TEEMU MURTOLA

Prostate Cancer Incidence Among Men Using Statins, Finasteride or Antidiabetic Drugs

A population-based study

ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Medicine of the University of Tampere,
for public discussion in the Auditorium of
Tampere School of Public Health, Medisiinarinkatu 3,
Tampere, on December 18th, 2009, at 12 o'clock.

UNIVERSITY OF TAMPERE

ACADEMIC DISSERTATION
University of Tampere, School of Public Health
Tampere University Hospital, Department of Urology
Central Finland Central Hospital, Department of Surgery
Doctoral Programs in Public Health (DPPH)
National Graduate School of Clinical Investigation (CLIGS)
Finland

Supervised by
Professor Anssi Auvinen
University of Tampere
Finland
Professor Teuvo Tammela
University of Tampere
Finland

Reviewed by
Professor Jan Adolfsson
Karolinska Institutet
Sweden
Professor Risto Huupponen
University of Turku
Finland

Distribution
Bookshop TAJU
P.O. Box 617
33014 University of Tampere
Finland

Tel. +358 3 3551 6055
Fax +358 3 3551 7685
taju@uta.fi
www.uta.fi/taju
http://granum.uta.fi

Cover design by
Juha Siro

Acta Universitatis Tamperensis 1482
ISBN 978-951-44-7925-0 (print)
ISSN-L 1455-1616
ISSN 1455-1616

Acta Electronica Universitatis Tamperensis 917
ISBN 978-951-44-7926-7 (pdf)
ISSN 1456-954X
http://acta.uta.fi

Tampereen Yliopistopaino Oy – Juvenes Print
Tampere 2009

Dedicated to the loves of my life:

my dear wife, Tiina

and my children, Kai and Eini

CONTENTS

10. ORIGINAL COMMUNICATIONS

LIST OF ORIGINAL PUBLICATIONS

1. Murtola TJ, Tammela TL, Määttänen L, Hakama M, Auvinen A (2007): Prostate cancer risk among users of finasteride and alpha-blockers – a population based case-control study. *Eur J Cancer 43:775-781*

2. Murtola TJ, Tammela TL, Määttänen L, Ala-Opas M, Stenman UH, Auvinen A. (2009): Prostate cancer incidence among finasteride and alpha-blocker users in the Finnish Prostate Cancer Screening Trial. *Br J Cancer*, 101, 834-838.

3. Murtola TJ, Tammela TL, Lahtela J, Auvinen A. (2007): Cholesterol-lowering drugs and prostate cancer risk: a population-based case-control study. *Cancer Epidemiol Biomarkers Prev 16:2226-2232*

4. Murtola TJ, Tammela TL, Määttänen L, Huhtala H, Platz EA, Ala-Opas M, Stenman UH, Auvinen A: Prostate cancer and PSA among statin users in the Finnish Prostate Cancer Screening Trial. *(Submitted)*

5. Murtola TJ, Tammela TL, Lahtela J, Auvinen A (2008): Antidiabetic medication and prostate cancer risk: a population-based case-control study. *Am J Epidemiol 168:925-931*

ABBREVIATIONS

ACE	angiotensin convertase-ezyme
5-ARI	5α-reductase inhibitor
AT	angiotensin receptor
BPH	benign prostatic hyperplasia
CI	confidence interval
CVD	Cardiovascular disease
DDD	defined daily dose
DM	diabetes mellitus
DRE	digital rectal examination
HMG-CoA	hydroxymethyl coenzyme-A
HR	hazard ratio

IU	international unit
LUTS	lower urinary tract symptoms
NSAID	non-steroidal anti-inflammatory drug
OR	odds ratio
PCPT	Prostate Cancer Prevention Trial
PSA	prostate-specific antigen
SII	Social Insurance Institution of Finland
WHO	World Health Organization

ABSTRACT

Introduction: Prostate cancer is the most common malignancy among men in Western countries and its incidence also in the developing world. In most countries it is among the three most lethal cancers. The high prevalence of the disease makes it an attractive target for prevention.

Recent evidence suggests that some commonly used medications could lower the risk of prostate cancer. Current evidence for most drug groups, however, is often controversial. The protective effect has been shown by a randomized clinical trial only for finasteride (a 5-α reductase inhibitor).

The present study used data from Finnish national registers and the Finnish Prostate Cancer Screening Trial to study prostate cancer incidence among users of statins, finasteride and antidiabetic drugs.

Materials and methods: Two distinct study populations were used. A case-control study including, as cases, all newly diagnosed prostate cancer cases in Finland during 1995-2002, and matched controls (24,723 case-control pairs) was formed using the Finnish Cancer Registry and the Population Register Centre. Another study population included all men participating in the screening arm of the Finnish Prostate Cancer Screening Trial during 1996-2004, forming a cohort of 23,320 men systematically screened for prostate cancer. Both populations were linked to the prescription database of the Social Insurance Institution of Finland to obtain detailed information on medication usage.

Results: Differences in results were observed between the case-control study and the cohort study.

In the case-control study, finasteride and alpha-blocker users had an increased prostate cancer incidence compared to the non-users. However, among men screened in the Finnish Prostate Cancer Screening Trial we observed a dose-dependent decrease in incidence of low grade/early stage prostate tumours among finasteride users.

The use of statins or other cholesterol-lowering drugs did not reduce overall prostate cancer risk in the case-control study, but there was a dose-dependent decrease in the incidence of advanced cancer among statin users. In the cohort study, on the other hand, statin use was associated with a dose-dependent decrease in overall prostate cancer incidence. Compared to non-users, median serum PSA concentration was slightly lower among users of statins and other cholesterol-lowering drugs, but this did not entirely explain the observed risk reduction among statin users.

Lastly, we observed decreased prostate cancer incidence among users of antidiabetic drugs in the case-control study. The decrease in risk was unrelated to the type of drug used, suggesting that diabetes, instead of medication use as such, is behind the association.

Conclusions: Our results demonstrate that prostate cancer incidence is associated with medication use at the population level. Thus, it seems possible to reduce the disease burden by manipulating this factor.

Differing results from the two study populations show the extent to which the differences in PSA testing activity impacts on the results of epidemiological studies; in the case-control study, prevalence of opportunistic PSA testing was low, albeit probably more common among medication users; whereas men in the cohort study were systematically screened. This underlines the importance of controlling for the PSA screening activity in any epidemiological study on prostate cancer incidence.

The previously reported chemopreventive effect of finasteride can be expected in men using the drug for symptomatic BPH. At the national level, however, the overall incidence is more strongly affected by the incidence increasing factors associated with BPH. Our finding of decreased prostate cancer risk among diabetic men brings further insight into the aetiology of prostate cancer. Cholesterol control with statins might be another promising avenue for prostate cancer prevention. Further mechanistic studies and, ultimately, also clinical studies are warranted to study statins as a prostate cancer chemopreventive agent.

TIIVISTELMÄ

Johdanto: Eturauhassyöpä on länsimaissa miesten yleisin syöpä ja sen ilmaantuvuus on nousussa myös kehitysmaissa. Se on useimmissa maissa yksi kolmesta yleisimmästä miesten syöpäkuoleman aiheuttajasta. Taudin yleisyys tekee sen ehkäisystä houkuttelevan vaihtoehdon.

Viimeaikaisten tutkimusten mukaan eräiden lääkeaineiden käyttö saattaa alentaa eturauhassyöpäriskiä. Useimpien lääkeaineiden kohdalla tulokset ovat kuitenkin ristiriitaisia. Suojavaikutus on todistettu satunnaistetussa kliinisessä tutkimuksessa ainoastaan finasteridin (5-α reduktaasin salpaaja) osalta.

Tutkimuksessamme yhdistimme kansallisista rekistereistä kerättyjä tietoja suomalaisen eturauhassyövän seulontatutkimuksen tietoihin arvioidaksemme eturauhassyövän ilmaantuvuutta finasteridin, statiinien ja diabeteslääkkeiden käyttäjien keskuudessa.

Aineistot ja menetelmät: Tutkimuksessa käytettiin kahta erillistä tutkimusaineistoa. Kaikki uudet eturauhassyöpätapaukset Suomessa vuosilta 1995-2002 ja näiden kaltaistetut verrokit sisältävä tapaus-verrokkiaineisto (24,723 tapaus-verrokkiparia) muodostettiin Syöpärekisterin ja Väestörekisterin avulla. Toinen tutkimuksessa käytetty väestö koostui suomalaisen eturauhassyövän seulontatutkimukseen sen seulontahaarassa vuosina 1996-2004 osallistuneista miehistä, muodostaen 23,320 eturauhassyövän suhteen seulotun miehen kohortin. Kummankin tutkimusväestön yksityiskohtaiset lääkkeidenkäyttötiedot haettiin KELA:n lääkekorvaustietokannasta.

Tulokset: Tulokset erosivat tutkimusasetelmien välillä. Tapaus-verrokkiväestössä eturauhassyövän ilmaantuvuus oli suurentunut finasteridin ja alfa-salpaajien käyttäjien keskuudessa ei-käyttäjiin verrattuna. Kuitenkin seulontatutkimuksen kohortissa hyvin erilaistuneiden ja paikallisten eturauhaskasvainten ilmaantuvuus laski suorassa suhteessa käytettyyn finasteridimäärään nähden.

Statiinien tai muiden kolesterolilääkkeiden käyttö ei laskenut eturauhassyövän ilmaantuvuutta yleisesti tapaus-verrokkiväestössä, mutta etäpesäkkeisen taudin ilmaantuvuus laski suorassa suhteessa käytettyyn statiinimäärään nähden. Kohorttiväestössä sen sijaan myös yleinen eturauhassyövän ilmaantuvuus oli alentunut. Statiinien ja muiden kolesterolilääkkeiden käyttäjillä oli keskimäärin hiukan matalampi PSA kuin lääkkeitä käyttämättömillä miehillä, mutta tämä ei täysin riittänyt selittämään lääkkeiden käyttäjien alentunutta eturauhassyövän ilmaantuvuutta.

Myös diabeteslääkkeiden käyttäjillä eturauhassyövän ilmaantuvuus oli muita miehiä alhaisempi tapaus-verrokkiväestössä. Ilmaantuvuuden alenema ei ollut yhteydessä käytettyyn lääketyyppiin. Löydös viittaa, että alentunut riski johtuu todennäköisemmin diabeteksesta kuin minkään yksittäisen lääkkeen käytöstä.

Johtopäätökset: Tuloksemme osoittavat että väestötasolla eturauhassyövän ilmaantuvuus riippuu lääkkeiden käytöstä. Niinpä taudin aiheuttaman haitan vähentäminen tähän tekijään vaikuttamalla näyttäisi mahdolliselta.

Tuloksissa havaitut erot kahden eri tutkimusväestön välillä osoittavat PSA testausaktiivisuuden suuren vaikutuksen epidemiologisen tutkimuksen tuloksiin; tapaus-verrokkiaineistossa opportunistinen seulonta oli harvinaista, vaikkakin todennäköisesti yleisempää lääkkeiden käyttäjien joukossa; kun taas kohorttiaineisto koostui seulotuista miehistä. Tämä osoittaa kuinka tärkeää PSA testausaktiivisuuden huomioiminen on eturauhassyövän ilmaantuvuutta selvittävissä epidemiologisissa tutkimuksissa.

Aiemmin osoitettu finasteridin eturauhassyövältä suojaava vaikutus pätee myös miehiin jotka käyttävät sitä eturauhasen hyvänlaatuisen liikakasvun hoitona. Kansallisella tasolla kuitenkin hyvänlaatuiseen liikakasvuun liittyvät, ilmaantuvuutta nostavat tekijät vaikuttavat enemmän kokonaisilmaantuvuuteen. Havaintomme diabeetikkomiesten alentuneesta eturauhassyöpäriskistä tuo uutta tietoa eturauhassyövän kehittymiseen vaikuttavista tekijöistä. Kolesterolitason alentaminen statiineilla saattaa osoittautua

lupaavaksi keinoksi alentaa eturauhassyöpäriskiä. Statiinien käyttökelpoisuus eturauhassyövän ehkäisyssä vaatii lisätutkimuksia jotka selvittävät vaikutuksen mekanismia sekä kliinistä merkitystä.

1. INTRODUCTION

Prostate cancer is an increasing health problem both in the Western world and in the developing world. The number of prostate cancer diagnoses per year has been steadily increasing for many years in most countries, especially after the introduction of the serum prostate-specific antigen (PSA) test (Ferlay et al., 2002). Most prostate tumours grow slowly and have a good prognosis. Indeed, localized prostate cancer is a common finding at autopsies of asymptomatic men (Franks, 1954; Breslow et al., 1977). However, fatal prostate cancer is not rare; prostate cancer is the second most common cause of male cancer death after lung cancer in most countries (Ferlay et al., 2002).

The aetiology of prostate cancer remains mainly unknown. The only well-established risk factors for prostate cancer are age, race and genetic predisposition (Crawford, 2009). Typically, prostate cancer occurs late in life, and is uncommon before the age of 40 years. African-American men have a higher prostate cancer risk than do Caucasian men (Crawford, 2009). Genetic predisposition accounts for 29-50% of the prostate cancer risk (Lichtenstein et al., 2000). Genetic liability for prostate cancer probably also increases the risk of stomach cancer (Matikainen et al., 2001).

Environmental factors have a great influence on the risk of clinically significant prostate cancer, as demonstrated by the changing incidence trends among Asian immigrants in the US (Pu et al., 2004). Asian men have a lower incidence of prostate cancer than have Western men, even though the prevalence of malignant precursors is equal. However, the incidence of prostate cancer among Asian immigrants increases more and more the longer their stay in the United States of America (US), ultimately rising to the level of their Western counterparts. Also, the traditionally low incidence of prostate cancer in Asia is increasing due to the westernization of lifestyles (Pu et al., 2004). A similar

change in prostate cancer incidence has also been reported among the Inuit population migrating to Denmark (Boysen et al., 2008). Nevertheless, despite active research, the role of any single environmental influence such as obesity or a high--fat diet as risk factors for prostate cancer remains controversial (Amling, 2005; Wu et al., 2006).

Recently, evidence has been emerging on the chemopreventive properties of some commonly used drug groups with respect to prostate cancer. These include 5α-reductase inhibitors finasteride and dutasteride, currently used in the treatment of benign prostatic hyperplasia (BPH) (Crawford, 2009). Finasteride is currently the only drug shown to decrease prostate tumour incidence in a placebo-controlled randomized clinical trial (Thompson et al., 2003). Cholesterol-lowering drugs statins (Murtola et al., 2008) and non-steroidal anti-inflammatory drugs (NSAIDs) (Harris et al., 2005) are also showing promise in this regard. Currently, the available evidence for these drug groups comes from experimental and epidemiological studies. Preliminary findings also suggest that the antidiabetic drug metformin (Ben Sahra et al., 2008) and some antihypertensive drug groups (Perron et al., 2004) could reduce the risk of -prostate cancer.

The aim of this thesis is to provide an epidemiological evaluation of associations in prostate cancer incidence among men using cholesterol-lowering drugs, drugs used in medical treatment of benign prostatic hyperplasia (finasteride and alpha-blockers) or antidiabetic drugs.

2. REVIEW OF THE LITERATURE

2.1. Definition and classification of prostate cancer

Prostate cancer is a disease of the prostate characterized by transformed epithelial cell populations with uncontrolled cell proliferation, ultimately causing the disease to spread outside the prostate, at first locally and ultimately to metastases in distant locations in the body. Prostate cancer is classified according to histology (grade) and by the extent of the spread of the disease (stage).

2.2. Diagnosis and pathology

The most common method for prostate cancer diagnosis is a transrectal prostate tissue biopsy performed on clinical suspicion, which usually results from an elevated level of serum prostate-specific antigen (PSA) or a suspicious finding during a digital rectal examination. A small proportion of the tumours are diagnosed as incidental findings in tissue samples from transurethral resection of the prostate performed for benign prostatic hyperplasia (Höltl W et al., 1990) or in a cystoprostatectomy specimen removed as treatment of bladder cancer (Kabalin et al., 1989; Montie et al. 1989).

2.2.1. Detection

The introduction of the serum PSA test into clinical practice in the late 1980s has enabled prostate cancer detection at the asymptomatic stage. Prior to the introduction of the PSA test, prostate cancer was generally not detectabled until palpable tumours were detected in a digital rectal examination

(DRE) or pain was caused by tumour metastases. Methods for non-invasive detection of asymptomatic, non-palpable prostate tumours were not available.

PSA is a biomarker that rises in prostatic diseases such as cancer, BPH and prostatitis. Currently, the only method available for differentiation between these conditions in the case of elevated PSA levels is a prostate biopsy for the histological examination of the prostate. The Finnish guideline for a biopsy threshold is PSA 3.,5 ng/ml or greater in men under 60 years of age (Lukkarinen O et al., 1999).

The introduction of the PSA test into routine clinical practice has significantly enhanced prostate cancer diagnostics. Data from the Finnish Cancer Registry shows a steep rise in age-adjusted prostate cancer incidence in Finland after the mid 1990s, the period of introduction of the PSA test in Finland (Finnish Cancer Registry, a). This rise is mainly due to more latent tumours being detected by the PSA test, as age-adjusted mortality from prostate cancer has remained unchanged in Finland (Finnish Cancer Registry, b). In the US, prostate cancer mortality has decreased after the introduction of the PSA test (Ferlay et al., 2002).

