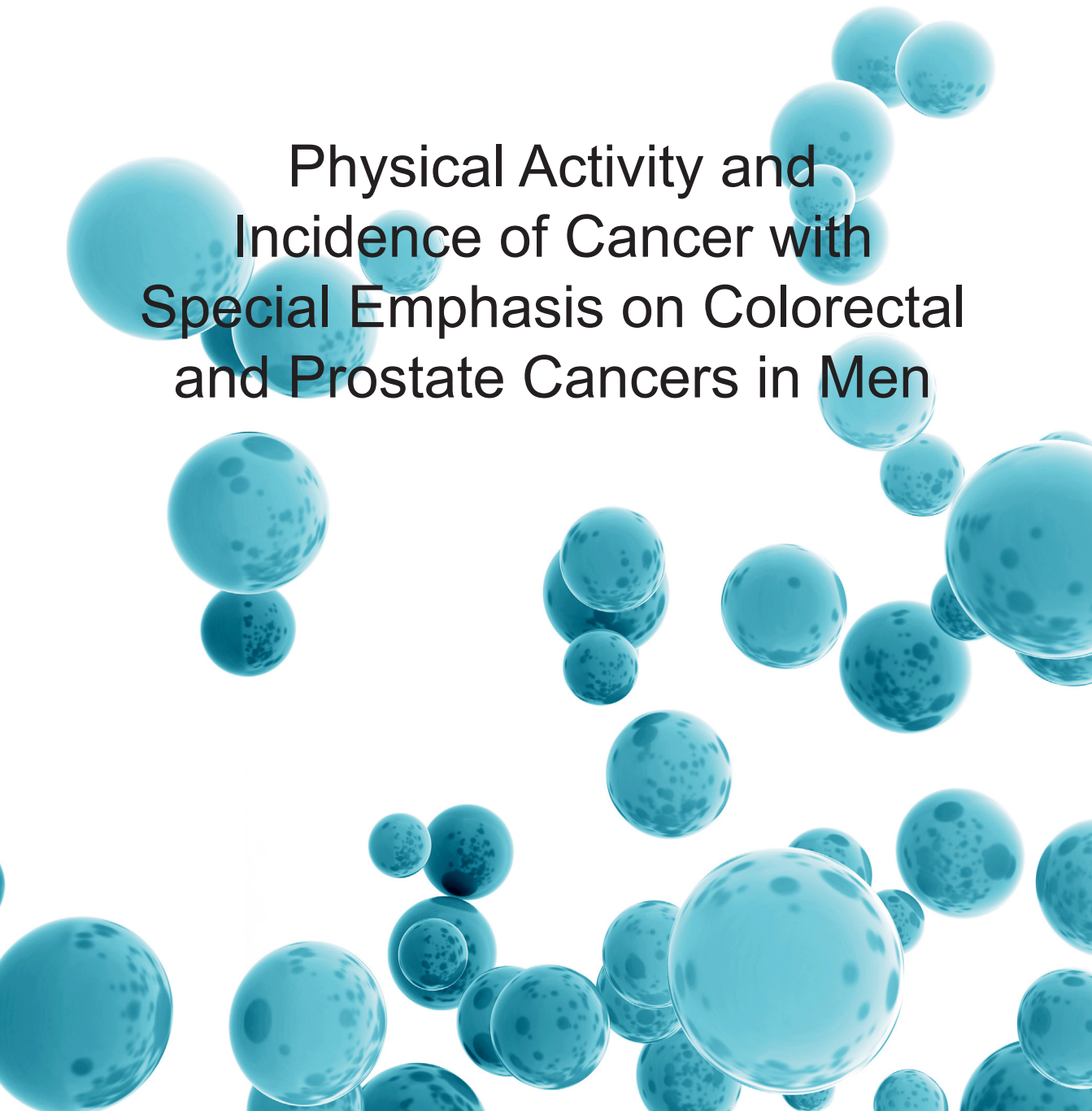
Acta Universitatis Tamperensis 2402

JORMA SORMUNEN

Physical Activity and Incidence of Cancer with Special Emphasis on Colorectal and Prostate Cancers in Men



JORMA SORMUNEN

Physical Activity and Incidence of Cancer with Special Emphasis on Colorectal and Prostate Cancers in Men

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty Council of Social Sciences
of the University of Tampere, for public discussion
in the Yellow Hall F025 of the Arvo building,
Arvo Ylpön katu 34, Tampere,
on 24 August 2018 at 12 o'clock.

UNIVERSITY OF TAMPERE

JORMA SORMUNEN

Physical Activity and Incidence of Cancer with Special Emphasis on Colorectal and Prostate Cancers in Men

Acta Universitatis Tamperensis 2402
Tampere University Press
Tampere 2018

UNIVERSITY
OF TAMPERE

ACADEMIC DISSERTATION
University of Tampere, Faculty of Social Sciences
Finnish Cancer Registry
Finland
International Agency for Research on Cancer (IARC)
France

Supervised by
Professor Eero Pukkala
University of Tampere
Finland

Reviewed by
Docent Liisa Pylkkänen
University of Turku
Finland
Docent Jóhanna Eyrún Torfadóttir
University of Iceland
Iceland

Cover design by
Mikko Reinikka

Acta Universitatis Tamperensis 2402
ISBN 978-952-03-0805-6 (print)
ISSN-L 1455-1616
ISSN 1455-1616

Acta Electronica Universitatis Tamperensis 1911
ISBN 978-952-03-0806-3 (pdf)
ISSN 1456-954X
http://tampub.uta.fi

Suomen Yliopistopaino Oy – Juvenes Print
Tampere 2018

ABSTRACT

In my PhD-dissertation research project I have studied the effects of physical activity and physical condition to the incidence of cancer with main emphasis on colorectal cancer (CRC) and prostate cancer (PCA) in men. There were two Finnish cohorts studied - the first one was the men born in 1958 (approximately 32,000 men) and the other one was a cohort of former elite male athletes (approximately 2,400 men). In addition there were two case-control studies, one for CRC (there were approximately 145,000 cases of colorectal cancer in men and 146,000 cases in women) and one for PCA (240,000 cancer cases were diagnosed during the study period). These case-control studies were embedded in the Nordic Occupational Cancer (NOCCA) study cohort.

In the cohort of men born in 1958 the data were collected from the time of their military service. The cancer cases of these men were collected from the Finnish Cancer Registry (FCR) until the end of 2014. Those men that were overweight or obese during the time of their military service had an increased, but statistically not significant, risk of cancer. Hazard Ratio (HR) was 1.08, 95% confidence interval (CI): 0.89-1.30. Men in good or excellent physical condition (PC) during military service had significantly reduced cancer risk later in life (HR 0.82, 95% CI: 0.71-0.95). Men of normal weight but in poor physical condition had an increased risk of all cancers combined (HR 1.18, 95% CI: 1.01-1.38) when compared to the men who were of normal weight and in good physical condition. Similarly those men that were overweight and in poor physical condition had even more increased risk of cancer (HR 1.30, 95% CI: 1.01-1.69). After adjusting these results for smoking, alcohol consumption and service class these associations decreased and became statistically insignificant. Men in this cohort are still relatively young and therefore a longer follow-up is needed for further conclusions on their cancer risk.

A Finnish cohort of 2448 elite male athletes and their 1712 referents was followed-up for cancer incidence from 1986 to 2010 through the Finnish Cancer Registry. The overall cancer incidence was lower in athletes than in the general population, standardized incidence ratio (SIR) was 0.89 (95% CI: 0.81-0.97). Middle-distance runners had the lowest cancer incidence (SIR 0.51, 95% CI: 0.22-1.01). A particularly low cancer incidence was detected also among long-distance runners

(SIR 0.57, 95% CI: 0.35-0.88) and jumpers (SIR 0.60, 95% CI: 0.37-0.92). The SIR of lung cancer among athletes was 0.40 (95% CI: 0.27-0.55). The lower risk can be attributed to lifestyle factors, especially less frequent smoking among the athletes and their better PC.

In the two case-control studies the associations between perceived physical workload (PPWL) at work and CRC and PCA were studied. Five population controls were selected for each cancer patient. Individuals were stratified to reference and different pre-determined groups based on their PPWL.

PPWL showed a bigger protective effect on colon cancer for men (odds ratio [OR] was 0.74 in the highest PPWL decile when compared with the lowest PPWL category, 95% CI: 0.72-0.77) than for women (OR 0.87, 95% CI: 0.81-0.95), with a significant trend for different levels of PPWL for both males and females. The OR of cancer in the descending colon for the highest PPWL decile of males was 0.61 (95% CI: 0.54-0.69). For females the protective effect was most notable in the transversal part of the colon (OR 0.83, 95% CI: 0.67-1.03). None of the results in this study for cancer incidence for females were statistically significant. The OR for rectal cancer in the highest PPWL decile for males was 0.87 (95% CI: 0.85-0.90) and for females 0.93 (95% CI: 0.83-1.04). Inclusion of further agents in multivariate (MV) analyses did not alter the ORs for PPWL.

The incidence of colon cancer and, to a lesser extent, rectal cancer was lowest in professions with the highest PPWL. The association is stronger in males than in females. The biggest protective effect appears to be in the descending colon in males.

The hazard ratios for PCA from the lowest to highest cumulative PPWL levels were 0.90 (95% CI: 0.89-0.91), 0.88 (95% CI: 0.87-0.89) and 0.93 (95% CI: 0.92-0.95) and all these results were statistically significant. There was no statistically significant dose response effect of the level of PPWL on PCA incidence. Inclusion of socioeconomic status (SES) in the model did not substantially change the result. The results were similar before Prostate Specific Antigen (PSA) testing and during the years of PSA testing in these countries.

Individuals with physical strain at work had a lower risk of invasive PCA when compared to individuals without physical strain at work.

TIIVISTELMÄ

Lääketieteen tohtoritutkimusprojektissani tutkin fyysisen aktiivisuuden ja kunnon vaikutuksia syöpäilmaantuvuuteen. Erityisinä mielenkiinnon aiheinani olivat paksu- ja peräsuolen sekä eturauhasen syövät. Tutkimuskokonaisuus perustui kahteen suomalaiseen kohorttiaineistoon: vuonna 1958 syntyneisiin miehiin (noin 32,000 miestä) ja huippu-urheilijoihin (noin 2,400 miestä) ja kahteen pohjoismaiseen tapaus-verrokkitutkimukseen. Näistä yhdessä tutkittiin paksu- ja peräsuolen syöpää (miehillä todettiin syöpiä tutkimusaikana yhteensä noin 145,000 ja naisilla noin 146,000) ja toisessa eturauhassyöpää (syöpiä todettiin tutkimusaikana yhteensä noin 240,000). Tapaukset ja verrokit poimittiin Nordic Occupational Cancer (NOCCA) tutkimuksen tietokannasta.

Vuonna 1958 syntyneiden miesten kohorttitukimusta varten kerättiin tietoja heidän varusmiespalvelunsa ajalta. Tämän jälkeen heille haettiin syöpäilmaantuvuusstiedot vuoden 2014 loppuun asti. Miehillä, jotka olivat ylipainoisia tai lihavia varusmiespalveluksen aikana, oli hieman suurentunut riski sairastua syöpään. Tämä riski ei kuitenkaan ollut tilastollisesti merkitsevä (kerroinsuhde, OR 1.08, 95 prosentin luottamusväli, 95% CI: 0.89-1.30). Hyvässä tai erinomaisessa fyysisessä kunnossa varusmiespalveluksen aikana olleilla riski sairastua syöpään myöhemmällä iällä oli merkitsevästi alentunut (OR 0.82, 95% CI: 0.71-0.95). Normaalipainoisten, mutta huonossa fyysisessä kunnossa olleiden miesten syöpäriski (kaikki syövät) oli suurentunut (OR 1.18, 95% CI: 1.01-1.38) verrattuna normaalipainoisiin ja hyvässä kunnossa olleisiin miehiin. Niillä miehillä, jotka olivat ylipainoisia ja huonossa fyysisessä kunnossa oli vielä tätäkin korkeampi riski sairastua syöpään (OR 1.30, 95% CI: 1.01-1.69). Kun nämä tulokset vakioitiin tupakoinnin, alkoholinkäytön ja palveluskelpoisuusluokan suhteen, tulokset eivät enää olleet tilastollisesti merkitseviä. Tutkimuskohortti on vielä suhteellisen nuori, ja pidempi seuranta on tarpeen, jotta tuloksista voidaan tehdä tarkempia päätelmiä.

Suomalaisten huippu-urheilijoiden kohorttiin kuuluvien 2448 miehen syöpäilmaantuvuutta seurattiin vuodesta 1986 vuoteen 2010. Kokonaissyöpäilmaantuvuus oli huippu-urheilijoilla alhaisempi kuin perusväestöllä, vakioitu ilmaantuvuussuhde (SIR) oli 0.89 (95% CI: 0.81-0.97). Keskimatkanjuoksijoilla oli matalin syöpäilmaantuvuus (SIR 0.51, 95% CI: 0.22-

1.01). Hyvin matala syöpäriski todettiin myös pitkänmatkanjuoksijoilla (SIR 0.57, 95% CI: 0.35-0.88) ja hyppääjillä (SIR 0.60, 95% CI: 0.37-0.92). Keuhkosyövän vakioitu ilmaantuvuussuhde urheilijoilla oli 0.40 (95% CI: 0.27-0.55). Alhaisempi riski voi johtua terveistä elämäntavoista, erityisesti huippu-urheilijoiden vähäisemmästä tupakoinnista sekä hyvästä fyysisestä kunnosta.

Kahdessa tapaus-verrokkitutkimuksessa tutkittiin yhteyttä koetun fyysisen työn kuormittavuuden (PPWL) ja paksu- ja peräsuolen syövän sekä eturauhassyövän ilmaantuvuuden välillä. Jokaiselle syöpään sairastuneelle henkilölle valittiin viisi kaltaistettua verrokkia. Tutkittavat jaettiin eri ryhmiin työn kuormittavuuden perusteella, ja syöpäilmaantuvuutta verrattiin ryhmään, jolla ei ollut merkittävää koettua fyysistä rasitusta työssä.

Työn fyysinen kuormittavuus suojasi paksu-ja peräsuolen syöviltä eniten niitä miehiä, jotka kuuluivat työn koetussa rasittavuudessa ylimpään kymmeneen prosenttiin (OR 0.74, 95% CI: 0.72-0.77) verrattuna ryhmään jolla ei ollut työssä fyysistä rasitusta. Naisten osalta todettu suojavaikutus oli pienempi (OR 0.87, 95% CI: 0.81-0.95).

Miehillä, jotka kuuluivat työn rasittavuudessa ylimpään kymmeneen prosenttiin, todettiin laskevan paksunsuolen alueella selkeästi vähemmän syöpiä kuin verrokkiryhmällä, kerroinsuhde oli 0.61 (95% CI: 0.54-0.69). Naisilla suurin suojavaikutus todettiin poikittaisen paksunsuolen alueella (OR 0.83, 95% CI: 0.67-1.03). Peräsuolisyövän kerroinsuhde miehille, jotka kuuluivat kuormittavuusarvion ylimpään kymmeneen prosenttiin, oli 0.87 (95% CI: 0.85-0.90) ja naisille 0.93 (95% CI: 0.83-1.04). Naisten syöpäesiintyvyydelle saadut tutkimustulokset eivät olleet tilastollisesti merkitseviä. Muiden tekijöiden mukaan ottaminen monimuuttuja-analyyseihin ei muuttanut kerroinsuhdetta merkittävästi.

Paksusuolensyövän ilmaantuvuus ja vähäisemmässä määrin myös peräsuolisyövän ilmaantuvuus on matalin ammateissa, jotka ovat fyysisesti raskaimpia. Tämä yhteys näkyy miehissä naisia selkeämmin. Suurin suojavaikutus todettiin miehillä laskevan paksunsuolen alueella.

Miehillä, joilla oli työhön kuuluvaa fyysistä rasitusta, oli pienempi riski sairastua eturauhassyöpään kuin miehillä, joilla ei ollut koettua fyysistä rasitusta työssä. Eturauhassyövän riskitiheyssuhteet matalimmasta korkeimpaan työn kuormittavuuden perusteella jaettujen ryhmien välillä olivat 0.90 (95% CI: 0.89-0.91) matalan altistuksen, 0.88 (95% CI: 0.87-0.89) keskisuuren altistuksen ja 0.93 (95% CI: 0.92-0.95) suuren altistuksen ryhmille. Tilastollisesti merkittävää yhteyttä työn kuormittavuustason ja eturauhassyövän ilmaantuvuuden välillä ei todettu. Sosiaaliluokan mukaanotto analyyseihin ei merkittävästi muuttanut tuloksia.

Tulokset olivat samanlaiset ennen PSA-mittausten yleistymistä 1990-luvulla ja niiden aikana 1990-luvun alun jälkeen.

TABLE OF CONTENTS

LIST OF ORIGINAL PUBLICATIONS

Sormunen J, Arnold M, Soerjomataram I, Pukkala E. Cohort profile: a nationwide cohort of Finnish military recruits born in 1958 to study the impact of lifestyle factors in early adulthood on disease outcomes. BMJ Open 2017;7:e016905. doi:10.1136/ bmjopen-2017-016905 (study #1)

Jorma Sormunen, Heli M. Bäckmand, Seppo Sarna Urho M. Kujala, Jaakko Kaprio, Tadeusz Dyba, Eero Pukkala: Lifetime physical activity and cancer incidence ‚Äí a cohort study of male former elite athletes in Finland. Journal of Science and Medicine in Sport. 2014(17)5:479-84. (study #2)

Jorma Sormunen, Madar Talibov, Jan Ivar Martinsen, Kristina Kjaerheim, Pär Sparen, Laufey Tryggvadottir, Elisabete Weiderpass, Eero Pukkala: Perceived Physical Strain at Work and Incidence of Colorectal Cancer - A Nested Case-Control Study, Cancer Epidemiology 43(2016) 100-104. (study #3)

Jorma Sormunen, Madar Talibov, Jan Ivar Martinsen, Kristina Kjaerheim, Pär Sparen, Laufey Tryggvadottir, Elisabete Weiderpass, Eero Pukkala: Perceived Physical Strain at Work and Incidence of Prostate cancer - A Case-Control Study (In press, Asian Pacific Journal of Cancer Prevention), 2018. (study #4)

ABBREVIATIONS

BMI=Body Mass Index
CI=Confidence Interval, ('Luottamusväli' in Finnish)
CRC=Colorectal cancer
DNA=Deoxyribonucleic-acid
EPIC-study= European Prospective Investigation Into Cancer and Nutrition -study
ETS=(Exposure to) Environmental Tobacco Smoke
FCR=Finnish Cancer Registry
FDF=Finnish Defence Forces
HPV=Human papiloma virus
HR=Hazard Ratio, ('Riskitiheyssuhde' in Finnish)
IARC=International Agency for Research on Cancer
JEM=Job Exposure Matrix
LTPA=leisure-time physical activity
MET=standard metabolic equivalent
MV=Multivariate
NIDDM=Non-Insulin Dependent Diabetes Mellitus
NOCCA-study=Nordic Occupational Cancer -study
OR=Odds Ratio, ('Kerroinsuhde' in Finnish)
PA=Physical Activity
PC=Physical Condition
PCA=Prostate cancer
PIC=Personal Identity Code
PSA=Prostate Specific Antigen
RR=Risk Ratio
RS=Relative Survival
SES=socio-economic status
SIR=Standardized Incidence Ratio, ('Vakioitu ilmaantuvuussuhde' in Finnish)
UV=Ultraviolet
WBV=Whole Body Vibration

1 INTRODUCTION

Cancers as well as the diseases of the circulatory system are by far the most important causes of death in the western world and the EU-area. (Eurostat 2017) In Finland men die several years younger than women. In year 2016 men's life expectancy at birth was 78.4 years and women's life expectancy was 84.1 years. Tumors were the second most important cause of death among men, explaining approximately 6,600 or 26% of deaths in men in year 2015. (Statistics Finland, 2017)

This study was aimed to answer to the question "what are the effects of physical activity (PA) and physical condition (PC) to the incidence of cancer" and ultimately - what could be done to decrease the number of cancers and the number of deaths from cancers. The main focus of this project was to evaluate how PA and PC affect the incidence of cancer. The biggest interest was in the incidence of men's CRC and PCA, but interesting results were found also for other cancers and the cancers of females.

1.1 All cancers

Cancer can be found in any organ of the human body. Age standardized incidence of all cancers (excluding non-melanoma skin cancer) in Finland in year 2012 was 423/100,000 for men and 324/100,000 for women. The most common cancers in men were cancers of the prostate, lung, colon and rectum, bladder as well as non-Hodgkin lymphoma. For women the most common cancer was breast cancer followed by CRC, cancer of the uterus, lung and non-Hodgkin lymphoma. (Ferlay et al. 2013) At the end of 2015 there were more than 110 000 men and almost 150 000 women living with cancer in Finland. (Syöpärekisteri 2018)

Symptoms of cancer vary widely depending on the organ of origin. The alarm symptoms of cancers can be e.g. a lump in an organ, occult blood stools, blood in urine or coughing for a prolonged period. (Svendsen et al. 2010) The symptoms of advanced cancer may be e.g. anorexia and cachexia, delirium, nausea and vomiting, electrolyte abnormalities, fatigue or constipation. (Lagman et al. 2005)

1.2 Colorectal cancer

Colon, which can also be called the large intestine is located between ileum (the final part of the small intestine) and rectum, and its parts are ascending (on the right side of the abdomen), transverse (across the upper part of the abdomen), descending (on the left side of the abdomen) and sigmoid colon (which is a curved part of colon right before the rectum). (Culligan et al. 2013) Rectum is located between sigmoid colon and anus. The function of colon is to remove water, salt and nutrients from digested nutrition in order to form stool. There is a large amount of bacteria living in the colon. The microbiota of the colon have an important role in all the functions of colon and rectum. (Shanahan 2012) The most typical symptoms of CRC are changes in bowel movements (bowel habits), abdominal discomfort, pain, occult blood in feces or diarrhea. (Majumdar, Fletcher, and Evans 1999)

Incidence of CRC is high in the developed world and low in the developing countries. At the beginning of the century (results from 1998-2002) the incidence of CRC varied from 4.1 in 100,000 men in certain regions in India to almost 60/100, 000 in men in Czech Republic. (Center et al. 2010) In high-risk populations the incidence ratio of colon to rectal cancers is close to 2:1. In lower risk countries the incidence of colon and rectal cancers are of the same magnitude. (Parkin et al. 2005) It is known that a part of colon cancer is hereditary, but it is now generally believed that environmental factors including diet and lack of exercise cause up to 80% of colon cancer cases in the Western World. (Bingham 2000)

Physical inactivity is one of the most important health hazards of our days (Kohl et al. 2012; Arem et al. 2013; I. M. Lee et al. 2012) and it is on the increase in our society. A substantial number of cancers could be avoided, if people were more physically active. (Torre et al. 2015; Brown et al. 2012; Wolin et al. 2009)

PA decreases the risk of CRC significantly – somewhat more in males than in females. It has been evaluated that insufficient PA is the reason for at least 10% of the CRC cases in Europe (Leitzmann et al. 2015) Huxley et al. (2009) made a meta-analysis on the lifestyle reasons of CRC. They noted e.g. that PA was significantly protective of CRC. The protective effects of PA were more pronounced in colon than rectum. In their meta-analysis Harriss et al. (2009) detected a inverse dose-response relationship for leisure time physical activity (LTPA) on colon cancer incidence in both genders. LTPA didn't seem to protect from rectal cancer. (Huxley et al. 2009; Harriss et al. 2009)

Diet has been recognized as an important risk factor of cancer and especially of CRC. The risk of CRC is increased by the intake of red and processed meat and

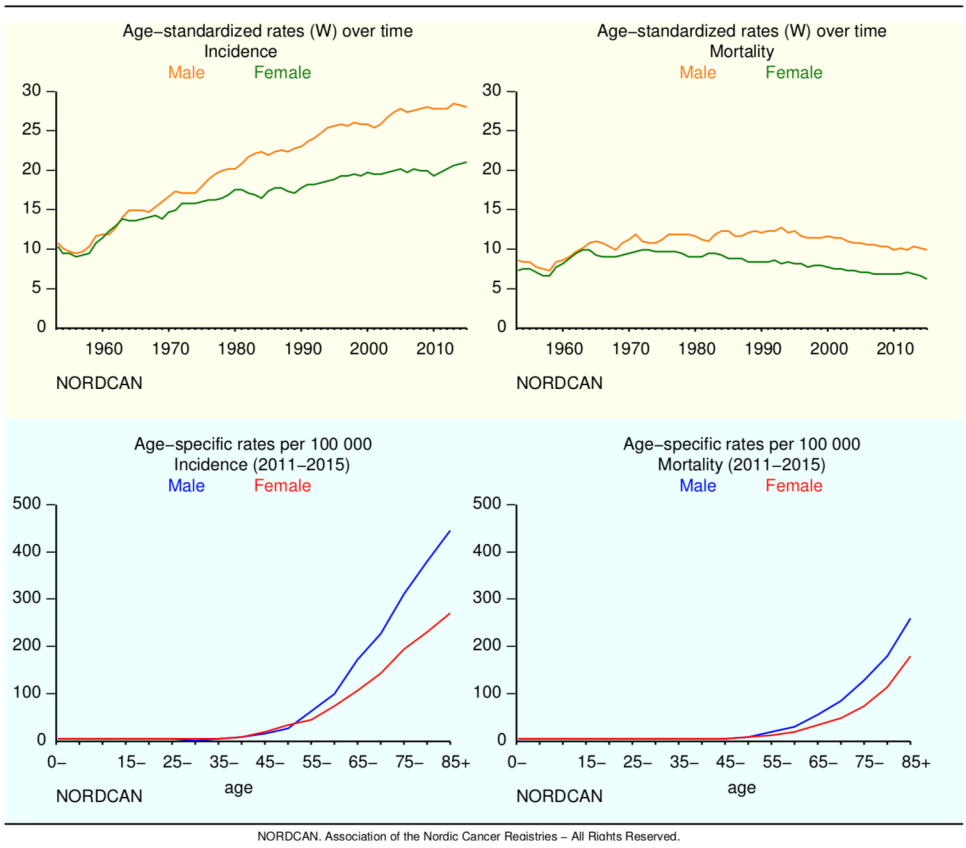
saturated fat. In addition a diet that contains small amounts of starch, non-starch polysaccharides, fiber and vegetables increase the risk of CRC. On the other hand – a healthy diet, which contains ample amounts of fruits, vegetables and whole-grain foods and fibers – and smaller amounts of red and processed meats and salt – reduce the risk of CRC. (Norat et al. 2015; Leenders et al. 2015; Vineis and Wild 2014; Bingham 2000)

Several studies suggest that many unhealthy habits related to eating and PA develop during childhood and adolescence. These unhealthy habits learned at childhood may increase the risk of some cancers including CRC. They may also increase the incidence and mortality of some other cancers (e.g. renal cancer and women's premenopausal breast cancer). (Fuemmeler, Pendzich, and Tercyak 2009) SES (socioeconomic status) modifies the incidence of many cancers including CRC. (Di Cesare et al. 2013; Rundle et al. 2013) Lately there has been interest on the early life SES and how it modifies the incidence of some cancers. (Akinyemiju et al. 2017)

There were approximately 1,600 new cases of CRC diagnosed every year for men and 1,400 cases for women between the years 2011and 2015 in Finland (Figure 1.). One year after the diagnosis 84% of men and 86% of men were alive. Five years after the diagnosis 65% of men and 68% of the women were still alive. When compared to other countries, the mortality-to-incidence -ratio of Finnish CRC-patients is on the same level as in other Nordic countries and e.g. United States. (Sunkara and Hébert 2015)

Age standardized CRC- incidence and mortality from 1954 to 2014 are presented in figure 1. It shows that especially in men the incidence has more than doubled over the follow-up period. In women the incidence has also increased, but not as much as in men. Age standardized CRC-mortality has increased only a little during the follow-up period, and it has decreased in men over the last two decades. In women a decreasing trend could be seen already earlier. Age specific incidence and mortality rates show that CRC is rare in young adults, and its incidence increases sharply after 60 years both in men and in women.

Figure 1. CRC-incidence and mortality in Finland between 1954-2015 for men. and women separately. (source: http://www-dep.iarc.fr/NORDCAN/english/frame.asp, accessed June 27, 2018, Nordcan)



The 5-year relative survival percentage for CRC in Finland was 52.5% (95% CI: 50.4-54.7) With the current treatment paradigms it can be expected that the current RS is higher. (Ferlay et al. 2013)

1.3 Prostate cancer

Prostate is located in male pelvis around the neck of the bladder and urethra. The mean prostatic volume for men between 50 and 80 years of age increases slowly from 24 to 38 cc. (Berges and Oelke 2011) The function of prostate is to produce mildly alkaline fluid, which makes an important part of the semen. When prostate grows it weakens the flow of the urine. This leads to slower flow of urine from the

urinary bladder and a need to urinate more often than before. This can be the only symptom of PCA. Other symptoms may include urinary hesitancy, pain or burning sensations during urination in the groin region, loss of bladder control, blood in urine or urinary infections. (Chen et al. 2014)

PCA is a very common old men's disease. The reasons for PCA have been studied widely but there are many areas where the evidence is still inconclusive.

Some risk factors that have been identified to increase the risk of PCA include

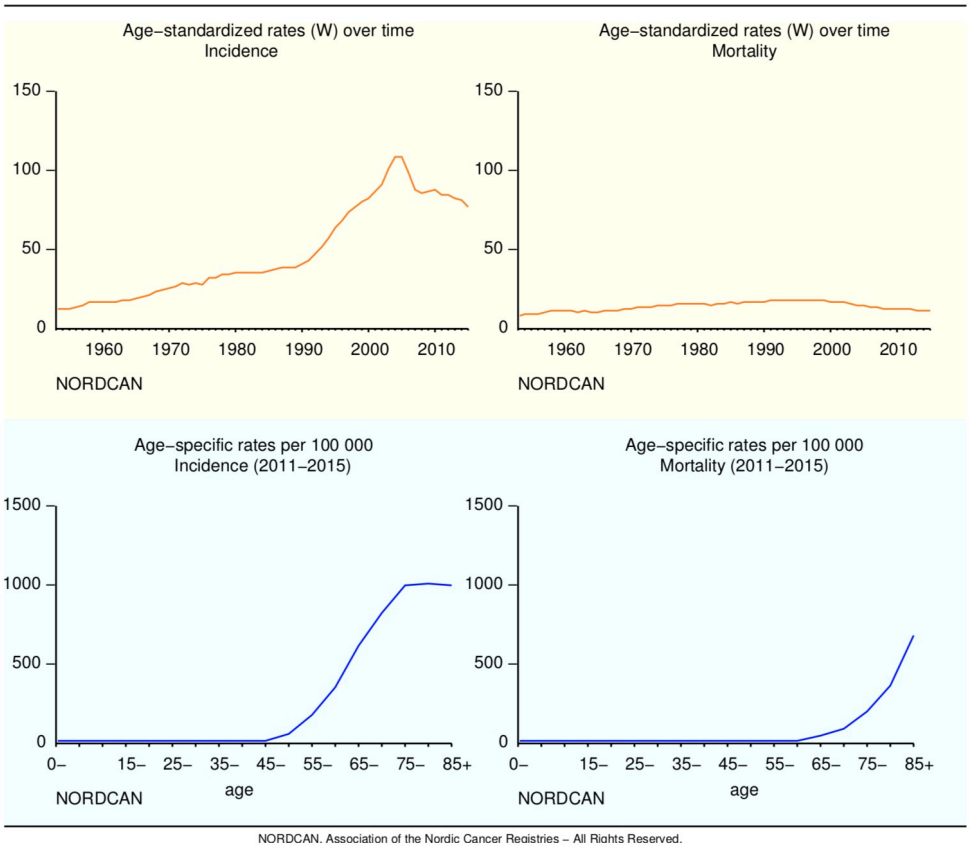
- Positive family history
  - Genetic predisposition of PCA, e.g. mutations of certain genes (Benafif and Eeles 2016; Raymond et al. 2013)
- Age
  - PCA incidence increases with age (Salinas et al. 2014)
- Race and ethnicity
  - Especially African origin (Mordukhovich et al. 2011)
- Geographical location
  - Incidence varies vastly in different regions (Globocan IARC 2012)

Prostate Specific Antigen (PSA) was discovered and purified in the 1970's by the team of Dr Wang at Roswell Park Cancer Institute in Buffalo, New York. These findings were published for the first time in 1979. (Wang et al. 1979) PSA's clinical significance in the diagnostics of PCA was realized very soon and it was quickly adopted to clinical use. FDA approved PSA-test in 1986 to monitor and follow the effects of PCA treatment and in the beginning of 1990's to screen for PCA in undiagnosed population. (Rao, Motiwala, and Karim 2008) In our days PSA-testing is possible to do in almost every laboratory around the World.

PCA morbidity and mortality in Finland are among the lowest in the Western World. The question of our times is whether PSA-testing should be done as a way of screening of asymptomatic men. (Hayes and Barry 2014)

Age standardized PCA incidence and mortality from 1954 to 2015 are shown in figure 2. It shows that the incidence rates increased shaprly in 1990's and early 2000's due to PSA-testing becoming available. Since the peak incidence was achieved in 2005, the numbers have decreased. There are approximately 4,500-5,000 new PCA cases diagnosed in Finland every year. Age standardized mortality has remained stable and low. Age specific incidence and mortality rates show that PCA is an old men's disease. There are very few cases diagnosed before the age of 60.

Figure 2. PCA incidence and mortality in Finland 1954-2015. (source: http://www-dep.iarc.fr/NORDCAN/english/frame.asp, accessed June 27, 2018, Nordcan)



The 5-year RS percentage for PCA patients in Finland was above 78% for men diagnosed between 1999 and 2003. (Bray et al. 2010; Coleman et al. 2008)

There were approximately 4,800 new PCA-cases diagnosed in Finland between the years 2011 and 2015 every year (Figure 2.). One-year survival rate for PCA patients was 99% and 5-year survival rate was 94%. At the end of year 2015 there were more than 49,000 people living with PCA in Finland. PCA survival has significantly increased in Finland between the years 1982 and 2002. (Kavasmaa et al. 2013)

There is very little evidence on any specific nutrition or dietary habit influencing the incidence of PCA. PCA is common in countries, where "western diet" is typical and increased risk may be connected to dietary consumption of saturated fat and beta-carotene. There is some evidence that low carbohydrate intake, soy protein, omega-3 fat, green tea as well as tomatoes (lycopene) in diet may reduce the risk of

PCA. Some vitamins (e.g. ascorbic acid and cholecalciferol) and minerals (e.g. calcium) may have a non-linear effect on PCA incidence. (Lin, Aronson, and Freedland 2015; Nelson, De Marzo, and Isaacs 2003; Bashir 2015).

PA decreases the incidence of several cancers, and it seems that PA has the same effect on the incidence of PCA. (Leitzmann et al. 2015) It is unclear how big the effect of PA can be. It is possible that PA influences on PCA incidence by decreasing body weight and changing the body composition and decreasing body adiposity. (World Cancer Research Fund and American Institute for Cancer Reseach 2007; Guh et al. 2009; Pischon et al. 2008).

2 REVIEW OF THE LITERATURE

Literature for this dissertation and this chapter have been collected over the period of these studies in several parts between years 2009 and 2018. The searches have been conducted at Pubmed-database as well as the websites of International Agency for Research on Cancer (IARC), especially its GloboCan and NordCan databases, FCR and Statistics Finland (Tilastokeskus). For this chapter the best quality publications and data have been collected. This review is not a complete collection of all scientific data on the issues discussed but rather a collection of articles of interest to the author. The articles of interest are mostly in English, but some are in Finnish, French or Spanish, which are the languages familiar to the author. Most of the articles have had at least an abstract in English.

2.1 What is cancer and what causes it?

First cancers in humans were described in a papyrus from Egypt some 1600 BC. (Feldman and Goodrich 1999) This document contained a description on how to surgically remove a lump from a breast. Since then, almost everything we know about cancers, their causes and how to treat them, has changed. Over the years there have been several different theories on the development of cancer – starting from humoral theory in Ancient Greece, which stated that if there was an imbalance between the four body fluids (humors) – blood, phlegm, yellow bile and black bile – this could lead to the formation of cancer.

In a healthy human body every function is in balance. All these functions are orchestrated by chromosomes and genes, which are stored as deoxyribonucleic -acid (DNA)-strains, that are located inside the cell's nucleus and mitochondria.

Cancer begins as damage or mutation in cell's DNA. (Chatterjee, Mambo, and Sidransky 2006) Most mutated cells are not viable, and most mutations can be repaired by the cells themselves, but this is not always the case. (Kitagishi, Kobayashi, and Matsuda 2013) This can be followed by uncontrollable growth of the mutated cell-line, growth of vessels and other life-supporting factors for the mutated tissue and thus it becomes a cancerous tumor. (Krishna Priya et al. 2016) In the 1970's the

roles of oncogenes (which cause normal cells into growing without control and becoming cancer cells) and tumor suppressor genes (which function in tissues to limit the division of cells, repair DNA and inform cells when it's their time to die) have been described in the development of cancer. (Sudhakar 2009)

An important characteristic of healthy tissue is its limited growth, i.e. the cells of a particular tissue do not multiply uninhibitedly. This function is genetically regulated by oncogenes and tumor suppressor genes. Oncogene is a mutated proto-oncogene, which regulate cell growth as well as their differentiation. After an activating mutation, gene amplification or a chromosomal translocation, a proto-oncogene becomes an oncogene. (Pierotti, Sozzi, and Croce 2003) Unlike oncogenes, tumor suppressor genes usually follow 'two-hit hypothesis' which means that two alleles of a gene coding for a particular protein need to be affected before the actual change is seen. If there is one affected allele, the correct protein is still being produced. Best known examples of this is TP53 gene, which encodes the tumor suppressing protein p53. (Chang et al. 1993; Akeshima et al. 2001; Greenblatt et al. 1994; el-Mahdani et al. 1997) Lately as the whole genome sequencing has become more affordable, new tumor suppressor genes have been identified. In addition to this, normal tissue may have other functions that define the death of the cells at the end of their lifecycle. (Schulte-Hermann et al. 1997)

Cancer cells may spread to other tissues either directly growing into them, spreading through blood (circulation) or lymph system. After attaching to a new organ, the cancer cells grow a new tumor, in case the body's own immune system doesn't react effectively enough to the new cancer cells that start growing. (Pagès et al. 2010)

Cancer is still, despite the development of molecular diagnostics, classified based on its origin and cell-type morphology, which are analyzed under a microscope using different stains (Kiernan 2008) and/or antibodies. (Gremel et al. 2014)

For example lung cancer is a cancer of lung tissue, and it can be divided to different subtypes of cancers based on several factors. In the case of lung cancer the rough division is 'small-cell' (Van Meerbeeck, Fennell, and De Ruysscher 2011) and 'non-small-cell'. (Goldstraw et al. 2011) Depending on the complexity of the disease and possible ways of separating different cell types or histology there can be further classification (in the case of lung cancer the non-small-cell lung cancers can be divided to large-cell lung cancers, adenocarsinomas and squamous-cell cancers). Further division is often needed, and sometimes particular genetic anomalies of cancers are nowadays used in the classification. (Leighl et al. 2014)

2.2 Short history of occupational cancer epidemiology

The reasons behind a regular 'healthy' tissues becoming a cancerous have been of interest to researchers for a long time. Italian Dr Bernardino Ramazzini was the first one to actually realize that there were more certain types of cancers in different populations. His studies, which were published in 1700 and 1713, contained data on the diseases of some 50-odd different occupations. He noticed e.g. that nuns had practically no cervical cancer, but instead had a higher incidence of breast cancer when compared to other women. (Araujo-Alvarez and Trujillo-Ferrara 2002) Later it would be found out that reasons for these findings pretty much were the same: lack of sexual contacts (i.e., HPV-infections) (Franco, Duarte-Franco, and Ferenczy 2001) and no pregnancies (i.e., hormonal reasons). (Gehring et al. 2016)

Another noteworthy early cancer epidemiologist, if that term may be used, was a British surgeon, Dr Percival Pott. He described in his publication in 1775 the cancer of the scrotum, which was more commonly found in chimney sweeps than the general population. (Waldron 1983) The reasons behind this finding would be the chemicals that were affecting the young boys and men working as chimney sweeps often from the age of 4 or 5 years of age cleaning the chimneys in the UK.

