Results

The mean age of participants (n= 9076) when entering the Reykjavik Study was 52.3 years (SD=8.6). During an average follow-up time of 24.3 years (SD=10.9), 1149 men were diagnosed with prostate cancer, of whom 387 had advanced disease. Mean age at cancer diagnosis was 73.8 years (SD=7.1).

Characteristics according to physical activity level

Table 1 shows the characteristics of the cohort (n= 8221) by level of RPA, stratified for OPA. Among those participants who were sedentary during working hours (n = 4423, low-OPA stratum), men participating in RPA (n = 1400, 32%) were taller and heavier and had lower blood and serum glucose levels than those physically inactive in their leisure time. The RPA/low-OPA men were also less likely to smoke but more likely to have a regular health check-up, prostate disease in the family, higher educational level and being raised in the capital area (Reykjavik) in childhood compared with the non-RPA/low-OPA group. Within the category of men in physically demanding jobs (n = 3798, high-OPA stratum), those participating in RPA (n = 764, 20%) were taller and had lower blood pressure than men not physically active in their leisure time. The RPA/high-OPA men were also less likely to smoke but more likely to have regular health checkup, higher educational level and first residency in the capital area (Reykjavik) than the non-RPA/high-OPA group.

Physical activity and prostate cancer

During an average follow-up period of 24.8 years (SD=10.7) among participants with valid information on RPA and OPA, 1052 men were diagnosed with prostate cancer, of whom 349 had advanced disease. For total, localized and advanced disease, no significant association was observed between non-stratified RPA and prostate cancer (Table 2). In the OPA analysis (Table 3), a statistically significant association was found for total (HR = 0.82 (95% CI = 0.72 to 0.94)) and localized prostate cancer (HR = 0.79 (95% CI = 0.67 to 0.92)) for the men mostly on the move during working hours as compared with men that were mostly sedentary at work, for the age-adjusted model. This association became non-significant when the multivariate model was employed, with HR = 0.85 (95% CI = 0.71 to 1.01) for localized disease and HR = 0.90 (95% CI = 0.78 to 1.04) for total prostate cancer. For advanced disease, a significant association was not observed in the OPA analysis.

When combined physical activity (TPA) was analyzed (Table 4), a statistically significant interaction was found between RPA and OPA (p = 0.0291, advanced disease). In the stratified RPA analysis (with regard to OPA, Table 5), there was no significant association observed between RPA and total prostate cancer or localized disease, for both high and low levels of OPA. However, a significantly reduced risk of advanced prostate cancer was found for men who were physically active both in their leisure time and during working hours, with HR of 0.59 (95% CI = 0.37 to 0.94), compared with those who were not participating in RPA but employed in a physically demanding job (Table 5, high-OPA stratum). Association between physical activity and advanced prostate cancer was not found among men in sedentary jobs (HR = 0.99, 95% CI = 0.72 to 1.37; Table 5, low-OPA stratum).

Sensitivity analysis

The results of the sensitivity analysis, excluding men who were diagnosed with prostate cancer within the first three years from study entry (five men with advanced disease), did not alter the point estimates significantly from that of the unrestricted multivariate analysis. Within the stratum of men employed in a physically demanding job, those participating in RPA had a HR of 0.62 (95% CI = 0.39 to 0.99) for advanced prostate cancer, as compared with men physically inactive in their leisure time.

Discussion

In this population-based prospective cohort study, we found that men in occupations demanding physical activity as well as with history of exercising regularly in their adult life had a 41% decreased risk of being diagnosed with advanced prostate cancer compared with men who didn´t exercise in leisure time but were employed in a physically demanding job. However, this risk reduction was not seen when analyzing separately data for those who were physically active only in their leisure time irrespective of occupational activity or only during working hours irrespective of leisure activity. We found no association between physical activity and total or localized prostate cancer.