The limitations of PSA as a prostate cancer biomarker have been well demonstrated by the PCPT trial. At the termination of this trial, all willing study participants were offered an end-of-study biopsy regardless of serum PSA level or DRE findings (Thompson et al., 2003). As a result, 7,472 men (40-% of the total) were biopsied despite a low PSA level and a normal DRE. An end-of-study biopsy was performed for 3,652 men in the finasteride arm and 3,820 men in the placebo arm, among whom 368 and 576 new cases of prostate cancer were diagnosed, respectively (Thompson et al., 2003). Of these, 25.3% and 15.8% were poorly differentiated tumours (Gleason score 7 or higher), respectively.

Moreover, the serum PSA level is influenced by environmental factors such as the serum cholesterol level (Hamilton et al., 2008) and body mass index (Skolarus et al., 2007). Current evidence suggests that these are associated with decreased serum PSA levels, potentially resulting in a lower number of diagnoses due to fewer prostate biopsies among these men. As a consequence, decreased PSA cut points for prostate biopsy have been suggested for men whose PSA level is thus affected.

Despite its weaknesses, PSA still remains the best available clinical marker for prostate cancer diagnostics. Other diagnostic biomarkers, such as Prostate Cancer Gene 3 (PCA3, a gene highly over-expressed in prostate cancer compared with normal tissue) have been studied, but they need further validation before implementation in routine clinical practice (Parekh et al., 2007).

2.2.2. Histological classification

Histological grading of prostate cancer is performed by a pathologist based on tissue samples most commonly obtained from a prostate biopsy, the resection material of a transurethral resection of the prostate or from the whole prostate removed at radical prostatectomy. If the samples are found to include tumour tissue, further determination of the disease stage and the choice of treatment are undertaken by a urologist.

2.2.2.1. Gleason grading system

The Gleason score is currently the most commonly used system for histopathological grading of prostate cancer samples (Engers, 2007). The stage of differentiation of the two most common cell types in the sample is made by a pathologist, based upon the degree of loss of the normal glandular tissue

architecture. The two most commonly occurring cell types are subjectively given primary grades ranging between 1 and 5.- Gleason grade 1 is given to well-differentiated cancer cells. Gleason grade 5 is the worst possible grade, and is given to very poorly differentiated cells. The two primary grades are then added together to form the total Gleason score, which ranges between 2 and 10 (Table 1). Gleason score 7 is normally considered as a separator of good and poor prognosis.

Table 1. Gleason grading system

	Primary grade based on loss of the normal glandular tissue architecture
Most common cancer cell type in the sample	1-5
Second most common cancer cell type in the sample	1-5
Total Gleason score	2-10

2.2.3. TNM-classification and staging

In Finland, the prostate cancer stage is classified according to the TNM classification system (Lukkarinen O et al., 1999). It describes the extent of the primary tumour (T stage), the absence or presence of spreading to nearby lymph nodes (N stage) and the absence or presence of distant metastases (M stage).

The T stages are further sub-classified into T1a-T1c by a method of cancer detection, and T2a-T2c, T3a-T3c, T4a or T4b according to the extent of the tumour spread in and around the prostate. Also, the N stage is sub-classified into N0-N3 cancers by the number of regional lymph nodes affected and the size of the lymph node metastases. The M stage is either M0 or M1, denoting whether cancer has or has not metastasized beyond the regional lymph nodes.

2.3. Occurrence

2.3.1. Incidence and prevalence

Prostate cancer is currently the most common malignancy among men in industrialized countries, and its incidence is also rising in the developing world (Ferlay et al., 2002). In Finland, the number of new prostate cancer cases diagnosed each year has been rising steadily, from 334 new cases in 1961-1965 to 4,189 new cases in 2007 (Finnish Cancer Registry, a). In the same period, the age-adjusted incidence has risen from 17.8 to 85.7/100 000 person-years (Finnish Cancer Registry, a).

Autopsy studies have shown that prevalence of asymptomatic, latent malignancy of the prostate is 10-fold greater than incidence of clinically significant cancer in the same age-group (Schröder et al., 2006). The prevalence of latent prostate cancer has been estimated to be 25% in men in their thirties (Sakr et al., 1993), going up to 40% among men in their eighties (Franks LM, 1954; Breslow et al., 1977). More recently, final results from the Prostate Cancer Prevention Trial (PCPT) demonstrated that prostate cancer, even high grade tumours, are common in men exhibiting no symptoms and with normal levels of serum PSA (Lucia et al., 2008).

2.3.2. Mortality and prognosis

Prostate cancer is the second most common cause of cancer death among men in Finland, causing on average 800 deaths annually and contributing to a yearly mortality rate of 15/100 000 person-years (Finnish Cancer Registry, b). However, despite the large number of deaths caused by prostate cancer, most prostate tumours have a slow growth rate and good prognosis (Lukkarinen O et al., 1999).

2.4.Aetiology

2.4.1. Age, race and genetic predisposition

The risk factors for developing prostate cancer are currently mainly unknown. The only well-established risk factors are age, race and genetic predisposition (Crawford, 2009).

Age is the most important risk factor for prostate cancer. In Finland, very few prostate cancer diagnoses are made for men under 40 years of age. However, in older age groups the incidence rises steeply, from 3/100,000 in men 40-44 years of age to 1,176/100,000 in the age group of 80-84 years (Finnish Cancer Registry, c).

Race affects prostate cancer risk, the risk being higher among African-American men as compared with Caucasian men (Crawford, 2009) (Table 2). The risk differs somewhat also between the Hispanic population and Caucasians.

Genetic predisposition is a strong risk factor (Table 2). However, genetic predisposition has been reported to cause only a small part of prostate cancers at the population level (Lichtenstein et al., 2000). Thus, environmental factors have- a greater influence on prostate cancer incidence.

Table 2. Impact of age, race and genetic predisposition on prostate cancer risk

Age*	Direct trend between age and prostate cancer incidence
Race*	Prostate cancer 1.6 times more common in black vs. white men
Genetic predisposition†	Prostate cancer incidence 2.5 times higher in men with first-degree relatives diagnosed with prostate cancer younger than 60 years of age

***** Crawford, 2009.
† Matikainen et al., 2001

2.4.2. Environmental influences

The fundamental importance of environmental factors on prostate cancer risk is well demonstrated by the evolving trends in prostate cancer incidence among Asian immigrants in North America (Pu et al., 2004). Asian men have a markedly lower incidence of clinical prostate cancer than have Western men, even though the prevalence of latent malignant precursors is equal among them. However, the incidence among Asian immigrants rises to the level of Western men in direct relation to the length of their stay in North America. Also, the traditionally low prostate cancer incidence in Asia is increasing due to the westernization of lifestyles (Pu et al., 2004). A similar change in prostate cancer incidence has also been reported among the Inuit population migrating to Denmark (Boysen et al., 2008). Thus, a profound change in the environment can lead to rapid changes in the incidence of prostate cancer at population level.

Environmental factors most commonly suggested to increase the risk of prostate cancer include those associated with the Western lifestyle such as a high--fat diet and obesity. A high--fat diet has been suggested to increase the overall prostate cancer risk (Ma And Chapman, 2009). Obese men probably have an elevated risk of advanced prostate cancer (Amling, 2005).

Hypercholesterolemia, a condition strongly associated with both a high--fat diet and obesity, is also likely to increases the risk of prostate cancer (Solomon and Freeman, 2008). Cholesterol is likely to promote prostate carcinogenesis *in vitro,* and prostate cancer cell growth appears to depend on intracellular cholesterol (Solomon and Freeman, 2008). The effect of hypercholesterolemia may be different in the different stages of prostate cancer (Platz et al., 2008).

Diabetes (Kasper and Giovannucci, 2006) and metabolic syndrome (Laukkanen et al., 2004; Tande et al., 2006) have been reported to associate with prostate cancer risk either positively or negatively. Any effect that these conditions have on prostate cancer risk could be due to decreased androgen levels occurring in these conditions (Barrett-Connor et al., 1990; Oh et al., 2002).

Other controversial risk factors for prostate cancer include the serum level and intake of vitamins such as vitamin D and vitamin E, and of minerals such as selenium and calcium (Dagnelie et al., 2004). Some studies have reported association between prostate cancer risk and anthropometric measures reflecting endogenous hormone metabolism, such as male pattern baldness (Giles et al., 2002). However, the available evidence on the role of these risk factors has not been conclusive.

2.5. Prevention

2.5.1. Primary prevention

Prostate cancer causes a high burden to public health and, hence, prevention of the disease would be desirable. Several agents have been studied in this context.

2.5.1.1. Finasteride

Finasteride, along with dutasteride, belongs to the group of drugs called 5α-reductase inhibitors (5-ARIs). The 5-ARIs reduce the conversion of testosterone into more potent androgen metabolite dihydrotestosterone (DHT) by inhibiting the enzyme 5α-reductase (Stoner, 1992). This causes apoptosis of prostatic cells (Sutton et al., 2006) and the involution of the prostate due to atrophy (Rittmaster et al., 1996). The current clinical indications for finasteride usage are treatment of BPH (at 5 mg/day dose) and male pattern baldness (at 1 mg/day dose).

A large randomized clinical trial, the Prostate Cancer Prevention Trial (PCPT) has reported a 24.8% relative reduction in prostate cancer risk among men receiving finasteride regularly for 7 years as compared to men who received placebo (Thompson et al., 2003).

However, the proportion of poorly differentiated tumours was found to be elevated among finasteride users, reducing the attractiveness of finasteride as a chemopreventive agent. Several explanations for this finding have been proposed, all concluding that the increased proportion of high grade tumours is probably a detection bias. A recent analysis from the PCPT study data suggests that finasteride treatment improves sensitivity of PSA test to detect high-grade prostate tumours (Thompson et al.,

2006). Additionally, it has been proposed that prostate involution during finasteride treatment leads to greater proportion of tumour tissue being harvested in prostate biopsy, enabling greater accuracy of histological grading (Lucia et al., 2007). This can lead to increased probability of small poorly differentiated foci within prostate tumour tissue to be included in the biopsy sample. Also, a grading artefact caused by low androgen levels during finasteride therapy has been offered as an explanation (Pinsky et al., 2008).

While decreased levels of DHT might reduce the initiation of prostatic malignancy, it could also be postulated that it can cause a selective pressure for survival of poorly differentiated, less androgen-dependent prostate cancer cell populations in genetically unstable malignant lesions. However, this hypothesis has not been studied and is purely speculative.

The PCPT trial had two special features in its study design: 1) a correction coefficient was used for the serum PSA values of men in the finasteride arm and 2) each participant was offered an end-of-study prostate biopsy regardless of the exposure status (Thompson et al., 2003). The use of the correction coefficient ensured that the observed decrease in the number of prostate tumours was a robust result and probably not due to decreased detection caused by a lower PSA and, hence, fewer biopsies among finasteride users. Performing an end-of-study biopsy for most men in the trial meant that the latent tumours were also detected; thus, the observed decrease in prostate cancer incidence concerned all tumours, not just the clinically detected ones.

However, the study population recruited in the PCPT trial consisted of men with no or only minor lower urinary tract symptoms (LUTS) (Thompson et al., 2003). Thus the study population differed

markedly from a typical finasteride user who uses the drug for treatment of symptomatic BPH. It is unclear whether similar results can be expected among this latter group of men.

It is also currently unclear whether finasteride use decreases prostate cancer mortality. These data are not available from the PCPT due to the low number of prostate cancer deaths within the study population. However, some model-based estimates have been made, suggesting a benefit, on average, of 3 months of longer survival in men treated with finasteride (Lotan et al., 2005) with an average cost of 130 000 dollars per ~~a~~ quality-adjusted life-year saved.

2.5.1.2. Statins

Statins lower serum cholesterol by inhibiting the enzyme 3-~~-~~hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase~~,~~ a key enzyme in the mevalonate-pathway, thus reducing endogenous cholesterol production (Igel et al., 2002). Experimental studies have reported inhibition of prostate cancer cell proliferation by cell cycle arrest and increased apoptosis after statin treatment (Murtola et al., 2008). These results suggest that statins could have prostate cancer preventive potential. However, most studies have demonstrated the effect only in cells representing advanced prostate cancer, and with very high, clinically irrelevant drug concentrations (Solomon and Freeman, 2008). Currently only one study has shown cell growth inhibition with clinically relevant statin concentrations in normal and early stage prostate cancer cells (Murtola et al., 2009)

Data from epidemiological studies mainly supports prostate cancer preventive effect of statins. Studies that have been able to evaluate the risk of advanced prostate cancer among statin users have consistently reported a decreased risk as compared with non-users (Bonovas et al., 2008; Friedman et

al., 2008; Murtola et al., 2008). However, results on the overall prostate cancer risk among statin users have been controversial (Agalliu et al., 2008; Boudreau et al., 2008; Farwell et al., 2008; Ford et al., 2007; Friedman et al., 2008; Haukka et al., 2009; Kuoppala et al., 2008; Murtola et al., 2008; Olsen et al., 1999; Taylor et al., 2008).

Most epidemiological studies have not been able to take into account the impact of PSA testing activity within their study populations. Statins are used either for primary prevention (treatment of hypercholesterolemia) or secondary prevention of cardiovascular disease (CVD). Men using statins for primary prevention are, in general, more health-oriented than non-users. They also are more likely to participate in opportunistic PSA testing (Brookhart et al., 2007). On the other hand, men using statins for secondary prevention usually have multiple comorbidities, such as diabetes mellitus and hypertension, leading to frequent contacts with physicians and probably also to more active PSA testing. This is a potential source of confounding for epidemiological studies, increasing the observed number of prostate tumours detected in statin users compared with those in non-users and masking the possible protective effect of statins.

Several clinical trials designed to study statins' efficacy in CVD prevention have measured cancer as a secondary study end-point. Meta-analyses of these trials have found no association between statin use and prostate cancer incidence (Baigent et al., 2005; Bonovas et al., 2006; Browning and Martin, 2007; Dale et al., 2006). In these studies, confounding by differing opportunistic PSA testing within the study populations is probably eliminated by random allocation of subjects between the study arms. However, follow-up times in these trials have been short (4 years on average). A longer treatment time would probably be needed to detect an effect in cancer incidence. Moreover, these studies measured cancer as a secondary end-point, lacking systematic case ascertainment of all prostate cancer cases arising in the

study population and leading to small numbers of prostate cancer cases included in the study population. Finally, the trials have not been able to separately analyze incidence of advanced prostate tumours.

Some previous studies have also suggested that statins could have an effect also against other types of cancers. One case-control study including 1,953 patients and 2,015 controls reported a 47-% reduction in relative risk of colorectal cancer among statin users (Poynter et al., 2005). One clinical study of 40 patients reported decreased proliferation and increased apoptosis of high-grade breast tumours in women randomized to receive 80 mg as compared to those receiving 20 mg of fluvastatin 3-6 weeks prior to surgery (Garwood et al., 2009).

Thus statins are currently a potential drug group for prostate cancer prevention, especially for advanced stages of the disease.

2.5.1.3. Other suggested chemopreventive agents

Non-steroidal anti-inflammatory drugs (NSAIDs), especially acetylsalisylic acid (aspirin), have been suggested to have chemopreventive potential against prostate cancer (Harris et al., 2005). Interest in this drug group is driven by established protective effect against colorectal cancer (Cuzick et al., 2009). NSAIDs exert their anti-inflammatory and analgesic effect by inhibiting cyclo-oxygenase (COX) enzyme isoforms, COX1 and COX2. *In vitro* NSAIDs inhibit prostate cancer cellular growth and decrease angiogenesis probably by both COX-dependent and independent mechanisms (Sooriakumaran et al., 2007). Epidemiological studies have mainly reported a protective effect of NSAIDs against prostate cancer (Harris RE, 2009). No clinical trials have been published on whether aspirin or other

NSAIDs reduce the risk of prostate cancer. However, some trials have reported benefits in treatment of existing prostate tumours (Sooriakumaran et al., 2009; Srinivas and Feldman, 2009).

Two experimental studies and one cohort study have suggested that quinazoline-derived alpha-blockers terazosine and doxazosin could protect against prostate cancer. Alpha-blockers reduce the contraction of smooth muscle cells in the prostate and other tissues by inhibiting alpha-adrenergic receptors, thus reducing the urinary outflow obstruction in the prostate. Alpha-blockers are clinically used in the treatment of LUTS. *In vitro* these drugs cause apoptosis in prostate cancer cells unrelated to the inhibition of alpha-adrenergic receptors (Kyprianou and Benning, 2000; Benning and Kyprianou, 2002). Thus far, only one cohort study has been undertaken on the subject, reporting decreased prostate cancer incidence in terazosin and doxazosin users (Harris et al., 2007). Tamsulosin and alfuzosin, the alpha-blockers in clinical use in Finland, have not been tested in this manner

Vitamin D is another agent suggested to affect prostate cancer risk. Vitamin D is a steroid hormone with a central role in the regulation of calcium homeostasis. Local vitamin D metabolism probably has significance in prostate cancer development, and serum vitamin D level may influence prostate cancer risk (Lou et al., 2004), although evidence is inconsistent (Travis et al., 2009). A recent large meta-analysis, pooling data from 45 published epidemiological studies, found no statistically significant association between vitamin D intake and prostate cancer risk (Huncharek et al., 2008).

Interest in vitamin E as prostate cancer chemopreventive agent was launched by a finding of decreased prostate cancer risk among men randomized to receive alpha-tocopherol (vitamin E) as compared to men receiving placebo in the Alpha-tocopherol, Beta Carotene Cancer Prevention Study (The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, 1994). Analyses based on up to 19 years

of follow-up of this study population have suggested continued risk lowering among men who received either supplement, the association being stronger for serum level than for dietary vitamin E (Weinstein et al., 2007). –Beta-carotene and vitamin E act as antioxidants and have been proposed to decrease chromosomal damage in prostate cancer cells (Dusinská et al., 2003), thus reducing chronic inflammation due to oxidative stress and lowering the cells' vulnerability to carcinogenesis (Federico et al., 2007). Selenium is another anti-oxidant that has been investigated for possible prostate cancer protective effects (Duffield-Lillico et al., 2003). However, recently results from two large randomized clinical trials were published showing no association between vitamin E (Gaziano et al., 2009) or selenium supplementation (Lippman et al., 2009) and prostate cancer risk. Thus, prostate cancer preventing value of antioxidant supplementation is uncertain.