2.2.1 Current data on work related cancers

There are more than 130 different carcinogenic workplace substances or agents in a Finnish registry, which has been maintained since 1979. In 1987 approximately 15,000 employees were exposed to one or several of these agents at their work. More than 80% of the workers exposed to carcinogenic agents were men, and 17% were women. The three most prevalent carcinogenic workplace agents were hexavalent chromium compounds, nickel and its inorganic compounds as well as asbestos. (Heikkilä and Kauppinen 1992; Kauppinen et al. 2007) It has been evaluated that 2-3% of cancers in Finland and other Nordic countries are work related, but physicians have difficulties in recognizing them. (Aitio and Kauppinen 1991; Pukkala and Härmä 2007)

People are exposed to cancer causing agents to a variable degree either at work or in their leisure time. Tobacco smoke is probably the most important workplace agent, which causes cancer. (Leon et al. 2015; Bradley and Golden 2005; Couraud et al. 2012) Over the past decades, however, smoking exposure at work as well as in restaurants and other public places has decreased significantly due to legislative

measures. Based on studies, reported exposure to tobacco smoke in bars and restaurants declined slowly after the launch of the renewed Tobacco Act. (Reijula and Reijula 2010) Some other important cancer causing agents at workplace are exposures to asbestos, radiation and infectious agents among many others. (Stellman and Stellman 1996) Also sedentary work has also been identified as an important cancer risk at work. (Boyle et al. 2011)

IARC classifies carcinogenic agents as follows

Table 1. Table 1. IARC classification of carcinogenic agents (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012)

IARC Class	Definition	Number of Agents	Examples
Group 1	Carcinogenic to humans	120 agents	Tobacco smoke, formaldehyde
Group 2A	Probably carcinogenic to humans	82 agents	Chloramphenicole, diethyl sulphate
Group 2B	Possibly carcinogenic to humans	299 agents	Isoprene, night shift work
Group 3	Not classifiable as to its carcinogenicity to humans	502 agents	Aniline, acrylic acid
Group 4	Probably not carcinogenic to humans	1 agent	Caprolactam

The classification helps in evaluating the possible carinogenicity and the need for protection from named workplace agents.

Examples of group 1 (carcinogenic to humans) agents at workplace are tobacco smoke and formaldehyde (used in the manufacture process of glues and cosmetic products). Over the past couple of decades protection at workplace from these carcinogenic agents has improved through legislative measures, most important of them being the ban of smoking at work and in other public places such as restaurants, first in 1995, and more strictly in 2007. (Tupakkalaki 2016)

Examples of group 2A (probably carcinogenic to humans) agents at workplace are chloramphenicole (an antibiotic) and diethyl sulphate (used e.g. in the process of preparing pigments and drugs).

Examples of group 2B (possibly carcinogenic to humans) agents at workplace are isoprene (used in preparation of rubber products) and night shift work, which has been associated with increased risk of breast cancer, especially for nurses and flight attendants. (Lin et al. 2015) Similar increasing effect of shift work on PCA has been suggested in some studies, but the finding has not been confirmed others. (Åkerstedt et al. 2017; Kubo et al. 2006)

Examples of group 3 (not classifiable) agents at workplace are aniline (used in the manufacture process of e.g. fabrics and polyuretan) and acrylic acid (used e.g. in the manufacture of plastic products).

The only agent in group 4, which has been classified as not carcinogenic to humans, is caprolactam. It is an organic compound used in the manufacture of nylon. (IARC Working Group on the Evaluation of Carcinogenic Risks to Humans 2012)

2.2.1.1 Current studies on cancer risk at work

The biggest epidemiological occupational cancer incidence study has been the NOCCA study. In the study the cancer incidence of approximately 15 million people in Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) aged between 20 and 64 years of age in the beginning of follow-up was followed for a maximum of 45 years, from 1961 to the end of 2005. During this time almost 3 million cancer cases were registered for people in the Nordic countries. The researchers collected information on each person's occupation and all incident cancer cases of the members of the cohort. For the final analysis the occupational data was classified in 54 categories. After the number of cancer cases in a professional group of people had been classified by country, sex, age, time period and professional group, it was then compared with the expected number of cancer cases (number of person years, incidence numbers in population) in order to calculate SIRs (i.e. observed/expected number of cancers) for each cancer in each occupational group. (Pukkala et al. 2009)

There are several other cohort studies that are currently collecting data on the cancer incidence at work in several countries. The aim of these studies is to evaluate the influence of different workplace agents to cancer incidence. The French investigators started inclusion to their cohort study "*Constances*" in 2011-2012. Their aim is to follow the cancer incidence of some 200,000 French randomly selected adults and evaluate, among other things, the effects of their workplace exposure to

cancer causing agents to their cancer incidence. (Goldberg et al. 2017) "*Amigo*"-study cohort in the Netherlands was set up to study occupational and environmental determinants of different diseases, including cancers, and people's well-being from a multidisciplinary and life course point of view. The study group has not reported results from this cohort yet. (Slottje et al. 2015) A relatively new cohort is Dutch "*Lifework*" -cohort, which has been set up to quantify the health effects of occupational and environmental exposures. (Reedijk et al. 2018)

2.3 Examples of some factors that modify (increase/decrease) cancer incidence

The reasons for a mutation to take place in a normal tissue cell and later on becoming cancerous are multiple. Quite often the reasons behind this change can't be identified. It should be noted that in most cases one single reason for a cancer can't be named. Often there are several reasons, which lead to the development of cancer. On a population level several risk factors and some protective factors have been identified, however.

2.3.1 Tobacco smoking and secondhand smoke

One of the first researchers to point out the increased incidence of cancers among smokers was German Dr Lickint, who published his first epidemiological studies in the 1920s and 1930s (Lickint 1930), but his studies were not taken seriously before the link between cigarette smoking and lung cancer was published in the 1964 Surgeon General's Report in the United States. (Hecht and Szabo 2014) In addition to lung cancer, tobacco smoking increases the incidence of several other cancers, e.g. cancers of pancreas, stomach and urinary bladder. (Malila et al. 2006; Leon et al. 2015)

The link between secondhand smoke or exposure to environmental tobacco smoke (ETS) and lung cancer has been proven in numerous studies. (Kim et al. 2014) In addition to lung cancer the risk is increased for other cancers including at least breast and urinary bladder cancer; possibly also cervix, nasal and sinus as well as kidney cancer. (Dossus et al. 2014; Tao et al. 2010; Lee, Thornton, and Hamling 2016)

In a meta-analysis investigators could establish a connection between smoking and the incidence of CRC (Liang, Chen, and Giovannucci 2009). The RR for heavy smokers was 1.38 ($p<0.0001$) when compared to non-smokers. RR for rectal cancer was higher than the RR for colon cancer.

The effects of smoking to PCA incidence have been studied widely. In a meta-analysis Islami et al (2014) reported that in studies completed before PSA-testing era (i.e. before 1995), ever smoking showed a positive association with PCA incidence (RR=1.06; 95% CI: 1.00-1.12). Smoking also seemed to increase mortality from PCA. (Islami et al. 2014)

2.3.2 Alcohol

Use of alcohol has been studied widely in the development of different cancers. Alcohol has been associated with an increased risk of cancers of e.g. oral cavity, pharynx, larynx, oesophagus, liver, colorectum as well as breast cancer in women. Increased risk has been detected even for those individuals that use low or moderate amounts of alcohol. (Parkin 2011; Scoccianti et al. 2015)

It has been reported that in Japanese population the use of alcohol increases the incidence of CRC significantly (Mizoue et al. 2008). It seems however that there are no other data that would support this finding. In a Dutch study (Bongaerts et al. 2008) the RR for incidence of colon cancer increased from proximal part of colon toward the end of the colon and rectum. Only the incidence of rectosigmoid and rectal cancers were significantly higher among alcohol users than among non-users.

The linkage between alcohol consumption and the risk of PCA have been inconsistent. In the EPIC-study (Rohrmann et al. 2008) neither baseline nor average lifetime consumption of alcohol were associated with an elevated risk of PCA. (Hsing et al. 2014; Albertsen and Grønbaek 2002)

2.3.3 Diet

Diet has a significant effect of cancer development, especially on the development of colon cancer. Willett et al. concluded that the women who belonged to the highest 20% of red-meat eaters had an increased RR of 1.9 of getting colon cancer when compared to the lowest red-meat eating quintile. (Willett et al. 1990) The exact reasons behind red meat's carcinogenicity (Kim, Coelho, and Blachier 2013) are not

known, but one possible candidate is iron in the form of heme, which could act as a pro-oxidant in colon. (Tappel 2007) In some studies patients suffering of non-insulin dependent diabetes mellitus (NIDDM) (La Vecchia 2011; Le Marchand et al. 1997; La Vecchia et al. 1991) have shown an elevated risk of CRC, which has led to a conclusion that CRC might be linked to metabolic syndrome and insulin metabolism.

There are many other dietary choices that have been studied as potential risk factors of colon cancer. (Akin and Tözün 2014) IARC has classified a few years ago processed red meat in group 1 (i.e. carcinogenic to humans) in its classification of carcinogenic agents. It's been evaluated that a daily dose of 50 grams of processed meat increases cancer risk by 18%. (World Health Organization 2015)

In a meta-analysis high intake of processed red meat was associated with an increased incidence of CRC. The RR was 1.16 (95% CI: 1.10-1.23). These associations were modified by sex – RR for men was 1.23 (95% CI: 1.07-1.42) and for women RR was 1.05 (95% CI: 0.94-1.16). (Alexander et al. 2010)

Among the probably protective dietary choices from CRC are fruits and vegetables (Terry et al. 2001), chicken and fish (Willett et al. 1990), calcium and dairy products (Cho et al. 2004) as well as anti-oxidants, especially beta-carotene. (West et al. 1989; Satia-Abouta et al. 2003)

There is also increasing amount of evidence of gut microbiota having an important role in the relationship between diet and the development of colon cancer. (Song, Garrett, and Chan 2015)

There are some data suggesting that lycopene (found e.g. in tomatoes) might reduce the incidence of PCA but in general there is very little knowledge on the effects of diet to PCA incidence. There seems to be some evidence between an increased incidence of advanced PCA and a diet high in saturated fat, well-done meats and high calcium content of diet. There are inconsistent results for a decreased incidence of PCA and intake of total meat, fruits, and vegetables. (Gathirua-Mwangi and Zhang 2014)

2.3.4 Inflammation and infections as reasons of cancer

Inflammatory Bowel Disease (IBD) patients have an increased risk of CRC. Similar molecular mechanisms that cause CRC are also a part of colitis-associated colon carcinogenesis. Risk of colon cancer in IBD increases with the duration of the disease, larger anatomic extent of colitis, the presence of sclerosing cholangitis,

family history of CRC and degree of inflammation in the bowel. (Xie and Itzkowitz 2008)

Approximately 12% cancers in human are caused by viruses that are called oncoviruses. Examples of oncoviruses are e.g. Epstein-Barr virus (EBV), human papillomaviruses (HPVs), hepatitis B and C viruses (HBV and HCV, respectively), human T cell lymphotropic virus-1 (HTLV-1), and Kaposi's sarcoma herpesvirus (KSHV). (Mesri, Feitelson, and Munger 2014) Human papillomavirus (HPV) infections can cause cancer at multiple anatomic sites in both men and women e.g. cervical vulvar and vaginal cancers in women, oropharyngeal and anal cancers in both men and women and penile cancers in men. (Giuliano et al. 2015) Patients with HPV-associated oropharyngeal cancers tend to be younger, and their survival is better than in the absence of HPV. (Syrjänen, Rautava, and Syrjänen 2017) HPV-vaccination is a cost-effective way to reduce the incidence of these cancers. (Arbyn et al. 2018) Human immunodeficiency virus (HIV) infection has been associated with increases in the incidence of Kaposis's sarcoma, non-Hodgkin's lymphoma, cervical, lung and liver cancers. The modern highly active antiretroviral therapy, however, has somewhat decreased the incidence of these cancers especially in the western World. (Engels et al. 2008) Cirrhosis due to chronic hepatitis B or hepatitis C is an important risk factor for hepatocellular carcinoma of the liver. (Mittal and El-Serag 2013)

2.3.5 Physical activity

2.3.5.1 Physical activity and colorectal cancer incidence

PA reduces the risk of colon cancer significantly. In a meta-analysis (Wolin et al. 2009) it was noted that especially men benefit of the protective effects of physical exercise. The evaluated Risk Ratio (RR) for men was 0.76 (95% CI: 0.71, 0.82). Women seemed to benefit less from exercise RR=0.79 (95% CI: 0.78, 0.88). Thune and Lund (1996) followed a population based cohort in Norway for approximately 16 years from 1970's for their CRC incidence. There were approximately 53,000 men and 28,000 women in the cohort. The researchers reported that PA at a level of e.g. walking at least four hours a week during leisure-time was associated with decreased risk of colon cancer in females when compared to the sedentary group (RR=0.62, 95% CI: 0.40-0.97). When occupational PA and LTPA were combined, an inverse dose-response with PA was detected (P for trend = 0.04) for both men and women.

The protective effect of PA was stronger in the ascending or proximal part of colon when compared to descending or distal part of colon. The researchers did not detect any association between PA and rectal cancer, neither for males nor females. (Thune and Lund 1996) In a Japanese case-control study high levels of job-related PA were associated with significant reduction of risk of cancer in the distal parts of colon and rectum in males. In females high levels of total PA was protective of the cancer of distal part of colon. (Isomura et al. 2006)

In a meta-analysis Thune and Furberg (2001) reported a protective effect of PA on cancer risk with a dose-response association between PA and colon cancer. The optimal level of PA remained unclear, but the findings supported that moderate activity (>4.5 MET) had a bigger effect than lighter activities (<4.5 MET). (Thune and Furberg 2001) In a more recent meta-analysis Harriss et al (2009) reported an inverse associations with LTPA and colon cancer for men (RR=0.80; 95% CI: 0.67-0.96) and women (0.86; 95% CI: 0.76-0.98). LTPA did not influence risk of rectal cancer. (Harriss et al. 2009) Boyle et al (2012) reported that the risk of proximal colon cancer was 27% lower among the most physically active people compared with the least active people (RR=0.73, 95% CI: 0.66 to 0.81). For distal part of the colon the risk reduction was almost identical. (RR=0.74, 95% CI: 0.68 to 0.80). (Boyle et al. 2012)

World Cancer Research Funds have published on their website a recent update on CRC. Being physically active is one of the key issues they present as a method to decrease colon cancer incidence. (Diet, Nutrition, Physical Activity and Colorectal Cancer 2018)

2.3.5.2 Physical Activity and prostate cancer incidence

The protective effect of PA has been studied in different settings. A publication by Johnsen et al (2009) on the large West European EPIC study (European Prospective Investigation Into Cancer and Nutrition) cohort concluded that a higher level PA at work was associated with a trend of lower incidence of advanced PCA. No association was found between LTPA and the risk of PCA. (Johnsen et al. 2009) In the EPIC study altogether 2446 men developed PCA during an 8.5 year follow-up period. The men with a bigger waist circumference or elevated waist-hip ratio had an elevated risk of advanced PCA but the total risk of PCA was not significantly elevated. (Pischon et al. 2008)

Moore et al (2008) reported a small protective effect (3%) of vigorous exercise in the adolescence for PCA (Moore et al. 2008), but their findings have not been confirmed by other researchers. Lifetime total occupational PA didn't prove to be protective of PCA in a Swedish study published in 2008. (Wiklund et al. 2008)

A protective effect of PCA was reported for men having a high level of PA at work for aerospace workers (OR=0.55; 95% CI: 0.32-0.95), but not for radiation workers (OR=0.95; 95% CI: 0.43-2.1). (Krishnadasan et al. 2008) Many other, larger studies have been inconclusive or negative. (Thune and Furberg 2001; Sass-Kortsak et al. 2007)

Hållmarker et al (2015) reported an increased PCA incidence in a cohort of men that participated in an endurance sport event (Vasaloppet), and were in good PC. (Hållmarker et al. 2015)

2.3.5.3 The physiological effects of physical activity that may reduce the incidence of cancer

There are several ways how PA might be linked to reduction of cancer incidence. First of all it has a direct effects to body weight, Body Mass Index (BMI, calculated by dividing the body mass by the square of the body height, and is universally expressed in units of kg/m^2) and body composition. (Mustelin et al. 2009; Schüz et al. 2015) It also changes the levels of hormones or hormonal effects in tissue. These can be associated with cancer induction and promotion on a cellular level. Examples of hormones or factors that may have such effects are growth factors (Thomas et al. 2013), stress hormones (Barbieri et al. 2015; Rundqvist et al. 2013) and estrogen. (Smith et al. 2013) In addition to this PA is effective in preventing obesity and its effects on insulin resistance (Exley et al. 2014; Kahn, Hull, and Utzschneider 2006), insulin like growth factor, IGF binding proteins (Bianchini, Kaaks, and Vainio 2002) and inflammation (Mraz and Haluzik 2014; Asghar and Sheikh 2017), which are all important factors in the development of metabolic and vascular changes in the development of cancer. Adipose tissue produces many bioactive molecules, e.g. adipokines, which have immunoregulatory properties (Exley et al. 2014) that have a role in the development of cancer.

In addition to other physiological changes, PA reduces the time of food to travel through the digestive system i.e. gastrointestinal transit time, and it has been postulated that this in itself may decrease the time of exposure to the carcinogens in the gastrointestinal tract. (Bernstein et al. 2005, Quadrilatero and Hoffman-Goetz 2003, Strid et al. 2011,Wertheim et al. 2009; Winzer et al. 2011)

2.3.5.4 Measurement of physical activity and physical condition

PA and PC can be measured in many ways. For epidemiological studies the most common method is questionnaire-based way to evaluate the amount of individual PA. (Silsbury, Goldsmith, and Rushton 2015)

In some studies PA has been measured by direct or indirect calorimetry, pedometers (to measure the number of steps), accelerometers, heart rate monitoring, GPS watches as well as motion sensors. (Aparicio-Ugarriza et al. 2015; Jörgensen et al. 2009)

Mobile technology based measurements are on the increase and offer new, more exact methods to measure PA in studies. These modern methods are more user friendly than some older methods. (Hong et al. 2015)

12-minute running test (Cooper) has been used widely in Finnish population, and it is a part of PC-measurement at the Finnish Defence Forces. It is considered accurate, quick and reliable method for evaluating the PC of conscripts. (Taanila et al. 2010)

2.3.6 Socio-economic-status

In addition to lifestyle, also socio-economic status (SES) has an effect on the incidence of cancer. Parts of these differences can be explained by diet, PA, smoking or alcohol consumption, but a part cannot be explained by these known factors.

Over years the incidence of cancers have changed, but the differences in cancer incidence between SES categories have remained similar. SES seems to be positively associated to the risk of breast and colon cancer incidence. For rectal cancer the data are inconsistent. An inverse association has been detected for lung, stomach, oropharyngeal and esophageal cancer. These differences in cancer incidence can be attributed to lifestyle factors, such as diet, alcohol consumption and reproductive factors. (van Loon et al. 1995) PA is a risk factor, which is likely to be associated with SES. (Meader et al. 2016)

In Finnish population the incidence of CRC increases with SES. Although a big part of the observed differences in cancer incidence could be explained by known etiological factors such as diet, PA, alcohol consumption, smoking, a part of the variation is apparently attributable to unknown factors.. (Weiderpass and Pukkala 2006)

Men of higher SES seem to have a higher PCA-incidence, but this can be attributed to better access to PSA-screening and earlier prostate biopsies to diagnose

PCA. (Rundle et al. 2013) This way these men's PCA is diagnosed earlier. This explains partly the fact that globally men of lower SES have higher mortality rates of PCA. (Shafique and Morrison 2013; Berglund et al. 2012) Even though SES differences in Finland are less pronounced than in some other countries, a similar finding has been reported in a recently published Finnish study: the researchers detected that men with a higher education level had a higher 10-year PCA specific survival than those with only basic education level. This difference in survival was apparent both before PSA-testing era and during it. (Seikkula et al. 2018)

In addition to adult life SES also the childhood SES affects people's cancer risk. (Akinyemiju et al. 2017) There are several reasons behind this finding, but most importantly children get used to their parents' lifestyle during childhood, dietary habits as well as PA and other lifestyle choices. In addition to these, also the childhood environment may modify the risks of cancer during adult years. One important risk factor is exposure to environmental tobacco smoke (ETS), or second-hand smoke that the children are exposed to when adults around them smoke.

A study analyzed ETS in Finland between years 1991 and 2009. ETS exposure decreased remarkably over years, as tobacco control measures were tightened, particularly among children of smoking parents. Differences defined by SES persisted, although they diminished over the study period. (Raisamo et al. 2014)

2.3.7 Other agents that may modify cancer incidence

Asbestos is a name commonly used for six naturally occurring silicate minerals, which were used in construction from 1920's. (Gee and Greenberg 2002) The use of asbestos was mostly terminated by early 1980's. Exposure to asbestos fibers increases the risk of mesothelioma and other cancers. Those who are diagnosed with work related mesothelioma, have often been exposed directly to asbestos for a number of years. (Plato et al. 2016; Koskinen et al. 2003) There are no studies linking the incidence of CRC or PCA to exposure to asbestos.

Ultraviolet (UV) radiation, which increases the endogenous production of amount of vitamin D3 (cholecalciferol) in the skin (Holick 1994), is an often neglected workplace carcinogen. UV-radiation increases significantly the risk of many types of skin cancers including melanoma. Examples of professions subjected to ample amounts of UV-radiation at work are farmers, fishermen and construction workers. In a meta-analysis Glanz et al (2007) noticed that men are more likely to wear hats and protective clothing and women are more likely to use sunscreen to

protect themselves from UV-radiation. The authors state that the sun-safety habits of outdoor workers may mirror the common gender norms for sun safety and may also be influenced by socioeconomic conditions. (Glanz, Buller, and Saraiya 2007) Exposure to UV-light might have a U-shaped association with PCA incidence, as a decrease has been noticed in some studies and an increased risk has been noticed in others. (Peters et al. 2016; Nair-Shalliker et al. 2012) There are some studies that link the incidence of CRC to increased vitamin D-levels in nutrition. (Garland et al. 1985) However, according to Jongbloet (2006) the epidemiological findings do not prove that higher levels of vitamin D would lower the risk of CRC. (Jongbloet 2006)

In a few studies workplace exposure to whole body vibration (WBV) has been associated with an increased incidence of PCA. A meta-analysis suggests that the effect of WBV to PCA incidence can't be ruled out. (Young et al. 2009) In a large Canadian cohort study WBV exposure was evaluated based on occupation in 1991 for more than one million men, who then were followed for PCA incidence until the end of 2003. The results showed that WBV-exposed men in certain professions (natural and applied sciences occupations) had a 37% elevated risk of PCA (95% CI: 1.09-1.72) whereas in some other occupations (trades, transport, and equipment operator occupations) a protective effect was detected – the men had a 9% reduced risk of PCA incidence (95% CI: 0.86-0.97). (Jones et al. 2014)

In the following tables some of the studies referred to earlier in the chapter have been collected. First table is a table presenting the studies on the incidence of all cancers. Second table presents the studies on the incidence of CRC. The third table presents the studies on the incidence of PCA.

Table 2. Epidemiological studies on cancer incidence in general and selected risk factors (mostly work related)

Authors	Year	Type of study	Cancer of interest	Exposure agent(s)	Number of cases	Results
Koskinen, Pukkala et al.	2003	Cohort	All cancers	Work related, Asbestos	1392 for men 55 for women	For men: increase all cancer SIR 1.07 (95% CI: 1.02-1.12), lung cancer (SIR 1.14, 95% CI:1.01-1.26), mesothelioma (SIR 2.77, 95% CI: 1.66-4.31) For women no increase detected
Malila, Virtanen et al.	2006	Intervention, cohort	All cancers Smoking related (incl. lung, mouth, pharynx, larynx, oesophagus, pancreas, stomach, liver, urinary bladder and kidney)	Smoking	5 944	Risk for all cancers: SIR 1.55 [95% CI: 1.51-1.59]. Risk for smoking related cancers: SIR 2.45 (95% CI: 2.35-2.56)
Pukkala, Martinsen et al.	2009	Cohort Study	All cancers	Work related	2,8 million	Different risks for different jobs*
Slottje, Yzermans et al.	2015	Cohort	All cancers, other health data	Work related, leisure time exposure	14829	No results yet
Moore, Lee et al.	2016	Cohort(s)	Several cancers	PA	186932	High vs low levels of leisure-time PA were associated with lower risks of 13 cancers: esophageal adenocarcinoma (HR 0.58; 95% CI: 0.37-0.89), liver (HR 0.73; 95% CI: 0.55-0.98), lung (HR 0.74; 95% CI: 0.71-0.77), kidney (HR 0.77; 95% CI: 0.70-0.85), gastric cardia (HR 0.78; 95% CI, 0.64-0.95), endometrial (HR 0.79; 95% CI, 0.68-0.92), myeloid leukemia (HR 0.80; 95% CI: 0.70-0.92), myeloma (HR 0.83; 95% CI: 0.72-0.95), colon (HR 0.84; 95% CI: 0.77-0.91), head and neck (HR 0.85; 95% CI: 0.78-0.93), rectal (HR 0.87; 95% CI: 0.80-0.95), bladder (HR 0.87; 95% CI: 0.82-0.92), and breast (HR 0.90; 95% CI: 0.87-0.93). Body mass index adjustment modestly attenuated associations for several cancers, but 10 of 13 inverse associations remained statistically significant after adjustment. Leisure-time PA was associated with higher risks of malignant melanoma (HR 1.27; 95% CI: 1.16-1.40) and PCA (HR 1.05; 95% CI: 1.03-1.08)
Goldberg, Carton et al.	2017	Cohort	All cancers, other health data	Work related,	200000 will be included	No results yet

				leisure time exposure		
Reedijk, Lenters et al.	2018	Cohort	All cancers, other health data	Work related, leisure time exposure	88466	No results yet

Table 3. Epidemiological studies on CRC incidence and selected risk factors

Authors	Year	Type of study	Cancer of interest	Exposure agent(s)	Number of cases	Results
West, Slattery et al.	1989	Case.control	CRC	Diet	231	High BMI increased risk for both sexes (OR for men 2.1, women 2.3), Fiber intake was protective especially for women.
Le Marchand, Wilkens et al.	1997	Case-Control	CRC	Energy intake, lifestyle (sedentary, diet etc.)	1192	High BMI and low PA-level for men increase OR 3.0; 95% CI: 1.8-5.0, and for women OR, 1.7; 95% CI: 1.0-3.2
Terry, Giovanucci et al.	2001	Cohort	CRC	Diet (fibers, fruit, vegetables)	460	Low vegetable and fruit consumers have increased risk of CRC (OR 1.65 (95% CI: 1.23-2.20)
Satia-Abouta, Galanko et al.	2003	Case-control	CRC	Micronutrients	613	Among caucasian (white) Americans the highest quartile of beta-carotene, vitamin C and Calcium intake had 40-60% lower CRC incidence. Among African Americans vitamin E was associated with 70% lower CRC incidence (OR 0.3, 95%CI:0.1-0.6) than the lowest quartile, vitamin C similarly had 50% protective effect (OR 0.5, 95% CI: 0.3-0.8).
Bongaerts, Van Den Brandt et al.	2008	Cohort	CRC	Alcohol	2323	Risk of CRC increased, HR 1.32, 95% CI: 1.06-1.65)
Liang, Chen et al.	2009	Meta-analysis of 34 cohort studies 2 case-control studies	CRC	Smoking	N/A	RR=1.38 for an increase of 40 cigarettes/day) RR=1.20 for an increase of 40 years of duration) RR=1.51 for an increase of 60 pack-years) RR=0.96 for a delay of 10 years in smoking initiation The association was stronger for rectal cancer than for colon cancer

Table 4. Epidemiological studies on PCA incidence and selected risk factors

Authors	Year	Type of study	Cancer of interest	Exposure agent(s)	Number of cases	Results
Norman, Moradi et al.	2002	Cohort	PCA	PA	92208	Rate Ratio for PCA was 1.11 (95% CI: 1.05-1.17) for men with sedentary jobs as compared with those whose jobs had very high/high PA-levels after MV-adjustment
Sass-Kortsak, Purdham et al.	2007	Case-control	PCA	Work related	760	Risk factors for increased incidence of PCA were detected to be WBV (OR: 1.38, 95% CI: 1.07-1.78) and workplace PA OR: 1.33 (95% CI: 1.02-1.74)
Kubo, Ozasa et al	2007	Cohort	PCA	Night shift work	14052	Rotating-shift workers were at an increased risk for PCA (RR= 3.0, 95% CI: 1.2-7.7). Fixed-night work was associated with a small and nonsignificant increase in risk.
Rohrmann, Linseisen et al.	2008	Cohort	PCA	Alcohol	2665	No increase of RR. For high-user-group RR= 0.88 [95% CI: 0.72-1.08]
Pischon, Boeing et al.	2008	Cohort	PCA	BMI, body size and shape	2446	For advanced PCA RR=1.06 (95% CI: 1.01-1.1) per 5-cm-higher waist circumference and RR=1.21 (95% CI: 1.04-1.39) per 0.1-unit-higher waist-hip ratio
Wiklund, Lageros et al.	2008	Cohort	PCA	Lifetime PA		OR 1.44 (95% CI: 1.08-1.92) of PCA risk for most active men when compared to the least active men
Krishnadasan, Kennedy et al.	2008	Case-control	PCA	PA, PPWL	362	High PPWL levels inversely associated with PCA incidence among aerospace workers (OR: 0.55; 95% CI:0.32-0.95), but not among radiation workers (OR: 0.95; 95% CI:0.43-2.1).

Orsini, Bellocco et al.	2009	Cohort	PCA	PA	2735	MV-adjusted incidence of PCA in the highest quartile of lifetime total PA risk reduction was 16% (95% CI:2-27%) compared with that in the lowest quartile of PA
Johnsen, Tjønneland et al.	2009	Cohort	PCA	PA	2458	Higher level of occupational PA associated with lower risk of advanced PCA (p-trend = 0.024)
Moore, Peters et al.	2009	Cohort	PCA	PA	9995	For black men, who participated in at least 4 hours/week in moderate/vigorous PA had a lower RR for PCA 0.65; 95% CI: 0.43-0.99 Among Caucasian men no protective effect of PA was detected
Hsing, Yeboah et al.	2014	Cohort	PCA	Genetics	73	7.0% of screened African men had PCA, investigators suggest role of genetics for this finding
Jones, HaRR=is et al.	2014	Cohort	PCA	WBV	1107700	WBV-exposed men in some occupations (Natural and Applied Sciences Occupations) had a 37% elevated risk of PCA, RR= 1.37 (95% CI: 1.09-1.72) WBV-exposed men in Trades, Transport, and Equipment Operator Occupations had a RR= 0.91(95% CI: 0.86-0.97). Differences in risk were seen for several occupational categories.

3 AIMS OF THE STUDY

The aims of this project were to study the effects of PA and PC to the incidence of cancer with main emphasis on CRC and PCA in men. In order to achieve this, the following were the aims of the sub-studies:

- To assess effects of PC, which was measured during military service, to the incidence of cancer later in life.
- To assess the effects of military fitness classification to the incidence of cancers after military service.
- To assess the effects of body weight and body mass index during military service to cancer incidence.
- To assess whether PPWL has protective effect against CRC.
- To quantify the protective effect of PPWL to CRC.
- To quantify the variation of the effect of PPWL to cancer incidence between colon subsites and rectum.
- To find out if there is a lower incidence of PCA in physically active men when compared to inactivity.
- To quantify the protective effects of PPWL to PCA if that is detected.

4 MATERIALS AND METHODS

4.1 A cohort study and a case-control study

The first and second studies were cohort studies, and studies three and four were case-control studies.

A cohort study is a study in which Individuals are followed for a certain time period for risk of developing a health outcome (in this case a cancer). They are observed in order to measure the frequency (number) of the health outcome among those that have been exposed to an agent that is suspected to cause the outcome of interest. During the follow-up period, the number of these expected cases is collected. (Blumenthal et al. 2001) In this case the number of cancer cases was collected.

A case-control study setup is different: in it the individuals already having the expected health outcome are compared to those people that belong to the same population, but are free from the expected health outcome. In this study type the sample size can be smaller, and these studies are faster to conduct as well as require less financial resources. Selection of control population may cause some issues (selection bias), information bias as well as the control of confounding variables. (Blumenthal et al. 2001)

Case-control studies are prone to selection bias and this should be kept in mind when selecting the controls for these studies. Wrongly selected controls may affect OR estimation. (Geneletti et al. 2011), similarly information bias (Han et al. 2013) and other confounding variables may affect it. (Moore et al. 2012)

4.2 The cohort study of Finnish military recruits born in 1958

This study was based on the cohort of men born in 1958. Data on their PC and other health aspects were recorded during their military service by the Finnish Defense Forces in paper based archives. These were then later digitized for this study by trained clerks.

The cancer incidence of these men was followed after military service. In this study their cancers were followed until the end of year 2014, by which time the men were 56 years old.

4.2.1 The baseline measurements

All baseline measurements were done by health-care professionals in the beginning of the military service of the men. Data on health-behavior (e.g. smoking habits and alcohol consumption) were collected during the medical check-up. A detailed list of all demographic, behavioral and health data items collected at baseline is presented in table 6. After the first health check, each man was given a fitness classification (A-E) based on their health.

- A-classification indicates that a conscript is in good physical and mental health and capable of normal field service.

- B-classified men are fit for lighter service. They may have health conditions that do not need regular treatment or medication, e.g., flat foot.

- C-classified men were liberated from peace time service due to more significant health issues and/or need of daily/regular medication

- D-classified conscripts are exempt from military service completely.

- E-classification means deferment for medical reasons for up to 3 years. Diagnoses, which lead to E-classification are usually young men's adjustment disorders. (Multimäki et al. 2005)

After the baseline medical check-up and fitness classification, the PC of the conscripts was measured by a 12-minute running test and a muscle strength test for the first time.

At the beginning of their service 91.5% of the men were healthy (classified to service class A), and 7.1% had minor health problems (service class B) (Table 5). In addition, 411 men were classified to service classes C, D or E before the end of the military service (beginning of the follow-up).

Over 80% of all men were of normal weight at recruitment (BMI 18.5-25 kg/m^2), approximately 11% were overweight (BMI 25-30 kg/m^2) and 1.4% were obese (BMI>30 kg/m^2).

Overall PC was excellent in 17.7%, good in 40.8%, and satisfactory or bad in 24.5% of the men in the cohort. Most men with BMI<25 kg/m^2 were also in a good or excellent PC, whereas the overweight and obese men (BMI≥25 kg/m^2) were more likely to be in a satisfactory or bad PC.

Approximately 52% of the men were non-smokers, and 26% did not drink any alcohol. All these data are presented in Table 5.

4.2.2 In the end of military service

PC is usually assessed at least twice during the military service. Medical check-ups were conducted in the beginning and in the end of military service. The medical check-up at the end of the military service is usually less rigorously followed than the medical check-up in the beginning. At the end of the military service self-perceived health is considered the most important health indicator. In case there were significant changes in this indicator, a rigorous medical check-up was conducted.

4.2.3 Linkage of the data

After all of the data from the military records were coded in digital format, the cohort data were linked with the FCR; National Population Registry and censuses (SES indicators), hospital discharge data (morbidity) and the cause-of-death register at Statistics Finland. (Pukkala et al. 2011) Approvals for these linkages were obtained from the Finnish Defense Forces and the National Institute of Health and Welfare in Finland (THL). The FCR data contain information on cancer including diagnosis date, type and topography, morphology, spreading of the cancer, and the treatment method. (Pukkala et al. 2017)

PIC was used in linking these data across different databases. First it was checked from the population database that every cohort member existed in the population either alive, or with date of emigration or death.

The linkage with Finnish Cancer Registry's data on cancer cases in this population was also done using the PIC as a key.

There was a built-in mechanism for checking the correct format of the PICs. Only an extremely small number of the recorded PICs were not found in the population registry, or were of wrong gender (27 PICs). These individuals were excluded from the cohort. The baseline characteristics of this cohort are presented in Table 5. The data collected on the recruits are presented in Table 6.

4.2.4 Statistical methods

Cox proportional hazard models with age as underlying time metric were fitted to estimate hazard ratios (HR) and 95% confidence intervals (CI) for the relation between each study variable and the risk of developing cancer by site. Subjects were censored as they emigrated from Finland or died before the end of follow-up (December 31, 2014), which ever occurred first. All analyses were carried out using Stata 13.

Table 5. The baseline characteristics of the Finnish Military Recruits born in 1958 -cohort

		Number	%
Service classification			
	A (healthy)	28 520	91.5%
	B (minor health problems)	2 227	7.1%
	C or D	192	0.6%
	Missing	219	0.7%
Smoking status			
	Yes	10 707	34.4%
	No	16 066	51.6%
	Missing	4 385	14.1%
Cigarettes/day among smokers			
	<10 cigarettes/day	2 010	18.8%
	10-19 cigarettes/day	5 657	52.8%
	≥20 cigarettes/day	2 862	26.7%
	Missing	178	1.7%
Alcohol consumption			
	Yes	19 052	61.1%
	No	8 097	26.0%
	Missing	4 009	12.9%
Body mass index			
	Underweight (BMI<18.5)	1 489	4.8%
	Normal weight (18.5≤BMI<25)	25 939	83.2%
	Overweight (25≤BMI<30)	3 294	10.6%
	Obesity (BMI≥30)	421	1.4%
	Missing	15	0.0%
Body surface area			
	<2 m^2	26 729	85.8%
	≥2 m^2	4 415	14.2%
	Missing	14	0.0%
Overall PC			
	Bad	1 326	4.3%
	Satisfying	6 294	20.2%
	Good	12 707	40.8%
	Excellent	5 503	17.7%
	Missing	5 328	17.1%
BMI & PC crosscategory			
	BMI<25 & good/excellent PC	16 930	54.3%
	BMI≥25 & good/excellent PC	1 277	4.1%
	BMI<25 & bad/satisfying PC	6 001	19.3%
	BMI≥25 & bad/satisfying PC	1 618	5.2%
	Missing	5 332	17.1%

Table 6. Data collected on the members of the Finnish Military Recruits born in 1958 -cohort.
Personal Identity Code of the individual
Professional group
Marital status
Beginning of military service (date)
End of military service (date)
Reason for preliminary discontinuation of military service (diagnosis)
Duration of military service
Military service classifications at different stages of the service
Classification diagnoses at different stages of the military service
Self-perceived health status in the beginning and in the end of the service
Height and weight at different stages of the service
Blood pressure at different stages of the service
PC test results at different stages of the service - 12-minute running test results - Muscle strength test results
Smoking status and amount smoked at different stages of the service
Use of alcohol and the amount smoked at different stages of the service

4.3 The cohort of the former elite athletes in Finland

In study #2 the effects of lifestyle were evaluated in the cohort of Finnish retired top athletes. Their lifestyle was charted and in this analysis it was used to evaluate how it affected the cancer incidence later in life.