Previous cohort studies exploring the association between physical activity and prostate cancer risk have reported inconsistent results (7-9, 14-37). That may, at least partly, be due to different methodologies used across studies, e.g. in obtaining information on physical activity, focus on different endpoints of prostate cancer (localized vs. advanced), as

well as varying study size and differences in duration of follow-up. Majority of the studies have focused on RPA (16-28), while others have explored both RPA and OPA (29-36) or OPA only (37). Very few cohort studies reported to date have analyzed combined RPA and OPA (30, 33, 34) and most studies have used information on current/recent physical activity during midlife or older adulthood only and not lifetime data. Our observed interaction between RPA and OPA (advanced disease) emphasizes the need for using stratified analysis when exploring the effects of leisure time and occupational physical activity.

Some researchers have analyzed total, advanced and localized prostate cancer separately (17-20, 25, 26, 32, 33, 35-37). Others have explored incident disease only (16, 21-24, 27-31, 34) and thus not been able to distinguish between potentially indolent prostate cancer and clinically aggressive forms of the disease.

Our finding of substantial risk reduction of advanced prostate cancer for men physically active both at work and in their leisure time is in agreement with a previous cohort study by Orsini et al. (33). They explored the risk of total, localized and advanced prostate cancer of Swedish men aged 45-79 years with regard to lifetime average RPA, OPA and TPA. When TPA was analyzed, a 25% risk reduction was found for advanced disease (16% for total disease). In two other cohort studies exploring TPA, one by Hartman et al. (34) and the other by Clarke and Whittemore (30), the lowest risk was seen for the most active men. The endpoint analyzed in these studies was, however, incident prostate cancer but not advanced disease. Both studies used information on recent physical activity in their analysis as compared to lifetime data in the study by Orsini et al. (33) and the present study (RPA data). This highlights the difficulties in comparing study results, due to differences in methodology across studies. Our results are not entirely in line with the findings of a recent meta-analysis by Liu et al. (7). In that study, a significantly reduced risk of total prostate cancer was found for TPA (10%), but when the analysis was stratified according to stage of disease (localized/advanced), the reduction was found to be non-significant. Differences in duration of follow-up and assessment of physical activity may possibly explain this discrepancy.

The exact biological pathways through which physical activity might reduce prostate cancer risk or progression remain unclear, but several mechanisms have been suggested. Physical activity may lower the levels of some of the endogenous growth factors and hormones that have been implicated in prostate cancer risk such as testosterone (38), serum insulin (39) and insulin-like growth factor-1 (40, 41). Being physically active is a key element in weight control and prevention of obesity, which has been associated with advanced prostate

cancer risk (42). However, in the present study we did not observe confounding effect of weight. Immune function may also improve (43) and chronic low-grade inflammation be prevented (44), and antioxidant defense mechanism may be augmented (45). Finally, regular physical activity combined with being in a physically demanding job might affect the quality of sleep during nights; where better sleep might offer a protection against advanced prostate cancer, as has been suggested among elderly men in a subgroup within this cohort (46).

Our study has several strengths. We used a large and well-described population based cohort, with information on physical activity in leisure time from early adulthood and onward. In addition, the available data on potential covariates were extensive, well characterized and obtained at the same time as the information on exposure. Another major strength of this study is the long and virtually complete follow-up for prostate cancer diagnosis and deaths via the linkage to the Icelandic cancer and mortality registries. As the meta-analysis by Liu et al. (7) shows, the length of the follow-up is very important. In their stratified analysis, risk reduction of prostate cancer was only observed for the studies with a follow-up of 10 years or more. This suggests that the effects of physical activity may be accumulative over time and/or need to be continuous during the induction time of prostate cancer, which tends to be long (7, 8). Finally, diminishing concerns of reverse causality, our sensitivity analysis excluding those participants diagnosed with prostate cancer within the first three years from entry to the study did not change the association results observed for the full-size cohort.

The present study has some limitations. First, information on physical activity was gathered through questionnaire at entry to the study only and not evaluated throughout the follow-up period. The men´s report of leisure time physical activity in the distant past is also likely to suffer from some recall-related errors. However, it is not likely that such biased recall is related to subsequent diagnosis of advanced prostate cancer in a way that would falsely construct the observed point estimates; in contrary, such nondifferential misclassification would affect the point estimates towards the null (47).