Green tea polyphenols, epigallate and epigallotechin gallate are powerful antioxidants and have been suggested as providing protection against a number of cancers, including prostate cancer (Boehm et al., 2009). A small clinical study has reported a decrease in PSA and other serum biomarkers among men with localized prostate cancer who were given green tea polyphenols for, on average, five weeks prior to radical prostatectomy (McLarty et al., 2009). A small placebo-controlled clinical trial has reported a lower rate of progression of prostatic intraepithelial neoplasia lesions among men randomized to receive green tea polyphenols for one year (Bettuzzi et al., 2006). These findings have been supported by epidemiological studies reporting lowered prostate cancer risk among men regularly consuming at least 3-5 cups of green tea per day (Boehm et al., 2009). Green tea would make an attractive chemopreventive agent as it is a popular beverage across the world. However, more evidence will be needed before green tea can be recommended for prostate cancer prevention, as the available epidemiological studies have been performed in Asia in countries renowned for their tea drinking

culture. Furthermore, the only available placebo-controlled clinical study on the subject is small and has a short follow-up period.

Current evidence on suggested prostate cancer chemopreventive effects of various substances has been summarized in Table 3.

Table 3. Published evidence on potential prostate cancer chemopreventive agents

		Median change in risk (range)	
Chemopreventive agent	Effects reported *in vitro*	Epidemiological studies	Clinical trials
Finasteride*	Increased apoptosis Decreased cell adhesion	-42%	-24.8 %
Statins†	Cell-cycle arrest Increased apoptosis	Overall risk: -4% (-63% - +30%) Advanced prostate cancer: -40% (-49% - 0%)	Overall risk: 0% (-3 - +46%)
NSAIDs, including aspirin‡	Decreased angiogenesis Inhibition of cellular proliferation and metastasis	-20 % (-39 % - +4%)	-
Alpha-blockers¶	Increased apoptosis	-32 %	-
Vitamin D intake§	Regulation of calcium homeostasis Cell-cycle arrest Increased apoptosis Enhanced cellular differentiation	pooled RR 1.16; 95% CI 0.98-1.38	-
Selenium**	Decreased chromosomal damage	-10%, (-41% - 0%)	+4% (-49% - +4%)
Vitamin E intake or supplementation**	Decreased chromosomal damage	0% (-24%, - +7%)	-3% (-34% - +13%)
Green tea (3-5 cups/day) ††	Decreased chromosomal damage Inhibition of cell proliferation	-73%, (-48% - -86%)	-26.7%

***** Irani et al., 2002; Rittmaster et al., 1996; Sutton et al., 2006; Thompson et al., 2003.
† Agalliu et al., 2008; Boudreau et al., 2008; Farwell et al., 2008; Friedman et al., 2008; Haukka et al., 2009; Murtola et al., 2008.

‡ Bosetti et al., 2006; Daniels et al., 2009; Dasgupta et al., 2006; García Rodríguez and González-Pérez, 2004; Irani et al., 2002; Jacobs et al., 2005; Platz et al., 2005; Sooriakumaran et al., 2007.
¶ Benning and Kyprianou, 2002; Harris et al., 2007; Kyprianou and Benning, 2000.
§ Huncharek et al., 2008; Lou et al., 2004.
** Bidoli et al., 2009; Chan et al., 1999; Duffield-Lillico, 2003; Gaziano et al., 2009; Kristal et al., 1999; Lippman et al., 2009; Peters et al., 2008; Rodriguez et al., 2004; The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, 1994; Schuurman et al., 2002; Weinstein et al., 2007; Zhang et al., 2009.
† † Bettuzzi et al., 2006; Boehm et al., 2009; Jian et al., 2004; Jian et al., 2007; Kurahashi et al., 2008.

2.5.2. Secondary prevention

2.5.2.1. Prostate cancer screening

As PSA testing provides a method for finding prostate cancer early in its course, prostate cancer screening with PSA has been suggested as a means to reduce prostate cancer mortality through earlier diagnosis and treatment. Prostate cancer fulfils many criteria set for diseases considered to be suitable for screening. It is a common disease causing extensive morbidity at the population level. The PSA test enables early diagnosis and the test is relatively cheap and easy to perform. A definitive therapy exists for both local and advanced prostate cancer.

A recent, multicenter randomized clinical trial has proven that PSA screening markedly reduces prostate cancer mortality (Schröder et al., 2009). However, a major problem for the implementation of prostate cancer screening is the high number of latent prostate cancers found when using this method. As autopsy studies have shown, the lifetime risk of developing an occult malignancy in the prostate is 10-fold greater than the risk of being diagnosed with clinical prostate cancer (Schröder et al., 2006). The implementation of PSA screening leads to overdiagnosis of prostate cancer, as a large proportion of latent tumours with unknown clinical significance is diagnosed (Andriole et al., 2009; Schröder et

al., 2009). Furthermore, there are currently no means to accurately predict which asymptomatic tumours will remain clinically insignificant and which will go on to develop into life-threatening cancer (Joniau and Van Poppel, 2008). Thus, in addition to overdiagnosis of prostate cancer, PSA screening also leads to overtreatment as many of these latent malignancies are radically treated, often unnecessarily, with all the accompanying treatment complications and associated costs. As a result, treatment-related morbidity increases.

Due to these uncertainties, systematic PSA screening of asymptomatic men is currently not recommended. Nevertheless, even without such recommendations, opportunistic testing (PSA testing without any clinical indications to do so) has been widely embraced in many Western countries (Ciatto et al., 2003; Swan et al., 2003). The prevalence of opportunistic PSA testing varies, being greater among men who are active users of health-services than among men who are not. For example, men using cholesterol-lowering drugs statins participate in PSA testing more often than do non-users (Brookhart et al., 2007). This is a potential source of bias in any epidemiological study estimating associations between medication use and prostate cancer incidence.

3. AIMS OF THE STUDY

The objective of this thesis is to provide a population-based estimate of associations between prostate cancer incidence and the use of finasteride, statins or antidiabetic drugs. The specific aims are the following:

1. Evaluation of associations between users of finasteride and alpha-blockers and prostate cancer incidence, as well as disease grade and stage by comparing medication users and non-users in two population-based studies.

2. Evaluation of prostate cancer incidence and disease grade and stage among users of cholesterol-lowering drugs with two population-based studies.

3. Exploration of possible associations between antidiabetic medication use and prostate cancer incidence.

4. SUBJECTS AND METHODS

4.1. Study settings and information sources

A summary of the study settings, study populations and the tested drug groups is provided in table 4.

Table 4. Summary of the study settings, populations and studied drug groups

Study setting	Population	Studied drug groups
Case-control	24,723 case-control pairs	Finasteride and alpha-blockers Cholesterol-lowering drugs Antidiabetic drugs
Cohort	23,320 PSA screened men	Finasteride and alpha-blockers Cholesterol-lowering drugs

4.1.1. Case-control study

We estimated the associations between medication use and prostate cancer incidence at the population-level with a case-control study which included all newly diagnosed prostate cancer cases in Finland during 1995-2002, a total of 25,029 men. Information on the cases was obtained from the Finnish Cancer Registry. The registry contains data on approximately 99% of all cancer cases diagnosed in Finland (Teppo et al., 1994). The data is being collected through mandatory notifications of cancer diagnoses made by all Finnish health care units, whether public or private and is maintained by the Finnish Cancer Organisations.

The information collected includes date and method of diagnosis. Virtually all (99.3%) of the cases were histologically confirmed (prostate biopsy, surgical specimen from transurethral resection of the

prostate or cystoprostatectomy, or from autopsy samples). Other methods of diagnosis included specific clinical (0.4%), radiological (0.3%) or laboratory findings (0.02% of cases). A total of 185 cases (0.7%) with an unknown method of diagnosis were excluded from the study population.

Information on the tumour stage was available for 13,616 men (55% of all cases). The tumour stage is recorded in the Finnish Cancer Registry in four categories: localized; locally advanced; metastatic and advanced to an unknown extent. In our study, the latter three categories were combined to form one group of advanced tumours. The proportion of the cases with missing information on tumour stage rose steadily during the study period, from 7% in 1995 to 21.8% in 2002 (Table 3). Information on grade or serum PSA values was not available for this study population.

Table 5. Median age and distribution of years of diagnosis among the 24,723 cases in the case-control study.

	Prostate cancer stage		
	No information	Localized	Advanced
n	11,107	9,940	3,676
Median age (y)	69	67	69
Year of diagnosis (%*)			
1995	7.0	10.7	13.0
1996	7.8	11.8	16.8
1997	8.7	13.8	14.4
1998	10.3	14.1	14.2
1999	11.6	13.6	12.5
2000	17.1	10.8	10.4
2001	15.6	14.1	10.5
2002	21.8	11.1	8.1

*Percentage distribution of cases by year of diagnosis.

Controls were selected from the Population Register Centre using individual matching for age and area of residence (municipality) within one year from the date of diagnosis of the corresponding case.- The Population Register Centre contains the date of birth and residence area for all Finnish citizens (Population Register Centre: Population information system). It also records the date and cause of death for deceased citizens. The information is gathered via mandatory notifications by citizens (for the data on area of residence) and by a number of health care institutions (dates of birth and death, causes of death). The Population Register Centre is maintained by the Finnish ministry of finance.

A total of 24,723 controls were identified using the incidence density sampling method, i.e. 963 men who were first included as controls, but were later diagnosed with prostate cancer, were included in the study population again as a case in another case-control pair, thus appearing twice in the analysis. For 121 cases in the oldest age groups, an age-matched control could not be found from the same area of residence (municipality). These cases were excluded from the analysis.

Information on exposure, i.e. medication use during 1995-2002 was obtained from the SII (Social Insurance Institution of Finland) prescription database. As part of the National Health Insurance Scheme, each Finnish citizen is entitled to reimbursement of the cost of most physician-prescribed medication purchases (Martikainen and Rajaniemi, 2002). This reimbursement is available when a drug is approved as reimbursable by the SII. The level of reimbursement varied during the study period from 50% to 100-%, depending on the severity of the disease. Most, but not all prescription drugs in clinical use in Finland are reimbursed by the SII.

Each reimbursed medication purchase is recorded in the prescription database. The database is nationally comprehensive:; e.g. in 1998-2004 it covered 94 to 96-% of total statin consumption outside

institutions in Finland (Halava et al., 2009). The data includes package size, number of packages, medication dose and the date of each purchase. Persons staying in a public nursing home or hospital for longer than 90 consecutive days are not eligible for reimbursements, and thus their drug purchases are not registered.

The database is fully computerized. All Finnish pharmacies have been included in the database since the beginning of 1995.

For each case-control pair, the use of medications was followed until the date the case was diagnosed. The yearly amount of reimbursed purchases for each drug was calculated as a sum of all purchases during that year, in milligrams or international units (IUs). The number of defined daily doses (DDDs) purchased each year was calculated by dividing the total mg or IU amount of medication purchases that year with the amount recommended by the World Health Organization (WHO) as one DDD (World Health Organization). The yearly DDDs were then added together for the total number of DDDs purchased during the study period.

The drugs and drug groups studied with the case-control population were drugs used in clinical management of benign prostatic hyperplasia (finasteride; alpha-blockers tamsulosin and alfuzosin);~~,~~ cholesterol-lowering drugs (statins: ~~(~~atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin and simvastatin); fibric-acid derivatives (bezafibrate, clofibrate, fenofibrate and~~,~~ gemfibrozil);~~,~~ bile-acid binding resins (cholestipol, cholestyramin~~)~~ and acipimox) and antidiabetic drugs (metformin; sulfonylureas (glibenclamide &~~,~~ glipizide); guar gum and insulin (human & recombinant)).

4.1.2. Cohort study

We used the participants of the screening arm of the Finnish Prostate Cancer Screening Trial as a cohort to estimate medication use and prostate cancer risk in a systematically screened population.

The Finnish Prostate Cancer Screening Trial primarily studies whether systematic prostate cancer screening with the PSA test reduces mortality resulting from the disease. The trial is the largest part of the multi-centered European Randomised Study of Prostate Cancer screening (Schröder et al., 2009).

A cohort of all men aged 55-67 years and residing in the areas of Helsinki and Tampere were identified from the population register of Finland (Määttänen et al., 1999). The cohort was linked to the Finnish Cancer Registry. After exclusion of prevalent prostate cancer cases, men were randomly assigned to either the screening or control arm during the period 1996-1999. A total of 78,484 men were included in the study. Of these, 30,196 were randomized to the screening arm of the trial.

Men in the screening arm were recruited by postal invitations to each screening round. After written informed consent was obtained from those invited to screening, a blood sample was drawn from these men. All men participating in screening also filled out a questionnaire on exposures and medical history, including family history of prostate cancer. An additional survey including questions on height and weight was mailed along with the third-round screening invitation. The population was linked annually to the Finnish Cancer Registry to identify and obtain information on prostate cancer cases diagnosed between the screening rounds.

The first screening round was completed during 1996-1999, during which time 22,536 men participated. A total of 18,612 men were screened during the second screening round in 2000-2003. The third round started in the beginning of 2004. By the end of 2004, 3,130 men had participated in the third round. A total of 23,320 men had had their PSA measured at least once during the study period 1996-2004. -The participation rate (73.8% overall) did not vary substantially by age.

The present cohort study comprised all men participating in the screening arm during 1996-2004, 23,320 men in total. During this period, a total of 1,594 new prostate cancer cases were diagnosed. Of these, 1,273 cases were detected in the screening, while 321 were interval cancers. The TNM-stage was known in 99.6% and the Gleason grade in 100% of the cases. Additionally, information on serum PSA from at least one screening was available for each participant.

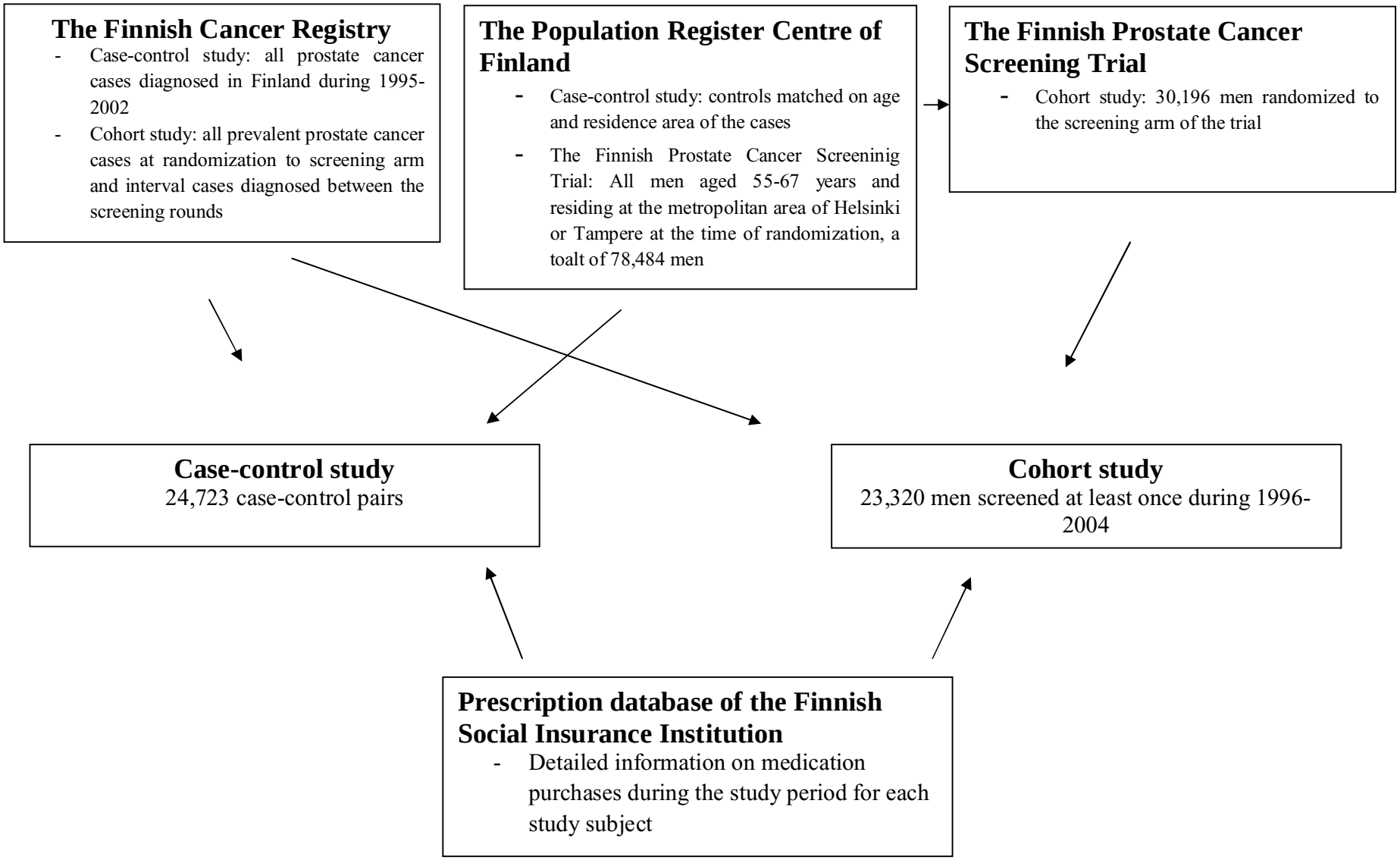
Again, information on medication use was obtained from the prescription database. Medication use for each cohort member was examined for the entire follow-up period; from the date of randomization until prostate cancer diagnosis, death, emigration from the study area or the –end of the follow-up period on December 31, 2004, whichever came first.