4.3.1 Data collected in the beginning of the follow-up

The original study cohort consisted of 2448 athletes and 1712 referents. In 1985, a questionnaire on PA and health was mailed to the survivors of the cohort and their referents. 85% of the athletes and 81% of the referents responded to the questions. Based on the questionnaires we could determine the most important health habits of the cohort members: body height and weight, LTPA, alcohol consumption, smoking status and amount smoked, SES,

The members of the top athlete -cohort were 55 years old on the average at the beginning of the follow-up. One in five members of the cohort exercised more than 45 MET*h/week (Metabolic Equivalent hours), while the median was 18 MET*h/week. Median alcohol consumption was 6.9 grams/week, and almost half of the men had never smoked. Average BMI was 25.6 kg/m2 and their SES was higher than that of their referents.

The cohort characteristics are presented in table 7.

4.3.2 Data linkage

We obtained PIC for every cohort member together with possible dates of emigration or death from the Population Register Centre of Finland. Follow-up for cancer through the files of Finnish Cancer Registry was done using the PIC as a key. We collected data on every incident cancer case of the cohort members between the 1st of January 1986 and the 31st of December 2010. The cohort members were censored at death or emigration from Finland, after which they were no longer followed up.

4.3.3 Statistical methods

Cox regression analyses comparing the risk of cancer in athletes vs. referents after adjustment for other factors were performed for lung cancer, all other smoking-related cancers, PCA and colon cancer. Adjustment for age in each analysis was made by using age as the time scale in the Cox models.

The smoking status (current smokers, former/unknown smoking status and others), pack-years of smoking, BMI, alcohol use, reported physical exercise in 1985 and socioeconomic status were also included in the regression analyses as potential confounders or covariates. The assumptions of the Cox model were also tested for proportionality.

Table 7. The baseline characteristics of the male former elite athletes in Finland -cohort on December 31,1985.

	Athletes	Referents
Age, years: median (min – max)	55.2 (35.6 – 93.8)	53.3 (38.0 – 87.5)
≤ 50 years	29.7%	35.6%
50 - 64 years	44.8%	45.3%
65 - 79 years	22.2%	17.3%
≥ 80 years	3.3%	1.9%
MET[a], MET*h/week: median (min - max)	18 (0 – 228)	6 (0 – 228)
Quintile I (< 3 MET*h/week)	13.5%	32.3%
Quintiles II – IV (3 – 45 MET*h/week)	66.4%	60.9%
Quintile V (> 45 MET*h/week)	20.1%	6.8%
Alcohol consumption, grams/week: median (min – max)	6.9 (0 – 144.5)	6.3 (0 – 151.9)
Abstainers (< 1 drinks/week)	11.9%	15.9%
Occasional users (1 – 3 drinks/week)	45.9%	46.6%
Moderate users (3 – 14 drinks/week)	29.1%	25.3%
Heavy users (≥ 14 drinks/week)	13.1%	12.2%
Cigarette smoking		
Never smokers	48.7%	28,2 %
Ex-smokers	35.2%	43.5%
Current smokers	16.0%	28.2%
Pack-years for current smokers: Median, during smoking period (min – max)	15 (0.4 – 87)	23 (0.4 – 72)
Body mass index (BMI), kg/m²: median (min - max)	25.6 (16.2 – 43.3)	26.1 (15.8 – 58.1)
Normal weight (BMI ≤ 24.99)	42.2%	36.8%
Overweight (BMI 25.00 – 29.99)	46.3%	50.4%
Obese (BMI ≥ 30.00)	11.6%	12.8%
SES		
Executives	26.7%	10.1%
Clerical workers	39.8%	23.3%
Skilled workers	26.8%	42.0%
Unskilled workers	2.0%	7.9%
Agricultural workers	4.4%	16.4%
Other	0.2%	0.3%

[a] The MET-index was calculated by assigning a coefficient of the resting metabolic rate to each activity and by calculating the product of intensity x duration x frequency.

4.4 The case-control studies on the association of physical activity to the incidence of colorectal cancer and prostate cancer

Studies #3 and #4 describe the patterns of cancer risk in physically demanding occupations with a focus to changes in risk patterns as a consequence of changes in overall work related PA. The role of PA was evaluated using Nordic Job Exposure Matrix (JEM).

Data from several Nordic countries was used in this study. For the study on CRC incidence, data from Finland, Sweden and Norway was used. In PCA study, data from Finland and Sweden was used.

4.4.1 Study Material

These studies were based on the NOCCA-cohort which is a joint database combining census occupations, cancer data and available data on non-occupational co-factors from all Nordic countries (Finland, Denmark, Norway, Sweden and Iceland) for altogether 15 million people. This cohort has been followed for up for 45 years from 1961 to 2005, which makes a total of 385 million person years. During this follow-up period 2.8 million cancers were diagnosed among the cohort members.

For these studies all CRC and PCA cases diagnosed during the follow-up time were extracted from the NOCCA -cohort. Five controls for every cancer case were selected among people who were had not been diagnosed with the respective cancer before the diagnosis of the cancer case (i.e. index date). Cases and controls were matched for birth year, sex, and home country. Everyone who was at least 20 years old on the index date, and had any occupational information available, were included in the studies.

For CRC -study, the cases and controls were from Finland, Sweden, Norway and Iceland. For PCA -study the cases and controls were from Finland and Sweden as we did not have access to the individual records neither for the Danish nor the Norwegian parts of the cohort. Occupational histories of individuals from Iceland were not available for us, thus these data were not included.

4.4.2 Job Exposure Matrix (JEM)

For everyone in these studies, cases and controls alike, the exposure to occupational factors was calculated based on conversions that were made from occupational codes to amounts of exposures with the NOCCA-JEM.

JEM is a way to define and quantify the different, harmful or potentially harmful – or potentially beneficial – exposures of a workplace.

There are many kinds of JEMs, in different countries e.g.

- US (McHugh et al. 2010; Hoar et al. 1980)
- UK (Pannett, Coggon, and Acheson 1985)
- France (Févotte et al. 2006)
- Sweden (Plato and Steineck 1993)
- Finland (Kauppinen, Toikkanen, and Pukkala 1998)

All of the JEMs evaluate the level of exposure to different agents, e.g. solvents, that are of interest to the study in question and which can be used to evaluate the (physical) health-hazards of a particular profession in epidemiological studies. In the case of this study project there was a particular interest for the PPWL of different professions.

It should be kept in mind that the levels of exposure were quantified on a population level, not on an individual level. Statistically it means, that 95% of the evaluated exposure (to an agent at a workplace) should be within +/- two standard deviations from the evaluated level. As work and life have changed over time, it has also been reflected in JEMs over different time periods, especially in longitudinal studies, such as the NOCCA-study is.

Foreign or ready-made JEMs could be used as an evaluation of occupational exposure in other countries (and this has been done (Kauppinen, Mutanen, and Seitsamo 1992; Benke et al. 2001)) but this always raises doubts of the validity of the exposure evaluation as workplace legislation and historical perspectives to work are different in different countries.

NOCCA-JEM was created with the Finnish-JEM on basis by a panel of Nordic experts from every country. (Kauppinen, Heikkilä, et al. 2009; Plato et al. 2011)

In order to use JEM in occupational studies, the following classes of variables have been estimated for each chemical or physical agent:

- Agents
- Occupations
- Time periods (beginning – end)

For NOCCA-JEM over 28 agents have been evaluated for more than 300 professions for different time periods: 1945–1959, 1960–1984, 1985–1994, 1995–1997, 1998–2000 and 2001–2003. (Kauppinen, Heikkilä, et al. 2009) The time periods were taken into use as the professional exposures to different workplace agents changed over years, and this change needs to be reflected in the exposure evaluations. This matrix consists of two cells of characterizing the occupational exposure to a workplace agent by the (P) proportion of the exposed and the (L) mean level of the exposure. There is a defined threshold limit of exposure for each agent.

4.4.2.1 Perceived physical workload

PA at work in these studies was expressed as (estimate of) PPWL. It was based on national surveys, which had questions about the perceived physical workload. If most of the workers in an occupational category reported that their workload was very heavy, the value approached one. On the other hand, if most people reported none or only a little heavy work, the value of exposure approached zero. If less than one in ten persons in the occupational category reported heavy or rather heavy physical work, the exposure to PPWL was set to zero ("unexposed").

The cumulative exposure to PPWL was calculated for all cases and controls. It was calculated by using the time (T) starting at the age of 20 (typical age to start working in non-academic occupations) until the age of 65 (typical retirement age) or until the index date (if earlier). This was used as a multiplier for the PPWL-exposure of the professional category of the individual. After this, the individuals (cases and controls) with PPWL above the baseline level, were divided to

- Baseline (for those people at zero PPWL-years) group in both studies (reference group)
- Low (lowest 50% of the non-zero P*L*T; <4.28 PPWL-years in study #3 for CRC and <7.37 PPWL years for study #4 for PCA)
- Moderate (between 50 and 90 percentiles; 4.28-17.2 PPWL-years for study #3 for CRC and 7.37-20.1 PPWL-years for study #4 for PCA)
- High (highest 10%; >17.2 PPWL-years for study #3 for CRC and >20.1 PPWL-years for study #4 for PCA) categories

These cut off points were selected in order to evaluate the effects of the jobs that were physically most demanding and compare those jobs to the other, less demanding jobs.

If the occupational codes changed from one census to another, it was assumed that the individual changed occupational groups in the middle of the period between the census years.

4.4.3 Methodology for perceived physical workload and colorectal cancer incidence

Individuals with baseline PPWL (or no exposure for the co-exposures) were used as the reference group. Variable selection for the final main-effect models was based-on the "purposeful covariate selection" procedure. (Hosmer and Lemeshow 2004) We estimated hazard ratios and 95% confidence intervals for each exposure by conditional logistic regression model. All occupational agents considered as potential confounders, and significantly associated (Wald test $p<0.25$) with CRC risk in univariate logistic regression models were selected for MV-model.

For the models analyzing the incidence of CRC in addition to PPWL, the following agents were included as co-variants: formaldehyde, benzene, ionizing radiation, wood dust, chlorinated hydrocarbon solvents and chromium. Analyses were made for different subsites of cancers of colon (ascending, transversal, descending, unknown) as well as for the cancers of the rectum for all and then separately for both genders. All analyses were conducted by using R statistical software version 3.4.1.

4.4.4 Methodology for perceived physical workload and prostate cancer incidence

We quantified the cumulative exposure to PPWL for all cases and controls as explained earlier to different exposure groups and used the baseline PPWL exposure group as referents.

There were no workplace agents in the NOCCA-JEM that would have influenced PCA incidence, so the only covariates included in this study were the time (before PSA-testing era i.e. 1990, or during PSA-testing era) as well as SES, which is known to influence how often individuals have PSA-test. All tested workplace agents were

not significantly (Wald test $p<0.25$) associated with PCA incidence. All analyses were conducted by using R statistical software version 3.4.1.

5 RESULTS

5.1 Finnish military recruits born in 1958 -cohort

31,158 men who were born in 1958 made up this cohort. They were followed-up for 34.4 years (range 0.1-39 years) from 20.0 years (range 17-31 years) to the end of 2014 (when they were 56 years old). 91.1% of all study participants were still alive at the end of the follow-up.

The most important result was that overweight and obesity (BMI≥25 kg/m^2) were associated with an increased risk of cancer (HR 1.08, 95% CI: 0.89-1.30). Good or excellent PC was associated with a significant 18% reduced cancer risk (HR 0.82, 95% CI: 0.71-0.95). The men who were of normal weight and bad PC had an increased risk of cancer (HR 1.18, 95% CI: 1.01-1.38, for all cancers) when compared to those with normal weight and good PC. This difference further increased if an individual was also overweight or obese (HR 1.30, 95% CI: 1.01-1.69). Men in service class B had a 46% increased risk of cancer (HR 1.46, 95% CI: 1.19-1.80, for all cancers) when compared to the men in service class A.

Most of these associations became statistically insignificant after MV-adjustment for smoking, alcohol consumption, service class and an interaction term between PC and overweight.

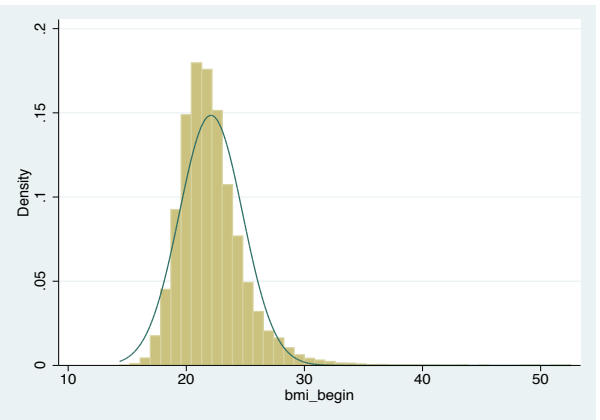
The increased risk of all cancers for men in service class B remained significant even after MV-adjustment. This was especially notable for advanced PCA, for which men in service class B were at a more than 3-fold risk when compared to those in service class A (HR 3.35, 95% CI: 1.14-9.90).

In this study it was also noticed that slim men gained weight and those that were overweight lost some weight during their military service.

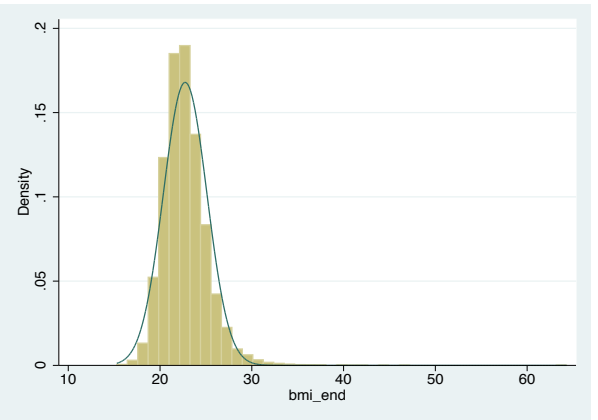
In Figure 3. the histograms of the BMIs of the men in the beginning (left side) and at the end (right side) are presented. In the beginning of the military service almost 90% of the men were either of underweight or of normal weight and a bit less than 12% were either overweight or obese. At the end of the military service approximately 55% were either under- or normal weight and 9% were either overweight or obese. It should be noted that these data was missing from more than one in three (36%) at the end of the military service.

Figure 3. Histograms of the BMI's of the Finnish military recruits born in 1958 -cohort

Histograms of the BMI's of the men in the beginning and the end of the military service



BMI's in the beginning of the military service



BMI's in the end of the military service

In the beginning of the military service almost 6 out of ten (58.5%) were in either in good or excellent PC, and one in four (24.4%) were in satisfying or poor PC.

We followed this cohort until the end of 2014 and collected information on all new cancer cases. During the follow-up period 1124 new cancer cases were diagnosed.

Data on the incidence of cancers (all cancers, smoking related, alcohol related, obesity related, CRC and PCA) in different subgroups are presented as forest plots in Figure 4.

At this stage the cohort is still relatively young – when it comes to cancer incidence – and even though there is an increase in e.g. alcohol related cancers in smokers, the increase is not yet statistically significant. We expect that this difference will become statistically significant in coming years.

Similarly an increased incidence is seen in smokers for smoking related cancers as well as for alcohol-related cancers (larynx, oral cavity, esophagus and liver, Dreyer et al. 1997) for men smoking 10-19 cigarettes daily.

Other non-significant increased HRs for obesity related cancers (thyroid, esophagus, stomach, pancreas, gallbladder, liver, CRC, kidney and multiple myeloma, Lauby-Secretan et al. 2016) were detected for groups that had:

- an increased body weight (BMI >25 kg/m2)
- high body surface area (BSA)
- service class B
- smokers

For CRC the risk factors for an increased HR were service class B and smoking. Service class B was the only significant factor for advanced PCA.

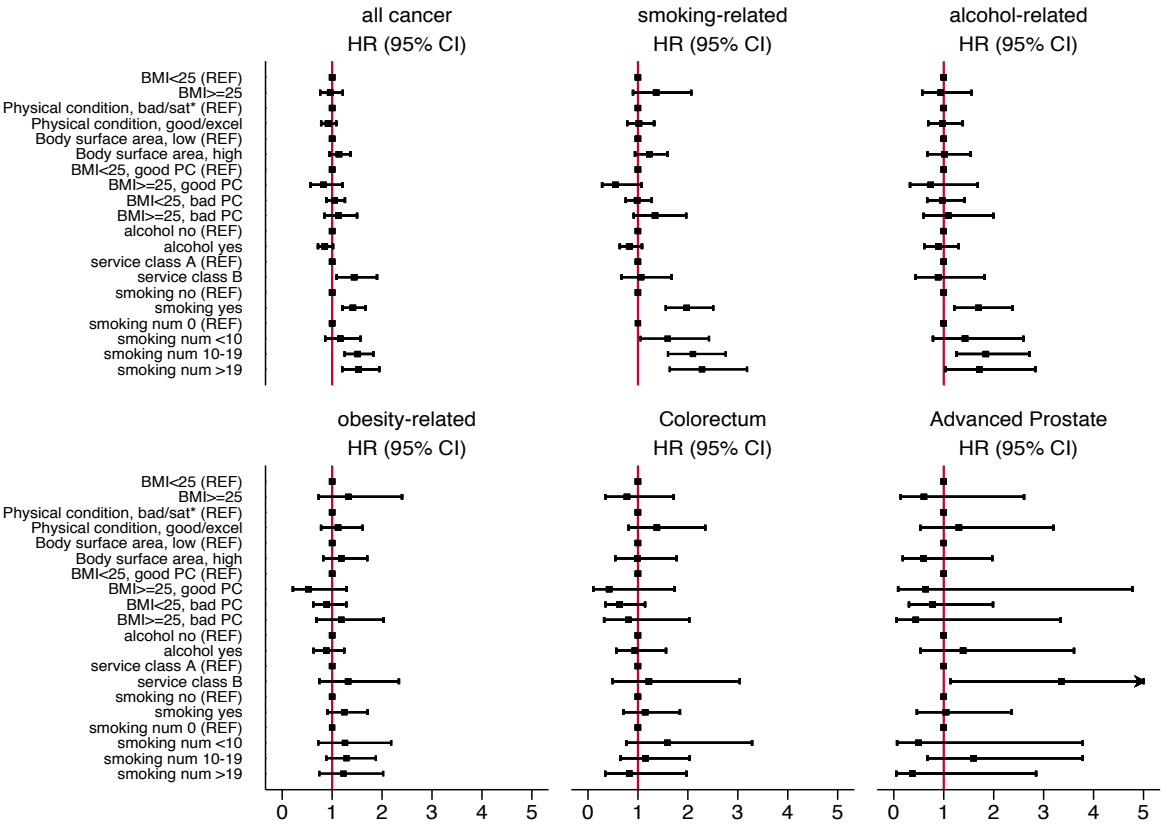


Figure 4. Forest plot of HR of all cancers for men in the Finnish military recruits born in 1958 -cohort

5.2 Former male elite athletes in Finland -cohort

Cancer incidence of Finnish world-class athletes in 1967-1999 was 20% lower than that of the general Finnish male population. (Pukkala et al. 2000) In this study the cancer incidence of these men was reported for a 20-year period from 1986 to 2006.

The cancer incidence was evaluated with consideration of cancer-related life-style factors from questionnaire based data, which was collected in 1985 from this group and their referents.

The overall cancer incidence for athletes was 12% lower than in the general population (SIR 0.88, 95%CI 0.79–0.97). The lowest SIRs were detected for lung cancer, SIR was 0.42 (95%CI 0.28–0.59) and for renal cancer SIR was 0.20 (95% CI: 0.04–0.58). There was an increased incidence of basal cell skin cancer for the cohort members.

The lowest overall cancer incidence was detected for middle-distance runners (SIR 0.51, 95%CI 0.22-1.01), long-distance runners (SIR 0.57, 95%CI 0.35-0.86) and jumpers (SIR 0.60, 95%CI 0.37-0.92). Among the referents the SIR for all cancers combined was 1.04 (95%CI 0.91–1.17). The site-specific differences between the observed and expected numbers among the referents were not statistically significant.

All results are presented in table 8.

Table 8. Observed and expected numbers of cancer cases for the former male elite athletes cohort

Observed and expected numbers of cancer cases for the former male elite athletes cohort						
Cancer site	**Athletes**			**Referents**		
	Observed number of cases	**Expected number of cases**	**SIR (95% CI)**	**Observed number of cases**	**Expected number of cases**	**SIR (95% CI)**
All sites	**372**	**422.6**	**0.88 (0.79-0.97)**	**239**	**230.3**	**1.04 (0.91-1.17)**
Strongly smoking-related cancers	**94**	**139.0**	**0.68 (0.55-0.83)**	**82**	**76.7**	**1.07 (0.85-1.33)**
Lung	30	71.7	0.42 (0.28-0.59)	49	39.5	1.24 (0.92-1.63)
Other	64	67.3	0.95 (0.73-1.21)	33	37.2	0.89 (0.61-1.24)
Larynx	4	4.0	1.00 (0.27-2.54)	3	2.3	1.29 (0.27-3.75)
Oral cavity and tongue	4	1.4	2.84 (0.77-7.26)	0	0.8	0.00 (0.00-4.84)
Pharynx	2	1.6	1.28 (0.15-4.62)	1	0.9	1.06 (0.03-5.92)
Oesophagus	3	5.0	0.61 (0.13-1.77)	2	2.8	0.72 (0.09-2.61)
Pancreas	14	14.6	0.96 (0.52-1.60)	8	8.0	1.00 (0.43-1.96)
Kidney, renal pelvis	3	15.1	0.20 (0.04-0.58)	6	8.6	0.70 (0.26-1.51)
Urinary bladder	34	24.6	1.38 (0.96-1.92)	13	13.2	0.99 (0.53-1.69)
Weakly smoking-related cancers	**26**	**39.2**	**0.66 (0.43-0.97)**	**19**	**21.2**	**0.90 (0.54-1.40)**
Lip	1	4.2	0.24 (0.01-1.31)	0	2.3	0.00 (0.00-1.62)
Liver	4	6.5	0.61 (0.17-1.57)	3	3.6	0.85 (0.17-2.47)
Stomach	11	19.6	0.56 (0.28-1.00)	11	10.5	1.05 (0.52-1.87)
Leukaemia	10	8.8	1.13 (0.54-2.07)	5	4.8	1.05 (0.34-2.45)
Alcohol-related cancers (all also related to smoking)	17	19.5	0.87 (0.51-1.39)	9	11.0	0.82 (0.37-1.54)
Other						
Stomach	11	19.6	0.56 (0.28-1.00)	11	10.5	1.05 (0.52-1.87)
Rectum, rectosigmoid, anus	15	17.1	0.88 (0.49-1.44)	7	9.4	0.74 (0.30-1.53)
Colon	20	22.1	0.90 (0.55-1.39)	14	12.0	1.17 (0.64-1.96)
Prostate	137	124.6	1.10 (0.92-1.29)	72	67.1	1.07 (0.84-1.35)

Skin melanoma	7	9.3	0.75 (0.30-1.55)	8	5.4	1.48 (0.64-2.91)
Skin, non-melanoma	22	15.7	1.40 (0.88-2.11)	8	7.8	1.02 (0.44-2.01)
Brain and central nervous system	12	7.7	1.56 (0.81-2.72)	3	4.6	0.66 (0.14-1.92)
Non-Hodgkin-lymphoma	14	13.9	1.01 (0.55-1.68)	10	7.8	1.28 (0.61-2.34)
Multiple Myeloma	5	5.5	0.92 (0.30-2.14)	5	3.0	1.70 (0.55-3.96)
Not included above:						
Skin, basal cell cancer	109	82.6	1.32 (1.08-1.57)	47	44.7	1.05 (0.77-1.39)

Athletes had less lung cancers than the referents even after adjustment for smoking status (HR 0.60, 95% 0.35-1.04). The difference was attenuated with further adjustment with pack-years (HR 0.83, 95% CI: 0.43-1.60).

Kidney cancer incidence was very low and due to the low number (n=3) among the athletes, Cox modelling was not possible for this cancer.

5.3 Case-control study for the effects of the physical strain at work to the incidence of colorectal cancer

In this study more than 85,000 colon cancer cases and more than 425,000 controls as well as a little more than 60,000 rectal cancer cases and more than 300,000 controls were identified for male population. The respective numbers for females for colon cancer were almost 97,000 colon cancer cases; 480,000 controls, and for rectal cancer 49,000 cases and 246,000 controls.

A statistically significantly decreased risk and inversed dose–response relationship was detected for the exposure of PPWL and colon and rectal cancers for the combined group of men and women.

The lowest risk for colon cancer was observed for the group that had their PPWL levels above the 90th percentile (HR 0.78, 95% CI: 0.76-0.79). The risk reduction for rectal cancer was less significant (HR 0.87, 95% CI: 0.85-0.89).

The HR for the highest PPWL level-group (90th percentile) for cancer of the ascending part of the colon was in men 0.76 (95% CI: 0.73-0.80) and in women 0.90 (95% CI: 0.79-1.03). For the cancer of the transverse part of colon the HR for males was 0.76 (95% CI: 0.71-0.82) and for females 0.83 (95% CI: 0.67-1.03).

For "other colon sites" (i.e. not defined cancer site or multiple sites) the risk for males in the highest PPWL level-group was 0.74 (95% CI: 0.71-0.77) and for females 0.85 (95% CI: 0.75-0.97). For this undefined cancer site of colon a statistically significant protective effect and a dose-response relationship was detected for all PPWL groups excluding the "low" exposure level for females.

The most significant difference in the findings between male and female population for the cancer risk was detected in the descending colon: the HR for men was 0.61 (95% CI: 0.54-0.69) and the HR for women was 0.99 (95% CI: 0.69-1.40). Inclusion of the occupational co-exposures did not change the results. These results are presented in the table 9. below.

Table 9. Hazard ratios and 95% confidence intervals (95% CI) for PPWL and CRC in the case-control study on perceived physical strain at work and incidence of CRC, by sex. PPWL is categorized based on 50th and 90th percentile of cumulative exposure distribution among exposed CRC cases and controls

Cancer location PPWL level	**Males**				**Females**			
	Cases	Controls	HR	95% CI	Cases	Controls	HR	95% CI
Ascending colon								
None	9579	43158	100		20278	100703	1.00	
Low	7195	35333	0.92	0.89-0.95	10531	52751	0.99	0.96-1.02
Moderate	8204	44077	0.84	0.81-0.86	5072	25819	0.97	0.94-1.01
High	2743	16037	0.76	0.73-0.80	265	1457	0.90	0.79-1.03
			p-trend <0.01				p-trend 0.06	
Transversal colon								
None	4280	19309	1.00		7956	38774	1.00	
Low	3367	16587	0.92	0.87-0.97	4040	21048	0.93	0.89-0.97
Moderate	3726	19958	0.84	0.80-0.88	2032	10232	0.96	0.91-1.02
High	1183	6926	0.76	0.71-0.82	97	571	0.83	0.67-1.03
			p-trend <0.01				p-trend 0.01	
Descending colon								
None	1615	6751	1.00		2577	12502	1.00	
Low	1185	5790	0.86	0.79-0.94	1305	6700	0.94	0.87-1.01
Moderate	1204	6872	0.73	0.67-0.79	585	3135	0.89	0.81-0.99
High	354	2377	0.61	0.54-0.69	38	188	0.99	0.69-1.40
			p-trend <0.01				p-trend 0.03	
Other colon sites								
None	14147	63123	1.00		23337	114914	1.00	
Low	10683	51523	0.93	0.90-0.96	12600	62996	0.98	0.96-1.01
Moderate	11752	64582	0.81	0.79-0.83	5680	29962	0.93	0.90-0.96
High	3820	22782	0.74	0.71-0.77	279	1608	0.85	0.75-0.97
			p-trend <0.01				p-trend <0.01	
All colon								
None	29621	132341	1.00		54148	266893	1.00	
Low	22430	109233	0.92	0.90-0.94	28476	143495	0.98	0.96-0.99
Moderate	24886	135489	0.82	0.80-0.83	13369	69148	0.95	0.93-0.97
High	8100	48122	0.74	0.72-0.77	679	3824	0.87	0.81-0.95
			p-trend <0.01				p-trend <0.01	
Rectum								
None	19350	94187	1.00		26889	132342	1.00	
Low	15830	76694	1.01	0.99-1.03	14667	75366	0.95	0.93-0.98
Moderate	18611	94765	0.96	0.94-0.98	7283	36361	0.98	0.96-1.01
High	6228	34449	0.87	0.85-0.90	369	1971	0.93	0.83-1.04
			p-trend <0.01				p-trend 0.01	

5.4 Case-control study on the effects of physical strain at work to the incidence of prostate cancer

In this study almost 240,000 PCA-cases and 1,200,000 controls were identified. The average age at PCA-diagnosis was 72 years. Almost 25% of the cancer cases were from Finland and the rest were from Sweden. More that 80,000 PCA cases were diagnosed before PSA-testing era, and almost 160,000 PCA cases were detected during PSA-testing era. There were 22 men who were diagnosed with PCA before the age of 40 years and more than 40,000 were over 80 years old at the time of diagnosis.

SES was determined by profession, and almost 25% belonged to the upper white collar (or highest) SES-group. Almost 6% were in the lowest (lower blue collar) SES group and 1.5% were economically inactive. Study population characteristics are presented in table 10.

The lowest risk for PCA was detected for subjects with moderate cumulative PPWL level. Their HR was 0.88 (95% CI: 0.87-0.89) when compared to the references. Reduced risk was observed also for subjects with low PPWL level (HR 0.90, 95% CI: 0.89-0.91) and for those with high PPWL level (HR 0.93, 95% CI: 0.92-0.95). The risk of PCA was decreased statistically significantly, but there was no clear dose-response pattern.

We also stratified the results based on the availability of PSA-testing. The cut-off point was year 1990. The risk for the low PPWL level (50th percentile) were (before PSA-testing HR was 0.90, 95% CI: 0.89-0.91 and during PSA-testing HR was 0.89, 95% CI: 0.88-0.90) practically the same.

The HRs both before and during PSA-testing era were then adjusted for SES, but the results changed only a little. SES seemed to explain some of the differences. After adjustment for SES the HRs increased by a few percentages, but remained significant. The HRs didn't change even if they were analyzed for times before and during the PSA-testing period. The results are presented in table 11.

Table 10. Characteristics of study population in PCA data in Finland and Sweden

Characteristics	Case		Control		Total	
	n	%	n	%	n	%
Total	239835	100	1199175	100	1439010	100
Age*						
<40	22	0,01	105	0,01	127	0,01
40-60	20198	8,4	101515	8,5	121713	8,5
60-80	175645	73,2	877070	73,1	1052715	73,2
>80	43970	18,3	220485	18,4	264455	18,4
Age (mean, SD)	72,16	8,4	72,16	8,5	72,16	8,5
Country						
Finland	58921	24,6	294605	24,6	353526	24,6
Sweden	180914	75,4	904570	75,4	1085484	75,4
PSA-period*						
pre-PSA	83772	34,9	418860	34,9	502632	34,9
post-PSA	156063	65,1	780315	65,1	936378	65,1
SES						
Upper white-collar (1)	59318	24,7	257201	21,5	316519	22,0
Lower white-collar (2)	83527	34,8	424643	35,4	508170	35,3
Upper blue-collar (3)	68317	28,5	358869	29,9	427186	29,7
Lower blue-collar (4)	14102	5,9	78631	6,6	92733	6,4
Farmers (5)	11066	4,6	53500	4,5	64566	4,5
Economically inactive (6)	3503	1,5	26331	2,2	29836	2,1

Table 11. Hazard ratio and 95% confidence interval (95% CI) for PCA, by cumulative PPWL exposure in Finland and Sweden, with an without adjustment for socioeconomic status (SES) in the case-control study for the perceived physical strain at work and PCA.

	Unadjusted			Adjusted for SES		
Exposure	HR	95% CI	p-trend	HR[2]	95% CI	p-trend
Cumulative PPWL[1]						
Reference	1.00	Ref.	<0.01	1.00	Ref.	<0.01
Low	0.90	0.89-0.91		0.94	0.93-0.95	
Moderate	0.88	0.87-0.89		0.94	0.92-0.95	
High	0.93	0.92-0.95		0.97	0.95-0.99	

[1] Cut-points are based on 50th and 90th percentile of exposure distribution among exposed subjects.

6 DISCUSSION

Several studies, before the ones presented at this work, have proven that PA and good PC reduce cancer incidence of several cancer types. Especially this has been proven for colon cancer e.g. by Wolin et al. (2009) who analyzed 52 studies in their meta-analysis and yielded an RR for men of 0.76 (95% CI: 0.71, 0.82) and for women 0.79 (95% CI: 0.71, 0.88). In case-control studies the risk seemed lower (RR=0.69, 95% CI: 0.65, 0.74) than in cohort studies (RR=0.83, 95% CI: 0.78, 0.88). (Wolin et al. 2009) Similar findings have been reported in several other publications. (Kamangar, Dores, and Anderson 2006; Isomura et al. 2006; Leitzmann et al. 2015)

Moore et al (2016) reported a reduced incidence of CRC associated with LTPA. For colon cancer HR was 0.84 (95% CI: 0.77-0.91), rectal cancer HR was 0.87 (95% CI: 0.80-0.95). A decreased incidence was also reported in association with LTPA for esophageal adenocarcinoma, myeloid leukemia and myeloma as well as cancers of liver, lung, kidney, gastric cardia, endometrial, head and neck, bladder and breast. An association of LTPA with increased risks for malignant melanoma (HR 1.27; 95% CI: 1.16-1.40) and PCA (HR 1.05; 95% CI: 1.03-1.08) were reported in the same study. (Moore et al. 2016)

In some other studies, e.g. Orsini (2009) however, a 16% decrease (95% CI:2-27) in PCA incidence was detected for the men belonging to the highest 25% of lifetime PA when compared to the lowest quartile. (Orsini et al. 2009)

Norman et al (2002) collected historical data from Swedish 1960 and 1970 censuses and analyzed two cohorts of men whose PA-level they could define based on their occupational titles. They reported a significantly increased risk of PCA for the men who had a low PA-level at work.(Norman et al. 2002)

In other studies protective effects of PA have been reported also for lung cancer incidence (Moore et al. 2016; Hållmarker et al. 2015; Pukkala et al. 2009; Paffenbarger, Hyde, and Wing 1987; Pukkala et al. 1993), endometrial cancer incidence (Moore et al. 2010; Friedenreich et al. 2010; Pukkala et al. 1993; Steven C. Moore et al. 2016), ovarian cancer incidence (Cottreau, Ness, and Kriska 2000; Bertone et al. 2002), testicular cancer incidence (Brownson et al. 1991; Thune and Lund 1994), pancreatic cancer incidence (Michaud et al. 2001), kidney cancer incidence (Pukkala et al. 1993; Paffenbarger, Hyde, and Wing 1987), urinary bladder

cancer incidence (Dosemeci et al. 1993; Wannamethee, Shaper, and Walker 2001) and the incidence of the cancers of hematopoietic origin (e.g. lymphomas) (Brownson et al. 1991; Wannamethee, Shaper, and Walker 2001; Cerhan 2002).

Based on literature it seems that PA at young age is more important than PA at an older age- This seems to be the case especially with breast cancer, but possibly this also applies to PCA (Moore et al. 2009) and some other cancers as well.

The studies we have conducted support this claim. There may be several reasons for this, but the most plausible reason for this is the fact that especially those young people that participate in high level of PA at young age (between 9 and 18 years of age) would continue this habit of participating in high level of adult PA also later in life (Telama et al. 2005). In addition to that PA has several different possible ways of reducing the incidence of cancer as discussed earlier (hormonal levels, circulation etc.) but it also influences other lifestyle factors, especially diet and smoking, both of which have important roles in the development of cancer.

Some of these above mentioned study results have already changed the recommendations that are given to the general public in order to reduce the incidence of cancer. A good example of this is the information that obesity and poor PC are associated with breast cancer (Fortner et al. 2016). Unfortunately this has not had much effect on the lifestyle. We have seen over the past decades, both in Finland and especially in other western countries, increase in average body weight, sedentary behavior/work and decreased time spent in LTPA. (Power and Thomas 2011; Berry et al. 2010; Vartiainen et al. 2010) These changes are especially visible in children and young people. Young people in general are now more obese and engage less in PA than e.g. 20 years ago. (Telama and Yang 2000; Telama et al. 2005) This will probably lead to increased numbers of the above mentioned, PA and obesity -related cancers in the future.

6.1 Finnish military recruits born in 1958

During the follow-up time we detected on a bit more than 1,100 cancer cases in this cohort. We noticed that those men that had been in good or excellent PC during their military service had a lower risk of cancer in general than those that were in satisfactory or poor condition. In our analyses this difference was not statistically significant due to the low number of cancer cases in the cohort at the time of analysis. As the cohort grows older, this difference will most likely become statistically

significant. In case the young men – in addition to being in poor PC were also obese – the difference was even bigger.

The strengths of this study are the fact that this is a population based study and it encompasses a very high percentage of men born in 1958. In addition we were able to collect a large amount of data on the conscripts and their PC, which was measured in a validated manner during military service. We also have almost 100% coverage on the cancer cases detected in this population.

The weaknesses of this study are the facts that the participants were healthy when they started military service. Those with chronic illnesses (diabetes, epilepsy etc.) were not included. When drawing further conclusions we have to remember that this cohort of men born in 1958 is still relatively young, and the number of cancer cases or deaths is still quite moderate. Further follow-up of this cohort will probably confirm the above discussed conclusions.

When we look at the present data it can be seen that the division between the 'healthy' and 'unhealthy' men (based on this cohort) happens already at a young age - before the age of 20 years. This means that it is of utmost importance to increase the amount of PA of every child and young person. In Finland the policy makers could make sure that e.g. school curricula have enough time for PA during school days. In addition the policies supporting natural inclusion of PA to daily life – at work or at studies – should be implemented. These policies would be also financially a wise investment: within years the aging society will be a challenge for the health care system as chronic illnesses and the incidence of cancers will increase. It would not be impossible to evaluate that up to 10% of incident cancer cases could be avoided by smart planning and integration of PA to people's daily life.

6.2 Former male elite athletes cancer incidence

The overall cancer incidence in athletes was significantly lower-than-expected and when compared to the cancer incidence of the general public. This is mostly due to the decreased incidence of lung cancer and other smoking related cancers among the athletes. Endurance athletes and jumpers had a lower than expected overall cancer incidence. The most probable reason for the low total cancer incidence of the endurance athletes is their low incidence of smoking.

In addition to smoking less, the athletes were physically more active and less obese than their referents. About 60% of former elite athletes continued an active and sports-oriented life-style throughout their adulthood, while only less than one in

five of their age-matched controls did this. (Sarna et al. 1993; Kujala et al. 2003) Physically active lifestyle is often combined with many other healthy lifestyle choices: healthy diet and non-smoking. (Pukkala et al. 2000)

The largest differences were detected between athletes and referents in the incidence of lung and kidney cancer. The extremely low incidence for kidney cancer cannot be explained by smoking, but possibly by other PA- and SES-linked lifestyle choices. In the presented study the prevalence of current smokers didn't fully explain the differences between the two groups, but as we added of the amount of smoking as pack-years in the statistical model, it decreased significantly the difference between the athletes and the referents.

Based on our results we can conclude that former elite athlete status modifies the risk factors of cancer incidence to a positive direction. Former athletes continue even after their careers a physically active lifestyle and healthy diet.

The strengths of this study are that the athlete cohort was comprehensively identified from several sources and their lifestyle was thoroughly examined by a questionnaire in 1985. In addition to this, the Finnish registries make accurate record linkage possible and a complete long-term follow-up for the cancer incidence with little losses to follow-up is possible.

The weaknesses of this study are the fact that the athletes are not general public. Their SES are higher, their PC and PA-levels are higher than that of their referents.