Although the use of questionnaires for historical recall of physical activity shows limited reliability and validity, especially at the individual level (47, 48), it is the only way to assess past activity and is believed to be useful as an activity-ranking instrument for large study populations (47). Second, the classification of OPA was based on current occupational activity at baseline and did not take into account previous or later occupations. Third, the incomplete data on tumor stage may have resulted in misclassification of disease level. Some men in our study with advanced prostate cancer at diagnosis might not have been classified as

such, most likely leading to underestimation of the association between physical activity and advanced prostate cancer.

In summary, we found that physically active men both in current work and leisure since early adulthood had a markedly reduced risk of being diagnosed with advanced prostate cancer later in life. Although the potential mechanisms underlying the observed association still needs to be explored, these results suggest that extensive physical activity may constitute an interesting intervention in future randomized studies targeting reduction in risk of advanced prostate cancer.

Acknowledgements

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Table 1. Demographic and health characteristics (at baseline) by level of RPA, stratified for OPA.

	Total (n = 8221)					
	Low-OPA (n = 4423)			High-OPA (n = 3798)		
	non-RPA/low-OPA (n = 3023)	RPA/low-OPA (n = 1400)		non-RPA/high-OPA (n = 3034)	RPA/high-OPA (n = 764)	
	mean (SD)	mean (SD)	p value	mean (SD)	mean (SD)	p value
Age, years	51.3 (8.0)	51.6 (8.2)	0.2523	52.0 (8.1)	52.6 (8.0)	0.0710
Height, cm	177.0 (6.2)	177.9 (6.4)	< 0.0001	175.7 (6.2)	176.3 (6.3)	0.0445
Weight, kg	81.3 (12.8)	82.2 (11.4)	0.0198	79.0 (11.8)	79.6 (11.1)	0.1738
Body mass index, kg/m²	25.9 (3.6)	26.0 (3.2)	0.6435	25.5 (3.4)	25.6 (3.2)	0.6633
Diastolic blood pressure, mm Hg	89.0 (10.5)	87.6 (10.4)	< 0.0001	87.9 (10.1)	86.6 (9.9)	0.0015
Systolic blood pressure, mm Hg	140.7 (18.9)	138.1 (18.5)	< 0.0001	139.9 (18.6)	138.0 (18.1)	0.0134
Serum cholesterol, mmol/L	6.40 (1.1)	6.37 (1.0)	0.3523	6.40 (1.1)	6.33 (1.0)	0.1079
Serum glucose, mg/dl	83.4 (15.5)	81.7 (11.3)	< 0.0001	82.6 (13.5)	82.8 (17.6)	0.7718
	n (%)	n (%)	p value	n (%)	n (%)	p value
Diabetes, type 2	139 (4.6)	51 (3.6)	0.145	114 (3.8)	28 (3.7)	0.9029
Smoking status			< 0.0001			< 0.0001
Never smoker	552 (18.3)	342 (24.4)		625 (20.6)	216 (28.3)	
Former smoker	710 (23.5)	358 (25.6)		625 (20.6)	169 (22.1)	
Current smoker	1761 (58.2)	700 (50.0)		1783 (58.8)	379 (49.6)	
Regular health check-up	643 (21.3)	412 (29.4)	< 0.0001	496 (16.3)	166 (21.7)	0.0005
Prostate disease in the family	299 (9.9)	169(12.1)	0.0283	203(6.7)	51(6.7)	0.9878
Education			< 0.0001			< 0.0001
Primary and secondary	2173 (71.9)	683(48.8)		2863(94.4)	652(85.4)	
College	467(15.4)	356(25.4)		136(4.5)	85(11.1)	
University	383(12.7)	361(25.8)		35(1.1)	27(3.5)	
Occupational physical activity			< 0.0001			N/A
mostly sitting	2096(69.3)	1157(82.6)		0	0	
mostly standing	927(30.7)	243(17.4)		0	0	
mostly on the move	0	0		3034 (100%)	764 (100%)	
Location of first residence*			< 0.0001			< 0.0001
Reykjavik	1106(36.9)	645(46.1)		955(31.5)	342(44.8)	
Seaside village	1008(33.3)	395(28.2)		1115(36.8)	238(31.2)	
Rural area	750(24.8)	294(21.0)		794(26.2)	160(20.9)	
Combination of rural area and seaside village	105(3.5)	38(2.7)		116(3.8)	20(2.6)	