Medication users who did not have medication purchases at the start of the follow-up period contributed person-time as nonusers until the first reimbursed purchase. After six months without purchases they were again categorized as non-users until the next purchase. The exposure status was allowed to change as often as necessary. –Similarly, the cumulative duration and the amount of medication use during the follow-up period increased according to the purchases made.

The drugs and drug groups studied with the cohort population were drugs used in the clinical management of benign prostatic hyperplasia (finasteride,~~;~~ alpha-blockers, tamsulosin and alfuzosin) and cholesterol-lowering drugs (statins: ~~(~~atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin and simvastatin); fibric-acid derivatives (bezafibrate, clofibrate, fenofibrate and~~,~~ gemfibrozil), bile-acid binding resins (cholestipol, cholestyramin~~)~~ and acipimox).

The sources of information for each study setting are outlined in Figure 1.

Figure 1. Information sources for case-control and cohort studies



4.2. Statistical methods

The conditional logistic regression-method was used to compare the odds ratio of prostate cancer between medication users and non-users in the case-control study (or between finasteride and alpha-blocker users in paper I). The model was adjusted for the matching factors; age at diagnosis (treated as a continuous variable) and for the municipality of residence of the study subjects. Additional adjustment was undertaken for simultaneous use of drugs in other drug groups that could possibly confound the association between the drug group under study and prostate cancer risk. The odds ratio (OR) and 95% confidence intervals (CI) are reported. The analyses were performed using Stata 8.2 (College Station, Texas, USA) statistical software.

The hazard ratios (HR) of prostate cancer among men screened in the trial were calculated with a time-dependent Cox proportional regression model adjusted for age, family history of prostate cancer at baseline, simultaneous use of other relevant drug groups, number of screening rounds attended, and the calendar period of screening (latest screening occurring before or after the year 2000). With the exception of family history of prostate cancer, all covariates included in the model were time-dependent, i.e., they could change during the follow-up period. At each time point in the follow-up period, the HR was compared between current users and non-users of the drug group under study, e.g., between current users and non-users of statins. Similarly, the current cumulative amount and duration of medication use was used in the analyses. Cox regression analyses were performed using SPSS 16.0 (Chigaco, Illinois, USA) statistical software package.

Age-adjusted geometric means (with 95% confidence intervals) of total PSA concentrations and free/total PSA ratios (percentage of free PSA) of current medication users and never-users in the cohort

study were compared. Linear regression with robust variance correction and adjustment for age was used for estimating a linear trend by the cumulative amount of medication use. The distribution of PSA and percentage of free PSA were right-skewed and were thus transformed using the natural logarithm. Stata 8.2 was used for PSA trend analyses.

4.3. Ethical considerations

The study protocol was approved by the ethical committee of the Pirkanmaa Hospital District (ETL R09159), the Data Protection Ombudsman of the National Institute of Health and Welfare, the Population Register Centre and the Social Insurance Institution of Finland. The study protocol of the Finnish Prostate Cancer Screening Trial has been approved by the ethics committees of each participating hospital.

5. RESULTS

5.1. Prostate cancer incidence in users of finasteride and alpha-blockers

5.1.1. Case-control study

Compared with non-users of medication, the overall prostate cancer risk was increased among finasteride and alpha-blocker users in the case-control study (OR 1.41, 95% CI 1.31-1.51 and OR 1.79, 95% CI 1.67-1.91 for finasteride and alpha-blocker users, respectively). The risk increase was greater for irregular medication use (less than 365 daily doses per year) than for regular use (365 daily doses per year), and concerned mainly localized tumours (Table 6). The risk of non-localized tumours, on the other hand, was borderline significantly decreased in men who had used the drugs for four years or more.

However, when compared with alpha-blocker users instead of medication non-users, the risk ratio of prostate cancer among finasteride users was non-significantly lower (OR 0.80, 95% CI 0.64-1.00).

Table 6. Prostate cancer incidence by stage in finasteride and alpha-blocker users in the case-control study.

	Duration of use	Pattern of use*	Localized cancer			Advanced cancer		
			No. of discordant pairs	OR†	95% CI	No. of discordant pairs	OR†	95% CI
Finasteride	< 4 years	Regular‡	133/101	1.32	1.01–1.72	35/41	0.86	0.54–1.34
		Irregular¶	623/319	1.95	1.71–2.23	114/128	0.89	0.69–1.14
	≥ 4 years	Regular	20/13	1.60	0.52–4.89	-	-	-
		Irregular	428/360	1.19	0.92–1.53	47/76	0.62	0.37–1.04
Alpha-blockers	< 4 years	Regular	119/77	1.55	1.16–2.06	28/26	1.08	0.63–1.84
		Irregular	707/347	2.04	1.79–2.32	132/119	1.11	0.87–1.43
	≥ 4 years	Regular	12/7	1.71	0.67–4.35	-	-	-
		Irregular	447/178	2.51	2.11–2.99	63/84	0.75	0.54–1.05

* Number of case–control pairs discordant to medication use. Case: user – control: non-user/Case: non-user – control: user.

† Odds ratio from the conditional logistic regression model adjusted for age and area of residence

‡ 365 daily doses per year

¶ Less than 365 daily doses per year

5.1.2. Cohort study

In the cohort study there was no change in overall prostate cancer risk among current finasteride (HR 0.87, 95% CI 0.63-1.19) or alpha-blocker users (HR 1.05, 95% CI 0.85-1.31) as compared with current non-users (Table 7). Increasing cumulative amount and duration of finasteride use were associated with a decreasing trend in the incidence of low-grade (Gleason 6 or less) tumours (p for trend 0.009 ad 0.019, respectively). The risk of high grade (Gleason 7-10) tumours was increased among long term finasteride users (1,087 doses or more; four years of use or longer) (Table 7). Alpha-blocker users, on the other hand, had a decreased risk of high grade tumours with a decreasing trend by cumulative amount and quantity of medication use (p for trend 0.053 and 0.044, respectively) (Table 8). The number of advanced tumours was too small for reliable risk estimation.

Table 7. Hazard ratio for prostate cancer by the amount and duration of use of finasteride and by prostate cancer stage and grade, results from the cohort study

	Overall		Gleason ≤ 6		Gleason 7-10		Organ-confined tumors*	
Quantity/duration of medication use	No. of cases	HR (95% CI) †	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)
Finasteride:								
Non-users	1,507	Reference	1,139	Reference	338	Reference	1,364	Reference
All users	87	0.87 (0.63-1.19)	55	0.59 (0.38-0.91)	26	1.33 (0.77-2.30)	81	0.89 (0.65-1.24)
Cumulative quantity of finasteride use (daily doses) ‡								
28-180	34	1.34 (0.74-2.42)	24	0.80 (0.33-1.92)	6	1.17 (0.29-4.74)	32	1.32 (0.70-2.46)
181-398	21	0.91 (0.50-1.65)	14	0.76 (0.36-1.60)	5	0.79 (0.20-3.20)	19	1.00 (0.55-1.81)
399-1,086	17	0.57 (0.27-1.19)	13	0.64 (0.29-1.43)	4	0.37 (0.05-2.68)	17	0.61 (0.29-1.28)
≥ 1,087	15	0.82 (0.47-1.46)	4	0.28 (0.09-0.87)	11	2.49 (1.27-4.89)	13	0.81 (0.45-1.48)
P_{trend}¶		0.204		0.009		0.114		0.275
Years of finasteride use‡								
1	41	0.89 (0.5-1.48)	30	0.62 (0.31-1.24)	7	0.57 (0.14-2.32)	39	0.91 (0.53-1.54)
2	19	0.96 (0.50-1.85)	13	0.84 (0.38-1.88)	5	1.02 (0.25-4.13)	19	1.03 (0.53-1.99)
3-4	11	0.72 (0.39-1.35)	7	0.48 (0.20-1.16)	4	1.60 (0.66-3.91)	10	0.70 (0.36-1.34)
> 4	16	1.00 (0.47-2.11)	5	0.40 (0.10-1.61)	10	2.61 (1.06-6.45)	13	1.07 (0.51-2.28)
P_{trend}¶		0.411		0.019		0.057		0.524

***** Men with $T_1N_{0/X}M_{0/X}$ and $T_2N_{0/X}M_{0/X}$ tumors combined

† From a Cox proportional hazard regression model adjusted for age, family history of prostate cancer, use of alpha-blockers, number of PSA screens and time period of screening (before or after year 2000)

‡ Stratification in quartiles of cumulative quantity/duration of finasteride use

¶ Estimated by including cumulative dose (DDDs) or duration (years) of finasteride use into Cox regression model as a continuous covariate. All statistical trends are inverse, i.e., indicating a decreased risk with larger amounts of medication use

Table 8. Hazard ratio for prostate cancer by the amount and duration of use of alpha-blockers and by prostate cancer stage and grade, results from the cohort study

	Overall		Gleason ≤ 6		Gleason 7-10		Organ-confined tumors*	
Quantity/duration of medication use	No. of cases	HR (95% CI) †	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)
Alpha-blockers:								
Non-users	1,399	Reference	1,041	Reference	330	Reference	1,262	Reference
All users	195	1.05 (0.85-1.31)	153	1.20 (0.94-1.52)	34	0.55 (0.31-0.96)	183	1.09 (0.87-1.36)
Cumulative quantity of alpha-blockers use (daily doses) ‡								
10-60	77	1.25 (0.83-1.87)	62	1.65 (1.09-2.49)	12	0.21 (0.03-1.52)	70	1.27 (0.83-1.93)
61-180	46	1.00 (0.64-1.56)	35	0.84 (0.48-1.49)	8	0.95 (0.39-2.30)	44	0.99 (0.62-1.58)
181-629	39	1.11 (0.75-1.64)	30	1.21 (0.77-1.88)	8	0.64 (0.24-1.72)	37	1.16 (0.78-1.73)
≥ 630	33	0.89 (0.59-1.36)	26	1.12 (0.72-1.75)	6	0.40 (0.13-1.25)	32	0.96 (0.64-1.46)
P_{trend}¶		0.975		0.345		0.053		0.700
Years of alpha-blockers use‡								
1	111	1.00 (0.73-1.38)	86	1.08 (0.75-1.55)	19	0.60 (0.27-1.35)	102	1.00 (0.72-1.39)
2	43	1.46 (1.00-2.15)	36	1.67 (1.09-2.56)	5	0.60 (0.19-1.89)	42	1.53 (1.03-2.26)
3-4	23	0.87 (0.55-1.37)	15	1.04 (0.63-1.70)	8	0.48 (0.15-1.52)	21	0.93 (0.59-1.47)
> 4	18	0.88 (0.42-1.86)	16	1.15 (0.51-2.60)	2	0.38 (0.05-2.73)	18	0.96 (0.45-2.03)
P_{trend}¶		0.858		0.186		0.044		0.580

***** Men with $T_1N_{0/X}M_{0/X}$ and $T_2N_{0/X}M_{0/X}$ tumors combined

† From a Cox proportional hazard regression model adjusted for age, family history of prostate cancer, use of alpha-blockers, number of PSA screens and time period of screening (before or after year 2000)

‡ Stratification in quartiles of cumulative quantity/duration of alpha-blocker use

¶ Estimated by including cumulative dose (DDDs) or duration (years) of alpha-blocker use into Cox regression model as a continuous covariate. All statistical trends are inverse, i.e., indicating a decreased risk with larger amounts of medication use

5.2. Serum PSA among finasteride and alpha-blocker users

Median PSA was considerably higher in current users of finasteride and alpha-blockers as compared with those who had never used such medications. When stratified in quartiles by the cumulative amount of medication use, the difference in PSA diminished among finasteride users but not among alpha-blocker users (Table 9).

Prostate cancer risk among BPH medication users was dependent on serum PSA level. Overall prostate cancer risk and risk of screen-detected cancer was decreased among finasteride users with PSA of 4 ng/ml or greater, but not among men whose PSA was below the prostate biopsy threshold level (Table 10). The same was true for alpha-blocker users. Incidence of interval cancer varied between finasteride and alpha-blocker users, being borderline significantly lower among finasteride users with PSA at 4 ng/ml or above, but elevated among alpha-blocker users with low PSA (Table 10).

Table 9. Age-standardized geometric mean of PSA and percentage of free PSA by cumulative quantity and duration of finasteride or alpha-blocker use, results from the cohort study

	Geometric mean (95% CI)	
	PSA	Percentage of free PSA
Finasteride use		
None	1.22 (0.27-7.72)	26.48 (10.40-52.80)
Overall	1.58 (0.24-11.05)	22.37 (9.49-48.36)
Cumulative quantity (tablets)		
28-180	1.95 (0.31-12.94)	22.87 (10.96-45.40)
181-398	1.72 (0.19-9.56)	22.67 (9.13-47.26)
399-1,086	1.49 (0.23-8.94)	21.22 (9.35-48.59)
≥ 1,087	1.31 (0.17-1.25)	21.12 (7.75-43.57)
Cumulative duration (years)		
1	1.78 (0.29-12.74)	23.07 (9.65-45.40)
2	1.63 (0.19-9.09)	21.62 (9.14-50.58)
3-4	1.40 (0.23-8.79)	22.22 (9.23-47.81)
> 4	1.42 (0.16-11.56)	20.67 (8.23-41.95)
Alpha-blocker use		
None	1.22 (0.26-7.67)	26.43 (10.30-52.80)
Overall	1.60 (0.28-9.46)	25.26 (10.56-50.96)
Cumulative quantity (doses)		
10-60	1.54 (0.26-8.64)	25.26 (10.50-50.99)
61-180	1.66 (0.19-9.07)	24.66 (9.90-47.47)
181-629	1.58 (0.29-9.58)	25.36 (10.85-54.85)
≥ 630	1.80 (0.36-11.66)	25.76 (10.76-52.53)
Cumulative duration (years)		
1	1.55 (0.26-8.94)	25.16 (9.83-50.68)
2	1.76 (0.24-9.43)	24.96 (11.31-53.91)
3-4	1.61 (0.32-11.54)	25.36 (10.80-49.56)
> 4	1.73 (0.35-11.11)	26.66 (10.56-54.52)

Table 10. Hazard ratio for screen-detected and interval prostate cancer among finasteride and alpha-blocker users, stratified by serum PSA level. Results from the cohort study.

	Overall		Screen-detected cancer		Interval cancer	
Quantity/duration of medication use	No. of cases (users/non-users)	HR (95% CI)*	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)
Finasteride:						
serum PSA < 4	19/214	0.87 (0.43-1.76)	5/134	0.64 (0.23-1.79)	14/80	1.26 (0.48-3.31)
serum PSA ≥ 4	68/1,293	0.62 (0.46-0.83)	46/1,084	0.61 (0.44-0.84)	22/209	0.49 (0.23-1.06)
Alpha-blockers:						
serum PSA < 4	48/185	1.75 (1.08-2.82)	20/119	1.40 (0.73-2.68)	28/66	2.46 (1.21-5.00)
serum PSA ≥ 4	147/1,214	0.72 (0.58-0.90)	97/1,033	0.66 (0.51-0.84)	50/181	1.06 (0.64-1.73)

* From a Cox proportional hazard regression model adjusted for age, family history of prostate cancer, finasteride or alpha-blocker use, number of PSA screens and time period of screening (before or after year 2000)

5.3. Prostate cancer incidence in users of statins or other serum cholesterol-lowering drugs

5.3.1. Case-control study

In the case-control study the overall prostate cancer risk was slightly elevated in statin users (OR 1.07, 95% CI 1.00-1.16), but no trend by cumulative quantity of statin use was observed (Table 11). No change in the overall risk was observed neither in users of fibrates (OR 1.05, 95% CI 0.86-1.27) nor in users of resins or acipimox (OR 1.16, 95% CI 0.80-1.68).

However, the risk of advanced prostate cancer was lower in statin users (OR 0.75, 95% CI 0.62-0.91) with a decreasing gradient by increasing cumulative amount of use (Table 11). A significant decrease in the risk of advanced prostate cancer was observed separately for atorvastatin (OR 0.61, 95% CI 0.37-0.98) and lovastatin (0.61, 95% CI 0.43-0.85). A borderline significant lowering of risk was also observed in simvastatin users (OR 0.78, 95% CI 0.61-1.01).

Table 11. Prostate cancer risk among statin users by quartiles of total cumulative quantity of medication use. Results from the case-control study.