6.3 Perceived physical workload and the incidence of colorectal cancer

As previously presented the association of an increased level of PA and a significant decrease in colon cancer incidence has been seen in many epidemiological studies before this study. The case of rectal cancer is a little different: the effects of PA to its incidence are either much smaller, or non-significant. (Leitzmann et al. 2015)

In the study #3 it was noticed that the incidence of CRC was inversely associated with the increase of PPWL level. The decrease was more pronounced in males than in females. The trend of risk reduction was significant in all groups that were analyzed and in every part of colon and rectum. The biggest protective effect was noticed in the distal or descending part of colon in males. In all subsites that were studied, the protective effect of PPWL was less pronounced in females.

The weaknesses of this study, as well as the one that was conducted for PCA, are that PPWL can be misclassified, because the generic JEM does not take into account

the individual differences in exposure levels in an occupational category. The incomplete work history data may also produce varying levels of misclassification on individual level. The data that we had were just snapshots with five years in between, and if a person had changed jobs from one census to another, it was estimated that the change had occurred halfway between these two censuses. This might not be true in individual case, but on population level, this accuracy is acceptable.

In addition to that we had census information from years 1960-1990 and the oldest persons may have started their work life 40 years before the first known census profession. It was concluded that if a person was still at a rather high age (in 1960 census) in a physically strenuous job, it was not likely that he would have earlier been in a physically less demanding job. This misclassification could bias our presumed OR values towards unity and lead to slightly too low estimate of the protective effect in our study.

In both of our PPWL-studies (for CRC and PCA) we could not control for several cancer causing agents: diet, smoking, alcohol use, BMI, body adiposity or genetic factors. For our study some of these issues might definitely be confounding factors as it is known that poor quality diet, smoking, excessive alcohol use as well as overweight are more frequent with people of lower SES. Those in lower SES work in professions that are physically more demanding (Kaikkonen et al. 2009), which – based on our study – protects them from colon cancer.

People in lower SES are more obese and overweight (Magnusson et al. 2014) than those in a higher SES. This could increase the incidence of CRC in lower SES-group. Even if BMI was not taken into account in our study, we were able to look at the SES. In our highest PPWL decile many of the professions belong to the lower SES-groups, and overweight and obesity are more common than in the lower PPWL-exposure groups. Based on this, the protective effect in the highest PPWL category would in reality be even stronger than what was seen in our results, if only we were able to control for BMI.

In addition to these factors, we were also unable to control for the LTPA. It can be assumed that the PA at work and leisure time would both decrease the incidence of CRC and possibly PCA.

In their meta-analysis of 21 different studies comparing the levels of PA and colon cancer subsites Boyle et al report (Boyle et al. 2012) a 27% decrease of the incidence of proximal colon cancer in the most physically active people when compared with the least active people (RR=0.73, 95% CI: 0.66-0.81). For distal colon cancer a 26% decreased risk was detected (RR=0.74, 95% CI: 0.68-0.80).

We had slightly different results. PA seemed to be in inverse dose response relationship with the incidence of CRC. There was more effect on the incidence of colon cancer in the descending part of the colon than in the ascending part of colon in men. This was not the case for women.

In our study there were only a few females in the highest decile of PPWL. Simnilarly the number of colon cancer cases in the distal part of the colon for females was small: there were 38 cases for the highest decile of PPWL. Still the 95% CI of the OR (0.69-1.40) does not overlap with that calculated for men (0.54-0.69).

There is a clear difference between the incidence of CRC in men and in women. As our analyses show, our method is robust in detecting even small differences in cancer incidence, this definitely warrants for more research.

6.4 Perceived physical workload and the incidence of prostate cancer

As previously presented data shows, there are some conflicting study results on the effects of PA to the incidence of PCA. There is some evidence supporting that PA reduces PCA incidence significantly. (Liu et al. 2011) Sedentary lifestyle is also a recognized risk factor to an increased risk of PCA. (Leitzmann et al. 2015)

Our study results show that the incidence of PCA was lower in individuals with some PPWL compared to individuals with a low PPWL, but there was no evidence of a dose-response relationship.

When interpreting our results, the same limitations of the methods – as previously mentioned in the case of CRC – should be kept in mind.

The associations between lifestyle, PA at work and the risk of PCA reported in previously published studies have been inconsistent. In a Swedish study published in 2008 lifetime total occupational PA did not prove to be protective of PCA. In this study an increased risk of PCA was detected for men that had a high amount of PA in their work. (Wiklund et al. 2008) In the US a significantly decreased risk was detected in high PA workers (Krishnadasan et al. 2008) but there are other studies, which have been modest, inconclusive or even negative. (Sass-Kortsak et al. 2007) Some of these results can be explained by small sample size and not long enough follow-up.

Advantages of the study are significant: the Nordic cancer registries have close to 100% accuracy and completeness when it comes to their data. (Pukkala et al 2017) For our follow-up – on aggregate level - we've had access to the job history of the

participants of this study to a very satisfactory degree. (Pukkala et al. 2009) These features, the completeness of the data, the long follow-up and the amount of the data make this dataset unique on a global scale.

Our study confirms the association between PA and the incidence of PCA: in fact even modest level of PA can reduce the incidence of PCA significantly.

In addition to this, we have also analyzed the results before the era of PSA-testing and during PSA-testing, and there are no significant differences. This study adds up to the findings presented earlier that especially the lack of PA and sedentary lifestyle seem to be associated with higher risk of PC than any level of PA.

6.5 Suggestions of future research

The 1958 born men's cohort is still relatively young and they are just approaching the years of increasing cancer incidence. As the cohort has now been set up and data are adding up, it is possible to study the effects of measured PC at a young age on different cancers. Some more longitudinal health data on the cohort could also be collected by the format of e.g. internet based questionnaires. This would also make the collection easier and analyzation of the data faster than in the previous and older studies.

The top athletes cohort is relatively mature already. It would be possible to collect and present mortality data on the cohort in the coming years. That way we would get information whether the healthy, young top athletes are also healthy elderly.

In the studies presented in my thesis I have been studying the effects of PA and PC to cancers with special focus on CRC and PCA.

PA seems to have a direct dose-response relationship into the incidence of CRC and many other cancers. The effects seem to vary by cancer site, and there is a big variation between the effects of PA in men and women. This should definitely be an area of interest for future studies.

PA has an effect on PCA incidence, but to our surprise there was no dose-response relationship. Anyone with a physically demanding job seems to have an approximately 10% less PCA than those in sedentary professions. The reasons behind this phenomenon are not fully understood. Maybe a longer follow-up of the Finnish Conscripts' cohort will reveal some new issues on the effects of PA and PC at a young age and how it affects PCA incidence later in life. This should also be kept in mind when planning for future studies.

7 SUMMARY AND CONCLUSIONS

These studies confirm the association between PA and the incidence of CRC as well as the incidence of PCA.

These observations support the previous study findings that the strength of the association between PPWL and colon cancer differs by subsite, which calls for further research for reasons behind this phenomenon.

In the presented studies no association was detected to the level of PA and the incidence rate of PCA. PA has effects on body BMI and body composition, but it seems that PA is also an independent modifying factor in addition to BMI. The conclusion of this finding can be that sedentary lifestyle increases PCA incidence and PA, even moderate, reduces it significantly.

In the top athlete cohort we detected that a good PC at a young age protects form many cancers later in life. In the 1958 born men's cohort it was detected that a poor PC at a young age is also an important prognostic factor for cancer incidence later in life. If a young individual – in our study a young man – is both overweight or obese and in poor PC, the association is even stronger. Based on other research this applies to females as well.

8 ACKNOWLEDGEMENTS

I couldn't have done this without you my friends and my colleagues. So many people have helped me along the way, sometimes even without knowing it, that I can't even start to mention all of your names.

Firstly I'd like to express my gratitude for my advisor professor Eero Pukkala for your tireless support, patience, immense knowledge and motivation over the several years of my PhD-studies. Without your help and guidance this work would never had been finalized.

I'd like to thank the Finnish cancer foundation for their 50 000 euro grant for making big parts of this project possible. I'd also like to thank the Finnish Cancer Registry and its personnel for allowing me to use their data and services in my research. The Nordic Cancer Union was for many years the main funder of the NOCCA -study which offered a major part of data used in my dissertation.

Besides professor Pukkala I'd like to express my gratitude to the immensely talented Mr Jan Ivar Martinsen and Dr Madar Talibov for your excellent work with the statistical analyses and for your patience to answer to all my questions.

I'd like to thank all my other co-authors – Dr Melina Arnold, Dr Heli Bäckmand, Dr Tadeusz Dyba, Prof Jaakko Kaprio, Dr Kristina Kjærheim, Prof Urho M. Kujala, Prof Seppo Sarna, Dr Isabelle Soerjomataram, Prof Pär Sparén, Prof Laufey Tryggvadottir, Prof Elisabete Weiderpass. Thank you for your vital input to the articles we have published over the last year. I hope there will be many more!

A big thank is also due for Dr Johanna Eyrun Torfadottir and Dr Liisa Pylkkänen for their help in reviewing the manuscript for this thesis.

This work would not have been possible without the important work done by Ms Päivi Haapakangas and Ms Anna Kaisa Pasanen, who collected and digitalized the data of the cohort of men born in 1958. Without your work, this study would not have been possible.

Finnish Defence Forces believed in our study proposal and gave us permission to dig into their confidential data on the men born in 1958 and I would like to thank them for it. Especially Mr Kari J. Laitinen, General Sakari Honkamaa and Prof Harri Pihlajamäki deserve a huge thank.

My co-workers, current ones and the ones I've had over these years – I thank you for your understanding and help. One very special person must be mentioned: Mr Anssi Pulkkinen – you are the one who actually opened this path to me. You told me I should do this – and so I did. I thank you for that crazy idea.

I'd like to thank my family, and especially my husband Mr Arthur Perfetto for your love, care, support and help. Thank you for moving to Finland with me and thank you for bearing with me, even those dark, cold winter nights. You are my rock.

I'd like to thank my brothers Jermu, Janne and Jyri for your love, care and the fact that you have been there when I've needed you. I am so sorry Janne, that I couldn't make this earlier so you would have still been here. This book is for you and for all the others who die too young from cancer.

9 REFERENCES

Aitio, A, and Kauppinen T. 1991. "Syöpä Ammattitautina." In Ammattitaudit 1991. Katsauksia., 121st ed. Helsinki: Työterveyslaitos.

Akeshima, R., Kigawa, J., Takahashi, M., Oishi, T., Kanamori, Y., Itamochi, H., Shimada, M., Kamazawa, S., Sato, S. and Terakawa, N. 2001. "Telomerase Activity and P53-Dependent Apoptosis in Ovarian Cancer Cells." British Journal of Cancer 84 (11): 1551–55. https://doi.org/10.1054/bjoc.2001.1812.

Akin, H., and Tözün, N. 2014. "Diet, Microbiota, and Colorectal Cancer." Journal of Clinical Gastroenterology 48: S67–69. https://doi.org/10.1097/MCG.0000000000000252.

Akinyemiju, T.F., Demb, J., Izano, M.A., Rehkopf, D.H., Fang, M.L., Hiatt, R.A. and Braithwaite, D. 2017. "The Association of Early Life Socioeconomic Position on Breast Cancer Incidence and Mortality: A Systematic Review." International Journal of Public Health. https://doi.org/10.1007/s00038-017-1060-8.

Albertsen, K. and Grønbaek, M. 2002. "Does Amount or Type of Alcohol Influence the Risk of Prostate Cancer?" The Prostate 52 (4): 297–304. https://doi.org/10.1002/pros.10120.

Alexander, D., Miller,A., Cushing, C. and Lowe, K. 2010. "Processed Meat and Colorectal Cancer: A Quantitative Review of Prospective Epidemiologic Studies." Eur J Cancer Prev.

Aparicio-Ugarriza, R., Mielgo-Ayuso, J., Benito, P.J., Pedrero-Chamizo, R., Ara, I. and González-Gross, M. 2015. "Physical Activity Assessment in the General Population; Instrumental Methods and New Technologies." Nutricion Hospitalaria. https://doi.org/10.3305/nh.2015.31.sup3.8769.

Araujo-Alvarez, J.M. and Trujillo-Ferrara, J.G. 2002. "De Morbis Artificum Diatriba 1700-2000." Salud Publica de Mexico. https://doi.org/10.1590/S0036-36342002000400010.

Arbyn, M., Xu, L., Simoens, C. and Martin-Hirsch, P.P.L. 2018. "Prophylactic Vaccination against Human Papillomaviruses to Prevent Cervical Cancer and Its Precursors." Cochrane Database of Systematic Reviews. https://doi.org/10.1002/14651858.CD009069.pub3.

Arem, H., Moore, S.C., Park, Y., Ballard-Barbash, R., Hollenbeck, A., Leitzmann, M. and Matthews, C.E. 2013. "Physical Activity and Cancer-Specific Mortality in the NIH-AARP Diet and Health Study Cohort." International Journal of Cancer. Journal International Du Cancer. https://doi.org/10.1002/ijc.28659.

Asghar, A. and Sheikh., N 2017. "Role of Immune Cells in Obesity Induced Low Grade Inflammation and Insulin Resistance." Cellular Immunology. https://doi.org/10.1016/j.cellimm.2017.03.001.

Barbieri, A., Bimonte, S., Palma, G., Luciano, A., Rea, D., Giudice, A., Scognamiglio, G. et al. 2015. "The Stress Hormone Norepinephrine Increases Migration of Prostate Cancer Cells in Vitro and in Vivo." International Journal of Oncology 47 (2): 527–34. https://doi.org/10.3892/ijo.2015.3038.

Bashir, M. N. 2015. "Epidemiology of Prostate Cancer." Asian Pacific Journal of Cancer Prevention. https://doi.org/10.7314/APJCP.2015.16.13.5137.

Benafif, S., and Eeles. R. 2016. "Genetic Predisposition to Prostate Cancer." British Medical Bulletin. https://doi.org/10.1093/bmb/ldw039.

Benke, G., Sim, M., Fritschi, L., Aldred, G., Forbes, A. and Kauppinen, T. 2001. "Comparison of Occupational Exposure Using Three Different Methods: Hygiene Panel, Job, Exposure Matrix (JEM), and Self Reports." Applied Occupational and Environmental Hygiene 16 (1): 84–91. https://doi.org/10.1080/104732201456168.

Berges, R. and Oelke, M. 2011. "Age-Stratified Normal Values for Prostate Volume, PSA, Maximum Urinary Flow Rate, IPSS, and Other LUTS/BPH Indicators in the German Male Community-Dwelling Population Aged 50 Years or Older." World Journal of Urology 29 (2): 171–78. https://doi.org/10.1007/s00345-010-0638-z.

Berglund, A., Garmo, H., Robinson, D., Tishelman, C., Holmberg, L., Bratt, O., Adolfsson, J., Stattin, P. and Lambe, M. 2012. "Differences According to Socioeconomic Status in the Management and Mortality in Men with High Risk Prostate Cancer." European Journal of Cancer. https://doi.org/10.1016/j.ejca.2011.07.009.

Bernstein, H., Bernstein, C., Payne, C. M., Dvorakova, K. and Garewal, H.. 2005. "Bile Acids as Carcinogens in Human Gastrointestinal Cancers." Mutation Research - Reviews in Mutation Research. https://doi.org/10.1016/j.mrrev.2004.08.001.

Berry, T. R., Spence, J. C. , Blanchard, C. , Cutumisu, N. , Edwards, J. and Nykiforuk, C. 2010. "Changes in BMI over 6 Years: The Role of Demographic and Neighborhood Characteristics." International Journal of Obesity 34 (8): 1275–83. https://doi.org/10.1038/ijo.2010.36.

Bertone, E.R., Newcomb, P.A., Willett, W.C., Stampfer, M.J. and Egan, K.M. 2002. "Recreational Physical Activity and Ovarian Cancer in a Population-Based Case-Control Study." International Journal of Cancer. Journal International Du Cancer 99 (3): 431–36. https://doi.org/10.1002/ijc.10365.

Bianchini, F., Kaaks, R. and Vainio, H. 2002. "Weight Control and Physical Activity in Cancer Prevention." Obesity Reviews : An Official Journal of the International Association for the Study of Obesity. https://doi.org/10.1046/j.1467-789X.2002.00046.x.

Bingham, S A. 2000. "Diet and Colorectal Cancer Prevention." Biochemical Society Transactions 28 (2): 12–16. https://doi.org/10.1042/bst0280012.

Blumenthal, U.J., Fleisher, J.M., Esrey, S.A. and Peasey, A. 2001. "Epidemiology: A Tool for the Assessment of Risk." In Guidelines, Standards, and Health : Assessment of Risk and Risk Management for Water-Related Infectious Disease, edited by Lorna Fewtrell and Jamie Bartram, 143–44. IWA Publishing.

Bongaerts, B.W.C., Van Den Brandt, P.A., Goldbohm, R.,A., De Goeij, A.F.P.M. and Weijenberg, M.P.. 2008. "Alcohol Consumption, Type of Alcoholic Beverage and Risk of Colorectal Cancer at Specific Subsites." International Journal of Cancer 123 (10): 2411–17. https://doi.org/10.1002/ijc.23774.

Boyle, T., Fritschi, L., Heyworth, J. and Bull, F. 2011. "Long-Term Sedentary Work and the Risk of Subsite-Specific Colorectal Cancer." American Journal of Epidemiology. https://doi.org/10.1093/aje/kwq513.

Boyle, T., Keegel, T., Bull, F., Heyworth, J. and Fritschi, L. 2012. "Physical Activity and Risks of Proximal and Distal Colon Cancers: A Systematic Review and Meta-Analysis." Journal of the National Cancer Institute. https://doi.org/10.1093/jnci/djs354.

Bradley, T.P., and Golden A.L. 2005. "Tobacco and Carcinogens in the Workplace." Clinics in Occupational and Environmental Medicine. https://doi.org/10.1002/mrc.1537.

Bray, F., Klint, Å., Gislum, M., Hakulinen, T., Engholm, G., Tryggvadóttir, L. and Storm, H.H. 2010. "Trends in Survival of Patients Diagnosed with Male Genital Cancers in the Nordic Countries 1964-2003 Followed up until the End of 2006." Acta Oncologica. https://doi.org/10.3109/02841860903575315.

Brown, J. C., Winters-Stone, K., Lee, A. and Schmitz, K.H. 2012. "Cancer, Physical Activity, and Exercise." In Comprehensive Physiology. https://doi.org/10.1002/cphy.c120005.

Brownson, R. C., Chang, J. C., Davis, J. R. and Smith, C. A. 1991. "Physical Activity on the Job and Cancer in Missouri." American Journal of Public Health 81 (5): 639–42. https://doi.org/10.2105/AJPH.81.5.639.

Center, M. M., Jemal, A., Smith, R. A. and Ward, E.. 2010. "Worldwide Variations in Colorectal Cancer." Diseases of the Colon and Rectum. https://doi.org/10.1007/DCR.0b013e3181d60a51.

Cerhan, J R. 2002. " Anthropometric Characteristics, Physical Activity, and Risk of Non-Hodgkin's Lymphoma Subtypes and B-Cell Chronic Lymphocytic Leukemia: A Prospective Study." American Journal of Epidemiology 156 (6): 527–35. https://doi.org/10.1093/aje/kwf082.

Cesare, M. D., Khang, Y.H., Asaria, P., Blakely, T., Cowan, M.J., Farzadfar, F., Guerrero, R. et al. 2013. "Inequalities in Non-Communicable Diseases and Effective Responses." The Lancet. https://doi.org/10.1016/S0140-6736(12)61851-0.

Chang, F., Syrjänen, S., Tervahauta, A. and Syrjänen, K. 1993. "Tumourigenesis Associated with the P53 Tumour Suppressor Gene." British Journal of Cancer 68 (4): 653–61. https://doi.org/10.1038/bjc.1993.404.

Chatterjee, A., Mambo, E.and Sidransky, D. 2006. "Mitochondrial DNA Mutations in Human Cancer." Oncogene 25 (34): 4663–74. https://doi.org/10.1038/sj.onc.1209604.

Chen, R. C., Chang, P., Vetter, R.J., Lukka, H., Stokes, W.A., Sanda, M.G., Watkins-Bruner, D., Reeve, B.B. and Sandler, H.M. 2014. "Recommended Patient-Reported Core Set of Symptoms to Measure in Prostate Cancer Treatment Trials." Journal of the National Cancer Institute 106 (7). https://doi.org/10.1093/jnci/dju132.

Cho, E., Smith-Warner, S. A., Spiegelman, D., Beeson, W.L., van den Brandt, P.A., Colditz, G.A., Folsom, A.R. et al. 2004. "Dairy Foods, Calcium, and Colorectal Cancer: A Pooled Analysis of 10 Cohort Studies." JNCI Journal of the National Cancer Institute 96 (13): 1015–22. https://doi.org/10.1093/jnci/djh185.

Coleman, M. P., Quaresma, M., Berrino, F., Lutz, J.M., De Angelis, R., Capocaccia, R., Baili, P., et al. 2008. "Cancer Survival in Five Continents: A Worldwide Population-Based Study (CONCORD)." The Lancet Oncology 9 (8): 730–56. https://doi.org/10.1016/S1470-2045(08)70179-7.

Cottreau, C M, Ness, R B. and Kriska, A. M. 2000. "Physical Activity and Reduced Risk of Ovarian Cancer." Obstetrics and Gynecology 96 (4): 609–14. https://doi.org/10.1016/S0029-7844(00)00972-8.

Couraud, S., Zalcman, G., Milleron, B., Morin, F. and Souquet, P.J. 2012. "Lung Cancer in Never Smokers - A Review." European Journal of Cancer. https://doi.org/10.1016/j.ejca.2012.03.007.

Culligan, K., F. H. Remzi, M. Soop, and J. C. Coffey. 2013. "Review of Nomenclature in Colonic Surgery - Proposal of a Standardised Nomenclature Based on Mesocolic Anatomy." Surgeon 11 (1): 1–5. https://doi.org/10.1016/j.surge.2012.01.006.

"Diet, Nutrition, Physical Activity and Colorectal Cancer." 2018. Diet, Nutrition, Physical Activity and Cancer: A Global Perspective. 2018. https://www.wcrf.org/sites/default/files/Colorectal-cancer-report.pdf.

Dosemeci, M., Hayes, R. B., Vetter, R., Hoover, R.N., Tucker, M., Engin, K., Unsal, M. and Blair, A. 1993. "Occupational Physical Activity, Socioeconomic Status, and Risks of 15 Cancer Sites in Turkey." Cancer Causes and Control 4 (4): 313–21. https://doi.org/10.1007/BF00051333.

Dossus, L., Boutron-Ruault, M-C., Kaaks, R., Gram, I.T., Vilier, A., Fervers, B., Manjer, J. et al. 2014. "Active and Passive Cigarette Smoking and Breast Cancer Risk: Results from the EPIC Cohort." International Journal of Cancer. Journal International Du Cancer. https://doi.org/10.1002/ijc.28508.

Dreyer, L, Winther, J. F., Andersen, A. and Pukkala, E. 1997. "Avoidable Cancers in the Nordic Countries. Alcohol Consumption." APMIS. Supplementum 76: 48–67.

El-Mahdani, N, Vaillant, J C Guiguet, M., Prévot, S., Bertrand, V., Bernard, C., Parc, R, Béréziat, G. and Hermelin, B. 1997. "Overexpression of P53 MRNA in Colorectal Cancer and Its Relationship to P53 Gene Mutation." British Journal of Cancer 75 (4): 528–36.

Engels, E. A., Biggar, R.J., Hall, H.I., Cross, H., Crutchfield, A., Finch, J.L., Grigg, R. et al. 2008. "Cancer Risk in People Infected with Human Immunodeficiency Virus in the United States." International Journal of Cancer. https://doi.org/10.1002/ijc.23487.

Eurostat. 2017. "Causes of Death Statistics." Http://Ec.Europa.Eu/Eurostat/Statistics-Explained/Index.Php/Causes_of_death_statistics. 2017. http://ec.europa.eu/eurostat/statistics-explained/index.php/Causes_of_death_statistics.

Exley, M. A., Hand, L., O'Shea, D. and Lynch, L. 2014. "Interplay between the Immune System and Adipose Tissue in Obesity." Journal of Endocrinology. https://doi.org/10.1530/JOE-13-0516.

Feldman, R. P., and Goodrich, J.T. 1999. "The Edwin Smith Surgical Papyrus." Child's Nervous System 15 (6–7): 281–84. https://doi.org/10.1007/s003810050395.

Ferlay, J., Steliarova-Foucher, E., Lortet-Tieulent, J., Rosso, S., Coebergh, J.W.W., Comber, H., Forman, D. and Bray, F. 2013. "Cancer Incidence and Mortality Patterns in Europe: Estimates for 40 Countries in 2012." European Journal of Cancer 49 (6): 1374–1403. https://doi.org/10.1016/j.ejca.2012.12.027.

Févotte, J, Luce, D., Arslan M, Dananché, B., Delabre, L., Ducamp, S. et al. 2006. "Surveillance Des Expositions d'origine Professionelle En Population Générale: Le Programme Matgéné." Bull Epidemiol Hebd, no. 46–47: 362–65.

Fortner, R. T., Katzke, V., Kühn, T. and Kaaks, R. 2016. "Obesity and Breast Cancer." In Recent Results in Cancer Research, 208:43–65. https://doi.org/10.1007/978-3-319-42542-9_3.

Franco, E.L., Duarte-Franco, E.L. and Ferenczy, A. 2001. "Cervical Cancer: Epidemiology, Prevention and the Role of Human Papillomavirus Infection." CMAJ.

Friedenreich, C. M., Cook, L.S., Magliocco, A.M., Duggan, M.A. and Courneya, K.S. 2010. "Case-Control Study of Lifetime Total Physical Activity and Endometrial Cancer Risk." Cancer Causes and Control 21 (7): 1105–16. https://doi.org/10.1007/s10552-010-9538-1.

Fuemmeler, B. F., Pendzich, M.K. and Tercyak, K.P. 2009. "Weight, Dietary Behavior, and Physical Activity in Childhood and Adolescence: Implications for Adult Cancer Risk." Obesity Facts. https://doi.org/10.1159/000220605.

Garland, C, Shekelle, R.B., Barrett-Connor, E., Criqui, M.H., Rossof, A.H. and Paul, O. 1985. "Dietary Vitamin D and Calcium and Risk of Colorectal Cancer: A 19-Year Prospective Study in Men." Lancet. https://doi.org/10.1016/S0140-6736(85)91694-0.

Gathirua-Mwangi, Wambui G, and Zhang, J. 2014. "Dietary Factors and Risk for Advanced Prostate Cancer." European Journal of Cancer Prevention : The Official Journal of the European Cancer Prevention Organisation (ECP). https://doi.org/10.1097/CEJ.0b013e3283647394.

Gee, D: and Greenberg, M. 2002. "Asbestos: From 'Magic' to Malevolent Mineral." Late Lessons from Early Warnings: The Precautionary Principle 1896-2000 22 (9 January 2002): 52–63.

Gehring, C., Siepmann, T., Heidegger, H. and Jeschke, U. 2016. "The Controversial Role of Human Chorionic Gonadotropin in the Development of Breast Cancer and Other Types of Tumors." The Breast 26: 135–40. https://doi.org/10.1016/j.breast.2016.01.010.

Geneletti, S., Best, N., Toledano, M.B., Elliott, P. and Richardson, S. 2011. "Uncovering Selection Bias in Case-Control Studies Using Bayesian Post-Stratification." Statistics in Medicine, 1–16. https://doi.org/10.1002/sim.0000.

Giuliano, A. R., Nyitray, A.G., Kreimer, A.R., Campbell, C.M.P., Goodman, M.T., Sudenga, S.L., Monsonego, J. and Franceschi, S. 2015. "EUROGIN 2014 Roadmap: Differences in Human Papillomavirus Infection Natural History, Transmission and Human Papillomavirus-Related Cancer Incidence by Gender and Anatomic Site of Infection." International Journal of Cancer. https://doi.org/10.1002/ijc.29082.

Glanz, K, Buller, D.B., and Saraiya, M. 2007. "Reducing Ultraviolet Radiation Exposure among Outdoor Workers: State of the Evidence and Recommendations." Environmental Health: A Global Access Science Source. https://doi.org/10.1186/1476-069X-6-22.

Globocan (IARC). 2012. "Prostate Cancer Estimated Incidence, Mortality and Prevalence Worldwide in 2012." Globocan 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.

Goldberg, M., Carton, M., Descatha, A., Leclerc, A., Roquelaure, Y., Santin, G., and Zins, M. 2017. "CONSTANCES: A General Prospective Population-Based Cohort for Occupational and Environmental Epidemiology: Cohort Profile." Occupational and Environmental Medicine. https://doi.org/10.1136/oemed-2016-103678.

Goldstraw, P, Ball, D., Jett, J.R., Le Chevalier, T., Lim, E., Nicholson, A.G. and Shepherd, F.A. 2011. "Non-Small-Cell Lung Cancer." Lancet 6736 (10): 1–14. https://doi.org/10.1016/S0140-6736(10)62101-0.

Greenblatt, M. S., Bennett, W.P., Hollstein, M. and Harris, C.C. 1994. "Mutations in the P53 Tumor Suppressor Gene: Clues to Cancer Etiology and Molecular Pathogenesis." Cancer Research 54 (18): 4855–78. https://doi.org/10.1016/0169-5002(94)92083-4.

Gremel, G., Bergman, J., Djureinovic, D., Edqvist, P-H., Maindad, V., Bharambe, B.M., Khan, W.A.Z., et al. 2014. "A Systematic Analysis of Commonly Used Antibodies in

Cancer Diagnostics." Histopathology 64 (2): 293–305. https://doi.org/10.1111/his.12255.
Guh, D. P., Zhang, W., Bansback, N., Amarsi, Z., Birmingham, C.L. and Anis, A.H. 2009. "The Incidence of Co-Morbidities Related to Obesity and Overweight: A Systematic Review and Meta-Analysis." BMC Public Health. https://doi.org/10.1186/1471-2458-9-88.
Han, D., Bonner, M.R., Nie, J. and Jo Freudenheim, L. 2013. "Assessing Bias Associated with Geocoding of Historical Residence in Epidemiology Research." Geospatial Health 7 (2): 369–74.
Harriss, D. J., Atkinson, G., Batterham, A., George, K, Cable, N.T., Reilly, T., Haboubi, N. and Renehan, A.G. 2009. "Lifestyle Factors and Colorectal Cancer Risk (2): A Systematic Review and Meta-Analysis of Associations with Leisure-Time Physical Activity." Colorectal Disease. https://doi.org/10.1111/j.1463-1318.2009.01767.x.
Hayes, J.H., and Barry, M.J. 2014. "Screening for Prostate Cancer with the Prostate-Specific Antigen Test." JAMA : The Journal of the American Medical Association 311 (11): 1143–49. https://doi.org/10.1001/jama.2014.2085.
Hecht, S.S., and Szabo, E. 2014. "Fifty Years of Tobacco Carcinogenesis Research: From Mechanisms to Early Detection and Prevention of Lung Cancer." Cancer Prevention Research. https://doi.org/10.1158/1940-6207.CAPR-13-0371.
Heikkilä, P. and Kauppinen, T. 1992. "Occupational Exposure to Carcinogens in Finland." American Journal of Industrial Medicine. https://doi.org/10.1002/ajim.4700210403.
Hoar, S K, Morrison, A.S., Cole, P. and Silverman, D.T. 1980. "An Occupation and Exposure Linkage System for the Study of Occupational Carcinogenesis." J.Occup.Med. 22 (11): 722–26.
Holick, M. F. 1994. "McCollum Award Lecture, 1994: Vitamin D - New Horizons for the 21st Century." In American Journal of Clinical Nutrition. https://doi.org/10.1093/ajcn/60.4.619.
Hong, Y.A., Goldberg, D., Ory, M.G., Towne, S.D., Forjuoh, S.N., Kellstedt, D. and Wang, S. 2015. "Efficacy of a Mobile-Enabled Web App (ICanFit) in Promoting Physical Activity Among Older Cancer Survivors: A Pilot Study." JMIR Cancer 1 (1): e7. https://doi.org/10.2196/cancer.4389.
Hosmer, D.W., and Lemeshow, S. 2004. Applied Logistic Regression Second Edition. Applied Logistic Regression. https://doi.org/10.1002/0471722146.
Hsing, A. W., Yeboah, E., Biritwum, R., Tettey, Y., De Marzo, A.M., Adjei, A., Netto, G.J. et al. 2014. "High Prevalence of Screen Detected Prostate Cancer in West Africans: Implications for Racial Disparity of Prostate Cancer." Journal of Urology 192 (3): 730–35. https://doi.org/10.1016/j.juro.2014.04.017.
Huxley, R. R., Moghaddam, A.A:, Clifton, P., Czernichow, S., Parr, C.L. and Woodward, M. 2009. "The Impact of Dietary and Lifestyle Risk Factors on Risk of Colorectal Cancer: A Quantitative Overview of the Epidemiological Evidence." International Journal of Cancer. https://doi.org/10.1002/ijc.24343.
Hållmarker, U., James, S., Michaëlsson, K., Ärnlöv, J., Sandin, F. and Holmberg, L. 2015. "Cancer Incidence in Participants in a Long-Distance Ski Race (Vasaloppet, Sweden) Compared to the Background Population." European Journal of Cancer 51 (4): 558–68. https://doi.org/10.1016/j.ejca.2014.12.009.
IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. 2012. "Chemical Agents and Related Occupations." IARC Monographs on the Evaluation

of Carcinogenic Risks to Humans / World Health Organization, International Agency for Research on Cancer. https://doi.org/now it's officially a carcinogen...

Islami, F., Moreira, D.M., Boffetta, P. and Freedland, S.J. 2014. "A Systematic Review and Meta-Analysis of Tobacco Use and Prostate Cancer Mortality and Incidence in Prospective Cohort Studies." European Urology. https://doi.org/10.1016/j.eururo.2014.08.059.

Isomura, K., Kono, S., Moore, M.A., Toyomura, K., Nagano, J., Mizoue, T., Mibu R. et al. 2006. "Physical Activity and Colorectal Cancer: The Fukuoka Colorectal Cancer Study." Cancer Science 97 (10): 1099–1104. https://doi.org/10.1111/j.1349-7006.2006.00282.x.

Johnsen, N. F., Tjønneland, A., Thomsen, B.L.R., Christensen, J., Loft, S., Friedenreich, C., Key, T.J. et al. 2009. "Physical Activity and Risk of Prostate Cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) Cohort." International Journal of Cancer 125 (4): 902–8. https://doi.org/10.1002/ijc.24326.

Jones, M.K., Harris, M.A., Peters, P.A., Tjepkema, M. and Demers, P.A. 2014. "Prostate Cancer and Occupational Exposure to Whole-Body Vibration in a National Population-Based Cohort Study." American Journal of Industrial Medicine. https://doi.org/10.1002/ajim.22354.

Jongbloet, P. H. 2006. "Do Sunlight and Vitamin D Reduce the Likelihood of Colon Cancer? Time for a Paradigm Shift?" International Journal of Epidemiology 35 (5): 1359–60.

Jørgensen, T., Andersen, L.B., Froberg, K., Maeder, U., Smith, L.V.H. and Aadahl, M. 2009. "Position Statement: Testing Physical Condition in a Population - How Good Are the Methods?" European Journal of Sport Science 9 (5): 257–67. https://doi.org/10.1080/17461390902862664.

Kahn, S. E., Hull, R.L. and Utzschneider, K.M. 2006. "Mechanisms Linking Obesity to Insulin Resistance and Type 2 Diabetes." Nature 444 (7121): 840–46. https://doi.org/10.1038/nature05482.

Kaikkonen, R., Rahkonen, O., Lallukka, T. and Lahelma, E. 2009. "Physical and Psychosocial Working Conditions as Explanations for Occupational Class Inequalities in Self-Rated Health." European Journal of Public Health 19 (5): 458–63. https://doi.org/10.1093/eurpub/ckp095.

Kamangar, F., Dores, G.M. and Anderson, W.F. 2006. "Patterns of Cancer Incidence, Mortality, and Prevalence across Five Continents: Defining Priorities to Reduce Cancer Disparities in Different Geographic Regions of the World." Journal of Clinical Oncology. https://doi.org/10.1200/JCO.2005.05.2308.

Kauppinen, T. P., Mutanen, P.O. and Seitsamo, J.T. 1992. "Magnitude of Misclassification Bias When Using a Job-Exposure Matrix." Scandinavian Journal of Work, Environment and Health 18 (2): 105–12. https://doi.org/10.5271/sjweh.1604.

Kauppinen, T., Toikkanen, T. and Pukkala, E. 1998. "From Cross-Tabulations to Multipurpose Exposure Information Systems: A New Job-Exposure Matrix." American Journal of Industrial Medicine 33 (4): 409–17. https://doi.org/10.1002/(SICI)1097-0274(199804)33:4<409::AID-AJIM12>3.0.CO;2-2.

Kauppinen, T., Heikkilä, P., Plato, N., Woldbæk, T., Lenvik, K., Hansen, J., Kristjansson, V. and Pukkala, E. 2009. "Construction of Job-Exposure Matrices for the Nordic Occupational Cancer Study (NOCCA)." Acta Oncologica 48 (5): 791–800. https://doi.org/10.1080/02841860902718747.

Kauppinen, T., Heikkilä, P., Plato, N., Woldbaek, T., Lenvik, K., Hansen, J., Kristjansson, V. and Pukkala, E. 2009. "Construction of Job-Exposure Matrices for the Nordic Occupational Cancer Study (NOCCA)." Acta Oncologica (Stockholm, Sweden) 48 (5): 791–800. https://doi.org/10.1080/02841860902718747.

Kauppinen, T., Saalo, A., Pukkala, E., Virtanen, A., Karjalainen, A., and Vuorela, R. 2007. "Evaluation of a National Register on Occupational Exposure to Carcinogens: Effectiveness in the Prevention of Occupational Cancer, and Cancer Risks among the Exposed Workers." The Annals of Occupational Hygiene. https://doi.org/10.1093/annhyg/mem030.

Kavasmaa, O.T., Tyomkin, D.B., Mehik, A., Parpala, T.M., Tonttila, P., Paananen, I., Kunelius, P., Vaarala, M.H., Ohtonen, P. and Hellström, P.A. 2013. "Changing Trends in Symptomatology, Diagnostics, Stage and Survival of Prostate Cancer in Northern Finland during a Period of 20 Years." World Journal of Surgical Oncology 11. https://doi.org/10.1186/1477-7819-11-258.

Kiernan, J.A. 2008. "Nuclear Stains." Cold Spring Harbor Protocols 3 (7). https://doi.org/10.1101/pdb.top50.

Kim, C. H., Lee, Y.C.A., Hung, R.J., McNallan, S.R., Cote, M.L., Lim, W.Y., Chang, S.C. et al. 2014. "Exposure to Secondhand Tobacco Smoke and Lung Cancer by Histological Type: A Pooled Analysis of the International Lung Cancer Consortium (ILCCO)." International Journal of Cancer. https://doi.org/10.1002/ijc.28835.

Kim, E, Coelho, D. and Blachier F. 2013. "Review of the Association between Meat Consumption and Risk of Colorectal Cancer." Nutrition Research. https://doi.org/10.1016/j.nutres.2013.07.018.

Kitagishi, Y., Kobayashi, M. and Matsuda, S. 2013. "Defective DNA Repair Systems and the Development of Breast and Prostate Cancer (Review)." International Journal of Oncology. https://doi.org/10.3892/ijo.2012.1696.

Kohl, H. W., Craig, C.L., Lambert, E.V., Inoue, S., Alkandari, J.R., Leetongin, G., Kahlmeier, S. et al. 2012. "The Pandemic of Physical Inactivity: Global Action for Public Health." The Lancet 380 (9838): 294–305. https://doi.org/10.1016/S0140-6736(12)60898-8.