Abbreviations: RPA = recreational physical activity; OPA = occupational physical activity
*Numbers do not add up to 100% due to missing values

Table 2. Prostate cancer risk by regular recreational physical activity (RPA) from the age of 20 years

	No. of participants			IR per 1000 person-yr	Age-adjusted HR (95% CI)	Multivariate HR[1] (95% CI)
	Total	Without PCa	With PCa			
Total PCa	8784					
No. of cases	1114					
RPA		1964	313	5.55	1.05 (0.92, 1.20)	0.95 (0.83, 1.09)
non-RPA		5706	801	5.09	1.0	1.0
Localized PCa	8408					
No. of cases	738					
RPA		1964	216	3.97	1.12 (0.96, 1.31)	1.01 (0.85, 1.19)
non-RPA		5706	522	3.45	1.0	1.0
Advanced PCa	8046					
No. of cases	376					
RPA		1964	97	1.88	0.93 (0.74, 1.17)	0.85 (0.66, 1.09)
non-RPA		5706	279	1.91	1.0	1.0

Abbreviations: PCa = Prostate cancer; RPA = recreational physical activity; IR = incidence rate; HR = hazard ratio; CI = confidence interval.

[1]Adjustment was made for the following covariates (values at baseline): birthyear, age, height, body mass index, type 2 diabetes, smoking, family history of prostate disease, education, residency in early life and regular health check-ups.

Number of individuals in multi-adjusted analysis was 3-4% lower than in the age-adjusted analysis (due to missing values for covariates).

Table 3. Prostate cancer risk by occupational physical activity (OPA).

	Total	No. of participants		IR per 1000 person-yr	Age-adjusted HR (95% CI)	Multivariate HR[1] (95% CI)
		Without PCa	With PCa			
Total PCa	8489					
No. of cases	1085					
Mostly sitting		2896	472	5.65	1.0	1.0
Mostly standing		1050	150	4.95	0.88 (0.73, 1.05)	0.95 (0.79, 1.15)
Mostly on the move		3458	463	4.80	0.82 (0.72, 0.94)	0.90 (0.78, 1.04)
Localised PCa	8130					
No. of cases	726					
Mostly sitting		2896	319	3.98	1.0	1.0
Mostly standing		1050	108	3.67	0.92 (0.74, 1.14)	0.98 (0.78, 1.23)
Mostly on the move		3458	299	3.20	0.79 (0.67, 0.92)	0.85 (0.71, 1.01)
Advanced PCa	7763					
No. of cases	359					
Mostly sitting		2896	153	2.00	1.0	1.0
Mostly standing		1050	42	1.52	0.76 (0.54, 1.07)	0.87 (0.61, 1.24)
Mostly on the move		3458	164	1.82	0.89 (0.71, 1.10)	1.01 (0.78, 1.30)

Abbreviations: PCa = Prostate cancer; OPA = occupational physical activity; HR = hazard ratio; CI = confidence interval.

[1]Adjustment was made for the following covariates (values at baseline): birthyear, age, height, body mass index, type 2 diabetes, smoking, family history of prostate disease, education, residency in early life and regular health check-ups.

Data on OPA were missing for 587 men.

Number of individuals in multi-adjusted analysis was 3-4% lower than in the age-adjusted analysis (due to missing values for covariates).