Prostate cancer risk:	No. of discordant pairs*	Crude OR	95% CI	Adjusted OR†	95% CI
Overall					
All statin users	2,253/2,067	1.09	1.02-1.15	1.07	1.00-1.16
14-167 DDD‡	576/533	1.08	0.96-1.22	1.06	0.94-1.19
168-446 DDD	559/527	1.06	0.97-1.15	1.04	0.95-1.13
447-914 DDD	558/526	1.06	0.95-1.20	1.05	0.93-1.18
915-6,781 DDD	560/483	1.16	1.03-1.31	1.13	1.00-1.28
Advanced:					
All statin users	196/272	0.72	0.60-0.87	0.75	0.62-0.91
14-167 DDD	66/73	0.91	0.65-1.27	0.94	0.67-1.31
168-446 DDD	46/71	0.65	0.45-0.94	0.68	0.47-0.99
447-914 DDD	44/71	0.62	0.43-0.90	0.64	0.44-0.94
915-6,781 DDD	40/56	0.71	0.48-1.07	0.74	0.49-1.11
		p for trend < 0.001		p for trend = 0.001	

* As conditional logistic regression is the analysis method, number of case-control pairs discordant in terms of statin use is reported. Case: user – control: non-user/ Case: non-user – control: user

† Adjusted for age, usage of diuretics, calcium-channel blockers, ACE-inhibitors, AT-blockers, metformin, sulphonylureas and human insulin

‡ Cumulative quantity of statins purchased during the observed time period. DDD = Defined Daily Dose

5.3.2. Cohort study

Again, the results differed between the cohort and the case-control study as in the former a decrease in overall prostate cancer risk was observed in current statin users as compared with current non-users (Table 12). An inverse relation between the cumulative amount of statin use and prostate cancer risk was observed (Figure 2). An inverse relation, albeit less clear, was also found for cumulative duration of statin use (Table 12). A risk decrease was observed for Gleason 6 or less, Gleason 7-10 and early stage (stage $T_1N_{0/X}M_{0/X}$ or $T_2N_{0/X}M_{0/X}$) tumours. A total of 22 advanced stage cases were observed among statin users, for overall HR of 0.93 (95% CI 0.54-1.58). The number of advanced cases was too low for stratification by cumulative amount or duration of statin use. The overall prostate cancer risk was decreased in atorvastatin users (HR 0.59, 95% CI 0.44-.079) and a negative trend with cumulative quantity of use was seen with fluvastatin and simvastatin (p for decreasing trend 0.008 and < 0.001. respectively). No trend in the risk was observed for users of other types of cholesterol-lowering drugs, although the risk estimates were consistently below one also among users of these drugs.

Table 12. Hazard ratio for prostate cancer by stage and grade among users of cholesterol-lowering drugs, results from the cohort study.

	Overall		Gleason 2-6		Gleason 7-10		Early stage tumors‡	
Quantity/duration of medication use	No. of cases	HR (95% CI)†	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)
Statins:								
Non-users	1,326	Refererence	994	Refererence	300	Refererence	1,183	Refererence
All users	268	0.75 (0.63-0.89)	202	0.76 (0.62-0.92)	66	0.72 (0.51-1.01)	246	0.73 (0.61-0.87)
Cumulative quantity of statin use (DDD)								
14-378	105	0.84 (0.65-1.09)	83	0.85 (0.63-1.14)	22	0.78 (0.44-1.36)	94	0.78 (0.59-1.04)
379-960	77	0.73 (0.55-0.97)	62	0.78 (0.57-1.06)	15	0.56 (0.30-1.07)	73	0.73 (0.55-0.98)
961-1,800	56	0.75 (0.55-1.03)	34	0.70 (0.48-1.02)	22	0.94 (0.54-1.63)	51	0.77 (0.56-1.06)
> 1800	30	0.58 (0.36-0.91)	23	0.59 (0.34-1.01)	7	0.54 (0.22-1.33)	28	0.56 (0.34-0.90)
P_{trend}*		<0.001		0.002		0.084		0.001
Years of statin use								
1	60	0.73 (0.54-0.98)	49	0.74 (0.53-1.04)	11	0.67 (0.36-1.28)	53	0.66 (0.47-0.91)
2-3	95	0.67 (0.50-0.90)	74	0.70 (0.50-0.98)	21	0.58 (0.31-1.11)	89	0.69 (0.51-0.93)
4-5	60	0.85 (0.65-1.11)	40	0.87 (0.64-1.19)	18	0.78 (0.45-1.36)	56	0.88 (0.67-1.15)
≥ 6	53	0.70 (0.45-1.08)	39	0.65 (0.38-1.12)	16	0.84 (0.40-1.74)	48	0.61 (0.38-0.99)
P_{trend}*		0.007		0.019		0.182		0.006
Other cholesterol-lowering drugs: ¶								
Non-users	1,579	Refererence	1,186	Refererence	357	Refererence	1,431	Refererence
All users	15	0.62 (0.28-1.38)	8	0.55 (0.21-1.48)	7	0.87 (0.22-3.52)	14	0.69 (0.31-1.55)
P_{trend} by cumulative quantity of medication use (DDD) *		0.353		0.216		0.703		0.286
P_{trend} by duration of medication use (years) *		0.205		0.090		0.578		0.167

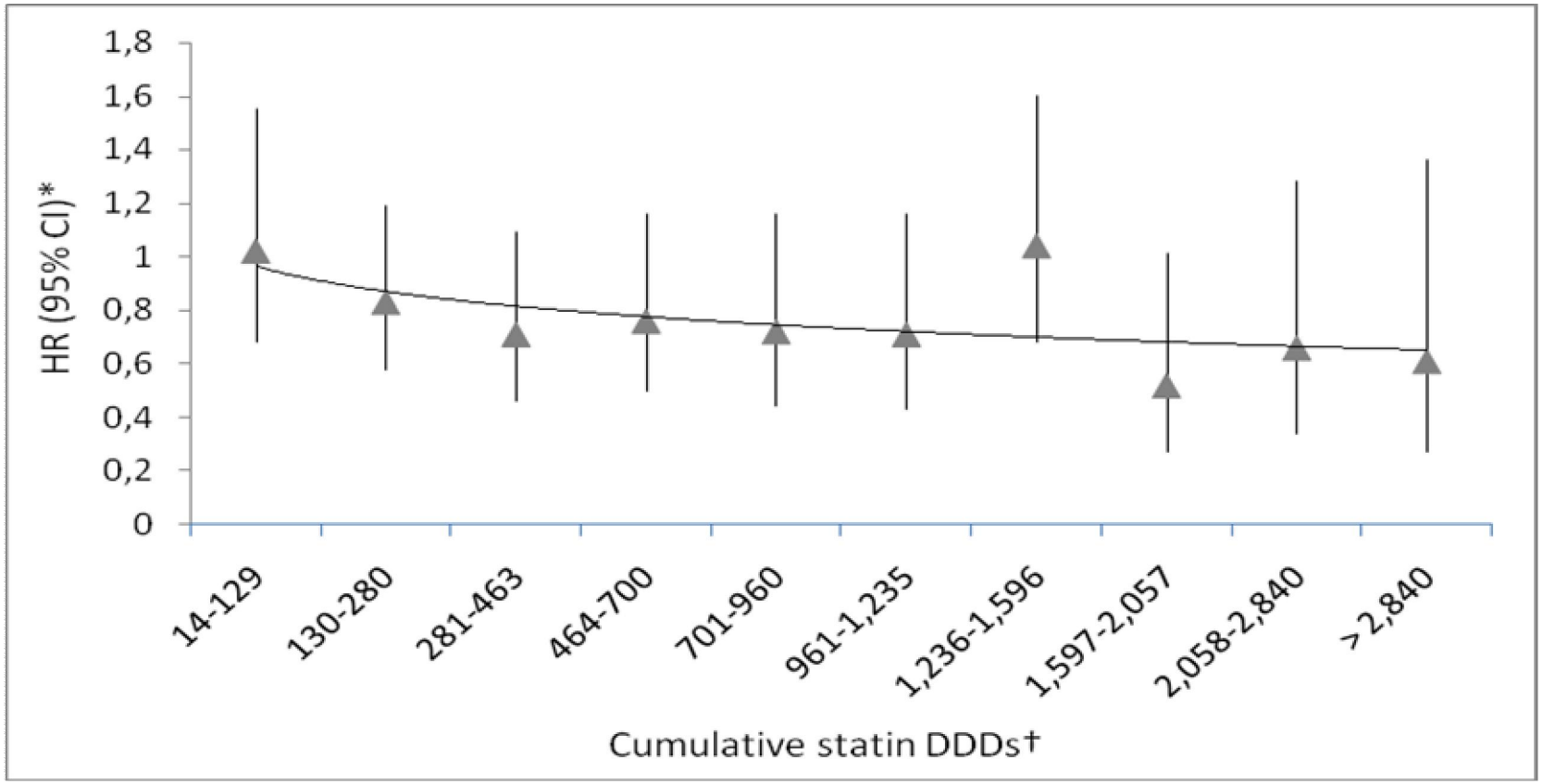
***** Estimated by including cumulative dose (DDDs) or duration (years) of medication use in a Cox regression model as a continuous covariate. All statistical trends are inverse i.e. indicating a decreased risk with larger amount of medication use

† From a Cox proportional hazard regression model adjusted for age, family history of prostate cancer, use of aspirin, antidiabetic drugs and/or antihypertensive drugs, number of PSA screens and calendar period of screening

‡ Men with stage $T_1N_{0/X}M_{0/X}$ or $T_2N_{0/X}M_{0/X}$ tumors combined

¶ Includes users of fibrates, resins and acipimox

Figure 2. Trend in the overall hazard ratio of prostate cancer by cumulative amount of statin DDDs purchased. Results from the cohort study.



* From a Cox proportional hazard regression model adjusted for age, family history of prostate cancer, use of aspirin, antidiabetic drugs and/or antihypertensive drugs, number of PSA screens and calendar period of screening.

† Medication users stratified in deciles by cumulative amount of statin use during the study period

5.4. Serum PSA among users of serum cholesterol-lowering drugs

Median serum PSA was slightly lower in current users of cholesterol-lowering drugs in all age-groups when compared with persons who had never used such medications (Table 13). This concerned especially users of fibrates, resins and acipimox. Also, the median PSA in statin users was slightly lower, but the difference was not statistically significant. However, no trend in PSA by cumulative amount of statin or other cholesterol-lowering drug use was observed (Table 13).

Conversely, the proportion of free PSA (percentage of free PSA) was higher in users of cholesterol-lowering medication than among non-users (Table 13). Again, the difference persisted in all age groups. A borderline significant increasing trend in percentage of free PSA was associated with an increasing cumulative amount of statin use (p for trend 0.056).

The association between overall prostate cancer risk for statin users and the risk of early stage tumours did not vary by PSA level (above or below the prostate biopsy threshold 4 ng/ml) (Table 14). A decreased prostate cancer incidence by current statin use was observed also among the 3,585 men undergoing prostate biopsy during the study period (HR 0.83, 95% CI 0.70-0.98).

Table 13. Age-standardized geometric means of serum PSA concentration and percentage free PSA among users and non-users of cholesterol-lowering drugs by age. Results from the cohort study.

Age group*	Geometric mean PSA (ng/ml) (95 % confidence interval)			β_1 (p-value) §	β_2 (p-value) §
	Cholesterol-lowering medication use				
	Statins†	Other†	None‡		
Overall	1.18 (0.25-7.44)	1.03 (0.23-5.78)	1.23 (0.27-7.82)	-0.012 (0.252)	0.033 (0.592)
55-59	0.93 (0.24-5.73)	0.64 (0.20-4.40)	0.91 (0.25-5.84)	-0.022 (0.251)	-0.217 (0.022)
60-63	1.01 (0.25-7.21)	0.93 (0.20-5.81)	1.10 (0.28-8.28)	-0.007 (0.647)	0.009 (0.920)
64-67	1.25 (0.26-9.12)	1.14 (0.29-8.89)	1.28 (0.29-9.77)	-0.007 (0.643)	0.138 (0.083)
68-72	1.54 (0.28-7.82)	1.35 (0.35-6.53)	1.59 (0.31-9.97)	-0.019 (0.259)	0.175 (0.097)
	Geometric mean percentage of free PSA (95 % confidence interval)				
Overall	27.51 (10.90-53.70)	28.78 (13.56-56.05)	26.18 (10.40-52.50)	0.010 (0.056)	0.004 (0.872)
55-59	26.85 (11.70-52.85)	29.98 (12.75-55.78)	26.59 (10.50-53.20)	0.025 (0.010)	0.065 (0.169)
60-63	27.27 (10.50-54.58)	30.56 (12.56-61.74)	26.01 (10.40-52.00)	0.013 (0.065)	0.022 (0.554)
64-67	27.49 (10.54-54.86)	28.19 (13.72-55.16)	25.63 (10.00-51.74)	0.002 (0.726)	-0.017 (0.622)
68-72	27.85 (10.80-53.56)	27.58 (11.10-46.70)	26.52 (10.60-52.40)	0.000 (0.970)	-0.068 (0.093)

* Study population stratified in quartiles by age at the time of PSA test

† Current use of statins or other cholesterol-lowering drugs (fibrates, resins or acipimox) at the time of PSA test

‡ Men without any cholesterol-lowering drugs during the study period

§ Correlation coefficient for the change in PSA or percentage of free PSA for one DDD change in cumulative quantity of statins (β_1) or other cholesterol-lowering drugs (β_2) used. P-value for trend between cumulative quantity of medication use and PSA. From linear regression with robust variance correction and adjustment for age, antidiabetic medication use and number of PSA tests

Table 14. Hazard ratio for prostate cancer among current statin users compared with non-users by serum PSA level, Gleason score and stage. Results from the cohort study.

PSA (ng/ml)*	Overall		Gleason 2-6		Gleason 7-10		Early stage tumors†	
	No.. of cases‡	HR (95% CI) §	No.. of cases	HR (95% CI)	No.. of cases	HR (95% CI)	No.. of cases	HR (95% CI)
0.0-3.9	43/190	0.66 (0.43-1.01)	31/130	0.79 (0.49-1.27)	12/50	0.46 (0.18-1.20)	39/174	0.62 (0.40-0.97)
≥ 4.0	211/1,150	0.85 (0.71-1.02)	157/876	0.86 (0.69-1.06)	50/252	0.84 (0.58-1.21)	195/1,034	0.83 (0.69-1.01)

***** Latest available PSA value

† Men with stage $T_1N_{0/X}M_{0/X}$ or $T_2N_{0/X}M_{0/X}$ tumors combined

‡ Number of cases among the exposed/number of cases among the unexposed men

§ From a Cox proportional hazard regression model adjusted for age, family history of prostate cancer, simultaneous use of other medication (aspirin, antidiabetic drugs and antihypertensive drugs), number of PSA screens and calendar period of screening

5.5. Prostate cancer risk in men using antidiabetic drugs: case-control study

A decreased overall prostate cancer risk was observed among men using antidiabetic medication in the case-control study (OR 0.84, 95% CI 0.79-0.90) (Table 15). When the antidiabetic drug groups were analyzed separately, a similar decrease was seen whether a man had used oral antidiabetic drugs (metformin, sulfonylureas or guar gum) or insulin. The risk decreased in association with increasing cumulative quantity of medication use (Table 15). The decreasing trend by increasing amount of antidiabetic medication use was observed for overall prostate cancer risk but not for advanced tumours. However, the time since the first antidiabetic medication purchase was inversely related with both overall and advanced prostate cancer risk (Table 16).

Table 15. Odds ratio for any prostate cancer and advanced prostate cancer risk by amount of antidiabetic medication use. Results from the case-control study.

Total amount of medication reimbursed (DDD) †	No. of discordant pairs‡	Overall cancer		Advanced cancer¶	
		OR§	95% CI	OR	95% CI
Oral drugs					
≤228	598/604	0.99	0.88-1.11	1.06	0.79-1.42
229-700	575/632	0.91	0.81-1.02	0.73	0.53-0.99
701-1,650	559/621	0.90	0.80-1.01	0.81	0.59-1.11
≥1,651	509/688	0.74	0.66-0.84	0.80	0.56-1.14
		p for trend < 0.001*		p for trend = 0.294	
Insulin					
≤288	148/172	0.86	0.69-1.08	0.49	0.27-0.87
289-744	142/290	0.70	0.56-0.86	0.65	0.37-1.14
745-1,707	142/192	0.74	0.60-0.93	0.74	0.40-1.35
≥1,708	156/184	0.85	0.68-1.05	0.63	0.35-1.16
		p for trend = 0.009		p for trend = 0.129	

***** p-values for trend computed by including the cumulative total quantity of medication purchases in the multivariable adjusted logistic regression model as a continuous covariate

† Medication users stratified by quartiles of reimbursements

‡ Number of pairs with exposed case and unexposed control relative to pairs with unexposed case and exposed control.

§ Adjusted for age, place of residence and simultaneous use of other medications (aspirin, cholesterol-lowering drugs or antihypertensive drugs).

¶ Locally or regionally invasive and metastatic prostate cancer

Table 16. Odds ratio for prostate cancer overall and for advanced prostate cancer by time since the onset of antidiabetic medication use. Results from the case-control study.

Time since first reimbursed purchase	No. of discordant pairs†	Overall cancer		Advanced cancer§	
		OR‡	95% CI	OR	95% CI
≤ 1 year	606/631	0.96	0.85-1.07	0.96	0.74-1.25
2 years	312/359	0.87	0.74-1.01	0.61	0.42-0.90
3 years	268/353	0.76	0.65-0.89	1.12	0.70-1.79
4 years	250/281	0.89	0.75-1.06	0.79	0.49-1.27
5 years	209/268	0.78	0.65-0.94	0.64	0.37-1.11
6 years	171/225	0.76	0.62-0.92	0.62	0.34-1.13
7 years	137/208	0.66	0.53-0.83	0.61	0.28-1.34
		p for trend < 0.001*		p for trend = 0.003	

***** p-values for trend computed by including the cumulative total quantity of medication purchases in the multivariable adjusted logistic regression model as a continuous covariate

† Number of pairs with exposed case and unexposed control relative to pairs with unexposed case and exposed control.

‡ Adjusted for age, place of residence and simultaneous use of other medications (aspirin, cholesterol-lowering drugs or antihypertensive drugs).