Koskinen, K., Pukkala, E., Reijula, K. and Karjalainen, A. 2003. "Incidence of Cancer among the Participants of the Finnish Asbestos Screening Campaign." Scandinavian Journal of Work, Environment and Health 29 (1): 64–70. https://doi.org/10.5271/sjweh.706.

Krishna P., Nagare, S., Sneha, R.P., Sidhanth, V.S., Bindhya, C., Manasa, C. and Ganesan, T. S. 2016. "Tumour Angiogenesis—Origin of Blood Vessels." International Journal of Cancer. https://doi.org/10.1002/ijc.30067.

Krishnadasan, A., Kennedy, N., Zhao, Y., Morgenstern, H. and Ritz, B. 2008. "Nested Case-Control Study of Occupational Physical Activity and Prostate Cancer among Workers Using a Job Exposure Matrix." Cancer Causes & Control : CCC 19 (1): 107–14. https://doi.org/10.1007/s10552-007-9076-7.

Kubo, T., Ozasa, K., Mikami, K., Wakai, K., Fujino, Y., Watanabe, Y., Miki, T. et al. 2006. "Prospective Cohort Study of the Risk of Prostate Cancer among Rotating-Shift Workers: Findings from the Japan Collaborative Cohort Study." American Journal of Epidemiology. https://doi.org/10.1093/aje/kwj232.

Kujala, U.M, Marti, P., Kaprio, J., Hernelahti, M., Tikkanen, H., and Sarna, S. 2003. "Occurrence of Chronic Disease in Former Top-Level Athletes. Predominance of

Benefits, Risks or Selection Effects?" Sports Medicine 33 (8): 553–61. https://doi.org/10.2165/00007256-200333080-00001.

Lagman, R. L., Davis, M.P., LeGrand, S.B. and Walsh, D. 2005. "Common Symptoms in Advanced Cancer." Surgical Clinics of North America. https://doi.org/10.1016/j.suc.2004.11.004.

Lauby-Secretan, B., Scoccianti, C., Loomis, D., Grosse, Y., Bianchini, F. and Straif, K. 2016. "Body Fatness and Cancer — Viewpoint of the IARC Working Group." New England Journal of Medicine 375 (8): 794–98. https://doi.org/10.1056/NEJMsr1606602.

Lee, I.M., Shiroma, E.J., Lobelo, F., Puska, P., Blair, S.N., Katzmarzyk, P.T., Alkandari, J.R. et al. 2012. "Effect of Physical Inactivity on Major Non-Communicable Diseases Worldwide: An Analysis of Burden of Disease and Life Expectancy." The Lancet 380 (9838): 219–29. https://doi.org/10.1016/S0140-6736(12)61031-9.

Lee, P. N., Thornton, A.J. and Hamling, J.S. 2016. "Epidemiological Evidence on Environmental Tobacco Smoke and Cancers Other than Lung or Breast." Regulatory Toxicology and Pharmacology. https://doi.org/10.1016/j.yrtph.2016.06.012.

Leenders, M., Siersema, P.D., Overvad, K., Tjonneland, A., Olsen, A., Boutron-Ruault, M-C., Bastide, N. et al. 2015. "Subtypes of Fruit and Vegetables, Variety in Consumption and Risk of Colon and Rectal Cancer in the European Prospective Investigation into Cancer and Nutrition." International Journal of Cancer. https://doi.org/10.1002/ijc.29640.

Leighl, N. B., Rekhtman, N., Biermann, W.A., Huang, J., Mino-Kenudson, M., Ramalingam, S.S., West, H., Whitlock, S. and Somerfield, M.R. 2014. "Molecular Testing for Selection of Patients with Lung Cancer for Epidermal Growth Factor Receptor and Anaplastic Lymphoma Kinase Tyrosine Kinase Inhibitors: American Society of Clinical Oncology Endorsement of the College of American Pathologists/Internat." Journal of Clinical Oncology 32 (32): 3673–79. https://doi.org/10.1200/JCO.2014.57.3055.

Leitzmann, M., Powers, H., Anderson, A.S., Scoccianti, C., Berrino, F., Boutron-Ruault, M-C., Cecchini, M. et al. 2015. "European Code against Cancer 4th Edition: Physical Activity and Cancer." Cancer Epidemiology 39: S46–55. https://doi.org/10.1016/j.canep.2015.03.009.

Leon, M. E, Peruga, A., McNeill, A., Kralikova, E., Guha, N., Minozzi, S., Espina, C. and Schüz, J. 2015. "European Code against Cancer, 4th Edition: Tobacco and Cancer." Cancer Epidemiol. 39 (Supplement 1): S20–33.

Liang, P.S., Chen, T-Y. and Giovannucci, E. 2009. "Cigarette Smoking and Colorectal Cancer Incidence and Mortality: Systematic Review and Meta-Analysis." International Journal of Cancer. Journal International Du Cancer 124 (10): 2406–15. https://doi.org/10.1002/ijc.24191.

Lickint, F. 1930. "Tabak Und Tabakrauch Als Ätiologischer Faktor Des Carcinoms." Zeitschrift Für Krebsforschung 30 (1): 349–65. https://doi.org/10.1007/BF01636077.

Lin, P. H., Aronson, W. and Freedland, S.J. 2015. "Nutrition, Dietary Interventions and Prostate Cancer: The Latest Evidence." BMC Medicine. https://doi.org/10.1186/s12916-014-0234-y.

Lin, X., Chen, W., Wei, F., Ying, M., Wei, W. and Xie, X. 2015. "Night-Shift Work Increases Morbidity of Breast Cancer and All-Cause Mortality: A Meta-Analysis of 16

Prospective Cohort Studies." Sleep Medicine. https://doi.org/10.1016/j.sleep.2015.02.543.
Liu, Y., Hu, F., Li, D., Wang, F., Zhu, L., Chen, W., Ge, J., An, R. and Zhao, Y. 2011. "Does Physical Activity Reduce the Risk of Prostate Cancer? A Systematic Review and Meta-Analysis." European Urology. https://doi.org/10.1016/j.eururo.2011.07.007.
Loon, A.J., Brug, J., Goldbohm, R.A., van den Brandt, P.A. and Burg, J.. "Differences in Cancer Incidence and Mortality among Socio-Economic Groups." Scandinavian Journal of Social Medicine.
Magnusson, M., Sørensen, T.I.A., Olafsdottir, S., Lehtinen-Jacks, S., Holmen, T.L., Heitmann, B.L. and Lissner, L. 2014. "Social Inequalities in Obesity Persist in the Nordic Region Despite Its Relative Affluence and Equity." Current Obesity Reports 3 (1): 1–15. https://doi.org/10.1007/s13679-013-0087-2.
Majumdar, S. R., Fletcher, R.H. and Evans, A.T. 1999. "How Does Colorectal Cancer Present? Symptoms, Duration, and Clues to Location." American Journal of Gastroenterology 94 (10): 3039–45. https://doi.org/10.1111/j.1572-0241.1999.01454.x.
Malila, N., Virtanen, M.J., Virtamo, J., Albanes, D. and Pukkala, E. 2006. "Cancer Incidence in a Cohort of Finnish Male Smokers." European Journal of Cancer Prevention 15 (2): 103–7. https://doi.org/10.1097/01.cej.0000197448.49239.60.
Marchand, L, Wilkens, L.R., Kolonel, L.N., Hankin, J.H., and Lyu, L.C. 1997. "Associations of Sedentary Lifestyle, Obesity, Smoking, Alcohol Use, and Diabetes with the Risk of Colorectal Cancer." Cancer Research 57 (21): 4787–94.
McHugh, M. K., Symanski, E., Pompeii, L.A. and Delclos, G. 2010. "The Feasibility of Adapting a Population-Based Asthma-Specific Job Exposure Matrix (JEM) to NHANES." American Journal of Industrial Medicine 53 (12): 1220–24. https://doi.org/10.1002/ajim.20879.
Meader, N., King, K., Moe-Byrne, T., Wright, K., Graham, H., Petticrew, M., Power, C., White, M. and Sowden, A.J. 2016. "A Systematic Review on the Clustering and Co-Occurrence of Multiple Risk Behaviours." BMC Public Health. https://doi.org/10.1186/s12889-016-3373-6.
Meerbeeck, J., P., Fennell, D.A. and De Ruysscher, D.K.M. 2011. "Small-Cell Lung Cancer." The Lancet 378 (9804): 1741–55. https://doi.org/10.1016/S0140-6736(11)60165-7.
Mesri, E.A., Feitelson, M.A. and Munger, K. 2014. "Human Viral Oncogenesis: A Cancer Hallmarks Analysis." Cell Host and Microbe. https://doi.org/10.1016/j.chom.2014.02.011.
Michaud, D. S., Giovannucci, E., Willett, W.C., Colditz, G.A., Stampfer, M.J. and Fuchs, C.S. 2001. "Physical Activity, Obesity, Height, and the Risk of Pancreatic Cancer." JAMA 286 (8): 921–29. https://doi.org/joc10229 [pii].
Mittal, S. and El-Serag, H. 2013. "Epidemiology of Hepatocellular Carcinoma: Consider the Population." In Journal of Clinical Gastroenterology. https://doi.org/10.1097/MCG.0b013e3182872f29.
Mizoue, T. I. M., Wakai, K., Nagata, C., Shimazu, T., Tsuji, I., Otani, T. et al. 2008. "Alcohol Drinking and Colorectal Cancer in Japanese: A Pooled Analysis of Results from Five Cohort Studies." American Journal of Epidemiology 167 (12): 1397–1406. https://doi.org/10.1093/aje/kwn073.
Moore, K., L., Neugebauer, R., Van der Laan, M.J. and Tager, I.B. 2012. "Causal Inference in Epidemiological Studies with Strong Confounding." Statistics in Medicine 31 (13): 1380–1404. https://doi.org/10.1002/sim.4469.

Moore, S. C., G. L. Gierach, A. Schatzkin, and C. E. Matthews. 2010. "Physical Activity, Sedentary Behaviours, and the Prevention of Endometrial Cancer." British Journal of Cancer. https://doi.org/10.1038/sj.bjc.6605902.

Moore, S.C., Lee, I-M., Weiderpass, E., Campbell, P.T., Sampson, J.N., Kitahara, C.M., Keadle, S.K. et al. 2016. "Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults." JAMA Internal Medicine 176 (6): 816. https://doi.org/10.1001/jamainternmed.2016.1548.

Moore, S.C., Peters, T.M., Ahn, J., Park, Y., Schatzkin, A., Albanes, D., Ballard-Barbash, R., Hollenbeck, A. and Leitzmann, M.F.. 2008. "Physical Activity in Relation to Total, Advanced, and Fatal Prostate Cancer." Cancer Epidemiology Biomarkers and Prevention 17 (9): 2458–66. https://doi.org/10.1158/1055-9965.EPI-08-0403.

Moore, S.C., Peters, T.M., Ahn, J., Park, Y., Schatzkin, A., Albanes, D., Hollenbeck,A. and Leitzmann, M.F. 2009. "Age-Specific Physical Activity and Prostate Cancer Risk among White Men and Black Men." Cancer 115 (21): 5060–70. https://doi.org/10.1002/cncr.24538.

Mordukhovich, I., Reiter, P.L., Backes, D.M., Family, L., McCullough, L.E., O'Brien, K.M., Razzaghi, H. and Olshan, A.F. 2011. "A Review of African American-White Differences in Risk Factors for Cancer: Prostate Cancer." Cancer Causes & Control 22 (3): 341–57. https://doi.org/10.1007/s10552-010-9712-5.

Mraz, M. and Haluzik, M. 2014. "The Role of Adipose Tissue Immune Cells in Obesity and Low-Grade Inflammation." Journal of Endocrinology. https://doi.org/10.1530/JOE-14-0283.

Multimäki, P., Parkkola, K., Sourander, A., Haavisto, A., Nikolakaros, G. and Helenius, H. 2005. "Military Fitness Class of Finnish 18-Year-Old Men. Prediction of Military Fitness Class at Call-up with the YASR and Sociodemographic Factors." Social Psychiatry and Psychiatric Epidemiology 40 (1): 57–63. https://doi.org/10.1007/s00127-005-0847-8.

Mustelin, L., Silventoinen, K,. Pietiläinen, K., Rissanen, A. and Kaprio, J. 2009. "Physical Activity Reduces the Influence of Genetic Effects on BMI and Waist Circumference: A Study in Young Adult Twins." International Journal of Obesity. https://doi.org/10.1038/ijo.2008.258.

Nair-Shalliker, V., Smith, D.P., Egger, S., Hughes, A.M., Kaldor, J.M., Clements, M., Kricker, A. and Armstrong, B.K. 2012. "Sun Exposure May Increase Risk of Prostate Cancer in the High UV Environment of New South Wales, Australia: A Case-Control Study." International Journal of Cancer. https://doi.org/10.1002/ijc.27400.

Nelson, W. G., De Marzo, A. and Isaacs, W.B. 2003. "Prostate Cancer." New England Journal of Medicine. https://doi.org/10.1056/NEJMra021562.

Norat, T., Scoccianti, C., Boutron-Ruault, M.C., Anderson, A., Berrino, F., Cecchini, M., Espina, C. et al. 2015. "European Code Against Cancer 4th Edition: Diet and Cancer. No Title." Cancer Epidemiology. https://doi.org/10.1016/j.canep.2014.12.016.

Norman, A, Moradi, T., Gridley, G., Dosemeci, M., Rydh, B., Nyrén, O. and Wolk, A. 2002. "Occupational Physical Activity and Risk for Prostate Cancer in a Nationwide Cohort Study in Sweden." British Journal of Cancer 86 (1): 70–75. https://doi.org/10.1038/sj.bjc.6600023.

Orsini, N., Bellocco, R, Bottai, M., Pagano, M., Andersson, S.O., Johansson, J.E., Giovannucci, E. , and Wolk, A. 2009. "A Prospective Study of Lifetime Physical Activity and Prostate Cancer Incidence and Mortality." British Journal of Cancer 101 (11): 1932–38. https://doi.org/10.1038/sj.bjc.6605404.

Paffenbarger, R. S., Hyde, R.T. and Wing, A. L. 1987. "Physical Activity and Incidence of Cancer in Diverse Populations: A Preliminary Report." American Journal of Clinical Nutrition 45 (1 Suppl): 312–17.

Pagès, F., Galon, J., Dieu-Nosjean, M-C., Tartour, E., Sautès-Fridman, C. and Fridman, W-H. 2010. "Immune Infiltration in Human Tumors: A Prognostic Factor That Should Not Be Ignored." Oncogene 29 (8): 1093–1102. https://doi.org/10.1038/onc.2009.416.

Pannett, B, Coggon, D. and Acheson, E.D. 1985. "A Job-Exposure Matrix for Use in Population Based Studies in England and Wales." British Journal of Industrial Medicine 42: 777–83. https://doi.org/10.1136/oem.42.11.777.

Parkin, D. M. 2011. "Cancers Attributable to Consumption of Alcohol in the UK in 2010." British Journal of Cancer. https://doi.org/10.1038/bjc.2011.476.

Parkin, D. M., Bray, F., Ferlay, J. and Pisani, P. 2005. "Global Cancer Statistics, 2002." CA: A Cancer Journal for Clinicians 55 (2): 74–108. https://doi.org/10.3322/canjclin.55.2.74.

Peters, C.E., Demers, P.A., Kalia, S., Hystad, P., Villeneuve, P.J., Nicol, A.M., Kreiger, N. and Koehoorn, M.W. 2016. "Occupational Exposure to Solar Ultraviolet Radiation and the Risk of Prostate Cancer." Occupational and Environmental Medicine, 2016. https://doi.org/10.1136/oemed-2016-103567.

Pierotti, M.A, Sozzi, G. and Croce, C.M. 2003. "Mechanisms of Oncogene Activation." In Holland-Frei Cancer Medicine, edited by Donald Kufe, Rafael Pollock, Ralph R Weichselbaum, Robert C Jr Bast, Ted S Gansler, James F Holland, and Emil Frei, 6th editio. BC Decker.

Pischon, T., Boeing, H., Weikert, S., Allen, N., Key, T., Johnsen, N.F., Tjønneland, A. et al. 2008. "Body Size and Risk of Prostate Cancer in the European Prospective Investigation into Cancer and Nutrition." Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology 17 (11): 3252–61. https://doi.org/10.1158/1055-9965.EPI-08-0609.

Plato, N., Kauppinen, T., Heikkilä, P. and Sparén, P. 2011. "Construction of the Swedish Job Exposure Matrix for a Nordic Occupational Cancer Study, NOCCA." Occupational and Environmental Medicine 68: A19.

Plato, N., Martinsen, J.I., Sparén, P., Hillerdal, G. and Weiderpass, E. 2016. "Occupation and Mesothelioma in Sweden: Updated Incidence in Men and Women in the 27 Years after the Asbestos Ban." Epidemiology and Health 38: e2016039. https://doi.org/10.4178/epih.e2016039.

Plato, N. and Steineck, G. 1993. "Methodology and Utility of a Job???Exposure Matrix." American Journal of Industrial Medicine 23 (3): 491–502. https://doi.org/10.1002/ajim.4700230312.

Power, C. and Thomas, C. 2011. "Changes in BMI, Duration of Overweight and Obesity, and Glucose Metabolism: 45 Years of Follow-up of a Birth Cohort." Diabetes Care 34 (9): 1986–91. https://doi.org/10.2337/dc10-1482.

Pukkala, E., Engholm, G., Højsgaard Schmidt, L.K., Storm, H., Khan, S., Lambe, M., Pettersson, D., Ólafsdóttir, E., Tryggvadóttir, L., Hakanen, T., Malila, N., Virtanen, A., Johannesen, T.B., Larønningen, S., Ursin, G. 2017. "Similarities and Differences of the Nordic Cancer Registries – an Overview of Their Procedures and Data

Comparability." Acta Oncologica, no. Dec 11: 1–16. https://doi.org/10.1080/0284186X.2017.1407039.

Pukkala, E., Poskiparta, M., Apter, D., and Vihko, V. 1993. "Life-Long Physical Activity and Cancer Risk among Finnish Female Teachers." European Journal of Cancer Prevention : The Official Journal of the European Cancer Prevention Organisation (ECP).

Pukkala, Eero. 2011. "Biobanks and Registers in Epidemiological Research on Cancer." In Methods in Biobanking, Methods in Molecuolar Biology, edited by Joakim Dillner, 77–78. Totowa, Humana Press. https://doi.org/10.1007/978-1-59745-423-0_3.

Pukkala, E., Engholm, G., Højsgaard Schmidt, L.K., , Storm, H., Khan, S., Lambe, M., Pettersson, D. et al. 2017. "Nordic Cancer Registries – an Overview of Their Procedures and Data Comparability." Acta Oncologica, 2017. https://doi.org/10.1080/0284186X.2017.1407039.

Pukkala, E. and Härmä, M. 2007. "Does Shift Work Cause Cancer?" Scandinavian Journal of Work, Environment and Health, 2007. https://doi.org/10.5271/sjweh.1152.

Pukkala, E., Kaprio, J., Koskenvuo, M., Kujala, U. and Sarna, S. 2000. "Cancer Incidence among Finnish World Class Male Athletes." International Journal of Sports Medicine 21 (3): 216–20. https://doi.org/10.1055/s-2000-8878.

Pukkala, E, Martinsen, J.I., Lynge, E., Gunnarsdottir, H.K., Sparen, P., Tryggvadottir, L., Weiderpass, E. and Kjaerheim, K. 2009. "Occupation and Cancer - Follow-up of 15 Million People in Five Nordic Countries." Acta Oncologica (Stockholm, Sweden) 48 (5): 646–790. https://doi.org/10.1080/02841860902913546.

Quadrilatero, J., and Hoffman-Goetz, L. 2003. "Physical Activity and Colon Cancer. A Systematic Review of Potential Mechanisms." The Journal of Sports Medicine and Physical Fitness.

Raisamo, S. U.,Doku, D.T., Heloma, A. and Rimpelä, A.H. 2014. "Persistence of Socioeconomic Differences in Adolescents' Environmental Tobacco Smoke Exposure in Finland: 1991–2009." Scandinavian Journal of Public Health. https://doi.org/10.1177/1403494813514301.

Rao, A. R., Motiwala, H.G.and Karim, O.M.A. 2008. "The Discovery of Prostate-Specific Antigen." BJU International. https://doi.org/10.1111/j.1464-410X.2007.07138.x.

Raymond, V. M, Mukherjee, B., Wang, F., Huang, S-C., Stoffel, E.M., Kastrinos, F., Syngal, S., Cooney, K.A. and Gruber, S.B. 2013. "Elevated Risk of Prostate Cancer among Men with Lynch Syndrome." Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology 31 (14): 1713–18. https://doi.org/10.1200/JCO.2012.44.1238.

"Reasons of Death in Finland in 2015." 2017. Statistics Finland, Reasons of Death in Finland in 2015. 2017. https://www.stat.fi/til/ksyyt/2015/ksyyt_2015_2016-12-30_tie_001_en.html.

Reedijk, M., Lenters, V., Slottje, P., Pijpe, A, Peeters, P.H., Korevaar, J.C., Bueno-de-Mesquita, B. et al. 2018. "Cohort Profile: LIFEWORK, a Prospective Cohort Study on Occupational and Environmental Risk Factors and Health in the Netherlands." BMJ Open. https://doi.org/10.1136/bmjopen-2017-018504.

Reijula, J.P., and Reijula, K. 2010. "The Impact of Finnish Tobacco Legislation on Restaurant Workers' Exposure to Tobacco Smoke at Work." Scandinavian Journal of Public Health. https://doi.org/10.1177/1403494810379168.

Rohrmann, S., Linseisen, J., Key, T.J., Jensen, M.K., Overvad, K., Johnsen, N.F., Tjønneland, A. et al. 2008. "Alcohol Consumption and the Risk for Prostate Cancer in the European Prospective Investigation into Cancer and Nutrition." Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology 17 (5): 1282–87. https://doi.org/10.1158/1055-9965.EPI-07-2888.

Rundle, A., Neckerman, K.N., Sheehan, D., Jankowski, M., Kryvenko, O.N., Tang, T. and Rybicki, B.A. 2013. "A Prospective Study of Socioeconomic Status, Prostate Cancer Screening and Incidence among Men at High Risk for Prostate Cancer." Cancer Causes & Control. https://doi.org/10.1007/s10552-012-0108-6.

Rundqvist, H., Augsten, M., Strömberg, A., Rullman, E., Mijwel, S., Kharaziha, P., Panaretakis, T., Gustafsson, T. and Östman, A. 2013. "Effect of Acute Exercise on Prostate Cancer Cell Growth." PLoS ONE 8 (7). https://doi.org/10.1371/journal.pone.0067579.

Salinas, C.A., Tsodikov, A., Ishak-Howard, M. and Cooney, K.A. 2014. "Prostate Cancer in Young Men: An Important Clinical Entity." Nature Reviews Urology. https://doi.org/10.1038/nrurol.2014.91.

Sarna, S., Sahi, T., Koskenvuo, M. and Kaprio, J. 1993. "Increased Life Expectancy of World Class Male Athletes." Medicine and Science in Sports and Exercise 25 (2): 237–44. https://doi.org/10.1249/00005768-199302000-00013.

Sass-Kortsak, A. M., Purdham, J.T., Kreiger, N., Darlington, G. and Lightfoot, N.E. 2007. "Occupational Risk Factors for Prostate Cancer." American Journal of Industrial Medicine 50 (8): 568–76. https://doi.org/10.1002/ajim.20495.

Satia-Abouta, J., Galanko, J.A., Martin, C.F:, Potter, J.D., Ammerman, A. and Sandler, R.S. 2003. "Associations of Micronutrients with Colon Cancer Risk in African Americans and Whites: Results from the North Carolina Colon Cancer Study." Cancer Epidemiol Biomarkers Prev 12 (8): 747–54.

Schulte-Hermann, R., Bursch, W., Grasl-Kraupp, B., Marian, B., Torok, L., Kahl-Rainer, P. and A Ellinger. 1997. "Concepts of Cell Death and Application to Carcinogenesis." Toxicol Pathol 25 (1): 89–93. https://doi.org/10.1177/019262339702500117.

Schüz, J., Espina, E., Villain, P., Herrero, R., Leon, M.E., Minozzi, S., Romieu, I. et al. 2015. "Physical Activity Reduces the Influence of Genetic Effects on BMI and Waist Circumference: A Study in Young Adult Twins." Cancer Epidemiology. https://doi.org/10.1016/j.canep.2015.05.009.

Scoccianti, Chiara, Michele Cecchini, Annie S. Anderson, Franco Berrino, Marie Christine Boutron-Ruault, Carolina Espina, Timothy J. Key, et al. 2015. "European Code against Cancer 4th Edition: Alcohol Drinking and Cancer." Cancer Epidemiology. https://doi.org/10.1016/j.canep.2015.01.007.

Seikkula, H. A., Kaipia, A.J., Ryynänen, H., Seppä, K., Pitkäniemi, J.M., Malila, N.K. and Boström, P.J. 2018. "The Impact of Socioeconomic Status on Stage Specific Prostate Cancer Survival and Mortality before and after Introduction of PSA Test in Finland." International Journal of Cancer. https://doi.org/10.1002/ijc.31109.

Shafique, K., and Morrison, D.S. 2013. "Socio-Economic Inequalities in Survival of Patients with Prostate Cancer: Role of Age and Gleason Grade at Diagnosis." PLoS ONE. https://doi.org/10.1371/journal.pone.0056184.

Shanahan, F. 2012. "The Colonic Microbiota and Colonic Disease." Current Gastroenterology Reports 14 (5): 446–52. https://doi.org/10.1007/s11894-012-0281-5.

Silsbury, Z., Goldsmith, R., and Rushton, A. 2015. "Systematic Review of the Measurement Properties of Self-Report Physical Activity Questionnaires in Healthy Adult Populations." BMJ Open. https://doi.org/10.1136/bmjopen-2015-008430.

Slottje, P., Yzermans, C.J., Korevaar, J.C., Hooiveld, M. and Vermeulen, R.C.H. 2015. "The Population-Based Occupational and Environmental Health Prospective Cohort Study (AMIGO) in the Netherlands." BMJ Open. https://doi.org/10.1136/bmjopen-2014-005858.

Smith, A. J., Phipps, W.R., Thomas, W., Schmitz, K.H. and Kurzer, M.S.. 2013. "The Effects of Aerobic Exercise on Estrogen Metabolism in Healthy Premenopausal Women." Cancer Epidemiology Biomarkers & Prevention 22 (5): 756–64. https://doi.org/10.1158/1055-9965.EPI-12-1325.

Song, M., Garrett, W.S. and Chan, A.T. 2015. "Nutrients, Foods, and Colorectal Cancer Prevention." Gastroenterology. https://doi.org/10.1053/j.gastro.2014.12.035.

Stellman, JM, and Stellman S.D. 1996. "Cancer and the Workplace." CA Cancer J Clin. https://doi.org/10.2307/3424537.

Strid, H., Simrén, M., Störsrud, S., Stotzer, P-O. and Sadik, R. 2011. "Effect of Heavy Exercise on Gastrointestinal Transit in Endurance Athletes." Scandinavian Journal of Gastroenterology. https://doi.org/10.3109/00365521.2011.558110.

Sudhakar, A. 2009. "History of Cancer, Ancient and Modern Treatment Methods." Journal of Cancer Science & Therapy 01 (02): i–iv. https://doi.org/10.4172/1948-5956.100000e2.

Sunkara, V., and Hébert, J.R. 2015. "The Colorectal Cancer Mortality-to-Incidence Ratio as an Indicator of Global Cancer Screening and Care." Cancer 121 (10): 1563–69. https://doi.org/10.1002/cncr.29228.

Svendsen, R. P., Støvring, H., Hansen, B.L., Kragstrup, J., Søndergaard, J. and Jarbøl, D.E. 2010. "Prevalence of Cancer Alarm Symptoms: A Population-Based Cross-Sectional Study." Scandinavian Journal of Primary Health Care. https://doi.org/10.3109/02813432.2010.505412.

Syrjänen, S., Rautava, J. and Syrjänen, K. 2017. "HPV in Head and Neck Cancer—30 Years of History." Recent Results in Cancer Research. https://doi.org/10.1007/978-3-319-43580-0_1.

Syöpärekisteri. 2018. "Syöpä Suomessa - Tärkeimpiä Tilastoja 2015." 2018. https://syoparekisteri.fi/syopa-suomessa/tarkeimpia-tilastoja/.

Taanila, H., Suni, J., Pihlajamäki, H., Mattila, V.M., Ohrankämmen, O., Vuorinen, P. and Parkkari, J. 2010. "Aetiology and Risk Factors of Musculoskeletal Disorders in Physically Active Conscripts: A Follow-up Study in the Finnish Defence Forces." BMC Musculoskeletal Disorders 11. https://doi.org/10.1186/1471-2474-11-146.

Tao, L., Xiang, Y.B., Wang, R., Nelson, H.H., Gao, Y.T., Chan, K.K., Yu, M.C. and Yuan, J-M. 2010. "Environmental Tobacco Smoke in Relation to Bladder Cancer Risk--The Shanghai Bladder Cancer Study." Cancer Epidemiology Biomarkers & Prevention. https://doi.org/10.1158/1055-9965.EPI-10-0823.

Tappel, Al. 2007. "Heme of Consumed Red Meat Can Act as a Catalyst of Oxidative Damage and Could Initiate Colon, Breast and Prostate Cancers, Heart Disease and Other Diseases." Medical Hypotheses 68 (3): 562–64. https://doi.org/10.1016/j.mehy.2006.08.025.

Telama, R. and Yang, X. 2000. "Decline of Physical Activity from Youth to Young Adulthood in Finland." Medicine & Science in Sports & Exercise, 1617–22. https://doi.org/10.1097/00005768-200009000-00015.

Telama, R., Yang, X., Viikari, J., Välimäki, I., Wanne, O and Raitakari, O. 2005. "Physical Activity from Childhood to Adulthood: A 21-Year Tracking Study." American Journal of Preventive Medicine 28 (3): 267–73. https://doi.org/10.1016/j.amepre.2004.12.003.

Terry, P., Giovannucci, E., Michels, K.B., Bergkvist, L., Hansen, H., Holmberg, L. and Wolk, A. 2001. "Fruit, Vegetables, Dietary Fiber, and Risk of Colorectal Cancer." Journal of the National Cancer Institute 93 (7): 525–33. https://doi.org/10.1093/JNCI/93.7.525.

Thomas, G. A., Kraemer, W.J., Comstock, B.A., Dunn-Lewis, C., Maresh, C.M., and Volek, J.S. 2013. "Obesity, Growth Hormone and Exercise." Sports Medicine. https://doi.org/10.1007/s40279-013-0064-7.

Thune, I, and Lund, E. 1994. "Physical Activity and the Risk of Prostate and Testicular Cancer: A Cohort Study of 53,000 Norwegian Men." Cancer Causes & Control : CCC 5 (6): 549–56.

———. 1996. "Physical Activity and Risk of Colorectal Cancer in Men and Women." British Journal of Cancer 73 (9): 1134–40. https://doi.org/10.1038/bjc.1996.218.

Thune, I. and Furberg, A-S.. 2001. "Physical Activity and Cancer Risk: Dose-Response and Cancer, All Sites and Site-Specific." Medicine and Science in Sports and Exercise 33 (Supplement): S530–50. https://doi.org/10.1097/00005768-200106001-00025.

Torre, L. A., Bray, F., Siegel, R.L., Ferlay, J., Lortet-Tieulent, J. and Jemal, A. 2015. "Global Cancer Statistics, 2012." CA: A Cancer Journal of Clinicians. 65 (2): 87–108. https://doi.org/10.3322/caac.21262.

Tupakkalaki. 2016. Helsinki: Suomen Eduskunta.

Vartiainen, E., Laatikainen, T., Peltonen, M., Juolevi, A., Männistö, S., Sundvall, J., Jousilahti, P., Salomaa, P., Valsta, L. and Puska, P. 2010. "Thirty-Five-Year Trends in Cardiovascular Risk Factors in Finland." International Journal of Epidemiology 39 (2): 504–18. https://doi.org/10.1093/ije/dyp330.

Vecchia, C., D'Avanzo, B., Negri, E. and Franceschi, S. 1991. "History of Selected Diseases and the Risk of Colorectal Cancer." Eur J Cancer 27 (5): 582–86.

Vecchia, Carlo La. 2011. "Diabetes Mellitus, Medications for Type 2 Diabetes Mellitus, and Cancer Risk." Metabolism: Clinical and Experimental, 2011. https://doi.org/10.1016/j.metabol.2011.03.011.

Vineis, P., and Wild., C.P. 2014. "Global Cancer Patterns: Causes and Prevention." The Lancet. https://doi.org/10.1016/S0140-6736(13)62224-2.

Waldron, H. A. 1983. "On the History of Scrotal Cancer." Annals of the Royal College of Surgeons of England 65 (6): 420–22. https://doi.org/10.1136/oem.40.4.390.

Wang, M. C, Valenzuela, L.A:, Murphy, G.P. and Chu, T.M. 1979. "Purification of a Human Prostate Specific Antigen." Investigative Urology 167 (2 Pt 2): 960-4; discussion 964-5. https://doi.org/10.1016/S0022-5347(02)80311-1.

Wannamethee, S. G., Shaper, A.G. and Walker, M. 2001. "Physical Activity and Risk of Cancer in Middle-Aged Men." British Journal of Cancer 85 (9): 1311–16. https://doi.org/10.1054/bjoc.2001.2096.

Weiderpass, E, and Pukkala, E. 2006. "Time Trends in Socioeconomic Differences in Incidence Rates of Cancers of Gastro-Intestinal Tract in Finland." BMC Gastroenterology 6. https://doi.org/10.1186/1471-230X-6-41.

Wertheim, B.C., Martínez, M.E., Ashbeck,cE.L., Roe, D.J., Jacobs, E.T., Alberts, D.S:, and Thompson, P.A. 2009. "Physical Activity as a Determinant of Fecal Bile Acid Levels." Cancer Epidemiology Biomarkers and Prevention 18 (5): 1591–98. https://doi.org/10.1158/1055-9965.EPI-08-1187.

West, D.W., Slattery, M.L., Robison, L.M., Schuman, K.L., Ford, M.H., Mahoney, A.W., Lyon, J.L., and Sorensen, A.W.. 1989. "Dietary Intake and Colon Cancer: Sex- and Anatomic Site-Specific Associations." American Journal of Epidemiology 130 (5): 883–94. https://doi.org/10.1093/oxfordjournals.aje.a115421.

Wiklund, F., Lageros, Y.T., Chang, E., Balter, K., Johansson, J-E., Adami, H-O., and Gronberg, H. 2008. "Lifetime Total Physical Activity and Prostate Cancer Risk: A Population-Based Case-Control Study in Sweden." European Journal of Epidemiology 23 (11): 739–46. https://doi.org/10.1007/s10654-008-9294-7.

Willett, W.C, Stampfer, M.J., Colditz, G.A., , Rosner, B.A. and Speizer, F.E.. 1990. "Relation of Meat, Fat and Fiber Intake to the Risk of Colon Cancer in a Prospective Study Among Women." NEJM 323: 1664–72.

Winzer, B. M, Whiteman, D.C. , Reeves, M.C., and Paratz, J.D. 2011. "Physical Activity and Cancer Prevention: A Systematic Review of Clinical Trials." Cancer Causes & Control : CCC 22 (6): 811–26. https://doi.org/10.1007/s10552-011-9761-4.

Wolin, K Y, Yan, Y., Colditz, G.A., and Lee, IM. 2009. "Physical Activity and Colon Cancer Prevention: A Meta-Analysis." British Journal of Cancer 100 (4): 611–16. https://doi.org/10.1038/sj.bjc.6604917.

World Cancer Research Fund, and American Institute for Cancer Research. 2007. Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective. Cancer Research. https://doi.org/978-0-9722522-2-5.

World Health Organization. 2015. "IARC Monographs Evaluate Consumption of Red Meat and Processed Meat and Cancer Risk." International Agency of Research on Cancer. https://doi.org/http://www.who.int/features/qa/cancer-red-meat/en/.

Xie, Jianlin, and Steven H. Itzkowitz. 2008. "Cancer in Inflammatory Bowel Disease." World Journal of Gastroenterology. https://doi.org/10.3748/wjg.14.378.

Young, E. K., Purdham, N. and Sass-Kortsak, A. 2009. "Prostate Cancer and Driving Occupations: Could Whole Body Vibration Play a Role?" International Archives of Occupational and Environmental Health. https://doi.org/10.1007/s00420-009-0403-z.

Åkerstedt, T, Narusyte, J, Svedberg,P, Kecklund, G, and Alexanderson, K. 2017. "Night Work and Prostate Cancer in Men: A Swedish Prospective Cohort Study." BMJ Open. https://doi.org/10.1136/bmjopen-2016-015751.

ORIGINAL PUBLICATIONS

BMJ Open

Cohort profile: a nationwide cohort of Finnish military recruits born in 1958 to study the impact of lifestyle factors in early adulthood on disease outcomes

Jorma Sormunen,[1,2] Melina Arnold,[3] Isabelle Soerjomataram,[3] Eero Pukkala[1,4]

To cite: Sormunen J, Arnold M, Soerjomataram I, *et al*. Cohort profile: a nationwide cohort of Finnish military recruits born in 1958 to study the impact of lifestyle factors in early adulthood on disease outcomes. *BMJ Open* 2017;**7**:e016905. doi:10.1136/bmjopen-2017-016905

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-016905).

Received 30 March 2017
Revised 13 July 2017
Accepted 10 August 2017

[1]Faculty of Social Sciences, University of Tampere, Tampere, Finland
[2]Department of Oncology, Tampere University Hospital, Tampere, Finland
[3]Section of Cancer Surveillance, International Agency for Research on Cancer, Lyon, France
[4]Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland

Correspondence to
Dr Jorma Sormunen;
jorma.sormunen@gmail.com

ABSTRACT

Purpose The cohort was set up to study the impact of lifestyle factors in early adulthood on disease outcomes, with a focus on assessing the influence of body composition and physical performance in early adulthood on subsequent cancer risk.

Participants Men born in 1958 who performed their military service between the ages of 17 and 30 years were included in this study (n=31 158). They were eligible for military service if they were healthy or had only minor health problems diagnosed at the beginning of their service. Men with chronic illnesses requiring regular medication or treatment were not eligible for service. Comprehensive health data including diagnosed illnesses, anthropometric measures and health behaviour were collected at the beginning and at the end of military service, including data from medical check-ups.

Findings to date During the follow-up, 1124 new cancer cases were diagnosed between baseline (ie, end of the military service for each individual) and end of the year 2014. In the end of the follow-up, 91% of the study participants were still alive. Overweight (body mass index (BMI) ≥25 kg/m^2) and obesity (BMI ≥30 kg/m^2) were associated with an overall increased risk of cancer. A good or excellent physical condition significantly reduced cancer risk.

Future plans The dataset offers the possibility of linkage with other databases, such as the Finnish Cancer Registry (eg, primary site of the tumour, morphology, time of detection, spreading and primary treatment), vital statistics (date of emigration or deaths), censuses (socioeconomic indicators), hospital discharge data (comorbidity) and population surveys (life habits).

Strengths and limitations of this study

- The large number of a proportion-representative sample of men born in 1958 in Finland included in this study.
- A thorough evaluation performed by medical personnel and measurement of different health variables in a uniform manner.
- Possibility for a wide range of linkages with different registries.
- The cohort is not fully representative of the male population born in 1958, which means that the results cannot be fully generalised to the entire population. Those suffering from chronically bad health before military service and those who chose to pursue their national service in civil service for any reason (ethical or religious) were not included in the cohort.
- We only have data from the military conscripts collected during their military service, when their average age was 20 years.