Table 4. Prostate Cancer risk by total physical activity (TPA = RPA + OPA)

		No. of participants			
	Total	Without PCa	With PCa	Age-adjusted HR (95% CI)	Multivariate HR[1] (95% CI)
Total PCa	8221				
non-RPA, low-OPA		2625	398	1.0	1.0
non-RPA, high-OPA		2674	360	0.87 (0.76, 1.01)	0.92 (0.79, 1.07)
RPA, low-OPA		1196	204	1.03 (0.87, 1.22)	0.94 (0.79, 1.13)
RPA, high-OPA		674	90	0.83 (0.66, 1.05)	0.83 (0.65, 1.04)
Localized PCa	7872				
non-RPA, low-OPA		2625	275	1.0	1.0
non-RPA, high-OPA		2674	222	0.79 (0.67, 0.95)	0.83 (0.69, 1.00)
RPA, low-OPA		1196	137	1.03 (0.84, 1.26)	0.94 (0.76, 1.16)
RPA, high-OPA		674	69	0.92 (0.71, 1.20)	0.88 (0.67, 1.16)
Advanced PCa	7518				
non-RPA, low-OPA		2625	123	1.0	1.0
non-RPA, high-OPA		2674	138	1.06 (0.83, 1.36)	1.15 (0.89, 1.49)
RPA, low-OPA		1196	67	1.08 (0.80, 1.46)	0.98 (0.72, 1.35)
RPA, high-OPA		674	21	0.61 (0.39, 0.97)	0.67 (0.42, 1.07)

Abbreviations: PCa = Prostate cancer; TPA = total physical activity; RPA = recreational physical activity; OPA = occupational physical activity; HR = hazard ratio; CI = confidence interval.

[1]Adjustment was made for the following covariates (values at baseline): birthyear, age, height, body mass index, type 2 diabetes, smoking, family history of prostate disease, education and regular health check-ups.

Number of individuals in multi-adjusted analysis was 3-4% lower than in the age-adjusted analysis (due to missing values for covariates).

*Data on OPA and/or RPA were missing or incomplete for 855 men, leaving 8221 men in the analytic cohort.

Table 5. Prostate cancer risk by recreational physical activity (RPA), stratified by level of occupational physical activity (OPA).

		No. of participants			
	Total	Without PCa	With PCa	Age-adjusted HR (95% CI)	Multivariate HR[t] (95% CI)
Total PCa					
Low OPA[2]	4423				
No. of cases		602			
RPA		1196	204	1.05 (0.88 to 1.24)	0.94 (0.79 to 1.12)
non-RPA		2625	398	1.0	1.0
High OPA[2]	3798				
No. of cases		450			
RPA		674	90	0.96 (0.76 to 1.21)	0.91 (0.72 to 1.16)
non-RPA		2674	360	1.0	1.0
Localised PCa					
Low OPA[2]	4233				
No. of cases		412			
RPA		1196	137	1.04 (0.85 to 1.28)	0.93 (0.75 to 1.15)
non-RPA		2625	275	1.0	1.0
High OPA[2]	3639				
No. of cases		291			
RPA		674	69	1.16 (0.89 to 1.52)	1.09 (0.82 to 1.44)
non-RPA		2674	222	1.0	1.0
Advanced PCa					
Low OPA[2]	4011				
No. of cases		190			
RPA		1196	67	1.10 (0.81 to 1.49)	0.99 (0.72 to 1.37)
non-RPA		2625	123	1.0	1.0
High OPA[2]	3507				
No. of cases		159			
RPA		674	21	0.58 (0.37 to 0.93)	0.59 (0.37 to 0.94)
non-RPA		2674	138	1.0	1.0

Abbreviations: PCa = Prostate cancer; RPA = recreational physical activity; OPA = occupational physical activity; HR = hazard ratio; CI = confidence interval.

[t]Adjustment was made for the following covariates (values at baseline): birthyear, age, height, body mass index, type 2 diabetes, smoking, family history of prostate cancer, education, residency in early life and regular health check-ups.

[2] Low OPA: mostly sitting or standing at work; High OPA: mostly on the move at work

Number of individuals in multi-adjusted analysis was 2-4% lower than in the age-adjusted analysis (due to missing values for covariates).

*Data on OPA and/or RPA were missing or incomplete for 855 men, leaving 8221 men in the analytic cohort.