§ Locally or regionally invasive and metastatic prostate cancer

6. DISCUSSION

6.1. General aspects

We have demonstrated that medication use is associated with prostate cancer incidence, even for advanced and poorly differentiated tumours. This suggests that the public health burden caused by prostate cancer could be reduced by modification of these factors. Further studies are definitely warranted.

The credibility of research depends on the critical assessment of the strengths and weaknesses in study design, conduct and analysis (von Elm et al., 2007). A major strength of the present study is the reliability and high quality of information on the study populations and their exposure. Using comprehensive national registers and data from the screening arm of the Finnish Prostate Cancer Screening Trial, we were able to perform both a nationwide case-control study and to study the influence of medication use in a population systematically screened for prostate cancer.

The two study populations both had their own strengths. In the cohort study, the impact of differential PSA testing was controlled by the systematic screening of the entire study population, allowing us to study changes in prostate cancer incidence between medication users and non-users while controlling this strong confounding factor. However, this does not reflect the current situation in most countries as systematic prostate cancer screening using a PSA test is currently not widespread and PSA testing activity, i.e., opportunistic testing, depends on the preferences and activity of both men and their

physicians. Results from our case-control study reflect the national level net effect of medication use on prostate cancer incidence in such a situation.

There are several potential limitations to our study that merit discussion. As often is the case in epidemiological research, our results could be affected by bias and confounding caused by unmeasured or unknown factors. We were able to adjust our analyses for age and family history of prostate cancer, as well as for simultaneous use of other types of drugs and prostate cancer screening activity. Still, the medication users could have had systematic differences as compared to the non-users, potentially causing confounding.

A fine example of this was observed in our analyses comparing the prostate cancer risk between finasteride users and non-users. Medication users were on average older than non-users, had higher age-adjusted median PSA and larger prostate volumes, confirming that the medication users were, indeed, men with BPH. This definitely caused bias, especially in the case-control study, as described above. In the cohort study, the higher PSA level could have resulted in more prostate biopsies among BPH medication users, possibly increasing prostate cancer incidence among them in relation to non-users. Thus, this bias does not affect our inference of a decreased prostate cancer risk among medication users.

Also, statin users differed from non-users. The recommended indications for statin use are treatment of hypercholesterolemia and primary or secondary prevention of cardiovascular disease. Previous research has suggested that men using statins for primary prevention of CVD are more health-oriented and have healthier lifestyles than have non-users (Brookhart et al., 2007), causing a so-called “healthy-user” bias in studies estimating statin use and various outcomes such as prostate cancer risk. However, in our

study the median BMI was higher and the use of aspirin, antidiabetic drugs and antihypertensive drugs was markedly more common among statin users than among non-users. Thus, statin users' overall health was actually worse than that of non-users, suggesting that statins were more commonly used for secondary rather than primary prevention of CVD. Also, long-term statin users are more likely to have multiple comorbidities, as previous research has shown a higher long-term persistence to statin therapy among these men (Helin-Salmivaara et al., 2008). Thus, the healthy-user bias probably does not explain either the decreased prostate cancer risk or the inverse association with cumulative amount of statin use observed in our study. Nevertheless, previous research has shown that, in Finland, atorvastatin prescriptions are preferred to simvastatin in younger and healthier population (Halava et al., 2009). Thus, the healthy user bias could in part explain the lower prostate cancer incidence among atorvastatin users as compared with other statins.

Users of antidiabetic medication most certainly differed from non-users with respect to diabetes and other associated factors, such as BMI and comorbidities. This could have possibly increased the risk in diabetic men compared to non-diabetic men, thus not explaining the inverse association observed. However, lower PSA levels among diabetic men (Werny et al., 2006; Waters et al., 2009) probably partly explain the relative risk decrease in the case-control study.

We did not have information on smoking, diet, vitamin and mineral (such as selenium and vitamin E) use or physical activity of study subjects in either population. However, their role as prostate cancer risk factors is controversial (Dagnelie et al., 2004) (Table 3).

Confounding by indication is another possible source of bias in our study. It is probable that some men had used finasteride or alpha-blockers for treatment of LUTS caused by prostate cancer undetected at

the time. This probably explains, in part, the increased prostate cancer incidence observed in the case-control study, but does not affect our inference of a lowered prostate cancer risk in the cohort study. Also, our analysis of prostate cancer incidence among antidiabetic medication users was most certainly affected by this bias, as a reduction in prostate cancer risk in diabetic men has been previously reported by multiple studies (Kasper and Giovannucci, 2006). Confounding by indication among men using cholesterol-lowering drugs for hypercholesterolemia is more uncertain. Serum cholesterol decreases spontaneously up to nine years before a cancer diagnosis, probably due to progressing carcinogenesis (Ahn et al., 2009). This could lead to less cholesterol-lowering drug use among cancer patients in the pre-diagnostic period, and thus to bias towards lower cancer incidence among statin users as compared with non-users. However, it could not explain the dose-dependent inverse association with statin use. On the other hand, bias in the opposite direction would be caused by reported decreased risk of advanced prostate cancer in men with low serum cholesterol (Platz et al., 2008; Platz et al., 2009).

Our follow-up on medication use started at the beginning of 1995 at the earliest, although most drugs studied, including finasteride, some statins, metformin and sulfonylureas, were licensed and introduced earlier to clinical use in Finland. Thus, some medication users might have had a longer history of usage than appeared in our study. This would create a bias towards the null in our results, and does not affect our inference of decreased or increased prostate cancer risk.

The prescription database did not have information on medication purchases for institutionalized persons. This probably resulted in an underestimation of medication use for some persons in the case-control study, and an immeasurable time bias in the cohort study, some current medication users being inadvertently categorized as current non-users. This would have caused a bias towards the null in our results.

The information in the SII prescription database is comprehensive for BPH medication, cholesterol-lowering medication, antidiabetic medication and antihypertensive medication. However, aspirin is commonly used without prescription in Finland, and our information on aspirin use (used for model adjustment in the Cox and logistic regression analyses) is an underestimation of the true prevalence of aspirin use.

We used the DDDs recommended by WHO to standardize consumption of drugs within the same drug category. This allowed us to combine, for example, purchases of, in the maximum, seven distinct statins into overall statin consumption. However, the DDDs recommended by the WHO do not necessarily reflect actual daily drug consumption; for example, the recommended DDD for insulin (whether human or recombinant) is 40 IU (World Health Organization), whereas individual treatment doses vary widely, sometimes rising up to hundreds of units per day.

In the case-control study, 963 men who were first included as controls were later diagnosed with prostate cancer and were again included in the study population, this time as a case in another case-control pair. This caused a slight bias towards the null in our results: for example the overall OR (95% CI) of prostate cancer among finasteride users was 1.41 (1.31-1.51), when the entire study population was used, versus 1.46 (1.36-1.57) after exclusion of case-control pairs with the men who appeared twice. However, this bias does not affect our conclusions concerning an increased or decreased risk.

6.2. Impact of varying PSA-measuring activity on the results of epidemiological studies of prostate cancer

The results between the two study populations differed for analyses of the effect of finasteride and statins. This difference is most probably caused by differing PSA-testing activity: in the case-control study, the prevalence of opportunistic PSA testing was low (Ciatto et al., 2003), albeit probably more common among medication users (Brookhart et al., 2007); whereas men in the cohort study were systematically screened regardless of medication use. This demonstrates how strongly the differing PSA testing activity between medication users and non-users can affect the results of epidemiological analyses on medication use and prostate cancer risk. Men in the cohort study could have been, in general, more health-oriented as they were living in urban areas of Finland and consented to participation in screening, whereas our case-control study was entirely register-based requiring no activity from the study subjects, and also included men living in rural areas. However, urban men also formed the majority of the study population in the case-control study. Thus, this difference is unlikely to affect the observed relation between medication use and prostate cancer risk to a great extent.

6.3. Medical treatment of benign prostatic hyperplasia and prostate cancer incidence

Our results on finasteride and prostate cancer risk in the cohort study are generally comparable to those of the Prostate Cancer Prevention Trial (PCPT). Men recruited to the PCPT had a low PSA level and no urological symptoms at baseline (Thompson et al., 2003), whereas in our study finasteride was used for treatment of symptomatic BPH. This was well demonstrated by the higher median PSA among finasteride and alpha-blocker users as compared with non-users.

In the case-control study, prostate cancer risk was elevated among men using BPH medications as compared to non-users. This is probably explained by more active case ascertainment: men with lower urinary tract symptoms undergo PSA testing as part of diagnostic work-up, i.e., the men are screened for prostate cancer due to being symptomatic, whereas the overall prevalence of opportunistic testing was low in Finland during the study period (Ciatto et al., 2003). Furthermore, as was seen in the cohort study, men using BPH medication have higher PSA levels than non-users. Thus, more prostate biopsies and more diagnoses of latent tumours are carried out in users of those medications. Some of the risk elevation is probably explained by a protopathic bias— BPH medications have been used to treat LUTS caused by yet undiagnosed prostate cancer.

When the influence of differing PSA testing was virtually eliminated in the cohort study by systematic testing of the entire study population there was no evidence of prostate cancer risk increase among BPH medication users. Instead, the risk of low-grade tumours was decreased among finasteride users. These findings suggest that the protective effect demonstrated in the PCPT can also be expected in men using finasteride for BPH in a population under systematic PSA screening. However, at the national level without such a screening programme, the influence of a higher PSA level and more active PSA testing is stronger, leading to an elevated risk among finasteride users instead.

A worrying observation was the increased risk of high-grade tumours among long-term finasteride users. A similar observation was reported also by the PCPT (Thompson et al., 2003), although later analyses have suggested this to be due to a bias caused by an increased sensitivity of PSA testing to detect high-grade tumours during finasteride therapy (Thompson et al., 2006). In any case, the long-term effects of dihydrotestosterone suppression with finasteride require more studies.

We also found a reduced number of high-grade tumours among alpha-blocker users. Previously, a few studies have reported that quinazoline-derived alpha-blockers terazosin and doxazosin could have prostate cancer preventative properties (Kyprianou and Benning, 2000; Benning and Kyprianou, 2002; Harris et al., 2007). Our results suggest that this could also be the case for tamsulosin and alfuzosin, the alpha-blockers in clinical use in Finland.

6.4. Medical treatment of hypercholesterolaemia and prostate cancer incidence

The results concerning decreased prostate cancer incidence among users of cholesterol-lowering drugs are encouraging. The decrease in risk was observed for all tumour grades and early stage tumours among statin users in the cohort study. The number of advanced cases was small in the cohort study; however, in the case-control study, the risk of advanced cancer was lower among statin users. Statin users' overall prostate cancer risk was not decreased in the case-control study, but this is again probably explained by more active case ascertainment, as statin users are more likely to undergo PSA testing than are non-users (Brookhart et al., 2007). Advanced prostate cancer, on the other hand, is usually detected on the basis of symptoms and is rarely missed even in the absence of PSA testing. Thus, the risk of advanced prostate cancer is probably less likely to be affected by detection bias.

The prostate cancer cell growth inhibiting potential of statins has been reported by multiple studies, as summarised by Murtola et al. (2008). These effects already occur at clinically relevant drug concentrations (Murtola et al., 2009). The mechanism for growth inhibition is probably related to a decrease in intracellular cholesterol content, leading to profound changes in cellular growth regulation

(Solomon and Freeman, 2008). Most probably, a reduction in serum cholesterol level also has significance *in vivo* (Platz et al., 2008; Platz et al., 2009). Decreased, albeit statistically non-significant, risk estimates were also observed among users of other types of cholesterol-lowering drugs than statins in both study populations, supporting the importance of reducing serum cholesterol. However, a dose-response in prostate cancer risk was observed only among statin users.

Currently, all epidemiological studies estimating the risk of advanced prostate cancer among statin users have reported lowered risk estimates (Friedman et al., 2008; Murtola et al., 2008). Such consistency is rare in the epidemiological literature. Results on statin users' overall prostate cancer risk, on the other hand, have been much more controversial (Agalliu et al., 2008; Boudreau et al., 2008; Farwell et al., 2008; Ford et al., 2007; Friedman et al., 2008; Haukka et al., 2009; Murtola et al., 2008; Olsen et al., 1999). A plausible explanation for the controversy is the differing ability of previous studies to control for PSA testing among their study populations. Our results support this notion as the overall risk was not decreased, but in fact slightly increased among statin users in the case-control study in which opportunistic prostate cancer testing could not be controlled for. On the other hand, in the cohort study with systematic prostate cancer screening a clear decrease in risk was found.

Previous studies have reported lower PSA values in men using statins as compared with other men (Hamilton et al., 2008). This has raised concerns as to whether the decreased prostate cancer incidence among statin users is due to fewer prostate biopsies made as a result of an elevated PSA level. We have shown that the inverse association in statin users does not depend on the serum PSA level, and remains significant even in the subgroup of men who have all undergone prostate biopsy. Thus, a lower PSA level does not explain the decrease in prostate cancer risk among statin users.

6.5. Diabetes and the incidence of prostate cancer

We observed a similar decrease in prostate cancer risk among users of antidiabetic drugs irrespective of the drug category. This suggests a common decrease among medication users, probably caused by the common indication for the medication use, diabetes mellitus. In this case, the dose-dependency with the cumulative amount and duration of medication use suggests that the risk decreases with the length of time since the onset of diabetes. These findings are in accordance with previous literature (Kasper and Giovannucci, 2006). A decreased prostate cancer risk among diabetic men has been reported before, but ours is the first study to comprehensively analyze the role of antidiabetic medication. The risk reduction is probably mediated by lower androgen levels in diabetic men (Barrett-Connor et al., 1990; Oh et al., 2002). However, decreased serum PSA has been reported in diabetic men (Werny et al., 2006; Waters et al., 2009), which could cause detection bias toward lowered risk due to fewer prostate biopsies. Nevertheless, a lowered PSA is not likely to explain the entire risk decrease in diabetic men (Waters et al., 2009). Further, the inverse association was observed even before the introduction of PSA testing in clinical practice (Kasper and Giovannucci, 2006). Thus, a reduction in prostate cancer risk seems to be a positive consequence of diabetes mellitus. However, we were not able to discriminate between type 1 and type 2 diabetes in our analysis, as we did not have information concerning indications for medication use. Thus, it is possible that the effect on prostate cancer is different between these two types of diabetes.

6.6. Future considerations

Prostate cancer preventive potential of statins is appealing as the cardiovascular benefits of this drug group are well established (Yusuf et al., 2009). Statins reduce the chance of cardiovascular events by 30% even in subjects with normal cholesterol levels (Collins et al., 2003; Collins et al., 2004). Furthermore, statins are cheap and well-tolerated even at high doses (Hebert et al. 1997; LaRosa et al., 1999; Wierzbicki et al., 2003). Adverse event rates are low, 0.6% for hepatic adverse events (elevated liver enzymes) and 1.3% for musculoskeletal adverse events for subjects receiving a high dose (80 mg) of atorvastatin (Wang et al., 2008). Still, the adverse events could be more common for certain subpopulations (Pasanen, 2008). Using a single drug group for both cardiovascular and cancer mortality reduction would be an appealing approach. However, the cancer preventive potential has to be confirmed by clinical trials before statins can be recommended for this purpose. Currently, only the prostate cancer preventive potential of finasteride has been confirmed by a randomized trial (Thompson et al., 2003). However, the prostate cancer preventive effect of finasteride needs to be weighed against a possibly increased risk of poorly differentiated tumours and sex-related side effects (such as decreased libido, decreased ejaculate volume, gynecomastia) observed during finasteride therapy (Thompson et al., 2003).

Nevertheless, even if the cancer preventive potential of statins was, in the future, confirmed by clinical trials it would be unrealistic to expect their use by all men. Even though statins have been shown to decrease cardiovascular mortality, a far more common cause of death than cancer, they are still mostly used for secondary, not primary, prevention of cardiovascular disease. This probably would not change even if more proof of statins' prostate cancer preventive potential was obtained.

In the future, a wise approach could be to study whether statins can prevent the development of prostate cancer in high-risk men, such as those with a strong family history, with elevated PSA and negative biopsy or prostatic intraepithelial neoplasia in biopsy. Another approach would be to study whether statins could be used in secondary prevention of prostate cancer, to delay or prevent the progression of clinically localized prostate tumours into advanced stages in men who are under active surveillance as part of the management of their prostate cancers.

For the general public, the best approach would be the continued recommendation of cholesterol control by diet and regular physical exercise, as the health benefits of these activities are already recognized and, as our results demonstrate, cholesterol-lowering could also lead to a reduction in prostate cancer risk.

Future epidemiological studies on medication use and prostate cancer incidence should control for the effect of differing PSA testing activity between medication users and non-users. An ideal solution would be to use a study population where no-one or, alternatively, everyone has been screened with PSA, eliminating the discrepancy between the exposed and the non-exposed. As this is usually not possible, detailed information on previous and current PSA testing should be collected, and analyses adjusted for this source of bias.

7. CONCLUSIONS

We have shown that epidemiological study results on prostate cancer incidence can be strongly influenced by PSA testing activity within the study population. Controlling for this strong potential confounding factor is crucial in future studies.

Our results demonstrate that the risk of prostate cancer is associated with regular medication use. The prostate cancer preventive potential of finasteride, previously demonstrated in men with a low PSA level and no lower urinary tract symptoms can also be expected in men using the drug for BPH, but the drug's long-term effect on the incidence of high-grade tumours and prostate cancer mortality warrant further studies.

Overall, the decrease in prostate cancer risk among antidiabetic drug users further confirms that diabetic men have a lower incidence of prostate cancer, which is probably due to lowered androgen levels.