INTRODUCTION

The Finnish Military Recruits Cohort was set up to study the impact of several lifestyle factors in early adulthood on disease outcomes. Military service in Finland is mandatory for men at the age of 17–30 years for a period of 8–11 months, meaning that virtually every Finnish man can be traced back in military records. In 2012, we started electronic transcription of the paper-based medical examination records at entry and exit of the mandatory military service of all men born in 1958, which was the oldest full dataset available to us. These records contain demographic information, data on common health risk factors such as tobacco smoking or height and weight, measurements of general physical performance, a standard medical examination such as blood pressure, results of basic urine examinations (sugar, proteins, leucocytes, nitrites and bacteria) and eyesight screening tests as well as self-reported health status.

One of the initial aims of this study was to document and assess the influence of early adulthood body composition and physical performance on adult cancer risk. This was motivated by the increasing burden of disease particularly in high-income countries such as Finland that has been linked to the growing proportion of the population with insufficient physical activity and high body weight. Regular physical activity (PA) and a healthy

body weight have been reported to positively impact general health and have been associated with lower risks of several non-communicable diseases including cardiovascular diseases,[1] diabetes[2] and cancer.[3 4]

In men, regular PA shows sufficient evidence to protect from colorectal cancer.[5 6] Similar associations have also been suggested for prostate[7–9] and bladder cancer, yet evidence is still inconsistent.[10 11] Previous research from Finland has shown that the incidence of cancer among world-class male athletes is reduced when compared with the general population, with the largest risk reduction seen in lung cancer (standardised incidence ratio (SIR) 0.40, 95% CI: 0.27 to 0.55) and kidney cancer (SIR 0.23, 95% CI: 0.06 to 0.57).[12 13] As for high body weight, certain cancer sites have been causally linked to body weight, including cancers of the oesophagus (adenocarcinoma), gastric cardia, colorectum, gallbladder, pancreas, liver, breast (postmenopausal), endometrium, ovary, kidney and prostate (non-localised).[14]

Two trained clerks performed the data extraction from paper-based military records (hard copy) into electronic format. The quality of the collected data was continuously monitored both by check-up tools built in the data input programme and by following the summary input statistics.

Cohort description

The cohort consists of men born in 1958, who served in the Finnish Defence Forces (FDF). There is a universal male conscription in Finland for either military service or civil service, which is usually completed at the age of 20 years. At the time of the service of the cohort in question (entry between 1975 and 1989), men were liable to serve between 240 and 330 days depending on the level of training they were to receive. Of the men born in 1958, almost 90% started their military service, whereas the rest either served in civil service or were completely liberated from the service.

In total, the cohort comprises 31 158 men born in 1958, who were randomly selected from the total population and represent 74% of all Finnish men born in 1958. The average age at study entry was 20 years (range 17–31 years). In the end of 2014, 91% of all study participants were still alive.

During their military service, the conscripts were followed-up by healthcare professionals at least twice (at the beginning and at the end of their military service). Their physical condition (PC) was recorded at least once during their military service. Owing to unique person identifiers, record linkage with health and administrative databases allows for a wide range of epidemiological studies on different outcomes in this cohort. Follow-up for incident cancers is currently available until the end of 2014, with annual updates envisaged depending on relevant research questions.

Box List of the variables collected at study entry for each member of the cohort

- Personal identity code of the individual
- Professional group
- Marital status
- Beginning of military service (date)
- End of military service (date)
- Reason for preliminary discontinuation of military service (diagnosis)
- Duration of military service
- Military service classifications at different stages of the service
- Classification diagnoses at different stages of the military service
- Self-perceived health status at the beginning and at the end of the service
- Height and weight at different stages of the service
- Blood pressure at different stages of the service
- Physical condition test results at different stages of the service
  - Twelve-minute running test results
  - Muscle strength test results
- Smoking status and amount smoked at different stages of the service
- Use of alcohol and the amount drunken at different stages of the service

WHAT HAS BEEN MEASURED?

At the start of military service (baseline)

All baseline measurements were performed by healthcare professionals (nurses, physicians and dentists) at the beginning of the military service (between 1975 and 1989). After an initial health check, a fitness classification (A–E) was assigned to each conscript, based on his health. Class A indicates good physical and mental health and capability of field service. Men with B-classification were fit for lighter service troops, with health conditions not needing regular treatment or medication, for example, flat foot. C-classified men were liberated from peacetime service, and D-classified men were exempted from military service completely. Men classified as C typically need regular treatment for their condition (eg, diabetes) but are otherwise healthy and can thus be drafted at wartime. D-classified men have a condition that affects their daily life so seriously that they cannot be drafted even during wartime. E-classification means deferment for medical reasons up to 3 years. Diagnoses leading to E-classification are typically young men's adjustment disorders.[15]

After the baseline medical check-up, the basic PC of the conscripts was measured by a 12 min running test and a test measuring muscle strength. Data on health behaviour (eg, smoking habits and alcohol consumption) were collected during the medical check-ups. A detailed list of all demographic, behavioural and health data items collected at baseline is presented in box. At recruitment, 91.5% of the men were healthy (classified to service class A), and 7.1% had minor health problems (service class B) (table 1). In addition, 411 men were classified to service classes C, D or E before the end of the military service (beginning of the follow-up). The majority of all men had a normal weight at recruitment (body mass index, BMI 18.5–25 kg/m^2), 10.6% were overweight (BMI 25–30 kg/m^2) and 1.4% were obese (BMI >30 kg/

Table 1 Cohort characteristics at study entry (n=31 158)

	n	%
Service classification		
A (healthy)	28 520	91.5
B (minor health problems)	2227	7.1
C or D	192	0.6
Missing	219	0.7
Smoking status		
Yes	10 707	34.4
No	16 066	51.6
Missing	4385	14.1
Cigarettes/day among smokers		
<10 cigarettes/day	2010	18.8
10–19 cigarettes/day	5657	52.8
≥20 cigarettes/day	2862	26.7
Missing	178	1.7
Alcohol consumption		
Yes	19 052	61.1
No	8097	26.0
Missing	4009	12.9
BMI		
Underweight (BMI <18.5)	1489	4.8
Normal weight (18.5≤BMI<25)	25 939	83.2
Overweight (25≤BMI<30)	3294	10.6
Obesity (BMI ≥30)	421	1.4
Missing	15	0.0
Body surface area		
<2 m^2	26 729	85.8
≥2 m^2	4415	14.2
Missing	14	0.0
Overall PC		
Bad	1326	4.3
Satisfying	6294	20.2
Good	12 707	40.8
Excellent	5503	17.7
Missing	5328	17.1
BMI and PC cross-category		
BMI <25 and good/excellent PC	16 930	54.3
BMI ≥25 and good/excellent PC	1277	4.1
BMI <25 and bad/satisfying PC	6001	19.3
BMI ≥25 and bad/satisfying PC	1618	5.2
Missing	5332	17.1

BMI, body mass index; PC, physical condition.

m^2). Overall PC was excellent in 17.7%, good in 40.8% and satisfactory or bad in 24.5%. Most men with BMI <25 were also in a good or excellent PC, whereas the overweight and obese men (BMI ≥25) were more likely to be in a satisfactory or bad PC. Overall, 51.6% of the men were non-smokers, and 26.0% stated at the beginning of their military service that they did not consume any alcohol. The number of men in service classes C and D was small so these data are not separately reported.

At the end of military service

Typically, assessments of PC take place at least twice during the military service of each conscript, including medical check-ups at the beginning and at the end of military service. The medical check-up at the end of military service has the same elements as the check-up at the beginning even though it is usually not as rigorously followed as the medical check-up at the beginning. This is because self-perceived health is considered the most important health indicator at the end of the service, only significant changes in this indicator lead to a rigorous medical check-up.

Follow-up via record linkage

After a complete transcription of the military records, the cohort data were linked with the Finnish Cancer Registry (FCR); National Population Registry (date of emigration or death) and censuses (socioeconomic indicators), hospital discharge data (morbidity) and the cause of death register at Statistics Finland. The linkage required approvals by the FDF and the National Institute of Health and Welfare in Finland. The high-quality FCR data contains information on cancer diagnosis date, type and location of the cancer (topography), morphology, spreading of the cancer and the primary treatment method.[16]

All record linkages were performed using the unique personal identity code (PIC) given to every resident of Finland and used as the key in all registries in Finland. PICs of the men in the cohort collected from the paper-based files were first linked to the Population Registry and checked that every person existed in the population either alive or with date of emigration or death.

In our raw data collection system, we had a built-in mechanism for checking the correct format of the PICs. Only 26 PICs were not found in the population registry. In addition, we had one PIC of wrong gender. These individuals were excluded from the cohort.

Statistical methods

Cox proportional hazard models with age as underlying time metric were fitted to estimate HRs and 95% CIs) for the relation between each study variable and the risk of developing malignant cancer by site. Subjects were censored as they emigrated from Finland or died before the end of follow-up (31 December 2014), whichever occurred first. All analyses were carried out using Stata 13.

Results: findings to date

In this first presentation of this cohort, we demonstrate the linkage that was done with the FCR to obtain data on cancer incidence. We furthermore assessed the

association between tobacco smoking, alcohol use and anthropometric measures as reported in young adulthood (at study baseline) and cancer risk. All men, except those with a missing service classification (n=219), those with service classification C or D (n=192) and those with a cancer diagnosis before the end of the military service (n=5) were included in the follow-up. The final study sample comprised 30 742 men.

During the follow-up, 1124 new cancer cases were diagnosed between baseline (ie, end of the military service for each individual) and end of the year 2014. Study variables were BMI (weight in kilogram divided by height in square metre), overall PC (excellent/good/satisfying/bad), service classification (A/B), smoking status (yes/no) and amount (cigarettes/day) and alcohol use (yes/no).

More than three decades after the end of their military service, this is the first epidemiological assessment of the impact of PC, body composition and certain lifestyle factors (eg, smoking and alcohol consumption), measured in young adulthood, on cancer risk later in life.

Overweight (BMI ≥25 kg/m^2) and obesity (BMI ≥30 kgm^2) were associated with an overall increased, but statistically not significant, risk of cancer (age-adjusted HR: 1.08, 95% CI: 0.89 to 1.30), a good or excellent PC significantly reduced cancer risk (HR: 0.82, 95% CI: 0.71 to 0.95). When compared with those with normal weight and good PC, those with normal weight but bad PC had an increased risk of all cancers combined (HR: 1.18, 95% CI: 1.01 to 1.38). Men who were in poor PC and also were overweight had an HR of 1.30 (95% CI: 1.01 to 1.69) when compared with those with normal weight and good PC. These associations however decreased and became statistically insignificant (respective HRs: 1.05 (95% CI: 0.88 to 1.26) and 1.13 (95% CI: 0.85 to 1.50)) when adjusted for smoking, alcohol consumption and service class. Men in service class B were at a more than threefold higher risk of advanced prostate cancer as compared with those in service class A (HR adjusted for age, PC, BMI, smoking and alcohol use: 3.35, 95% CI: 1.14 to 9.90).

To further validate health indicators available for this cohort, we also observed a dose–response relationship between the number of cigarettes smoked daily and total cancer incidence. The HR among those who smoked 20 cigarettes or more per day was 1.54 (95% CI: 1.25 to 1.89). Increased risk was most pronounced for incidence of lung cancer (HR: 9.65, 95% CI: 4.83 to 19.27).

Main strengths and weaknesses

The main strength of this study is the large number of a proportion-representative sample of men born in 1958 in Finland included in this study. A thorough evaluation performed by medical personnel and measurement of different health variables including general health and PC were measured in a uniform manner. The FDF have a thorough training protocol for all military and medical personnel especially for classifying service class and to measure PC. Over the 14-year period (1975–1989) during which the men in the cohort completed their service, there were neither new service class classifications nor PC measurement methods introduced in the FDF. We believe that the data we collected from the military records are of high quality.

Situated in Finland, this cohort provides the possibility for a wide range of linkages with different registries. In this first study, we linked the cohort data to the FCR and validated associations with BMI, PC and smoking.

Usually, ill-health seems to be associated with poor PC or high BMI, which in turn are related to some other factors typical with low socioeconomic status (SES). Finland has tried to take steps in order to decrease these risks. Owing to cheap universal health coverage in Finland, all Finns have similar access to healthcare independent of their financial or SES. In addition to this, most Finnish municipalities encourage people to improve their health by physical exercise and by offering planned activities for people of all ages, even people with disabilities.

Some weaknesses should be noted in relation to these data. First, the cohort is not fully representative of the male population born in 1958, which means that the results cannot be fully generalised to the entire population. Those suffering from chronically bad health (eg, development disorders or mental disorders) before military service and those who chose to pursue their national service in civil service for religious, ethical or other reasons were not included in the cohort, but their proportion is small.

Second, we only have data from the military conscripts collected during their military service, lasting between 8 and 11 months. The conscripts were between the ages of 17 and 30 years at the beginning of their military service. We do not have data on the possible changes in their health habits after the completion of their service. Considering the relatively stable life habits in the majority of the population and the long lag related to cancer development, we believe that the changes in the health habits do not markedly confound our results. In the future, linkage with national population survey data, such as the FINRISK study (extensive population study on risk factors behind chronic diseases, whici is carried out by the National Institute for Health and Welfare THL), which is conducted every 5 years since 1972,[17] will allow for better understanding of the magnitude of changes in the risk factors measured during the military service, as well as other risk factors. A marked proportion of the young-age cancers detected up-to-date may have a genetic background which was not taken into account in the present analyses. It is, however, possible to identify first-degree family members of the men in our cohort from the Finnish Population Registry and then link their PICs to the FCR to get information on cancer cases in the family.

At present, the cohort is still relatively young, with moderate number of cancer cases or deaths. However, preliminary results of this cohort show that it can already

be used for epidemiological purposes and will become even more interesting as the cohort grows older.

Acknowledgements We thank the important work done by Päivi Haapakangas and Anna Kaisa Pasanen, who collected and digitalised the data. Without their work, this study would not be possible.

Contributors JS, EP, MA and IS were responsible for the planning, data collection, data analysis and preparing of the manuscript. All authors have contributed equally. The project has been managed by JS.

Funding This work was supported by a grant of €50 000 from the Finnish Cancer Foundation.

Competing interests None declared.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The study data are not freely available due to confidentiality reasons, but the research team welcomes potential collaboration with other researchers. For further information, contact the author EP at the Finnish Cancer Registry (eero.pukkala@cancer.fi) or JS (jorma.sormunen@fimnet.fi).

REFERENCES

1. Vanhees L, De Sutter J, GeladaS N, *et al*. Importance of characteristics and modalities of physical activity and exercise in defining the benefits to cardiovascular health within the general population: recommendations from the EACPR (Part I). *Eur J Prev Cardiol* 2012;19:670–86.
2. Lamb MJ, Westgate K, Brage S, *et al*. Prospective associations between sedentary time, physical activity, fitness and cardiometabolic risk factors in people with type 2 diabetes. *Diabetologia* 2016;59:110–20.
3. Brenner DR. Cancer incidence due to excess body weight and leisure-time physical inactivity in Canada: implications for prevention. *Prev Med* 2014;66:131–9.
4. de Vries E, Soerjomataram I, Lemmens VE, *et al*. Lifestyle changes and reduction of colon cancer incidence in Europe: a scenario study of physical activity promotion and weight reduction. *Eur J Cancer* 2010;46:2605–16.
5. Boyle T, Keegel T, Bull F, *et al*. Physical activity and risks of proximal and distal colon cancers: a systematic review and meta-analysis. *J Natl Cancer Inst* 2012;104:1548–61.
6. Friedenreich CM, Neilson HK, Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. *Eur J Cancer* 2010;46:2593–604.
7. De Nunzio C, Presicce F, Lombardo R, *et al*. Physical activity as a risk factor for prostate cancer diagnosis: a prospective biopsy cohort analysis. *BJU Int* 2016;117.
8. Johnsen NF, Tjønneland A, Thomsen BL, *et al*. Physical activity and risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Int J Cancer* 2009;125:902–8.
9. Darlington GA, Kreiger N, Lightfoot N, *et al*. Prostate cancer risk and diet, recreational physical activity and cigarette smoking. *Chronic Dis Can* 2007;27:145–53.
10. Liu Y, Hu F, Li D, *et al*. Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis. *Eur Urol* 2011;60:1029–44.
11. Keimling M, Behrens G, Schmid D, *et al*. The association between physical activity and bladder cancer: systematic review and meta-analysis. *Br J Cancer* 2014;110:1862–70.
12. Sormunen J, Bäckmand HM, Sarna S, *et al*. Lifetime physical activity and cancer incidence—a cohort study of male former elite athletes in Finland. *J Sci Med Sport* 2014;17:479–84.
13. Pukkala E, Kaprio J, Koskenvuo M, *et al*. Cancer incidence among Finnish world class male athletes. *Int J Sports Med* 2000;21:216–20.
14. Anderson AS, Key TJ, Norat T, *et al*. European code against cancer 4th Edition: obesity, body fatness and cancer. *Cancer Epidemiol* 2015;39:S34–S45.
15. Multimäki P, Parkkola K, Sourander A, *et al*. Military fitness class of Finnish 18-year-old men—prediction of military fitness class at call-up with the YASR and sociodemographic factors. *Soc Psychiatry Psychiatr Epidemiol* 2005;40:57–63.
16. Teppo L, Pukkala E, Lehtonen M. Data quality and quality control of a population-based cancer registry. Experience in Finland. *Acta Oncol* 1994;33:365–9.
17. Borodulin K, Vartiainen E, Peltonen M, *et al*. Forty-year trends in cardiovascular risk factors in Finland. *Eur J Public Health* 2015;25:539–46.

BMJ Open

Cohort profile: a nationwide cohort of Finnish military recruits born in 1958 to study the impact of lifestyle factors in early adulthood on disease outcomes

Jorma Sormunen, Melina Arnold, Isabelle Soerjomataram and Eero Pukkala

*BMJ Open*2017 7:
doi: 10.1136/bmjopen-2017-016905

Journal of Science and Medicine in Sport 17 (2014) 479–484

Contents lists available at ScienceDirect

Journal of Science and Medicine in Sport

journal homepage: www.elsevier.com/locate/jsams

Original research

Lifetime physical activity and cancer incidence—A cohort study of male former elite athletes in Finland

Jorma Sormunen[a,*], Heli M. Bäckmand[b,c], Seppo Sarna[b], Urho M. Kujala[d], Jaakko Kaprio[b,e,f], Tadeusz Dyba[g], Eero Pukkala[a,g]

[a] University of Tampere, School of Health Sciences, Finland
[b] University of Helsinki, Department of Public Health, Finland
[c] City of Vantaa, Health and Social Welfare Department, Finland
[d] University of Jyväskylä, Department of Health Sciences, Finland
[e] University of Helsinki, Institute for Molecular Medicine FIMM, Finland
[f] National Institute for Health and Welfare (THL), Finland
[g] Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Finland

ARTICLE INFO

Article history:
Received 22 April 2013
Received in revised form
21 September 2013
Accepted 4 October 2013
Available online 26 October 2013

Keywords:
Epidemiology
Endurance
Exercise
Ageing
Statistical review

ABSTRACT

Objectives: Physical activity has been shown to decrease the risk of certain cancers. Objective of this study was to assess the effect of physical activity on cancer incidence in former male athletes in older age.
Design: A cohort of 2448 elite male athletes and 1712 referents was followed-up for cancer incidence during 1986–2010 through the Finnish Cancer Registry.
Methods: Standardised incidence ratios were calculated with the general male population as the reference. Self-reported questionnaire-based data on covariates were used in Cox regression analyses comparing the risk of cancer in athletes and referents.
Results: The overall cancer incidence was lower in athletes than in the general population, standardised incidence ratio 0.89 (95% confidence interval 0.81–0.97). It was lowest among middle-distance runners (standardised incidence ratio 0.51, 95% confidence interval 0.22–1.01), long-distance runners (standardised incidence ratio 0.57, 95% confidence interval 0.35–0.88) and jumpers (standardised incidence ratio 0.60, 95% confidence interval 0.37–0.92). The standardised incidence ratio of lung cancer among athletes was 0.40 (95% confidence interval 0.27–0.55) and that of kidney cancer 0.23 (95% confidence interval 0.06–0.57). The hazard ratio for lung cancer between athletes and referents increased from the unadjusted ratio of 0.29 (95% confidence interval: 0.18–0.48) to 0.61 (95% confidence interval: 0.30–1.26) after adjustment for smoking status and pack-years of smoking.
Conclusions: Former male elite athletes evidently have less cancer than men on the average. The lesser risk can be attributed to lifestyle factors, notably less frequent smoking among the athletes.

1. Introduction

In addition to the well-recognized role of smoking, alcohol consumption and unhealthy diet in the aetiology of many cancers, increasing evidence implicates physical inactivity as a risk factor for some cancers. In 2002 the International Agency for Research on Cancer (IARC) estimated that excess body weight and physical inactivity could account for one quarter to one third of cancers of colon, kidney and oesophagus.[1] Since especially leisure-time physical activity is usually associated with a generally healthier lifestyle,[2,3] the independent role of physical activity in the aetiology of cancer may be difficult to demonstrate.

Several studies have reported links between physical activity and reduced risk of certain cancers, especially breast[4,5] and colon cancer.[6–8] There is conflicting evidence from the studies on prostate, lung and kidney cancer among physically active men. Some studies have suggested that the risks of these cancers are lower among the more physically active[9,10] but not all studies agree with this finding.[11,12]

Cancer incidence of Finnish world-class athletes in 1967–1995 was reported to be one-fifth lower than that of the general Finnish male population.[13] This was mainly explained by smaller incidence

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; IARC, International Agency for Research on Cancer; LTPA, leisure-time physical activity; MET, standard metabolic equivalent; PIC, personal identity code; SES, socio-economic status; SIR, standardised incidence ratio.

* Corresponding author.
E-mail address: Jorma.Sormunen@fimnet.fi (J. Sormunen).

1440-2440/$ – see front matter © 2013 Sports Medicine Australia. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jsams.2013.10.239

of smoking-related cancers in the athletes, but individual-level risk factor data prior to 1985 were not available. The value of studying elite athletes is that there is a documented period of intensive physical activity needed to achieve elite status and this information is available historically obviating the need to study young adults prospectively into the period of high risk for cancer decades later. However, elite athletes differ also for other cancer risk factors, which need to be accounted for in a rigorous analysis of the relationship of elite athlete status with future cancer. We now report the cancer incidence of these individuals for a period of 21 years from 1986 to 2010, with due consideration of cancer-related life-style factors collected in 1985.

The aim of this study was to evaluate the effects of an athlete status and their lifestyle covariates in incidence of different cancers.

2. Methods

The study cohort consisted of Finnish male athletes, who had represented Finland between the years 1920 and 1965 at least once in international or inter-country competitions (for details, see Sarna et al.[14]). The following sports were selected: track and field athletics, cross-country skiing, soccer, ice hockey, basketball, boxing, wrestling, weight lifting, and shooting. Sport disciplines were chosen based on the numbers of Finnish Olympic games participants. In addition it was made sure that endurance, speed, power and team sports disciplines were included in the cohort. One referent for each athlete was selected from the archives of the registry of men liable for military service, matched for year of birth and area of residence. The referent had to have been classified as completely healthy ("A1 category") at the compulsory medical examination for induction into military service at age of 20 years (referents were born between years 1898 and 1948). No eligible referent was traced for 15% of athletes because ice hockey, basketball, weight lifting, and shooting were retrospectively included in the study after selection of the referents.

The original study cohort consisted of 2448 athletes and 1712 referents. In 1985 a questionnaire on physical activity and health was mailed to the survivors of the cohort and their referents. The response proportion was 85% for the athletes and 81% for the referents. We had no reason to expect recall bias between the two groups. Out of the responders 1324 athletes and 754 of referents had no missing values on the main covariates. All persons with non-missing values of variables included in the models were included in the Cox regression analyses.

Everyone residing in Finland since 1967 has been assigned a unique personal identity code (PIC), which is used in all main registers. PICs for every cohort member together with possible dates of emigration or death were obtained from the Population Register Centre of Finland. Follow-up for cancer through the files of the population-based countrywide Finnish Cancer Registry was done using the PIC as a key.

In this article we report the cancer incidence of the survivors of the cohort on the 1st of January 1986 from 1st of January 1986 to death or 31st of December 2010.

The ethics committee of the University of Helsinki approved the study, and all subjects have provided informed consent.

Assessment of leisure-time physical activity (LTPA) was based on three structured questions on participation in recreational physical activity. The activity-MET index was used as a measure of physical activity level in 1985 and expressed as the score of MET-hours per week. It was further classified into five groups by four quintiles (lowest quintile value 3 and highest 45 MET-hours per week) (Table 1). For Cox regression analyses the three middle fifths (II–IV) were combined. Athletes exercised more MET-hours weekly than their referents (Table 1).

Table 1
Distribution of the background characteristics of the study subjects on December 31, 1985.

Characteristic	Athletes	Referents
Age	*N* = 1609	*N* = 1046
Years: median (min–max)	55.2 (35.6–93.8)	53.3 (38.0–87.5)
≤50 years	31.1%	36.3%
50–64 years	45.9%	45.5%
65–79 years	20.3%	16.5%
≥80 years	2.7%	1.6%
Leisure time physical activity (LTPA)	*N* = 1257	*N* = 731
MET[a], MET * h/week: median (min–max)	18 (0–228)	6 (0–228)
Lowest fifth (<3 MET * h/week)	13.6%	32.6%
Intermediate (fifth II, III & IV (3–45 MET * h/week)	65.9%	60.5%
Highest fifth V (>45 MET * h/week)	20.5%	7.0%
Alcohol consumption	*N* = 1238	*N* = 723
Abstainers (<1 drinks/week)	11.7%	15.5%
Occasional users (1–3 drinks/week)	45.4%	46.7%
Moderate users (3–14 drinks/week)	29.7%	25.4%
Heavy users (≥14 drinks/week)	13.2%	12.3%
Cigarette smoking status	*N* = 1247	*N* = 725
Never smokers	48.9%	28.0%
Occasional smokers	4.7%	2.5%
Ex-smokers	30.6%	40.7%
Current smokers	15.9%	28.8%
Pack-years for current smokers: median, during smoking period (min–max)	15 (0.4–87)	23 (0.4–72)
Body mass index (BMI)	*N* = 1264	*N* = 735
kg/m^2: median (min–max)	25.6 (16.2–43.3)	26.1 (15.8–58.1)
Normal weight (BMI ≤ 24.99)	41.8%	36.5%
Overweight (BMI 25.00–29.99)	46.4%	50.9%
Obese (BMI ≥ 30.00)	11.9%	12.7%
Socio-economic status	*N* = 1579	*N* = 962
Executives	26.4%	10.3%
Clerical workers	40.5%	23.4%
Skilled workers	26.5%	41.6%
Unskilled workers	2.1%	7.9%
Agricultural workers	4.3%	16.5%
Other	0.3%	0.3%

[a] The metabolic equivalent (MET) index was calculated by assigning a coefficient of the resting metabolic rate to each activity and by calculating the product of intensity × duration × frequency.

Alcohol consumption was evaluated by quantity-frequency measures of beverages. Respondents were categorised as abstainers, light, moderate and heavy users of alcohol based on number of drinks per week.[15]

Smoking status was based on a detailed smoking history.[16] Respondents were classified into four categories: never, ex-, occasional or current (daily or almost daily) smokers. Current smokers were defined as persons, who had smoked more than 100 cigarettes in their lifetime and smoked daily or almost daily at the time of the 1985 questionnaire. For Cox regression analyses the groups occasional and current smokers were combined.

Duration of smoking was based on age of onset of smoking and age in 1985 (for current smokers), or age at cessation (for former smokers). In the calculation of pack-years of smoking for current smokers in 1985, the daily smoking was classified as follows: those who smoked 1–15 cigarettes daily were given value of 0.4 packs (8 cigarettes/day); for those who smoked more than 15, but less than 25 cigarettes/day were given a value of 1.0 pack; and for those who smoked >25 cigarettes/day were given a value of 1.5 packs. The numbers of pack-years was then packs smoked daily multiplied by the number of years of smoking.

Self-reported data on height (m) and weight (kg) were used to calculate the body mass index (BMI) as weight divided by height squared (kg/m^2).

Table 2
Observed (Obs) and expected (Exp) numbers of cancer cases, and standardised incidence ratios (SIR) with 95% confidence intervals (CI) for most common and all smoking related cancers among the athletes and referents.

Cancer site	Athletes			Referents		
	Obs	Exp	SIR (95%CI)	Obs	Exp	SIR (95%CI)
All sites	452	509.8	0.89 (0.81–0.97)	289	281.0	1.03 (0.91–1.15)
Strongly smoking-related cancers	109	163.8	0.67 (0.55–0.80)	93	91.1	1.02 (0.82–1.25)
Lung	33	82.9	0.40 (0.27–0.55)	54	46.1	1.17 (0.88–1.52)
Other	76	80.9	0.94 (0.74–1.17)	33	37.2	0.89 (0.61–1.24)
Larynx	4	4.5	0.89 (0.24–2.27)	3	2.6	1.14 (0.24–3.33)
Oral cavity and tongue	4	1.7	2.40 (0.65–6.14)	0	1.0	0.00 (0.00–3.71)
Pharynx	2	1.9	1.07 (0.13–3.86)	1	1.1	0.89 (0.02–4.96)
Oesophagus	5	5.9	0.85 (0.28–1.98)	3	3.3	0.91 (0.19–2.65)
Pancreas	17	17.8	0.95 (0.55–1.52)	10	9.9	1.01 (0.49–1.86)
Kidney, renal pelvis	4	17.7	0.23 (0.06–0.57)	7	10.2	0.69 (0.28–1.42)
Urinary bladder	40	29.3	1.36 (0.97–1.85)	15	15.7	0.95 (0.53–1.57)
Weakly smoking-related cancers	39	46.9	0.83 (0.59–1.14)	23	25.4	0.91 (0.57–1.36)
Lip	1	4.7	0.21 (0.01–1.19)	0	2.5	0.00 (0.00–1.46)
Liver	7	8.5	0.82 (0.33–1.69)	4	4.7	0.85 (0.23–2.18))
Stomach	16	22.0	0.73 (0.42–1.18)	12	11.8	1.02 (0.53–1.77)
Leukaemia	14	10.9	1.29 (0.70–2.16)	5	5.9	0.84 (0.27–1.97)
Alcohol-related cancers (all also related to smoking)	22	24.6	0.91 (0.57–1.37)	9	11.0	0.82 (0.37–1.54)
Other						
Rectum, rectosigmoid, anus	20	20.7	0.97 (0.59–1.49)	10	11.6	0.87 (0.42–1.59)
Colon	24	27.2	0.88 (0.57–1.31)	16	14.9	1.08 (0.62–1.74)
Prostate	159	152.6	1.04 (0.89–1.21)	84	83.7	1.00 (0.80–1.24)
Skin melanoma	8	11.8	0.68 (0.29–1.33)	11	6.9	1.60 (0.80–2.85)
Skin, non-melanoma	25	21.8	1.15 (0.74–1.69)	11	11.0	1.00 (0.50–1.78)
Brain and central nervous system	13	9.1	1.43 (0.76–2.44)	4	5.4	0.74 (0.20–1.90)
Non-Hodgkin-lymphoma	15	16.7	0.90 (0.50–1.48)	13	9.5	1.37 (0.73–2.34)
Multiple myeloma	7	6.7	1.05 (0.42–2.15)	5	3.7	1.37 (0.45–3.19)
Not included above						
Skin, basal cell cancer	126	106.5	1.18 (0.99–1.39)	55	58.2	0.94 (0.71–1.22)

The socioeconomic status was based on data on subject's occupation collected partly from the Central Population Register of Finland and partly from the questionnaire of year 1985. A much larger proportion of athletes than referents belonged to the highest socio-economic categories (Table 1).

Person-years at risk during 1986–2010 were counted by five-year age groups and by five-year calendar time periods. The expected number of cancer cases was calculated by multiplying the number of person-years in each stratum by the corresponding cancer incidence rate in the overall Finnish male population. The standardised incidence ratio (SIR) was calculated as the ratio of the observed to the expected number of cases. The 95% confidence intervals (CI) were obtained assuming a Poisson distribution of the number of cases.

Finnish Cancer Registry includes accurate information of more than 99% of cancers diagnosed in Finland since 1953.[17] All cancer cases that were reported to Finnish cancer registry were included in the analyses. Smoking-related cancers were analysed in three groups: (i) lung cancer; (ii) other cancers that have a strong confirmed association with smoking (cancers of the larynx, upper digestive track, oral cavity and tongue, pharynx, pancreas, urinary tract, kidney and urinary bladder); and (iii) cancers that have a weak association with smoking (cancers of the lip, liver and stomach, and leukaemia).[18]

Cox regression analyses[19] comparing the risk of cancer in athletes vs. referents after adjustment for other factors were performed for lung cancer, all other smoking-related cancers, prostate cancer and colon cancer. Adjustment for age in each analysis was made by using age as the time scale in the Cox models. The smoking status (current smokers, former/unknown smoking status and others), pack-years of smoking, BMI, alcohol use, reported physical exercise in 1985 and socioeconomic status were also included in the regression analyses as potential confounders or covariates. The results of Cox regression analyses are reported as hazard ratios (HR). The assumptions of the Cox model were tested for proportionality. All Cox regression calculations were performed with Stata software, release 10 (Stata Corp., College Station, TX, USA).

3. Results

Athletes were somewhat older than their referents, their median age was 55 years when the median age of the referents was 53 years. Athletes also engaged more in leisure time physical activity (LTPA) – one fifth of the athletes exercised more than 45 MET * h/week, when only 7% of the referents did so (Table 1).

The athletes used a bit more alcohol (median 6.9 g/day) than their referents (median 6.3 g/day). Current smoking was less common among athletes (16%) than among referents (29%) in 1985. The median number of pack-years for smoking athletes was 15 and for referents who smoked 23. The athletes were also somewhat leaner than referents (Table 1).

The overall cancer incidence for athletes was lower than in the general population (SIR 0.89, 95%CI 0.81–0.97) (Table 2). We noticed a significant reduction for two smoking related cancers: the SIR for lung cancer was 0.40 (95%CI 0.27–0.55) and for renal cancer 0.23 (95%CI 0.06–0.57).

The overall cancer incidence was lowest for middle-distance runners (SIR 0.51, 95%CI 0.22–1.01), long-distance runners (SIR 0.57, 95%CI 0.35–0.86) and jumpers (SIR 0.60, 95%CI 0.37–0.92). The athlete group specific SIRs for all cancer types with expected number of cases ≥5 in any group are reported in the Appendix Table.

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jsams.2013.10.239.

The SIR for all cancers combined among the referents was 1.03 (95%CI 0.91–1.15). None of the site-specific differences between the observed and expected numbers among the referents were statistically significant (Table 2).

The Cox regression analysis showed an age-adjusted HR of 0.92 (95%CI 0.79–1.07) for overall cancer between the athletes and referents (Table 3). Adjustment for smoking status, pack-years of

Table 3
Hazard ratios of selected cancers for athletes compared with referents derived from Cox regression analyses. The alternative models include smoking status (no/ex/current), pack-years of smoking for current smokers, leisure-time physical activity (LTPA as metabolic equivalent index, MET) and socioeconomic status (SES) reported in 1985.

Cancer variables in the model	Hazard ratio (95% confidence interval)
All cancer sites	
None	0.92 (0.79–1.07)
Smoking status	0.92 (0.80–1.20)
Smoking status + pack-years + LTPA	0.99 (0.81–1.21)
LTPA	0.93 (0.80–1.09)
Socioeconomic status	0.86 (0.73–1.01)
Socioeconomic status + smoking status + pack-years + LTPA	0.97 (0.79–1.20)
Lung cancer	
None	0.29 (0.18–0.48)
Smoking status	0.39 (0.24–0.64)
Smoking status + pack-years	0.61 (0.30–1.26)
Smoking status + pack-years + LTPA	0.59 (0.29–1.23)
LTPA	0.29 (0.18–0.47)
Socioeconomic status	0.38 (0.22–0.64)
Socioeconomic status + smoking status + pack-years + LTPA	0.89 (0.42–1.90)
Other strongly smoking related cancers[a]	
None	1.02 (0.65–1.59)
Smoking status	1.11 (0.71–1.75)
Smoking status + pack-years	0.99 (0.56–1.78)
Smoking status + pack-years + LTPA	1.00 (0.55–1.80)
LTPA	1.05 (0.67–1.65)
Socioeconomic status	0.86 (0.53–1.37)
Socioeconomic status + smoking status + pack-years + LTPA	0.87 (0.47–1.60)
Colon cancer	
None	0.70 (0.33–1.47)
Smoking status	0.78 (0.36–1.67)
Smoking status + pack-years	1.13 (0.43–2.99)
Smoking status + pack-years + LTPA	1.19 (0.45–3.18)
LTPA	0.44 (0.20–0.97)
Socioeconomic status	0.71 (0.32–1.57)
Socioeconomic status + smoking status + pack-years + LTPA	1.17 (0.43–3.24)
Prostate cancer	
None	1.03 (0.77–1.37)
Smoking status	0.95 (0.71–0.27)
Smoking status + pack-years	1.09 (0.75–1.58)
Smoking status + pack-years + LTPA	1.07 (0.74–1.56)
LTPA	0.91 (0.69–1.20)
Socioeconomic status	0.99 (0.73–1.35)
Socioeconomic status + smoking status + pack-years + LTPA	1.12 (0.76–1.65)
Renal cancer	
None	0.19 (0.04–0.96)
Smoking status	0.19 (0.04–0.97)
Smoking status + pack-years	0.13 (0.01–1.26)
Smoking status + pack-years + LTPA	0.12 (0.01–1.14)
LTPA	0.19 (0.04–0.96)
Socioeconomic status	0.23 (0.04–1.28)
Socioeconomic status + smoking status + pack-years + LTPA	0.17 (0.02–1.80)

[a] Cancer types strongly related to tobacco smoking: larynx, oral cavity and tongue, pharynx, oesophagus, pancreas, kidney and urinary bladder.

smoking and LTPA in 1985 raised the HR to 0.99, 95%CI 0.81–1.21. After adjustment for socio-economic status (SES) the HR for cancer incidence was 0.86 (95%CI 0.73–1.01).

Compared to referents athletes had less lung cancer even after the result was adjusted for smoking status (HR 0.39, 95%CI 0.24–0.64), but this was strongly attenuated after further adjustment with pack-years (HR 0.61, 95%CI 0.30–1.26) (Table 3). Lung cancer was the only cancer that remained significant between athletes and referents after adjustment for socioeconomic status (SES) alone (HR 0.38, 95%CI 0.22–0.64), but when adjusted also for smoking status, pack-years and SES, the difference disappeared (HR = 0.97, 95% CI 0.79–1.20). Other strongly smoking-related cancers showed HRs of about 1.0 for athletes, irrespective of the presence or absence of smoking variables in the model.

The hazard ratio for colon cancer of athletes in comparison to the referents was 0.70 (95%CI 0.33–1.47) in the crude model and was attenuated in the models including smoking variables. When the result was adjusted for LTPA, the protective effect was statistically significant (HR 0.44, 95%CI 0.20–0.97), but not significant in a model, which included also smoking (HR 1.19, 95% CI 0.45–3.18). Hazard ratios for prostate cancer for athletes were close to 1.0 in all models (Table 3). Adding other variables to the models did not change the results significantly.

There were only four cases of renal cancer among athletes vs. 17.7 expected. The risk factors for renal cancer include smoking, obesity and possibly hypertension[20] and/or hypertensive medication[20]. Despite the small number of cases (8) Cox regression analyses for renal cancer yielded some significant results. When adjusted for LTPA the HR was 0.19 (0.04–0.96) and when smoking was added to the model the HR stayed the same: 0.19 (0.04–0.97). Adding other variables (amount of smoking in pack-years, socioeconomic status) yielded even lower HRs but the results lost their statistical significance. Hence the cofactors seem not to give satisfactory explanation for such an extremely low incidence of renal cancer among athletes.