We have demonstrated that cholesterol-lowering drugs, especially statins, probably have prostate cancer preventive benefits. Whether statins and finasteride could reduce prostate cancer mortality is a highly interesting topic for future research.

8. ACKNOWLEDGEMENTS

This study was carried out at the University of Tampere, School of Public Health; Tampere University Hospital, Department of Urology and Central Finland Central Hospital, Department of Surgery.

I wish to express my most sincere gratitude to my supervisors, professor Anssi Auvinen and professor Teuvo Tammela. Beginning from the first planning meetings and carrying on throughout the research project, both have continuously supported me. During this process Anssi has taught me a great deal about scientific thinking in general and about epidemiology in particular. Furthermore, he has served as an example on how to effectively run a research group of many professionals at the researcher meetings of the Finnish Prostate Cancer Screening Trial. It was Teuvo whom I first contacted when I wanted to start a research project. Right away he set up a meeting with me and Anssi to come up with a research plan. From the start his support for me has been remarkable. Teuvo's enthusiasm and commitment never cease to inspire me.

I would like to cordially thank Mrs. Liisa Määttänen, who has been effectively managing the practical issues and maintaining the database of the Finnish Prostate Cancer Screening Trial for so many years. She has always been very helpful when I have needed any information or data from the trial.

Professor emeritus Matti Hakama and Dr Juha Koskimäki were in the on the dissertation follow-up group. Matti has always had the time to share his wide knowledge on epidemiology. He has given many good and often critical suggestions on my research, which usually have led me to see research questions in a new angle. Juha has given me lots of guidance in clinical work with his own steady style during my time at the Tampere University Hospital.

Sincere thanks go to the co-authors of the papers in this thesis for their contribution and for sharing their expertise. Specifically I would like to mention Mrs. Heini Huhtala. Many times she has helped me solve problems on statistical issues, and thus has helped me overcome major obstacles in my research. I am truly grateful to her. I would also like to thank professor emeritus Ulf-Håkan Stenman for his critical revision of the articles and Dr Jorma Lahtela for sharing his insights on internal medicine, an area often obscure for simple surgeons like me.

My friend, Neill Booth from the school of public health and his wife Anu Planting reviewed the language of the dissertation, of which I am thankful for.

I would like to thank assistant professor Elizabeth Platz from Johns Hopkins Bloomberg School of Public Health, Baltimore, USA, for helping me with the data analyses and making me feel most welcome during my research visit to Baltimore in April, 2009. She agreed to sit down with me help to me with the data analyses in the middle of her busy congress poster presentation. I would also like to thank her research group, especially Alison Mondul, David Lopez, Shondelle Wilson, Samah Nour and Corrie Luino for all the good times we had during my visit.

Warm thanks to Heimo Syvälä, Merja Bläuer, Pasi Pennanen, Mirja Hyppönen and Timo Ylikomi from the department of anatomy and from the Cell Research Center, University of Tampere. They supported me in my first attempts on scientific research, and have also had an integral role in starting an extension of this thesis work, a cell research project estimating the effect of various medications, especially statins, on the growth of prostatic epithelial cells. Apart from being distinguished professionals, they are also good friends of mine.

I would also like to acknowledge good friends whom I have made while doing this research: Dr. Kari Tikkinen, Mika Helminen, Jani Raitanen and all the other guys at the school of public health. We have had some good times.

I thank my colleagues from the Department of Surgery in Central Finland Central Hospital. The chief of department, Jukka-Pekka Mecklin, has ensured that the clinical training in the clinic has been of high quality, with occasions every now and then to have time off for research. I would also like to thank doctors Mikko Tuuliranta and Kerkko Karjalainen for patiently teaching me the basic operative techniques and principles of surgery.

This work would not have been possible without research grants from the Competitive Research Funding of Tampere University Hospital and Central Finland Central Hospital District; Pirkanmaa Regional Fund of the Finnish Cultural Foundation; Irja Karvonen cancer trust; The Finnish Cancer Organizations and by non-restricted grants from Astellas, Coloplast, Schering Foundation, Lilly foundation, research foundation of Orion Pharma, Pfizer, Abbott Pharma and AstraZeneca.

Last but definitely not least, I thank my family. Firstly, my parents and my brother, Tommi for standing by me at all times. Loving thanks to my wife, Tiina, and to my beautiful and smart children, Kai and Eini. They are the ultimate joy of my life, both in times of success and in times of failure. You are there for me, and I am there for you, and in the end that is what really matters. I love you.

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10. ORIGINAL COMMUNICATIONS

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Prostate cancer risk among users of finasteride and alpha-blockers – A population based case–control study

Teemu J. Murtola[a,*], *Teuvo L.J. Tammela*[b], *Liisa Määttänen*[c], *Matti Hakama*[a], *Anssi Auvinen*[a,d]

[a]*University of Tampere, School of Public Health, 33014 Tampere, Finland*
[b]*Department of Urology, Tampere University Hospital and Medical School, University of Tampere, Teiskontie 35, 33520 Tampere, Finland*
[c]*The Finnish Cancer Registry, Liisankatu 21 B, 00170 Helsinki, Finland*
[d]*The Finnish Cancer Institute, Liisankatu 21 B, 00170 Helsinki, Finland*

ARTICLE INFO

Article history:
Received 3 October 2006
Received in revised form
30 November 2006
Accepted 1 December 2006
Available online 23 January 2007

Keywords:
Prostatic neoplasms
Prostatic hyperplasia
Drug therapy
Epidemiology
Case–control study

ABSTRACT

Finasteride has been reported to reduce prostate cancer risk in asymptomatic men. However, in clinical practice finasteride and alpha-blockers are used to treat benign prostatic hyperplasia (BPH). We evaluated prostate cancer risk among users of BPH pharmacotherapy at the population level. Comprehensive Finnish national registries provided information on 24723 prostate cancer cases and controls. Overall, prostate cancer risk was elevated among users of both drug categories compared to non-users (odds ratio, OR = 1.41; 95% confidence interval, CI 1.31–1.51 for finasteride and OR = 1.79; 95% CI 1.67–1.91 for alpha-blockers). However, the risk was lower among finasteride users when compared with alpha-blocker users (OR = 0.80; 95% CI 0.64–1.00). Regular finasteride users had the lowest risk. The increased risk is probably due to enhanced diagnostics of prostate cancer in men with BPH. Finasteride use does not decrease prostate cancer incidence compared with non-users. Nevertheless, the risk is lower when compared with alpha-blocker users.

1. Introduction

Prostate cancer is the most common malignancy among men in most countries.[1] An estimated 225227 new cases of prostate cancer were diagnosed in Europe in 2002.[1] Prostate cancer is among the three most common causes of cancer death in men in most European countries.[1]

Benign prostatic hyperplasia (BPH) is a common disease affecting up to 40% of men in the oldest age groups.[2] Incidence of both BPH and prostate cancer increases with age. However, association between these two conditions has not been established.[3]

Alpha-blockers and 5α-reductase inhibitors are currently used for medical management of BPH.[4] The 5α-reductase inhibitors decrease prostate size by inhibiting formation of the active androgen metabolite, dihydrotestosterone. Finasteride was the only 5α-reductase inhibitor licensed in Finland during the study period. Alpha-blockers reduce lower urinary tract symptoms (LUTS) of BPH by relaxing smooth muscle in the prostate.[4] The principal indication for both drug groups is symptomatic BPH. However, the effect of alpha-blocker treatment commences more rapidly than finasteride. Thus, men with severe BPH symptoms are more often treated with alpha-blockers.

Results from the Prostate Cancer Prevention Trial (PCPT) have shown a reduction in prostate cancer risk in finasteride users.[5] To be eligible for inclusion in the trial, the men had to have only little or no LUTS.[5] However, currently the only

* *Corresponding author:* Tel.: +358 3 3551 6168; fax: +358 3 3551 6057.
E-mail address: teemu.murtola@uta.fi (T.J. Murtola).
0959-8049/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2006.12.001

official indications for finasteride use are treatment of symptomatic BPH and male pattern baldness.

Some alpha-blockers have been reported to inhibit growth of prostate cancer cells *in vitro*.[6] Alpha-blockers licensed in Finland are tamsulosin and alfuzosin.

This study was undertaken to examine prostate cancer risk among users of BPH pharmacotherapy at the population level.

2. Patients and methods

2.1. Study population

All 25029 newly diagnosed prostate cancer cases in Finland during 1995–2002 were identified from the Finnish Cancer Registry, which covers more than 99% of all prostate cancer patients in Finland.[7] The register information includes primary site of cancer, histology, date and method of diagnosis. Information on stage was available in 55% of cases (13616 patients). Of these 73% were localised. The registry does not routinely record differentiation, such as Gleason score, nor serum prostate specific antigen (PSA) values.

Practically all the cases were histologically confirmed (99.3%). Also cases with the diagnosis based solely on clinical (0.4%), radiological (0.3%) or specific laboratory findings (0.02% of cases) were included. A total of 185 cases (0.7%) with an unknown method of diagnosis were excluded.

The Population Register Centre of Finland selected 24723 male controls with individual matching on age and geographical area of the cases at the time of the diagnosis. A total of 963 controls were subsequently diagnosed with prostate cancer during the study period, thus appearing twice in the analysis. Population size in Finnish municipalities ranges from less than 200 to 560000.[8] For 121 cases in the oldest age group, matched controls could not be found from the same municipality, resulting in their exclusion. A total of 24723 case–control pairs were included in the analyses.

Following approval from the ethics committee of the Pirkanmaa health care district, Finland, obtaining informed consent from the study population was not undertaken due to the large size of the population, and due to part of the population being unattainable (deceased or moved abroad) by the time of the study.

2.2. Drug exposure data

Information on BPH pharmacotherapy prescribed to the study population and reimbursed by the Social Insurance Institution of Finland during 1995–2002 was obtained from the comprehensive nationwide prescription database of the Social Insurance Institution of Finland (SII). The database provided individual information on quantity and time of the medication use.

SII manages the national public health insurance in Finland, providing reimbursements for the cost of medicines prescribed by a physician (with the exception of hospital inpatients).[9] The prescription database covers all reimbursements paid by the SII, which are available for all Finnish citizens for every drug purchase. However, not all drugs are approved as reimbursable, thus not covered in the prescription database.

Finasteride was licensed for use and approved for reimbursement for treatment of BPH in Finland in 1992. Therefore, information on finasteride use for this indication was available for the entire follow-up period. Finasteride is not reimbursed for treatment of androgen-induced alopecia; thus information on this use was not available. Tamsulosin was approved for basic reimbursement in 1996 and alfuzosin in 1997. The only official indication for both alpha-blockers is the symptoms of BPH.

The defined daily doses (DDDs) of finasteride, tamsulosin and alfuzosin available for the treatment of BPH in Finland are 5 mg, 0.4 mg and 10 mg, respectively. Medication use was quantified by calculating the number of DDDs bought each year based on package size and the number of packages bought.

2.3. Statistical analysis

Only the medication purchases prior to the month of diagnosis were included in the analyses. For controls, the month of diagnosis of their matched case was used as the reference month for medication purchases.

Prostate cancer may cause symptoms similar to BPH. Therefore, some medication purchases were likely prescribed to treat symptoms of prostate cancer while diagnostic process was under way. To reduce this bias, all cases and controls whose only purchases were 100 DDD or less of either drug-group within six months preceding the reference month were excluded from the analysis. Thus 1910 cases and 375 controls were excluded.

A conditional logistic regression model stratified by age and geographical area was used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) for prostate cancer related to pharmacotherapy using STATA 8.2 software. For analyses comparing the risk between finasteride and alpha-blocker users, a stratified unconditional model was used due to low number of matched case–control pairs available in these two groups.

To estimate the time relation between medication use and prostate cancer diagnosis, the time period preceding the diagnosis was extended 12 months at a time running backwards from the reference month. Only the case–control pairs with the information available for the entire time period (1–8 years prior to the reference month) were included in these analyses.

Regularity of medication use was assessed based on two variables: the number of years during which each person had reimbursements and the number of DDDs reimbursed each year. Regular users had been reimbursed at least 365 DDDs during each year of the analysed time period. Irregular users' reimbursements covered each year, but were less than 365 DDD/year. Short-term users had at least one year without reimbursements during the analysed time period. Also analyses were carried out, where persons who had been reimbursed 350 DDD or more per year were considered regular users. However, the results were not changed.

For analyses on prostate cancer stage a four year cutoff point was used for duration of medication use, since the number of men with longer duration would not have allowed

stratified analyses. Additionally, the prostate cancer risk difference between treatment arms in the PCPT was evident already after four years of treatment.[5]

3. Results

3.1. Prevalence of BPH pharmacotherapy

A total of 7715 men (15.6% of the overall study population) had used BPH pharmacotherapy. Of them 1578 had used both types of formulations. Finasteride use was more frequent among cases than controls (Table 1). The difference was greatest among users of smallest quantities of finasteride and diminished with increasing total cumulative quantity.

A similar pattern in prevalence was observed in tamsulosin users (Table 1). In alfuzosin users the prevalence differed only when the total cumulative quantity was 365 DDD or less.

3.2. Finasteride and prostate cancer risk

Overall, finasteride use was associated with an increased prostate cancer risk (OR = 1.41; 95% CI 1.31–1.51). The risk was increased among short-term users regardless of length of the analysed time period (Table 2a). Among the irregular users the risk was elevated only when the analysed time period was the year preceding the reference month. Prostate cancer risk among regular finasteride users did not differ from that of the non-users.

Finasteride use did not affect prostate cancer risk if usage had been discontinued prior to the reference month (data not shown). The effect of finasteride did not significantly vary between age groups (data not shown).

Finasteride use for less than four years was associated with an increased risk for localised prostate cancer (Table 3). However, the risk of advanced cancer was not affected by finasteride usage.

Table 1 – Prevalence of BPH pharmacotherapy among Finnish prostate cancer cases diagnosed in 1995–2002 and their matched controls

Pattern of use[a]	Finasteride		Tamsulosin		Alfuzosin	
	Cases	Controls	Cases	Controls	Cases	Controls
Ever-users	2534	1761	4244	2108	410	186
Never-users	22189	22962	20479	22615	24313	24537
Cumulative dose (DDD)[b]						
0	89.4	92.9	80.6	90.7	97.9	99.0
1–365	6.5	3.5	15.8	6.6	1.9	0.8
366–730	1.8	1.5	2.0	1.3	0.1	0.1
731–1095	0.95	0.8	0.9	0.6	0.05	0.05
1096–1460	0.5	0.5	0.4	0.4	0.01	0.01
1461–1825	0.35	0.4	0.2	0.2	–	–
1826–2190	0.2	0.3	0.1	0.0	–	–
⩾2191	0.1	0.1	0.01	0.005	–	–

Distribution of users according to the total cumulative quantity of medication reimbursements.
a Total number of men in each category.
b Total cumulative quantity of DDDs reimbursed during the study period. Reported as percentages of men in each category.

Table 2a – Odds ratios of prostate cancer among finasteride users in the study population of all Finnish prostate cancer cases diagnosed in 1995–2002 and their matched controls

Period of exposure[a]	Regular use[b]			Irregular use[c]			Short-term use[d]		
	No. of discordant pairs[e]	OR	95% CI	No. of discordant pairs	OR	95% CI	No. of discordant pairs	OR	95% CI
1 year	345/332	1.04	0.90–1.21	394/277	1.42	1.21–1.65	415/256	1.62	1.39–1.89
2 years	111/113	0.98	0.76–1.28	312/286	1.09	0.93–1.28	1102/755	1.46	1.33–1.61
3 years	49/36	1.36	0.88–2.09	235/240	0.98	0.82–1.18	1181/772	1.53	1.40–1.68
4 years	56/72	0.78	0.55–1.10	114/113	1.00	0.77–1.30	1132/745	1.52	1.39–1.67
5 years or more	25/26	0.96	0.56–1.66	98/100	0.98	0.74–1.29	1067/721	1.48	1.34–1.62

a Length of the time period included in the analysis. Measured as consecutive years running backwards from the reference month.
b Each person categorised as regular user has been reimbursed at least 365 DDD of finasteride during each year of the exposure period.
c Irregular users have been reimbursed less than 365 DDD of finasteride during each year of the exposure period.
d Finasteride users with one or more years without reimbursements during the exposure period are categorised as short-term users.
e Number of case–control pairs discordant to finasteride use. Case: user – control: non-user/Case: non-user – control: user.

Table 2b – Odds ratios of prostate cancer among alpha-blocker users in the study population of all Finnish prostate cancer cases diagnosed in 1995–2002 and their matched controls

Period of exposure[a]	Regular use[b]			Irregular use[c]			Short-term use[d]		
	No. of discordant pairs[e]	OR	95% CI	No. of discordant pairs	OR	95% CI	No. of discordant pairs	OR	95% CI
1 year	96/49	1.95	1.34–2.83	996/524	1.90	1.70–2.13	595/242	2.46	2.10–2.88
2 years	199/141	1.41	1.11–1.77	290/180	1.61	1.32–1.96	1227/529	2.32	2.09–2.57
3 years	109/78	1.40	1.01–1.94	174/117	1.49	1.15–1.92	1183/616	1.92	1.74–2.12
4 years	54/34	1.60	0.97–2.64	116/73	1.59	1.14–2.20	1052/581	1.81	1.63–2.00
5 years or more	15/5	2.79	1.00–7.74	53/27	1.96	1.22–3.14	1704/1058	1.61	1.47–1.77

a Length of the time period included in the analysis. Measured as consecutive years running backwards from the reference month.
b Each person categorised as regular user has been reimbursed at least 365 DDD during each year of the exposure period.
c Irregular users have been reimbursed less than 365 DDD during each year of the exposure period.
d Users with one or more years without reimbursements during the exposure period are categorised as short-term users.
e Number of case–control pairs discordant to alpha-blocker use. Case: user – control: non-user/Case: non-user – control: user.