In addition to the results presented in Table 3, Cox regression analyses were made with SES, smoking status, pack-years, LTPA and alcohol use, but these analysis did not have any significant effect on the presented results. BMI was not included in the analyses due to the fact that BMI for athletes is elevated due to muscular build instead of body fat and does not necessarily reflect the same risks attributed to fat mass as it does in general population.[21]

4. Discussion

We observed a lower overall cancer incidence in athletes than in the general population or among the men in the reference cohort. It has also been seen in other studies that aerobic exercise protects from many cancers[1] possibly due to hormonal changes,[22] body-fat alterations[22] or shorter intestinal transit time.[23] In our study exceptionally low overall cancer incidence rates were observed among athletes with aerobic exercise, i.e., middle-distance and long-distance runners, but not in cross-country skiers. The SIRs were 0.51 (95%CI 0.22–1.01), 0.57 (95% CI 0.35–0.86), and 0.84, (95%CI 0.54–1.23), respectively. Nearly all the decrease in overall cancer incidence among the athletes is due to low incidence of lung cancer. The difference between observed and expected number of cases was about 58 cases overall, of which 50 was due to lung cancer alone. The incidence of renal cancer in athletes was also markedly lower than expected.

The incidence for lung cancer among athletes was less than half of that of both the general population and the referents. The hazard ratio rose to 0.89 (95%CI 0.42–1.90) and lost statistical significance when the amount smoked (in pack-years), LTPA and socioeconomic status were added in the model. These findings are in line with the information that the prevalence of smokers among athletes was lower than among the referents and that athlete smokers smoked less than referents who smoked. Our findings are in line with a recently published meta-analysis.[24] A similar pattern was observed for other tobacco-related cancers.

In this study a 30% non-significantly lower incidence of colon cancer was detected among the athletes when compared to their referents, and the difference totally disappeared after adjustment for covariates. It may be that intense physical activity as young

adults is not the period yielding the most protection, but physical activity would need to be continued later in life (which is consistent with the low risk observed when adjusted only for later leisure-time physical activity). The small number of cases in the cohort population limits the possibilities for more extensive analyses.

The athletes and referents had exactly same prostate cancer incidence, when the result was adjusted for socio-economic status. A part of prostate cancer incidence in the Nordic countries (with the exception of Denmark) since the 1990s may be related to frequency of PSA-testing[25] but other factors cannot be excluded. A recent meta-analysis suggests that physical activity is associated with a 10% reduced risk of prostate cancer, but the risk is lower for occupational physical activity (relative risk 0.81) than for leisure-time physical activity (0.95, 95%CI 0.89–1.00). Our estimate is fully compatible with the meta-analysis.[26]

While none of the invasive cancer types showed elevated risk among the athletes, we observed a borderline non-significant 18% excess incidence of basal cell cancer of skin. The risk for other non-melanoma skin cancer was also elevated, but this excess was not statistically significant. Skin melanoma was less common in the athletes than in the average population or among the referents. The risk of non-melanoma skin cancer is elevated in professions that include exposure to ultraviolet light (work outdoors, e.g. farmers),[25,27] while outdoor workers tend to have low risk of skin melanoma.[25] Many athletes exercise and compete outdoors during their athletic careers and which might explain the similarity of their skin cancer risk pattern with that of Finnish outdoor workers.[25] It has also been observed before that physical exercise does not protect from non-melanoma skin cancer.[28] Finally, very vigorous exercise may induce immunosuppression, which is known to increase the risk of non-melanoma skin cancers.[29]

This study gives a realistic picture of cancer pattern of athletes. The cohort was comprehensively identified from a variety of sources and the Finnish registries, which enable accurate record linkage and complete long-term follow-up for the cancer incidence of this cohort, with no losses to follow-up. Unfortunately not enough women could be identified as elite athletes during the inclusion period of the present cohort and hence no results can be given on elite athlete status and cancer in women. The last athletes in the cohort were included before the increase in use of performance-enhancing doping agents, so these agents are unlikely to have marked effect on the results that we have seen.

The athletes of this cohort differ from the general population by the level of their physical activity and some other health habits: they smoke less and they are less obese than their referents.[30] This could be analysed in an unbiased way as the former athletes responded well to the 1985 questionnaire. About 60% of former elite athletes continued an active and sports-oriented lifestyle throughout their adulthood, while only less than 20% of their age-matched controls did so.[14] Physically active lifestyle is often combined with other features of a healthy lifestyle such as healthy diet and non-smoking.[13]

The referent population was recruited from "A1-classified" men at military service. Although these men were rated as completely healthy in age 20, their cancer incidence rates later in life did not differ from the rates of the entire population. Hence the reference cohort appears to represent quite well the general population and is an acceptable reference for the analyses of cancer in former elite athletes.

Our main conclusion is that former elite athlete status has – especially among endurance athletes – modified the life-long pattern of risk factors of cancer to generally positive direction. Former athletes have continued their physically active lifestyle, healthy diet and low smoking. This lifestyle has given them protection against several types of cancers up to their old ages.

5. Conclusions

Former male elite athletes evidently have less cancer than men on the average. Much of the lesser risk is due to the lifestyle factors, notably less frequent smoking among the athletes.

6. Practical implications

- Athletes have fewer cancers than general population. The incidence is lowest among those engaged in endurance sports.
- Especially notable is the difference in lung and renal cancer.
- Most, if not all, of this is due to healthy lifestyle, especially less frequent smoking.
- The healthy lifestyle may also be a consequence of the training and other requirements for being an elite athletes, hence making it difficult to attribute causal effects based on this data alone.

Acknowledgments

The authors would like to thank professor Timo Hakulinen, the former director of the Finnish Cancer Register, for his participation in the study. The study group has no competing interests. The research project on physical condition and cancer in men received funding from the Finnish Cancer Organisations. The study group has copyright for the presented material.

References

1. IARC. IARC handbooks of cancer prevention: weight control and physical activity, In: Vainio H, Bianchini F, editors. *IARC handbooks of cancer prevention*, vol. 6. Lyon, World Health Organization, 2002, p. 314.
2. Mensink GB, Loose N, Oomen CM. Physical activity and its association with other lifestyle factors. *Eur J Epidemiol* 1997; 13:771–778.
3. Backmand H, Kujala U, Sarna S et al. Former athletes' health-related lifestyle behaviours and self-rated health in late adulthood. *Int J Sports Med* 2010; 31:751–758.
4. Rintala PE, Pukkala E, Paakkulainen HT et al. Self-experienced physical workload and risk of breast cancer. *Scand J Work Environ Health* 2002; 28:158–162.
5. Angeles-Llerenas A, Ortega-Olvera C, Perez-Rodriguez E et al. Moderate physical activity and breast cancer risk: the effect of menopausal status. *Cancer Causes Control* 2010; 21:577–586.
6. Vena JE, Graham S, Zielezny M et al. Lifetime occupational exercise and colon cancer. *Am J Epidemiol* 1985; 122:357–365.
7. Lee IM. Physical activity and cancer prevention – data from epidemiologic studies. *Med Sci Sports Exerc* 2003; 35:1823–1827.
8. Wolin KY, Yan Y, Colditz GA et al. Physical activity and colon cancer prevention: a meta-analysis. *Br J Cancer* 2009; 100:611–616.
9. Albanes D, Blair A, Taylor PR. Physical activity and risk of cancer in the NHANES I population. *Am J Public Health* 1989; 79:744–750.
10. Lee IM, Paffenbarger Jr RS. Quetelet's index and risk of colon cancer in college alumni. *J Natl Cancer Inst* 1992; 84:1326–1331.
11. Lee IM, Sesso HD, Paffenbarger Jr RS. A prospective cohort study of physical activity and body size in relation to prostate cancer risk (United States). *Cancer Causes Control* 2001; 12:187–193.
12. Tardon A, Lee WJ, Delgado-Rodriguez M et al. Leisure-time physical activity and lung cancer: a meta-analysis. *Cancer Causes Control* 2005; 16:389–397.
13. Pukkala E, Kaprio J, Koskenvuo M et al. Cancer incidence among Finnish world class male athletes. *Int J Sports Med* 2000; 21:216–220.
14. Sarna S, Sahi T, Koskenvuo M et al. Increased life expectancy of world class male athletes. *Med Sci Sports Exerc* 1993; 25:237–244.
15. Jarvenpaa T, Rinne JO, Koskenvuo M et al. Binge drinking in midlife and d ementia risk. *Epidemiology* 2005; 16:766–771.
16. Kaprio J, Koskenvuo M. A prospective study of psychological and socioeconomic characteristics, health behavior and morbidity in cigarette smokers prior to quitting compared to persistent smokers and non-smokers. *J Clin Epidemiol* 1988; 41:139–150.
17. Teppo L, Pukkala E, Lehtonen M. Data quality and quality control of a population-based cancer registry. Experience in Finland. *Acta Oncol* 1994; 33:365–369.
18. IARC. *Tobacco Smoke and Involuntary Smoking IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, 2002. p. 83.
19. Fisher LD, Lin DY. Time-dependent covariates in the Cox proportional-hazards regression model. *Annu Rev Public Health* 1999; 20:145–157.
20. McLaughlin JK, Chow WH, Mandel JS et al. International renal-cell cancer study. VIII. Role of diuretics, other anti-hypertensive medications and hypertension. *Int J Cancer* 1995; 63:216–221.

21. Wallner-Liebmann SJ, Kruschitz R, Hubler K et al. A measure of obesity: BMI versus subcutaneous fat patterns in young athletes and nonathletes. *Coll Antropol* 2013; 37(2):351–357.
22. Siiteri PK. Adipose tissue as a source of hormones. *Am J Clin Nutr* 1987; 45:277–282.
23. Oettle GJ. Effect of moderate exercise on bowel habit. *Gut* 1991; 32:941–944.
24. Buffart LM, Singh AS, van Loon EC et al. Physical activity and the risk of developing lung cancer among smokers: a meta-analysis. *J Sci Med Sport* 2013, pii: S1440-2440(13)00047-9.
25. Pukkala E, Martinsen JI, Lynge E et al. Occupation and cancer follow-up of 15 million people in five Nordic countries. *Acta Oncol* 2009; 48:646–790.
26. Liu Y, Hu F, Li D et al. Does physical activity reduce the risk of prostate cancer? A systematic review and meta-analysis. *Eur Urol* 2011; 60:1029–1044.
27. Adams BB. Dermatologic disorders of the athlete. *Sports Med* 2002; 32: 309–321.
28. Moehrle M. Outdoor sports and skin cancer. *Clin Dermatol* 2008; 26:12–15.
29. Ramsay HM, Fryer AA, Hawley CM et al. Non-melanoma skin cancer risk in the Queensland renal transplant population. *Br J Dermatol* 2002; 147:950–956.
30. Kujala UM, Marti P, Kaprio J et al. Occurrence of chronic disease in former top-level athletes. Predominance of benefits, risks or selection effects? *Sports Med* 2003; 33:553–561.

Appendix Table (for online publishing only): Observed (Obs) and expected (Exp) numbers of cancer cases, and standardised incidence ratios (SIR) with 95% confidence intervals (CI) for cancers with ≥5 expected cases in any group of athletes by type of sports.

Cancer/site	Short distance running/hurdles/decathlon			Jumps			Middle distance running			Long distance running			Cross-country skiing		
	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)
All sites	51	51.8	0.98 (0.73-1.29)	20	33.2	0.60 (0.37-0.92)*	8	15.6	0.51 (0.22-1.01)	21	37.0	0.57 (0.35-0.86)**	25	29.8	0.84 (0.54-1.23)
Smoking. strong association[1]	10	8.3	1.21 (0.58-2.22)	3	5.3	0.57 (0.12-1.65)	0	2.5	0.00 (0.00-1.49)	4	5.8	0.69 (0.19-1.76)	3	4.7	0.64 (0.13-1.88)
Lung	7	8.8	0.80 (0.32-1.63)	1	5.6	0.18 (0.00-0.99)*	1	2.6	0.38 (0.01-2.10)	0	6.1	0.00 (0.00-0.60)**	1	5.1	0.19 (0.00-1.08)
Pancreas	2	1.8	1.12 (0.14-4.03)	2	1.2	1.73 (0.21-6.25)	0	0.5	0.00 (0.00-6.90)	0	1.3	0.00 (0.00-2.88)	1	1.0	0.98 (0.02-5.45)
Kidney	0	1.9	0.00 (0.00 - 1.99)	0	1.2	0.00 (0.00-3.13)	0	0.6	0.00 (0.00-6.57)	0	1.2	0.00 (0.00-2.96)	0	1.0	0.00 (0.00-3.79)
Bladder. ureter. urethra	7	3.0	2.31 (0.93-4.76)	1	2.0	0.51 (0.01-2.85)	0	0.9	0.00 (0.00-4.14)	2	2.2	0.90 (0.11-3.24)	2	1.9	1.08 (0.13-3.91)
Smoking. weak association[2]	2	4.8	0.42 (0.05-1.51)	0	3.1	0.00 (0.00-1.18)	3	1.4	2.09 (0.43-6.11)	1	3.5	0.29 (0.01-1.59)	3	2.9	1.04 (0.21-3.03)
Stomach	2	2.4	0.84 (0.10-3.04)	0	1.6	0.00 (0.00-2.34)	2	0.7	2.80 (0.34-10.1)	0	1.8	0.00 (0.00-2.09)	1	1.5	0.68 (0.02-3.80)
Leukemia	0	1.1	0.00 (0.00-3.43)	0	0.7	0.00 (0.00-5.27)	1	0.3	3.07 (0.08-17.1)	1	0.8	1.26 (0.03-7.03)	2	0.6	3.11 (0.38-11.21)
Alcohol dependant[3]	1	2.4	0.42 (0.01-2.33)	0	1.5	0.00 (0.00-2.41)	0	0.7	0.00 (0.00-5.08)	2	1.6	1.23 (0.15-4.44)	0	1.3	0.00 (0.00-2.89)
Colon	1	3.3	0.30 (0.01-1.67)	3	2.1	1.41 (0.29-4.11)	0	1.0	0.00 (0.00-3.58)	2	2.4	0.85 (0.10-3.06)	0	1.8	0.00 (0.00-2.03)
Rectum. anus	2	2.1	0.96 (0.12-3.46)	1	1.3	0.74 (0.02-4.15)	0	0.6	0.00 (0.00-5.85)	0	1.5	0.00 (0.00-2.50)	2	1.2	1.70 (0.21-6.14)
Prostate	16	15.3	1.04 (0.60-1.69)	5	9.8	0.51 (0.17-1.19)	3	4.6	0.65 (0.13-1.89)	12	11.0	1.09 (0.56-1.90)	11	8.8	1.25 (0.61-2.23)
Non-Hodgkin lymphoma	2	1.7	1.17 (0.14-4.21)	0	1.1	0.00 (0.00-3.38)	0	0.5	0.00 (0.00-7.10)	0	1.2	0.00 (0.00-3.14)	1	0.9	1.10 (0.03-6.12)
Myeloma	0	0.7	0.00 (0.00-5.56)	1	0.4	2.32 (0.06-12.9)	1	0.2	4.98 (0.13-27.8)	1	0.5	2.06 (0.05 – 11.5)	1	0.4	2.55 (0.06-14.2)
Skin melanoma	2	1.2	1.74 (0.21-	1	0.7	1.37 (0.03-	0	0.4	0.00 (0.00-	1	0.8	1.33 (0.03-	0	0.6	0.00 (0.00-

			6.30)			7.63)			10.6)			7.42)			6.65)
Skin. non-melanoma	4	1.9	2.06 (0.56-5.28)	0	1.3	0.00 (0.00-2.93)	0	0.6	0.00 (0.00-6.71)	1	1.6	0.64 (0.02-3.57)	2	1.3	1.58 (0.19-5.69)
Basal cell carcinoma of the skin[4]	20	10.2	1.97 (1.20-3.03)**	9	6.5	1.38 (0.63-2.61)	4	3.0	1.33 (0.36-3.41)	8	7.3	1.09 (0.47-2.15)	6	5.9	1.02 (0.38-2.22)
Cancer/site	**Ice hockey**			**Football**			**Basketball**			**Throws**			**Wrestling**		
	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)
Total cancer	35	32.2	1.09 (0.76-1.51)	50	45.7	1.09 (0.81-1.44)	14	15.3	0.92 (0.50-1.53)	24	27.7	0.87 (0.55-1.28)	44	43.4	1.02 (0.74-1.36)
Smoking. strong association[1]	4	5.2	0.77 (0.21-1.96)	11	7.3	1.50 (0.75-2.69)	3	2.5	1.21 (0.25-3.52)	1	4.5	0.22 (0.01-1.25)	7	6.9	1.01 (0.41-2.09)
Lung	7	5.3	1.31 (0.53-2.70)	2	7.8	0.26 (0.03-0.92)*	1	2.6	0.39 (0.01-2.15)	1	4.7	0.21 (0.01-1.18)	2	7.4	0.27 (0.03-0.98)*
Pancreas	0	1.1	0.00 (0.00-3.27)	2	1.6	1.27 (0.15-4.59)	1	0.5	1.90 (0.05-10.6)	0	1.0	0.00 (0.00-3.82)	4	1.5	2.66 (0.72-6.80)
Kidney	0	1.2	0.00 (0.00-3.03)	0	1.7	0.00 (0.00-2.18)	0	0.6	0.00 (0.00-5.94)	0	1.0	0.00 (0.00-3.62)	0	1.5	0.00 (0.00-2.39)
Bladder. ureter. urethra	2	1.8	1.12 (0.14-4.03)	6	2.6	2.32 (0.85-5.04)	1	0.8	1.27 (0.03-7.08)	1	1.6	0.63 (0.02-3.50)	3	2.5	1.19 (0.25-3.47)
Smoking. weak association[2]	0	2.9	0.00 (0.00-1.28)	3	4.1	0.73 (0.15-2.13)	0	1.3	0.00 (0.00-2.88)	3	2.6	1.18 (0.24-3.44)	3	4.0	0.74 (0.15-2.17)
Stomach	0	1.4	0.00 (0.00-2.61)	2	2.0	0.99 (0.12-3.56)	0	0.6	0.00 (0.00-6.03)	0	1.3	0.00 (0.00-2.89)	1	2.0	0.50 (0.01-2.77)
Leukemia	0	0.7	0.00 (0.00-5.58)	1	0.9	1.08 (0.03-5.99)	0	0.3	0.00 (0.00-12.4)	1	0.6	1.75 (0.04-9.73)	1	0.9	1.10 (0.03-6.11)
Alcohol dependant[3]	3	1.6	1.91 (0.39-5.59)	3	2.2	1.39 (0.29-4.04)	1	0.8	1.27 (0.03-7.10)	1	1.3	0.77 (0.02-4.27)	2	2.0	1.00 (0.12-3.61)
Colon	3	1.7	1.79 (0.37-5.23)	3	2.4	1.26 (0.26-3.69)	1	0.8	1.27 (0.03-7.07)	0	1.5	0.00 (0.00-2.54)	6	2.3	2.64 (0.97-5.74)
Rectum. anus	2	1.3	1.51 (0.18-	0	1.9	0.00 (0.00	0	0.6	0.00 (0.00-	0	1.1	0.00 (0.00-	2	1.8	1.14 (0.14-

			5.46)			1.98)			5.81)			3.26)			4.13)
Prostate	14	9.5	1.47 (0.80-2.46)	18	13.5	1.33 (0.79-2.10)	4	4.6	0.88 (0.24-2.25)	12	8.2	1.47 (0.76-2.56)	14	12.8	1.10 (0.60-1.83)
Non-Hodgkin lymphoma	0	1.1	0.00 (0.00-3.28)	4	1.6	2.58 (0.70-6.59)	1	0.6	1.77 (0.04-9.83)	1	0.9	1.07 (0.03-5.98)	4	1.4	2.81 (0.77-7.19)
Myeloma	0	0.4	0.00 (0.00-9.07)	0	0.6	0.00 (0.00-6.38)	1	0.2	5.33 (0.13-29.7)	0	0.4	0.00 (0.00-10.4)	0	0.6	0.00 (0.00-6.61)
Skin melanoma	1	0.8	1.25 (0.03-6.97)	0	1.1	0.00 (0.00-3.46)	0	0.4	0.00 (0.00-8.83)	0	0.6	0.00 (0.00-5.80)	1	1.0	1.06 (0.03-5.87)
Skin. non-melanoma	1	1.1	0.91 (0.02-5.08)	2	1.5	1.30 (0.16-4.68)	0	0.4	0.00 (0.00-9.08)	1	1.0	1.02 (0.03-5.68)	3	1.6	1.83 (0.38-5.34)
Basal cell carcinoma of the skin[4]	9	6.3	1.43 (0.65-2.70)	12	8.9	1.35 (0.70-2.36)	4	2.9	1.37 (0.37-3.50)	9	5.4	1.67 (0.76-3.16)	4	8.5	0.47 (0.13-1.20)

Cancer/site	**Weight lifting**			**Boxing**			**Shooting**		
	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)
Total cancer	19	22.4	0.85 (0.51-1.32)	32	38.0	0.84 (0.58-1.18)	29	30.6	0.95 (0.64-1.36)
Smoking. strong association[1]	8	3.6	2.24 (0.97-4.40)	6	6.1	0.98 (0.36-2.13)	2	4.8	0.42 (0.05-1.50)
Lung	2	4.0	0.50 (0.06-1.81)	3	6.6	0.46 (0.09-1.33)	2	5.0	0.40 (0.05-1.44)
Pancreas	1	0.8	1.30 (0.03-7.26)	1	1.3	0.75 (0.02-4.20)	0	1.1	0.00 (0.00-3.46)
Kidney	2	0.8	2.49 (0.30-8.97)	1	1.4	0.72 (0.02-4.03)	0	1.0	0.00 (0.00-3.72)
Bladder. ureter. urethra	4	1.3	3.00 (0.82-7.68)	3	2.2	1.36 (0.28-3.98)	2	1.9	1.06 (0.13-3.82)
Smoking. weak association[2]	2	2.1	0.96 (0.12-3.47)	4	3.6	1.11 (0.30-2.85)	2	3.1	0.66 (0.08-2.37)
Stomach	0	1.0	0.00 (0.00-3.53)	3	1.8	1.65 (0.34-4.83)	0	1.6	0.00 (0.00-2.35)

Leukemia	2	0.5	4.33 (0.52-15.6)	0	0.8	0.00 (0.00-4.62)	1	0.7	1.47 (0.04-8.20)
Alcohol dependant[3]	1	1.0	0.98 (0.02-5.46)	2	1.3	0.76 (0.02-4.21)	2	1.8	1.12 (0.14-4.03)
Colon	0	1.2	0.00 (0.00-3.14)	1	2.0	0.51 (0.01-2.82)	1	1.6	0.62 (0.02-3.43)
Rectum. anus	1	0.9	1.11 (0.03-6.19)	2	1.6	1.29 (0.16-4.64)	3	1.2	2.46 (0.51-7.19)
Prostate	6	6.5	0.92 (0.34-1.99)	10	11.0	0.91 (0.44-1.67)	12	9.0	1.33 (0.69-2.32)
Non-Hodgkin lymphoma	0	0.7	0.00 (0.00-5.04)	1	1.3	0.80 (0.02-4.44)	0	0.9	0.00 (0.00-3.92)
Myeloma	0	0.3	0.00 (0.00-12.8)	0	0.5	0.00 (0.00-7.48)	0	0.4	0.00 (0.00-8.94)
Skin melanoma	0	0.5	0.00 (0.00-7.75)	1	0.8	1.19 (0.03-6.61)	0	0.6	0.00 (0.00-6.32)
Skin. non-melanoma	0	0.8	0.00 (0.00-4.53)	3	1.3	2.25 (0.46-6.56)	5	1.3	3.73 (1.21-8.70)*
Basal cell carcinoma of the skin[4]	2	4.4	0.46 (0.06-1.65)	14	7.3	1.91 (1.04-3.20)*	8	6.0	1.34 (0.58-2.63)

1) Cancers included: larynx, oral cavity, tongue, pharynx, oesophagus, pancreas, kidney, renal pelvis, urinary bladder

2) Cancer sites included: lip, liver, stomach and leukaemia

3) Cancer sites included: larynx, oral cavity, tongue, pharynx, oesophagus, liver (all of them also related to smoking)

4) Basal cell carcinoma of the skin not included in “Total cancer” or “Skin, non-melanoma”

* $p<0.05$

** $p<0.01$

Cancer Epidemiology 43 (2016) 100–104

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

Perceived physical strain at work and incidence of colorectal cancer: A nested case–control study

Jorma Sormunen[a,b,*], Madar Talibov[a], Jan Ivar Martinsen[c], Kristina Kjaerheim[c], Pär Sparen[d], Laufey Tryggvadottir[e,f], Elisabete Weiderpass[c,d,g,h], Eero Pukkala[a,i]

[a] School of Health Sciences, University of Tampere, Tampere, Finland
[b] Tampere University Hospital, Lahti Unit of Radiation Therapy, Lahti, Finland
[c] Department of Research, Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway
[d] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[e] Icelandic Cancer Registry, Reykjavik, Iceland
[f] Faculty of Medicine, University of Iceland, Reykjavik, Iceland
[g] Genetic Epidemiology Group, Folkhälsan Research Center, Helsinki, Finland
[h] Department of Community Medicine, University of Tromsø, The Arctic University of Norway, Tromsø, Norway
[i] Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland

ARTICLE INFO

Article history:
Received 15 March 2016
Received in revised form 23 June 2016
Accepted 4 July 2016
Available online 13 July 2016

Keywords:
Epidemiology
Colon cancer
Physical workload

ABSTRACT

The evidence for a relationship between colon cancer incidence and physical activity is not fully convincing, and the association between physical activity and rectal cancer is also unclear.

We studied the association between perceived physical workload (PPWL) at work and colorectal cancer, stratified by subsite, in a nested case–control setting in the Nordic Occupational Cancer (NOCCA) data from Finland, Iceland, Norway and Sweden. Five population controls were selected for each cancer patient.

PPWL showed a bigger protective effect on colon cancer for males (odds ratio [OR] 0.74 in the highest PPWL decile as compared with the lowest PPWL category, 95% confidence interval [95% CI]: 0.72–0.77) than for females (OR 0.87, 95% CI: 0.81–0.95), with a significant trend for different levels of PPWL for both males and females. In males, the OR of cancer in the descending colon for the highest PPWL decile of males was 0.61 (95% CI: 0.54–0.69). For females the protective effect was most notable in the transversal part of the colon (OR 0.83, 95% CI: 0.67–1.03). The OR for rectal cancer in the highest PPWL decile for males was 0.87 (95% CI: 0.85–0.90) and for females 0.93 (95% CI: 0.83–1.04). Inclusion of further agents in multivariate analyses did not alter the ORs for PPWL.

The incidence of colon cancer and, to a lesser extent, rectal cancer is lowest in professions with the highest PPWL. The association is clearer in males than in females. The biggest protective effect appears to be in the descending colon in males.

1. Introduction

Globally colorectal cancers are among the most common cancers. Their incidence is particularly high in the Western World [1] and in the developed Asian countries [2]. The incidence has increased in most countries over the past decades, possibly due to lifestyle changes and changes in diet [3].

Physical activity can be one of the key lifestyle factors that may significantly reduce the risk of colon cancer. According to a meta-analysis published in 2009 [4] both men and women benefit from the protective effect of exercise. When comparing the most and the least active individuals across all studies, the protective effect in men seemed a bit more pronounced than in women (24% versus 21%). Physical activity also reduces the risk of rectal cancer, but the effect is not as strong as that in colon cancer [5,6].

Reduced incidence of colon cancer has been reported in those with professions that required continuous daily physical activity, such as people involved in agricultural and related jobs, farmers, fishermen and hunters [6,7]. In a Japanese study Isomura et al. observed that the protective effect of physical activity was greatest

* Corresponding author at: Tampere University Hospital, Lahti Unit of Radiation Therapy, Keskussairaalankatu 7, 15850 Lahti, Finland.
E-mail address: Jorma.Sormunen@gmail.com (J. Sormunen).

http://dx.doi.org/10.1016/j.canep.2016.07.001
1877-7821/

in the distal part of colon, especially in women [8]. Nilsen et al. detected a hazard ratio (HR) of 0.44 (95% CI: 0.25–0.78) for cancer in the transverse colon, comparing people who reported high versus no leisure-time physical activity [9]. For cancer in the sigmoid colon the HR was 0.48 (95% CI: 0.31–0.75).

The aim of the current study is to confirm that there is a protective effect related to physical activity at work, and that this effect is stronger in men than in women. We also assess the variation of this effect between colon and rectum, and between subsites of the colon.

2. Materials and methods

This study employed a case–control design nested in the Nordic Occupational Cancer Study (NOCCA) cohort. The NOCCA study cohort consists of 14.9 million people from Nordic countries (Finland, Iceland, Norway, Denmark, and Sweden) who participated in population censuses in 1960, 1970, 1980/1981, and/or 1990. A detailed description of the NOCCA cohort has been given by Pukkala et al. [10]. Because we did not have access to the individual records of the Danish part of the cohort, their data were not included. Occupational information was obtained from digital census records from 1960 and later censuses in Sweden and Norway, and from 1970 and later censuses in Finland. In Iceland, the only computerized census records available were from a 1981 census [10].

Unique personal identity codes for all residents were first introduced in Sweden in 1947, last in Denmark in 1968, and in other countries between these time points. Personal identity codes were used for linking the census records with the data from cancer registries and national population registries for information on cancer, death, and emigration [10].

The cancer registries in all Nordic countries collect information on almost 100% of cancer cases diagnosed in each country [11]. We have no reason to expect that there would have been occupation-related selection in the missing cancer cases. The cancer cases have been collected in all participating Nordic countries since the 1950s.

For this study, all incident colon and rectal cancer cases diagnosed between the first available census and 2005 were extracted from the NOCCA cohort. Five controls for each cancer case were randomly selected among persons who were alive and free from colon and rectal cancer on the date of diagnosis of the case (hereafter the 'index date' of the case–control set). Cases and controls were matched for the year of birth, sex, and country. Individuals with a minimum age of 20 years at the index date, and having occupational information from at least one census record before the index date, were included in the present study.

For each case and control, the exposure to occupational factors was estimated on the basis of conversions of occupational codes to quantitative amounts of exposure with the NOCCA job exposure matrix (JEM). It is used for defining the specific occupational exposures to different, potentially harmful or beneficial, workplace conditions, e.g., exposure to different chemicals or the physical stress of the work [12].

The exposure is characterized by probability of being exposed, P, and the average exposure level among the exposed persons, L (e.g. mg/m^3). The physical activity at work was expressed as (estimate of) 'perceived physical workload' (PPWL), and it was based on physical workload as reported in national interview surveys. The unit of exposure was defined as a score among those workers reporting heavy or rather heavy physical work in a national interview survey, which was conducted in 1990 as a part of the national 'Quality of Work Life Survey' in Finland [13]. When most workers in an occupational category report very heavy workload in their profession, the value approaches one. If most respondents report only fairly heavy work, the value approaches zero. If <10% persons in the occupation report heavy or rather heavy physical work, the PPWL was set to zero ('unexposed').

We quantified the cumulative exposure to PPWL for all cases and controls. Physical workload of all individuals was calculated by using the time (T) between the age of 20 (typical age to start working in non-academic occupations) and the age of 65 (typical retirement age) or index date as a multiplier for the P * L exposure of the profession of the individual (Table 1). After this, the individuals (cases and controls) with PPWL above the baseline level, which was defined as P * L * T being zero, were divided into low (lowest 50% of the non-zero P * L * T; <4.28 PPWL years), moderate (between 50 and 90%; 4.28–17.2 PPWL years) and high (highest 10%; >17.2 PPWL years) categories. If there were different occupational codes in census records for an individual, he/she was assumed to have changed occupations in the middle of the period between known census years.

The following agents have in some studies been found to be related to either colon or rectal cancer: aromatic hydrocarbon solvents (benzene, and cyclic hydrocarbon solvents) [14], wood dust [15], diesel engine exhaust [15], ionizing radiation [16], chromium [17], formaldehyde [18]; all of these were considered as potential confounders in the analysis. The NOCCA JEM-based exposure categories were defined for these factors using a procedure similar to that described above for PPWL.

We estimated hazard ratios and 95% confidence intervals for each exposure by conditional logistic regression. Individuals with baseline PPWL (or no exposure for the co-exposures) were used as the reference group.

Variable selection for the final main-effect models was based on the 'purposeful covariate selection' procedure [19]. We used univariate analyses to assess which agents were associated with colorectal cancer risk, and considered such agents as potential confounders. Variable selection suggested that co-exposures to benzene, formaldehyde, ionizing radiation, wood dust, chlorinated hydrocarbon solvents and chromium (in addition to PPWL) could be of interest as they can have a moderate effect on the incidence of colorectal cancers. A correlation check was then done between these cofactors: benzene was highly correlated with chlorinated hydrocarbon solvents and chromium, and therefore these cofactors were not used for same model. The resulting models were (1) PPWL + benzene + formaldehyde + ionizing radiation and wood dust and (2) PPWL + chlorinated hydrocarbon solvents + chromium + formaldehyde + ionizing radiation and wood dust.

Table 1
Annual Physical Workload for *Probability (P) and Level* (L) of being exposed to physical workload in different professions (all professions with a value of P * L ≥ 0.28) NOCCA Job Exposure Matrix.

Occupation	P * L
Reinforced concrete layers, stonemasons etc.	0.69
Concrete shutterers and finishers	0.68
Rod layers	0.58
Labourers	0.56
Assisting construction workers, nec	0.54
Assisting building workers	0.51
Butchers and sausage makers	0.50
Farmers, silviculturists, horticulturists	0.45
Bath attendants etc.	0.43
Homehelps (municipal)	0.42
Building occupations, nec	0.40
Sheet metal workers	0.37
Bricklayers, plasterers and tile setters	0.36
Forestry workers and lumberjacks	0.34
Charworkers	0.31
Fur farm workers	0.31
Headwaiters, restaurant waiters	0.28
Metal smelting furnacemen	0.28
Insulation workers	0.28

Analyses were made for different subsites of cancers of the colon (ascending, transversal, descending, unknown) as well as for the cancers of the rectum for all and then separately for both genders.

3. Results

Altogether 85,037 male colon cancer cases and 425,185 controls, and 60,019 rectal cancer cases and 300,095 controls were identified during the study period. The respective numbers for females for colon cancer were 96,672 and 483,360, and for rectal cancer 49,208 cases and 246,040 controls.

We observed a statistically significantly decreased risk and an inverse dose–response relationship (*P*-values for trends are presented in Table 2) for the exposure of PPWL and cancers of colon and rectum for males and females combined (Table 2). The lowest risk estimate for colon cancer was observed for cumulative PPWL levels above the 90th percentile of exposed persons (OR 0.78, 95% CI: 0.76–0.79). For the subsite analysis of colon cancer we observed the lowest risk for cancer of the descending colon (OR 0.66, 95% CI: 0.59–0.75). Reduced risks were also observed for high PPWL categories for ascending colon (OR 0.80, 95% CI: 0.77–0.84) and transversal colon (OR 0.78, 95% CI: 0.73–0.84). The risk reduction for rectal cancer was less pronounced (OR 0.87, 95% CI: 0.85–0.89) than for colon cancer.

The OR for the highest PPWL level for cancer of the ascending part of the colon was 0.76 in males (95% CI: 0.73–0.80) and 0.90 in females (95% CI 0.79–1.03). For the transverse part of colon the OR for males was 0.76 (95% CI 0.71–0.82) and that for females was 0.83 (95% CI 0.67–1.03). The most pronounced difference in the findings between male and female populations for the risk of cancer of the descending colon were: OR for males 0.61 (95% CI 0.54–0.69) and OR for females 0.99 (95% CI 0.69–1.40). Detailed results are presented in Table 3.

Inclusion of the occupational co-exposures did not change the results.

Table 2
Odds ratios (OR) and 95% confidence intervals (95% CI) for perceived physical workload (PPWL) and colorectal cancer. PPWL is categorized based on 50th and 90th percentile of cumulative exposure distribution among exposed colorectal cancer cases and controls.

Cancer location	Number of individuals		OR	95% CI
PPWL level	Case	Control		
Ascending colon				
None	29857	143861	1.00	Reference
Low	17726	88084	0.97	0.94–0.99
Moderate	13276	69896	0.90	0.88–0.92
High	3008	17494	0.80	0.77–0.84
p-trend <0.01				
Transversal colon				
None	12236	58083	1.00	Reference
Low	7407	37635	0.93	0.89–0.96
Moderate	5758	30190	0.89	0.86–0.92
High	1280	7497	0.78	0.73–0.84
p-trend <0.01				
Descending colon				
None	4192	19253	1.00	Reference
Low	2490	12490	0.91	0.86–0.96
Moderate	1789	10007	0.79	0.75–0.85
High	392	2565	0.66	0.59–0.75
p-trend <0.01				
Other colon sites				
None	37484	178037	1.00	Reference
Low	23283	114519	0.96	0.94–0.98
Moderate	17432	94544	0.86	0.84–0.88
High	4099	24390	0.77	0.74–0.79
p-trend <0.01				
All colon				
None	83769	399234	1.00	Reference
Low	50906	252728	0.95	0.94–0.97
Moderate	38255	204637	0.87	0.86–0.89
High	8779	51946	0.78	0.76–0.79
p-trend <0.01				
Rectum				
None	46239	226529	1.00	Reference
Low	30497	152060	0.98	0.97–0.99
Moderate	25894	131126	0.96	0.94–0.98
High	6597	36420	0.87	0.85–0.89
p-trend <0.01				

4. Discussion

Our study shows that the incidence of colorectal cancer decreases along with increasing PPWL, more so in males than in females. The trend of risk reduction along with increasing PPWL was significant in all groups and in all subsites of the colon as well as in the rectum. The biggest protective effect was noticed in the distal part of the colon in males. The protective effect was less pronounced in females in all subsites.

When interpreting our results, one potential limitation of the present study is exposure misclassification, which may arise from two sources. First, the generic JEM does not take into account the individual variety of exposure levels within an occupational category.

The incomplete data on work history is another factor possibly contributing to exposure misclassification. People's work histories were based on census records that are merely snapshots of jobs held in the year before the time of the census. The data did not provide accurate information on changes of the job or tasks during the entire career. The census information was known from years 1960–1990, and the oldest persons might have started their work life more than 40 years before the first known census occupation. If the person is still at rather an old age in a physically demanding job, it is unlikely that he/she would have been at the beginning of his/her career in a physically less demanding job than later in life, while the change to a physically less demanding job in older ages is more common. Therefore it is likely that the persons classified to the highest PPWL category truly belong in that category, but there may be persons on the no-PPWL category with PPWL exposure. This misclassification would bias the OR values towards unity and lead to slightly too low an estimate of the protective effect in our study.

We could not control for diet, smoking, alcohol usage, body mass index, adiposity or genetic factors that have been linked to cancers of colorectal cancer [20,21]. In a meta-analysis [22] investigators were able to establish a connection between smoking and colorectal cancer. Relative risk for smoking in rectal cancer seemed to be higher than the risk in colon cancer. The investigators detected a dose–response relationship, and the relative risk for incidence in the high exposure group was up to 1.5 for those with an exposure of ≥60 pack-years of cigarette smoking. For our study this issue might be a confounding factor as we are aware that smoking is more frequent in people of lower socioeconomic class [23]. Those in lower socioeconomic classes work in professions that are physically more demanding [24], which protects from colon cancer. For some of the professions in our highest decile of PPWL we noticed an increased risk ratio for lung cancer (highest in male waiters RR 1.90, 95% CI: 1.75–2.05) and a decreased risk ratio for some (lowest in female farmers, RR 0.46, 95% CI: 0.44–0.49). This big variability shows that this should not be expected to be a confounding effect in this study.

Table 3
Odds ratios (OR) and 95% confidence intervals (95% CI) for PPWL and colorectal cancer for men and women separately. Cumulative PPWL is categorized based on 50th and 90th percentile of cumulative exposure distribution among exposed colorectal cancer cases and controls.

Cancer location	Males				Females			
PPWL level	Cases	Controls	OR	95% CI	Cases	Controls	OR	95% CI
Ascending colon								
None	9579	43158	100	Reference	20278	100703	1.00	Reference
Low	7195	35333	0.92	0.89–0.95	10531	52751	0.99	0.96–1.02
Moderate	8204	44077	0.84	0.81–0.86	5072	25819	0.97	0.94–1.01
High	2743	16037	0.76	0.73–0.80	265	1457	0.90	0.79–1.03
p-trend <0.01					p-trend 0.06			
Transversal colon								
None	4280	19309	1.00	Reference	7956	38774	1.00	Reference
Low	3367	16587	0.92	0.87–0.97	4040	21048	0.93	0.89–0.97
Moderate	3726	19958	0.84	0.80–0.88	2032	10232	0.96	0.91–1.02
High	1183	6926	0.76	0.71–0.82	97	571	0.83	0.67–1.03
p-trend <0.01					p-trend 0.01			
Descending colon								
None	1615	6751	1.00	Reference	2577	12502	1.00	Reference
Low	1185	5790	0.86	0.79–0.94	1305	6700	0.94	0.87–1.01
Moderate	1204	6872	0.73	0.67–0.79	585	3135	0.89	0.81–0.99
High	354	2377	0.61	0.54–0.69	38	188	0.99	0.69–1.40
p-trend <0.01					p-trend 0.03			
Other colon sites								
None	14147	63123	1.00	Reference	23337	114914	1.00	Reference
Low	10683	51523	0.93	0.90–0.96	12600	62996	0.98	0.96–1.01
Moderate	11752	64582	0.81	0.79–0.83	5680	29962	0.93	0.90–0.96
High	3820	22782	0.74	0.71–0.77	279	1608	0.85	0.75–0.97
p-trend <0.01					p-trend <0.01			
All colon								
None	29621	132341	1.00	Reference	54148	266893	1.00	Reference
Low	22430	109233	0.92	0.90–0.94	28476	143495	0.98	0.96–0.99
Moderate	24886	135489	0.82	0.80–0.83	13369	69148	0.95	0.93–0.97
High	8100	48122	0.74	0.72–0.77	679	3824	0.87	0.81–0.95
p-trend <0.01					p-trend <0.01			
Rectum								
None	19350	94187	1.00	Reference	26889	132342	1.00	Reference
Low	15830	76694	1.01	0.99–1.03	14667	75366	0.95	0.93–0.98
Moderate	18611	94765	0.96	0.94–0.98	7283	36361	0.98	0.96–1.01
High	6228	34449	0.87	0.85–0.90	369	1971	0.93	0.83–1.04
p-trend <0.01					p-trend 0.01			

Overweight and obesity are definite factors that increase the incidence of colorectal cancers [25]. People in lower socioeconomic classes are also more obese/overweight [26], and this could increase the incidence of CRC. Even if we couldn't take BMI into account in our study, we were able to look at socioeconomic class. In our highest PPWL decile many of the professions belong to the lower socioeconomic groups, and thus overweight/obesity can be expected to be more common than in the lower PPWL exposure groups. Therefore, the protective effect seen in the highest PPWL category would be even stronger than that seen in our results, if we were able to control for BMI.

We were also unable to control for the leisure-time physical activity of the subjects. It can be assumed that the physical activity at work and leisure time would have similar, but weaker, effects for the incidence of colorectal cancer. This has been the finding of a few other studies that have looked at physical activity at work and leisure time [27]. Thus the effect of leisure-time physical activity could possibly decrease the incidence rates.

According to our results physical activity is in a significant inverse dose–response relationship with the incidence of colorectal cancer. There is more effect on the incidence of colon cancer in the distal part (descending) of the colon than in the proximal (or ascending) part of colon in the male population, but not in the female population. Isomura et al. [8] noticed a similar finding in colon cancer subsites among men, but a completely different result for the females: the study suggested a bigger protective effect for females, especially in the distal part (in our study: descending part) of colon.

In our study the number of colon cancer cases in the descending part of the colon for females was quite small: only 38 for the highest decile of PPWL. Despite the small number of cancer cases in women, the 95% CI of the OR (0.69–1.40) does not overlap with that calculated for men (0.54–0.69). A Norwegian study [28] found a stronger preventive effect for self-reported physical activity in males in the proximal part than in the distal part of colon. They noticed that the range of self-reported physical activity was greater in males than in females. In our study there were also only a few females in the highest decile of PPWL.

Our study confirms the inverse association between physical activity and the incidence of colorectal cancer. Our observations support previous study findings that the strength of the association between PPWL and colon cancer differs by subsite; this calls for further research into the reasons behind this phenomenon.

Conflict of interest

None.

Authorship contribution

1. Jorma Sormunen: Planning of the study, Statistical analysis, Collection of data, Authoring the manuscript.
2. Madar Talibov: Planning of the study, Statistical analysis, Collection of data, Authoring the manuscript.
3. Jan Ivar Martinsen: Statistical analysis, Collection of data, Authoring the manuscript.
4. Kristina Kjaerheim: Collection of data, Authoring the manuscript.
5. Pär Sparen: Collection of data, Authoring the manuscript.
6. Laufey Tryggvadottir: Statistical analysis, Collection of data, Authoring the manuscript.
7. Elisabete Weiderpass: Statistical analysis, Collection of data, Authoring the manuscript.
8. Eero Pukkala: Planning of the study, Statistical analysis, Collection of data, Authoring the manuscript.

References

[1] W.C. Willett, Diet and cancer: one view at the start of the millennium, Cancer Epidemiol. Biomarkers Prev. 10 (1) (2001) 3–8.
[2] M. Arnold, N. Pandeya, G. Byrnes, A.G. Renehan, G.A. Stevens, M. Ezzati, et al., Global burden of cancer attributable to high body-mass index in 2012: a population-based study, Lancet Oncol. 16 (1) (2015) 36–46.
[3] N.M. Pham, T. Mizoue, K. Tanaka, I. Tsuji, A. Tamakoshi, K. Matsuo, et al., Meat consumption and colorectal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population, Jpn. J. Clin. Oncol. 44 (7) (2014) 641–650.
[4] K.Y. Wolin, Y. Yan, G.A. Colditz, I.M. Lee, Physical activity and colon cancer prevention: a meta-analysis, Br. J. Cancer 100 (4) (2009) 611–616.
[5] I. Thune, A.S. Furberg, Physical activity and cancer risk: dose-response and cancer, all sites and site-specific, Med. Sci. Sports Exerc. 33 (6 Suppl) (2001) S530–S550 discussion S609-10.
[6] T. Moradi, G. Gridley, J. Bjork, M. Dosemeci, B.T. Ji, H.J. Berkel, et al., Occupational physical activity and risk for cancer of the colon and rectum in Sweden among men and women by anatomic subsite, Eur. J. Cancer Prev. 17 (3) (2008) 201–208.
[7] M. Dosemeci, R.B. Hayes, R. Vetter, R.N. Hoover, M. Tucker, K. Engin, et al., Occupational physical activity, socioeconomic status, and risks of 15 cancer sites in Turkey, Cancer Causes Control 4 (4) (1993) 313–321.
[8] K. Isomura, S. Kono, M.A. Moore, K. Toyomura, J. Nagano, T. Mizoue, et al., Physical activity and colorectal cancer: the Fukuoka colorectal cancer study, Cancer Sci. 97 (10) (2006) 1099–1104.
[9] T.I. Nilsen, P.R. Romundstad, H. Petersen, D. Gunnell, L.J. Vatten, Recreational physical activity and cancer risk in subsites of the colon (the Nord-Trondelag Health Study), Cancer Epidemiol. Biomarkers Prev. 17 (1) (2008) 183–188.
[10] E. Pukkala, J.I. Martinsen, E. Lynge, H.K. Gunnarsdottir, L. SparÈn Pr Tryggvadottir, et al., Occupation and cancer follow-up of 15 million people in five Nordic countries, Acta Oncol. 48 (2009) 646–790.
[11] G. Engholm, J. Ferlay, N. Christensen, F. Bray, M.L. Gjerstorff, A. Klint, et al., NORDCAN—a Nordic tool for cancer information, planning, quality control and research, Acta Oncol. 49 (5) (2010) 725–736.
[12] T. Kauppinen, P. Heikkila, N. Plato, T. Woldbaek, K. Lenvik, J. Hansen, et al., Construction of job-exposure matrices for the Nordic occupational cancer study (NOCCA), Acta Oncol. (2009) 1–11.
[13] Quality of Work Life Surveys, Statistics Finland, Helsinki, 1990 http://www.stat.fi/tk/el/tyoolot_aineisto_en.html (accessed 6.07.16).
[14] C. Paulu, A. Aschengrau, D. Ozonoff, Tetrachloroethylene-contaminated drinking water in Massachusetts and the risk of colon-rectum, lung, and other cancers, Environ. Health Perspect. 107 (4) (1999) 265–271.
[15] R. Fang, N. Le, Band P Identification of occupational cancer risks in British Columbia, Canada: a population-based case-control study of 1,155 cases of colon cancer, Int. J. Environ. Res. Public Health 8 (10) (2011) 3821–3843.
[16] A. Auvinen, K. Seppa, K. Pasanen, P. Kurttio, T. Patama, E. Pukkala, et al., Chernobyl fallout and cancer incidence in Finland, Int. J. Cancer 134 (9) (2014) 2253–2263.
[17] E. Weiderpass, H. Vainio, T. Kauppinen, K. Vasama-Neuvonen, T. Partanen, E. Pukkala, Occupational exposures and gastrointestinal cancers among Finnish women, J. Occup. Environ. Med. 45 (3) (2003) 305–315.
[18] J. Hansen, J.H. Olsen, Formaldehyde and cancer morbidity among male employees in Denmark, Cancer Causes Control 6 (4) (1995) 354–360.
[19] D.L.S. Hosmer, Applied Logistic Regression, 2nd ed., John Wiley & Sons, New York, 2004.
[20] M. Morita, L. Le Marchand, S. Kono, G. Yin, K. Toyomura, J. Nagano, et al., Genetic polymorphisms of CYP2E1 and risk of colorectal cancer: the Fukuoka Colorectal Cancer Study, Cancer Epidemiol. Biomarkers Prev. 18 (1) (2009) 235–241.
[21] G. Yin, S. Kono, K. Toyomura, T. Hagiwara, J. Nagano, T. Mizoue, et al., Methylenetetrahydrofolate reductase C677T and A1298C polymorphisms and colorectal cancer: the Fukuoka colorectal cancer study, Cancer Sci. 95 (11) (2004) 908–913.
[22] P.S. Liang, T.Y. Chen, E. Giovannucci, Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis, Int. J. Cancer 124 (10) (2009) 2406–2415.
[23] J. Jankovic, M. Eric, D. Stojisavljevic, J. Marinkovic, S. Jankovic, Socio-economic differences in cardiovascular health: findings from a cross-sectional study in a middle-Income country, PLoS One 10 (10) (2015) e0141731.
[24] R. Kaikkonen, O. Rahkonen, T. Lallukka, E. Lahelma, Physical and psychosocial working conditions as explanations for occupational class inequalities in self-rated health, Eur. J. Public Health 19 (5) (2009) 458–463.
[25] Y. Ma, Y. Yang, F. Wang, P. Zhang, C. Shi, Y. Zou, et al., Obesity and risk of colorectal cancer: a systematic review of prospective studies, PLoS One 8 (1) (2013) e53916.
[26] M. Magnusson, T.I. Sorensen, S. Olafsdottir, S. Lehtinen-Jacks, T.L. Holmen, B.L. Heitmann, et al., Social inequalities in obesity persist in the nordic region despite its relative affluence and equity, Curr. Obes. Rep. 3 (2014) 1–15.
[27] L.H. Colbert, T.J. Hartman, N. Malila, P.J. Limburg, P. Pietinen, J. Virtamo, et al., Physical activity in relation to cancer of the colon and rectum in a cohort of male smokers, Cancer Epidemiol. Biomarkers Prev. 10 (3) (2001) 265–268.
[28] I. Thune, E. Lund, Physical activity and risk of colorectal cancer in men and women, Br. J. Cancer 73 (9) (1996) 1134–1140.

Perceived Physical Strain at Work and Incidence of Prostate cancer – A Case-Control Study in Sweden and Finland

Authors: Jorma Sormunen[1,2]*, Madar Talibov[1], Pär Sparén[3], Jan Ivar Martinsen[4], Elisabete Weiderpass[3-6#], Eero Pukkala[1,7#]

*Corresponding author.
Mailing address:
Dr Jorma Sormunen
Tampere University Hospital
Department of Oncology, Teiskontie 35,
35320 Tampere, Finland
e-mail: Jorma.Sormunen@gmail.com

Shared last authorship.

[1] Faculty of Social Sciences, University of Tampere, Tampere, Finland
[2] Tampere University Hospital, Department of Oncology, Tampere, Finland
[3] Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
[4] Department of Research, Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway
[5] Genetic Epidemiology Group, Folkhälsan Research Center, Helsinki, Finland
[6] Department of Community Medicine, University of Tromsø, The Arctic University of Norway, Tromsø, Norway
[7] Finnish Cancer Registry, Institute for Statistical and Epidemiological Cancer Research, Helsinki, Finland

Abstract

The evidence that prostate cancer is associated to physical inactivity is inconsistent.

We studied the association of perceived physical workload (PPWL) at work and incidence of prostate cancer in a case-control setting. We used data from the Nordic Occupational Cancer study from Finland and Sweden. Five population controls were selected for each prostate cancer patient, matched on age and country. We had 239,835 cases and 1,199,175 controls in our study.

For each case and control we estimated cumulative PPWL based on probability, level and duration of PPWL using the NOCCA Job Exposure Matrix.

We then stratified individuals as having no exposure (reference category), low physical activity (below 50th percentile of the exposed), moderate exposure (50th-90th percentile) and high exposure (90th percentile and higher). The hazard ratios for prostate cancer from the lowest to highest cumulative PPWL levels were 0.90 (95% confidence interval 0.89-0.91), 0.88 (0.87-0.89) and 0.93 (0.92-0.95). There was no statistically significant dose response effect of PPWL on prostate cancer incidence. Inclusion of socioeconomic status in the model did not substantially change the result. The results were similar before Prostate Specific Antigen (PSA) testing and during the years of PSA testing in these countries.

In summary, individuals with physical strain at work had a lower risk of invasive prostate cancer as compared to individuals without physical strain at work.

Contents

Keywords: Epidemiology, Invasive Prostate cancer, Physical Workload

Abbreviations: P-Professional exposure, L-level (of exposure), T-time, PPWL-Perceived Physical Workload, PC-Prostate Cancer, PA-Physical Activity

What's new?

Perceived Physical workload (PPWL) at work was associated with a decreased risk of invasive prostate cancer. The association between PPWL and prostate cancer was not dose-dependent. The results were similar before and during the active PSA-testing years.
Adjustment for socio-economic status did not influence risk estimates.

Introduction

Prostate cancer (PC) is the most common cancer in older men in the western world.[1] Incidence rates increased steadily from the beginning of 1970's to the end of 1980's [2]. After the introduction of prostate specific antigen (PSA) testing in the late 1980's PC incidence rates have soared, due to detection of asymptomatic early state PCs.[3] Some of the PCs detected in PSA test are of low risk of progression, and can safely be followed-up clinically without active treatment for years, and may still later be treated surgically or with radiation therapy if PC becomes more aggressive.[4] Despite this PC mortality rates in the developed countries have stayed quite constant over the years.

Physical activity (PA) is one of the most important lifestyle factors that may reduce the risk of several cancer forms[5]. Reduced risk of prostate cancer has been reported in the Nordic Occupational Cancer (NOCCA) study in professions that require continuous physical activity, i.e., gardeners, fishermen, forestry workers, miners and quarry workers, smelting workers as well as several others.[6] In a recently published study it was noted that early onset-PC (men diagnosed before the age of 50) was most common in public safety workers and military personnel.[7] The reasons behind this finding require further research.

In a meta-analysis published in 2012, an inverse linear association was noted between localized PC and body mass index (BMI, defined as weight in kg/ height in meters squared), while f or advanced PC there was a linear positive association with BMI.[8] It has been postulated that BMI might not be an ideal marker of body composition, especially for PC studies, as the positive association seen in some studies between BMI and PC incidence could be caused by lean body mass or muscle mass, which are associated with increased circulating androgen levels.[9]

Socioeconomic status (SES) seems to predict active PSA-screening.[10] In a Norwegian cohort study the incidence of PC, probably due to increased PSA-testing, was elevated among men of high SES when compared to low SES (RR = 1.30; 95% CI 1.05-1.61). Men who were highly educated had similarly an increased risk for PC-diagnosis when compared to those with least education (RR = 1.56; 95% CI 1.11-2.19). In the same study a 20-percent protective effect was detected with leisure-time physical activity (RR = 0.80; 95% CI 0.62-1.03 for high vs low activity).[11] In another study SES was studied in relation to cancers of male genital organs in Finnish men aged 45-69 years of age between years 1971-95. The incidence of prostate cancer was 40-50% higher in men of the highest SES than men of the lowest SES. The difference diminished significantly in the 1990s.[12]

The aim of this study is to assess effect of perceived physical workload (PPWL) at work and the incidence of invasive prostate cancer in Finland and Sweden.

Materials and methods

We used a nested case-control design within the Nordic Occupational Cancer Study (NOCCA) cohort. This cohort consists of 14.9 million people from Nordic Countries (Finland, Iceland, Norway, Denmark, and Sweden) who participated in population censuses in 1960, 1970, 1980/1981, and/or 1990. A detailed description of the NOCCA cohort has been given by Pukkala et al.[6] As we did not have access to the individual records neither of the Danish nor

the Norwegian parts of the cohort, their data were not included. Occupational histories of individuals from Iceland were not available for us, thus these data were not included.

Occupational data was obtained from digital census records from 1960 and later censuses in Sweden and from 1970 and later censuses in Finland. Unique personal identity codes were used for linking the records from census with cancer registry data and national population registries for information on death, and emigration from the country.[6]

The cancer registries in Finland and Sweden have collected information on almost every single cancer case diagnosed since the 1950s, and their data is of high quality.[13]

For this study all incident prostate cancer cases diagnosed between the first available census and the 31st of December 2005 were extracted from the NOCCA cohort. Five controls for each cancer case were randomly selected among men who were alive and without a reported diagnosis of prostate cancer on the date of diagnosis of the case (hereafter the "index date" of the case–control set). Cases and controls were matched for year of birth and country. Individuals with minimum age of 20 years at index date, and having occupational information from at least one census record before the index date, were included in this study. Having a cancer diagnosis before prostate cancer incidence (for cases) or inclusion date (for controls) was not considered an exclusion criteria

For each case and control, the PPWL was estimated based on conversion of occupational codes to quantitative amounts of PPWL with the NOCCA Job Exposure Matrix (JEM).[14]

The PPWL is characterized by probability (P) and average PPWL (L). The unit of exposure was defined as a score of workers reporting heavy or rather heavy physical work in a national interview survey, which was conducted in 1990 as a part of the national 'Quality of Work Life Survey' in Finland.[15] When most workers in an occupational category reported very heavy workload in their profession, the value approaches one. If most respondent reported only fairly heavy work, the value approaches zero. If <10% persons in the occupation reported heavy or rather heavy physical work, the PPWL was set to zero. The estimated PPWL was highest among reinforced concrete layers, stonemasons, and concrete shutters (Annex Table 1).

We quantified the cumulative exposure to PPWL for all cases and controls. Physical workload of all individuals was calculated by using the time (T) between the age of 20 (typical age to start working in non-academic occupations) and the age of 65 (typical retirement age) or index date as a multiplier for the P*L-exposure of the profession of the individual (Table 1). After this, the individuals with PPWL above the baseline level, which was defined as P*L*T being zero, were divided to low (lowest 50% of the non-zero P*L*T; <7.37 PPWL-years), moderate (between 50 and 90 percentiles; 7.37-20.1 PPWL-years) and high (highest 10%; >20.1 PPWL-years) categories. If there were different occupational codes in census records for an individual, he was assumed to have changed occupations in the middle of the period between known census years.

<< Table 1. here>>
Table 1. Characteristics of study population in prostate cancer data in Finland and Sweden

Based on the introduction of PSA-testing at the end of 1980's, as well as the possible SES-bias in access to it, we conducted stratified analyses for the period before and after 1990 in order to evaluate the effect of PSA-testing on our main results. We used year 1990 as a cut-point because PSA-testing became widely available that time.[16]

Results

Altogether 239,835 PC-cases and 1,199,175 controls were identified during the study period (Table 1). The average age at diagnosis was 72.2 years. Most men were over 60 years old when they were diagnosed with PC, but there were a few cases that were diagnosed also in men under the age of 30.

The lowest risk estimate for PC was observed for moderate cumulative PPWL level; the HR was 0.88 (95% CI 0.87-0.89) when compared to the reference population. Reduced risks were also observed for low PPWL level (HR=0.90, 95% CI 0.89-0.91) and for high PPWL level (HR=0.93, 95% CI: 0.92-0.95). We observed statistically significantly decreased risk of PC, though without a clear dose-response pattern. (Table 2).

After adjustment for SES the HRs were 0.94 (95% CI 0.93-0.95), 0.94 (0.92-0.95) and 0.97 (0.95-0.99) for the low, moderate and high PPWL groups (Table 2).

<< Table 2 here >>
Table 2a. Hazard ratio and 95% confidence interval (95% CI) for PPWL exposure and prostate cancer in Finland and Sweden, with and without adjustment for socio-economic status (SES)

The HRs were virtually identical before and during the PSA-testing period (Table 3).

<< Table 3. here>>
Table 3. Hazard ratio and 95% confidence interval (95% CI) for PPWL exposure and prostate cancer in Finland and Sweden stratified by PSA-period.

Discussion

Our study shows that the incidence of PC was lower in individuals with PPWL compared to individuals without PPWL, but there was no evidence of a dose-response relationship.

When interpreting our results, one potential limitation of the present study is exposure misclassification, which may arise from the following sources. First, the generic JEM does not take into account the variation of PPWL between individuals in the same occupation category, but an average PPWL is given to every individual in the same occupational category. NOCCA-JEM does not account for industries but only occupational groups. PPWL intensity and prevalence may vary by industry included into the same occupational group.[17] Hence, a lack of information on industry may also contribute to misclassification, in the case of this study of physical strain at work, and bias the association between exposure and outcome of interest.[18]

The incomplete data on work history may also contribute to exposure misclassification. People's work histories were based on census records that are merely snapshots of jobs held in the year before the time of the census. The data did not provide exact information on the

changes of the job or tasks during the entire career. The census information was known from years 1960-1990, and the oldest individuals may have started their work life more than 40 years before the first known census occupation. If the person was still at rather high age in a physically demanding job, it was unlikely that he would have been in the beginning of his/her career in a physically less demanding job, while the change to physically less demanding job in older age is more common. Therefore it is likely that the persons classified to the highest PPWL category truly belonged in that category but there may be persons in the reference category with some PPWL exposure. This misclassification would bias the HR values towards unity and lead to slightly too low estimates of the protective effect in our study.

The associations between lifestyle, physical activity at work and the risk of PC reported in previously published studies have been inconsistent. Lifetime total occupational physical activity did not prove to be protective of PCs in a Swedish study published in 2008.[19] On the contrary, there was an increased risk of PC for men that had a high amount of physical activity in their work. There was a significantly decreased risk in high physical activity workers in the US[20] but several other studies have been inconclusive or negative[21]. Often these results can be explained by small sample size and short follow-up.

We were unable to control for the leisure time physical activity of the subjects. However, on population level we were able to assess the effects of independent lifestyle factors to a satisfactory degree. Some studies have reported a small decrease in PC risk for increased leisure time PA[22], but recently some conflicting findings have been reported: an increased PC incidence has been reported in a meta-analysis of 12 different studies from US and Europe comprising of 1.44 million adults. Intense leisure-time physical activity was associated with a 5% increased risk of prostate cancer (HR, 1.05; 95% CI, 1.03-1.08).[23]

Advantages of the study are important. The Nordic[13] cancer registries have reportedly a very high accuracy and completeness when it comes to their data. In addition to that we've had access to the accurate job history of the participants of this study[6] to a very satisfactory degree. The completeness and the amount of the data makes this dataset unique.

In addition to this the general lifestyle and access to healthcare for all social classes, thanks to tax funded health care, is almost identical to everyone living in Finland and Sweden. In addition to that in both countries the local municipalities support different health promoting activities e.g. cheap access to sports facilities.

Our study confirms the association between physical activity and the incidence of PC: in fact even modest levels of physical activity (PA) at work can reduce the incidence of PC significantly[24]. In addition, the results were almost identical at the time before the era of PSA-testing and during PSA-testing. Most importantly our study adds up to the finding presented by earlier research that especially the lack of physical activity and sedentary lifestyle seem to be associated with higher risk of PC than any level of physical activity.

References

1. Wong MCS, Goggins WB, Wang HHX, Fung FDH, Leung C, Wong SYS, Ng CF, Sung JJY. Global Incidence and Mortality for Prostate Cancer: Analysis of Temporal Patterns and Trends in 36 Countries. *Eur Urol* 2016;70:862–74.
2. Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer statistics, 2003. *CA Cancer J Clin* 2003;53:5–26.
3. Potosky AL, Miller BA, Albertsen PC KB. The role of increasing detection in the rising incidence of prostate cancer. *JAMA* 1995;7:548–52.
4. Herden J, Ansmann L, Ernstmann N, Schnell D, Weissbac L. The Treatment of Localized Prostate Cancer in Everyday Practice in Germany. *Dtsch Arztebl Int* 2016;113:329–36.
5. Leitzmann M, Powers H, Anderson AS, Scoccianti C, Berrino F, Boutron-Ruault MC, Cecchini M, Espina C, Key TJ, Norat T, Wiseman M, Romieu I. European Code against Cancer 4th Edition: Physical activity and cancer. *Cancer Epidemiol* 2015;39:S46–55.
6. Pukkala E, Martinsen JI, Lynge E, Gunnarsdottir HK, Sparen P, Tryggvadottir L, Weiderpass E, Kjaerheim K. Occupation and cancer - follow-up of 15 million people in five Nordic countries. *Acta Oncol* 2009;48:646–790.
7. Barry KH, Martinsen JI, Alavanja MCR, Andreotti G, Blair A, Hansen J, Kjærheim K, Koutros S, Lynge E, Sparèn P, Tryggvadottir L, Weiderpass E, Berndt SI, Pukkala E. Risk of early-onset prostate cancer associated with occupation in the Nordic countries. *Eur J Cancer* 2017;87:92–100.
8. Discacciati A, Orsini N, Wolk A. Body mass index and incidence of localized and advanced prostate cancer-a dose-response meta-analysis of prospective studies. *Ann. Oncol.*2012;23:1665–71.
9. Severson RK, Grove JS, Nomura a M, Stemmermann GN. Body mass and prostatic cancer: a prospective study. *BMJ* 1988;297:713–5.
10. Burns R, Walsh B, O'Neill S, O'Neill C. An examination of variations in the uptake of prostate cancer screening within and between the countries of the EU-27. *Health Policy (New York)* 2012;108:268–76.
11. Lund Nilsen TI, Johnsen R, Vatten LJ. Socio-economic and lifestyle factors associated with the risk of prostate cancer. *Br J Cancer* 2000;82:1358–63.
12. Pukkala E, Weiderpass E. Socio-economic differences in incidence rates of cancers of the male genital organs in Finland, 1971-95. *Int J Cancer* 2002;102:643–8.
13. Pukkala E., Engholm G., Højsgaard Schmidt LK., Storm H, Khan S, Lambe M, Pettersson D, Ólafsdóttir E, Tryggvadóttir L, Hakanen T, Malila N, Virtanen A, Johannesen TB, Larønningen S, Ursin G. Similarities and differences of the Nordic Cancer Registries – an overview of their procedures and data comparability. *Acta Oncol* 2017;Accepted for publication.
14. Kauppinen T, Heikkil P, Plato N, Woldbæk T, Lenvik K, Hansen J, Kristjansson V, Pukkala E. Construction of job-exposure matrices for the Nordic Occupational Cancer Study (NOCCA). *Acta Oncol* 2009;48:791–800.
15. Content areas of Quality of Work Life Surveys [Internet]. *Stat. Finl.*1990 [cited 2017 Oct 25];Available from: http://www.stat.fi/tk/el/tyoolot_aineisto_sisalto_en.html
16. Oesterling JE, Jacobsen SJ, Klee GG, Petterson K, Piironen T, Abrahamsson PA, Stenman UH, Dowell B, Lovgren T, Lilja H. Free, Complexed and Total Serum Prostate Specific Antigen: The Establishment of Appropriate Reference Ranges for their Concentrations and Ratios. *J Urol* 1995;154:1090–5.
17. Wang R, Zhang Y, Lan Q, Holford TR, Leaderer B, Hoar Zahm S, Boyle P, Dosemeci M,

Rothman N, Zhu Y, Qin Q, Zheng T. Occupational exposure to solvents and risk of non-Hodgkin lymphoma in Connecticut women. *Am J Epidemiol* 2009;169:176–85.
18. Stewart PA, Herrick RF. Issues in performing retrospective exposure assessment. *Appl Occup Environ Hyg* 1991;6:421–7.
19. Wiklund F, Lageros YT, Chang E, Balter K, Johansson J-E, Adami H-O, Gronberg H. Lifetime total physical activity and prostate cancer risk: a population-based case-control study in Sweden. *Eur J Epidemiol* 2008;23:739–46.
20. Krishnadasan A, Kennedy N, Zhao Y, Morgenstern H, Ritz B. Nested case-control study of occupational physical activity and prostate cancer among workers using a job exposure matrix. *Cancer Causes Control* 2008;19:107–14.
21. Sass-Kortsak AM, Purdham JT, Kreiger N, Darlington G, Lightfoot NE. Occupational risk factors for prostate cancer. *Am J Ind Med* 2007;50:568–76.
22. Littman AJ, Kristal AR, White E. Recreational physical activity and prostate cancer risk (United States). *Cancer Causes Control* 2006;17:831–41.
23. Moore SC, Lee I-M, Weiderpass E, Campbell PT, Sampson JN, Kitahara CM, Keadle SK, Arem H, Berrington de Gonzalez A, Hartge P, Adami H-O, Blair CK, Borch, KB, Boyd E, Check DP, Fournier A, Freedman ND, Gunter M, Johannson M, Khaw K-T, Linet M, Orsini N, Park Y, Riboli E, Robien K, Schairer C, Sesso H, Spriggs M, Van Dusen R, Wolk A, Matthews CE, Patel AV. Association of Leisure-Time Physical Activity With Risk of 26 Types of Cancer in 1.44 Million Adults. *JAMA Intern Med* 2016;176:816.
24. Cuzick J, Thorat MA, Andriole G, Brawley OW, Brown PH, Culig Z, Eeles RA, Ford LG, Hamdy FC, Holmberg L, Ilic D, Key TJ, Vecchia CL, Lilja H, Marberger M, Meyskens FL, Minasian LM, Parker C, Parnes HL, Perner S, Rittenhouse H, Schalken J, Schmid HP, Schmitz-Dräger BJ, Schröder FH, Stenzl A, Tombal B, Wilt TJ, Wolk A. Prevention and early detection of prostate cancer. *Lancet Oncol.*2014;15(11);e484–92.

Table 1. Characteristics of study population for prostate cancer data in Finland and Sweden.

Characteristics	Case		Control	
	n	%	N	%
Total	239835	100	1199175	100
Age at index date				
<40	22	0.0	105	0.0
40-60	20198	8.4	101515	8.5
60-80	175645	73.2	877070	73.1
>80	43970	18.3	220485	18.4
Country				
Finland	58921	24.6	294605	24.6
Sweden	180914	75.4	904570	75.4
Period				
Before 1990 (pre-PSA)	83772	34.9	418860	34.9
1990-2005 (PSA)	156063	65.1	780315	65.1
Socio-economic status				
Upper white-collar	59318	24.7	257201	21.5
Lower white-collar	83527	34.8	424643	35.4
Upper blue-collar	68317	28.5	358869	29.9
Lower blue-collar	14102	5.9	78631	6.6
Farmer	11066	4.6	53500	4.5
Economically inactive	3503	1.5	26331	2.2

Table 2. Hazard ratio (HR) and 95% confidence interval (95% CI) for prostate cancer, by cumulative PPWL exposure in Finland and Sweden, with an without unadjustment for socioeconomic status (SES).

	Unadjusted			Adjusted for SES		
Exposure	**HR**	**95% CI**	**p-trend**	**HR[2]**	**95% CI**	**p-trend**
Cumulative PPWL[1]						
Reference	1.00	Ref.		1.00	Ref.	
Low	0.90	0.89-0.91		0.94	0.93-0.95	
Moderate	0.88	0.87-0.89		0.94	0.92-0.95	
High	0.93	0.92-0.95	<0.01	0.97	0.95-0.99	<0.01

[1] Cut-points are based on 50th and 90th percentile of exposure distribution among exposed subjects.

Table 3. Hazard ratio (HR) and 95% confidence interval (95% CI) for PPWL exposure and prostate cancer in Finland and Sweden stratified by PSA-period, with and without adjustment for socioeconomic status (SES).

Cumulative PPWL[1]	Case	Control	Unadjusted			Adjusted for SES		
			HR	95% CI	p-trend	HR	95% CI	p-trend
Before 1990 (pre-PSA period)								
Reference	30205	144069	1..00	Ref.		1..00	Ref.	
Low	22290	114081	0.90	0.89-0.91		0.94	0.92-0.96	
Moderate	21980	114294	0.88	0.87-0.89		0.94	0.92-0.96	
High	9297	46416	0.93	0.92-0.95	<0.01	0.99	0.95-1.02	0.01
1990 and later (PSA period)								
Reference	56720	261649	1.00	Ref.		1.00	Ref.	
Low	54533	282317	0.89	0.88-0.90		0.94	0.92-0.95	
Moderate	38548	204829	0.87	0.86-0.88		0.93	0.92-0.95	
High	6262	31520	0.92	0.89-0.95	<0.01	0.96	0.93-1.00	<0.01

[1] Cut-points are based on 50th and 90th percentile of exposure distribution among exposed subjects.

Annex table for online publication. Annual Physical Workload for *Probability (P) and Level* (L) of being exposed for physical workload in different professions (all professions with a value of P*L≥0.001) NOCCA Job Exposure Matrix.

Occupation	P*L
Reinforced concrete layers. stonemasons etc.	0.69
Concrete shutterers and finishers	0.68
Rod layers	0.58
Labourers	0.56
Assisting construction workers. Nec	0.54
Assisting building workers	0.51
Butchers and sausage makers	0.50
Farmers. silviculturists. horticulturists	0.45
Bath attendants etc.	0.43
Homehelps (municipal)	0.42
Building occupations. Nec	0.40
Sheet metal workers	0.37
Bricklayers. plasterers and tile setters	0.36
Forestry workers and lumberjacks	0.34
Charworkers	0.31
Fur farm workers	0.31
Headwaiters. restaurant waiters	0.28
Metal smelting furnacemen	0.28
Insulation workers	0.28
Occupations below this line never reach the highest cumulative PPWL category of 17.2 PPWL-years	
Laundry workers	0.27
Turners. toolmakers and machine-tool setters	0.27
Occupations in smelting. metallurgical and foundry work. nec	0.25
Cabinetmakers and joiners etc.	0.25
Construction carpenters	0.24
Cold- and hot-rolling metal workers	0.24
Chimney sweeps	0.24
Stone cutters	0.24
Hairdressers and barbers	0.23
Concrete-mixer operators and cast concrete product workers	0.23
Plumbers	0.23
Postmen and sorters	0.22
Warehousemen	0.22
Painters. lacquerers and floor layers	0.21
Commercial garden and park workers	0.20
Wooden boat builders. coach-body builders etc.	0.20
Sugar processing workers	0.20
Pursors and hostesses	0.20
Kitchen assistants	0.20
Plywood and fibreboard workers	0.20
Processed foods workers	0.19
Maintenance crews and supervisors	0.18
Wooden surface finishers	0.17
Foundry workers	0.17
Fishermen	0.17
Bakers	0.17
Wire and pipe drawers	0.16
Occupations in the food industry. nec	0.16

Bench carpenters	0.16
Dairy workers	0.15
Sawyers	0.15
Cannery workers	0.15
Metal plating and coating work	0.15
Glaziers	0.14
Masseurs etc.	0.14
Heat treaters. hardeners. temperers etc.	0.14
Newspaper delivery work	0.14
Door-to-door salesmen	0.14
Assemblers and other machine and metalware occupations	0.14
Smiths	0.13
Cooks etc.	0.13
Chocolate and confectionery manufacturers	0.13
Farm workers	0.13
Brewers. beverage makers and kilnmen	0.12
Woodworking machine operators etc.	0.12
Woodworking occupations. Nec	0.12
Welders and flame cutters	0.11
Institutional child care staff	0.11
Fur farmers	0.11
Machine setter operators (not in textile industry) and riggers	0.11
Physical education instructors. trainers. coaches etc.	0.11
Shop personnel. shop supervisors and department chiefs	0.11
Grain millers	0.11
Reindeer breeders	0.10
Timbermen	0.10
Directors and nursing staff at child day care centres	0.10
Machine and engine mechanics	0.10
Occupations in agriculture. horticulture and animal husbandry. nec	0.10
Nurses	0.10
Concentration plant workers	0.09
Well drilling and quarrying	0.09
Firemen	0.09
Miners. shot firers etc.	0.09
Asphalt workers	0.09
Stevedores etc.	0.09
Farm supervisors	0.09
Other occupations related to health care and medical work	0.09
Fitter-assemblers etc.	0.09
Housekeepers (private service). child care in families and at home	0.08
Physiotherapists. occupational therapists	0.08
Caretakers	0.08
Occupations below this line never reach the Moderate cumulative PPWL category of 4.28 PPWL-years	
Messengers and delivery boys etc.	0.07
Assistant nurses and affendants	0.07
Packers and labellers etc.	0.07
Flight operations officers	0.07
Midwives	0.07
Crushers. grinders and calender operators (chemical processing)	0.07
Occupations in manufacturing. nec	0.06
Paper products workers	0.06
Glass and ceramics kilnmen	0.06
Cashiers in shops and restaurants	0.06
Paper and cardboard mill workers	0.05

Non-commissioned officers in corresponding positions	0.05
Deck crew	0.05
Fish farmers	0.05
Engine-room crew	0.05
Rubber products workers	0.04
Glass moulders etc.	0.04
Hotel and restaurant matrons	0.04
Waiters in bars and cafes etc.	0.04
Tanners. fellmongers and pelt dressers	0.04
Potters	0.04
Customs officers and border guards	0.04
Distillers	0.04
Plastic product workers	0.04
Telephone installation crew. linemen and cable jointers	0.03
Service station attendants	0.03
Electricians	0.03
Beauticians etc.	0.03
Guards (civil duties)	0.03
Enlisted military personnel	0.02
Military personnel	0.02
Photographic laboratory assistants	0.02
Research and consultative work in forestry	0.02
Electric machine fitters (high voltage)	0.02
Occupations related to building caretaking and cleaning. nec	0.02
Housekeeping managers	0.02
Printers	0.02
Cookers and furnacemen (chemical processes)	0.02
Tobacco industry workers	0.02
Occupations and guarding security. nec	0.02
Refinery workers. other occupations in the chemical industry	0.01
Prison guards etc.	0.01
Occupations related to medical and nursing work. nec	0.01
Forklift operators etc.	0.01
Bookbinders	0.01
Electric machine operators	0.01
Upholsterers	0.01
Secondary school rectors. teachers and instructors	0.01
Construction machinery operators etc.	0.01