3.3. *Alpha-blockers and prostate cancer risk*

Alpha-blocker use was associated with substantially increased prostate cancer risk (OR = 1.79; 1.67–1.91). The risk remained elevated regardless of regularity of use or length of the analysed time period (Table 2b).

Alpha-blocker use did not affect prostate cancer risk among men who had discontinued medication prior to the reference month (data not shown). The risk increase tended to be stronger among the youngest age group (60 years or younger) compared to the oldest age group (77 years or older) (OR = 2.78, 2.38–3.25 *versus* OR = 1.45, 1.23–1.71, respectively).

Only the risk of localised prostate cancer was affected among alpha-blocker users (Table 3). The risk was increased among regular users for less than four years and non-regular users for both duration categories.

3.4. *Prostate cancer risk among BPH medication users*

The risk among users of both drug categories was elevated compared with that among non-users (OR = 1.49; 95% CI 1.34–1.65).

However, when compared with the alpha-blocker users the overall prostate cancer risk in finasteride users was decreased (OR = 0.80; 95% CI 0.64–1.00). A significant decrease was observed among regular and irregular users (Table 4). The odds ratio tended to be less than one also among the short-term users, but significant differences were not observed. There were no clear trends in risk associated with duration of finasteride use.

4. Discussion

Our results show an increased risk of prostate cancer in men using either group of BPH phrarmacotherapy. The risk increase is most likely caused by increased detection of latent prostate cancers due to differential diagnostics of BPH. However, the risk was lower among finasteride users compared with the alpha-blocker users. Our results emphasise that prostate cancer risk in symptomatic finasteride users is strongly affected by not only the biological effect of finasteride , but by the clinical practices and diagnostics in the management of LUTS and BPH as well.

Ours is the first study to examine prostate cancer risk among finasteride users in a population-based setting and compare it to that of alpha-blocker users.

Due to the comprehensive national health care registers of Finland, we were able to evaluate the effect of medication use on prostate cancer risk at the population level. Enrollment of

Table 3 – Prostate cancer stage in finasteride and alpha-blocker users in the study population of all Finnish prostate cancer cases diagnosed in 1995–2002 and their matched controls

Duration of medication use		Pattern of use	Localised cancer			Non-localised cancer		
			No. of discordant pairs[a]	OR	95% CI	No. of discordant pairs	OR	95% CI
Finasteride	<4 years	Regular	133/101	1.32	1.01–1.72	35/41	0.86	0.54–1.34
		Non-regular[b]	623/319	1.95	1.71–2.23	114/128	0.89	0.69–1.14
	⩾4 years	Regular	20/13	1.60	0.52–4.89	–	–	–
		Non-regular	428/360	1.19	0.92–1.53	47/76	0.62	0.37–1.04
Alpha-blockers	<4 years	Regular	119/77	1.55	1.16–2.06	28/26	1.08	0.63–1.84
		Non-regular	707/347	2.04	1.79-2.32	132/119	1.11	0.87–1.43
	⩾4 years	Regular	12/7	1.71	0.67–4.35	–	–	–
		Non-regular	447/178	2.51	2.11–2.99	63/84	0.75	0.54–1.05

a Number of case–control pairs discordant to medication use. Case: user – control: non-user/Case: non-user – control: user.
b Includes irregular and short-term medication users.

Table 4 – Prostate cancer risk among finasteride users compared with alpha-blocker users

Period of exposure[a]	Regular use[b]			Irregular use[c]			Short-term use[d]		
	No. of exposed cases	OR	95% CI	No. of exposed cases	OR	95% CI	No. of exposed cases	OR	95% CI
1 year	356	0.61	0.51–0.72	423	0.83	0.69–0.99	1042	1.06	0.89–1.26
2 years	114	0.65	0.49–0.85	323	0.72	0.60–0.85	1507	0.88	0.78–1.00
3 years	45	0.93	0.59–1.45	221	0.64	0.53–0.78	1041	0.98	0.87–1.11
4 years	52	0.57	0.39–0.82	102	0.71	0.54–0.95	1041	0.99	0.87–1.13
5 years or more	24	0.72	0.41–1.26	96	0.76	0.57–1.02	1135	1.04	0.92–1.19

Study population of all Finnish prostate cancer cases diagnosed in 1995–2002 and their matched controls.
a Length of the time period included in the analysis. Measured as consecutive years running backwards from the reference month.
b Each person categorised as regular user has been reimbursed at least 365 DDD during each year of the exposure period.
c Irregular users have been reimbursed less than 365 DDD during each year of the exposure period.
d Medication users with one or more years without reimbursements during the exposure period are categorised as short-term users.

all the prostate cancer cases in Finland during 1995–2002 and their controls led to a large study population with minimal influence of chance or selection bias.

Finasteride and alpha-blocker use for BPH was fully documented by the prescription database since they were available only through physician's prescription during the study period. Thus we were able to estimate detailed exposure information from the prescription database in an unbiased fashion and with extensive coverage. In 2002, a total of 4.69 DDD/1000 persons/day of finasteride and 6.41 DDD/1000/day of alpha-blockers were purchased in Finland for BPH treatment.[10] In our data, the men had been reimbursed 4.42 DDD/1000/day of finasteride and 6.15 DDD/1000/day of alpha-blockers. Hence the validity and representativeness of our results are high.

An 89% prevalence of LUTS has been estimated among Finnish men 50 years of age or older, with 24% having severe symptoms.[11] The 15.6% overall prevalence of BPH pharmacotherapy observed in our study population suggests that only a small portion of these men seek medical help, presumably those with most severe LUTS. Severe symptoms are more often treated with quicker acting alpha-blockers, explaining their observed greater prevalence of use.

A portion of BPH pharmacotherapy was used to treat symptoms of prostate cancer, as shown by the substantially increased risk among men whose only medication purchases had occurred within six months of the reference date (OR = 3.19; 95% CI 2.60–3.90 and OR = 6.02; 95% CI 5.25–6.89 for finasteride and alpha-blockers, respectively). However, exclusion from the analyses controlled the bias caused by these men.

Finasteride was licensed in Finland in 1992, though information on medication purchases was available since 1995. As a result some of the users may have longer history of use than appeared in our study and some previous users may appear falsely as non-users, thus diluting the observed effect of finasteride. However, the distortion is likely to be small as the estimates based on cases diagnosed during the early period (with less complete coverage of recent use) gave similar results than analyses based on later cases.

The observed difference in prostate cancer risk between alpha-blocker and finasteride users could have been slightly diluted by the fact that alpha-blockers were licensed in Finland later than finasteride, as 681 previous finasteride users switched to alpha-blockers in 1996 and 1997. However, the exclusion of these men from the analyses changed the results only marginally.

Finasteride used in the treatment of androgen-induced alopecia is not recorded by the prescription database, possibly leading to underestimation of the treatment effect. However, finasteride is not commonly used for this indication; in 2002 the consumption in Finland was 0.41 DDD/1000 persons/day.[10]

Age and ethnicity are well known risk factors for prostate cancer.[12] We controlled the confounding effect of age by individual matching of cases and controls. Confounding by ethnicity is minimal due to the homogeneity of the Finnish population with over 98% being Caucasian.[8] Inherited predisposition for prostate cancer is a strong risk factor, estimated to account for 5–10% of all Finnish prostate cancers.[13] Thus if the medical treatment for BPH is assumed to be 1.1–1.5 times more common among men with a family history of prostate cancer, this confounding factor could have caused 0.5–5% of excess risk observed in our study. However, hereditary prostate cancer has not been found to affect the risk of BPH.[14]

Other possible risk factors such as body mass index, dietary fat, vitamin D and vitamin E[12] were not accounted for in the selection of study population, since data were not available. Thus, they can potentially cause a confounding factor in our results, but their role as risk factors has not been well established.

We found the odds ratio of prostate cancer to be increased similarly in users of both drug groups of BPH pharmacotherapy, even though the drugs act through very distinct mechanisms. Since BPH is not associated with prostate cancer risk,[3] non-causal explanations must be considered. Differential diagnostics in men with LUTS includes measuring of serum PSA and performing a digital rectal examination, with prostate biopsy for the exclusion of prostate cancer in men with suspicious findings.

Prostate cancer is a disease of slow growth rate and long latency. Autopsy studies have reported a 34% prevalence of latent prostate cancer for men older than 50 years.[15,16] A 42% average prevalence of incidental prostate cancer has been reported in men undergoing cystoprostatectomy for

bladder cancer.[17,18] The autopsy and cystoprostatectomy prevalences have been estimated to exceed the lifetime risk of death from prostate cancer by at least 10-fold.[19] The present diagnostic techniques have been shown to be capable of diagnosing a large proportion of these latent cancers, leading to overdetection.[20]

Routine prostate cancer screening with PSA-test in asymptomatic men was not recommended in Finland during the study period. The exception was men participating in the Finnish Prostate Cancer screening trial, initiated in 1996.[21] The overall prevalence of opportunistic screening has been reported to be 10% in Finnish population during 1996–1999.[22]. Since a majority of the population was unscreened, the prevalence of undiagnosed latent malignancies of prostate was presumably high leading to increased detection rate in men whose PSA was systematically measured due to LUTS, causing detection bias. The observed risk being increased only for localised prostate cancer supports this assumption.

Prostate cancer risk was increased among alpha-blocker users regardless of regularity of use. However, in finasteride users the risk increase was observed only among short-term users in all categories of exposure time and irregular users when the analysed time period was the year preceding the reference month. Among regular finasteride users the risk was not elevated at any time period. It is likely that the risk is elevated also among regular users at the initiation of the therapy, but the subsequent decrease in risk among long-term regular users diminishes the overall increase observed.

BPH is a progressive disease,[23] and discontinuation of medication use eventually leads to recurrence of LUTS unless surgery is commenced. Thus irregular and short-term users likely had more frequent contacts with a physician due to LUTS than the regular users, leading to more frequent PSA measurements and an increased likelihood of prostate cancer diagnosis.

The biological effect of finasteride use could more properly be evaluated when prostate cancer risk among finasteride users was compared to that of alpha-blocker users since both groups undergo differential diagnostics of BPH, increasing comparability. The risk did not differ between short-term medication users with one or more years without purchases during the analysed time periods. However, in men with purchases each year, i.e. regular and irregular users, the risk decrease was significant. It is plausible that only consistent exposure to finasteride on a yearly basis is sufficient for a risk decreasing effect. Among regular and irregular finasteride users for five years or longer the odds ratios were below one, but the difference was not significant due to small number of men in these categories.

The risk difference between finasteride and alpha-blocker users could also be affected by the PSA lowering effect of finasteride.[24] Due to lower average PSA-level there could have been fewer indications for prostate biopsies among finasteride users. However, the PSA lowering effect has been reported to be stronger when PSA is elevated due to BPH than when elevated due to cancer.[25] Thus the prostate cancer detection sensitivity of PSA has been reported to improve during finasteride therapy, presumably counterbalancing the detection bias caused by lower PSA-levels.

We report an increased prostate cancer risk among BPH pharmacotherapy users compared to non-users in previously mainly unscreened population. The increase is due to enhanced detection of latent prostate cancers associated with clinical practice of BPH diagnosis and management. However, the risk is decreased among finasteride users when compared with alpha-blocker users, who are subject to similar diagnostics. The results suggest a chemopreventive effect of finasteride on prostate cancer at the population level in men treated for BPH. Nevertheless, possible detection bias caused by the PSA lowering effect of finasteride must be considered when interpreting the results.

Conflict of interest statement

None.

Acknowledgements

The study was supported in part by grants from Academy of Finland (Grant number 205 862), Sigrid Juselius Foundation and the Finnish Cancer Society.

Teemu Murtola's work was supported by grants from the Pirkanmaa Regional Fund of the Finnish Cultural Foundation, the Medical Research Fund of Tampere University Hospital and by non-restricted grants from Schering foundation, Astellas, Lilly Foundation and the Medical Research Fund of AstraZeneca.

We thank Dr. Roger S Rittmaster, MD, for his helpful comments on the manuscript.

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British Journal of Cancer (2009), 1 – 6

www.bjcancer.com

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Prostate cancer incidence among finasteride and alpha-blocker users in the Finnish Prostate Cancer Screening Trial

TJ Murtola[*,1,2], TLJ Tammela[3,4], L Määttänen[5], M Ala-opas[6], UH Stenman[7] and A Auvinen[1]

[1]School of Public Health, University of Tampere, 33101 Tampere, Finland; [2]Department of Surgery, Central Finland Central Hospital, 40620 Jyväskylä, Finland; [3]Department of Urology, Tampere University Hospital, 33521 Tampere, Finland; [4]Medical School, University of Tampere, 33101 Tampere, Finland; [5]The Finnish Cancer Registry, 00130 Helsinki, Finland; [6]Department of Urology, Helsinki University Hospital, 00029 Helsinki, Finland; [7]Department of Clinical Chemistry, University of Helsinki, 00014 Helsinki, Finland

BACKGROUND: The Prostate Cancer Prevention Trial has shown a protective effect of finasteride on prostate cancer in low-risk men. It is uncertain whether similar results can be expected when finasteride is used to treat benign prostatic hyperplasia.

METHODS: We performed an observational cohort study within the Finnish Prostate Cancer Screening Trial. Using a comprehensive prescription database on medication reimbursements during 1995–2004 of men using finasteride or alpha-blockers for benign prostatic hyperplasia, we evaluated prostate cancer incidence among 23 320 men screened during 1996–2004.

RESULTS: Compared to medication non-users, overall prostate cancer incidence was not significantly affected in finasteride users (hazard ratio 0.87; 95% CI 0.63–1.19). Incidence of Gleason 2–6 tumours, however, was decreased among finasteride users (HR 0.59; 95% CI 0.38–0.91), whereas incidence of Gleason 7–10 tumours was unchanged (HR 1.33; 95% CI 0.77–2.30). The protective effect concerned mainly screen-detected tumours. Overall prostate cancer risk was not significantly reduced among alpha-blocker users relative to non-users, but decreased incidence of high-grade tumours was observed (0.55; 95% CI 0.31–0.96).

CONCLUSIONS: The detection of low-grade, early-stage tumours is decreased among men who use finasteride for symptomatic BPH. The protective effect of finasteride can also be expected in men with benign prostatic hyperplasia.

British Journal of Cancer advance online publication, 4 August 2009; doi:10.1038/sj.bjc.6605188 www.bjcancer.com

Keywords: alpha-blockers; benign prostatic hyperplasia; finasteride; epidemiology; prostatic neoplasms; screening

Finasteride, a 5-alpha reductase enzyme-inhibitor that inhibits conversion of testosterone into active androgen metabolite dihydrotestosterone, thereby lowering prostate volume and serum prostate-specific antigen (PSA) level (Marberger, 2006), is used for treatment of benign prostatic hyperplasia (BPH) and male pattern baldness. The Prostate Cancer Prevention Trial (PCPT) has reported a 25% decrease in prostate cancer incidence in men receiving finasteride compared with placebo (Thompson *et al*, 2003). The trial participants had baseline PSA 3.0 ng ml^{-1} or less and low symptom score of lower urinary tract symptoms (LUTS). The restrictive inclusion criteria limit the generalisability of the findings. It is not known whether the results are applicable to men using finasteride for symptomatic BPH.

α1-Adrenoceptor antagonists (alpha-blockers) are used in the medical management of symptoms of benign prostatic hyperplasia. Alpha-blockers lower smooth muscle tension in the prostate and urinary tract, thereby improving urinary flow and decreasing LUTS (Ishizuka *et al*, 2002). Some experimental studies have reported increased prostate cancer cell apoptosis after treatment with quinazoline-derived alpha-blockers, terazosin and doxazosin (Kyprianou and Benning, 2000; Benning and Kyprianou, 2002). One cohort study has reported a decreased incidence among alpha-blocker users (Harris *et al*, 2007).

We evaluated the effect of finasteride and alpha-blocker usage on prostate cancer incidence in a cohort of men participating in the screening arm of the Finnish Prostate Cancer Screening Trial during 1996–2004.

MATERIALS AND METHODS

The Finnish Prostate Cancer Screening Trial is a part of the European Randomized Study of Prostate Cancer Screening. The trial assesses whether screening can reduce prostate cancer mortality (Määttänen *et al*, 1999) The ethical committees of each participating hospital approved the study protocol. In 1996–1999, all men aged 55–67 years and residing in the metropolitan areas of Helsinki and Tampere (80 484 men) were identified from the population register of Finland and randomly assigned into either the screening arm (32 000 men) or the control arm (48 484 men) of the trial. The detailed protocol has been described previously (Määttänen *et al*, 1999). For exclusion of prevalent prostate cancer cases at randomisation, the cohort was linked to the comprehensive Finnish Cancer Registry (Teppo *et al*, 1994).

Men in the screening arm were recruited with mailed invitations to undergo a PSA screening test at 4-year intervals. After a written informed consent, a blood sample was drawn. All participants also filled in a questionnaire on prostate cancer family history and

*Correspondence: Dr TJ Murtola, School of Public Health, University of Tampere, Medisiinarinkatu 3, University of Tampere, FIN-33014 Tampere, Finland; E-mail: teemu.murtola@uta.fi
Received 8 April 2009; revised 16 June 2009; accepted 22 June 2009

previous prostatic diseases. Participants of the third screening round were asked to provide information on height and weight for calculation of the body mass index (BMI). The population was linked annually to the Finnish Cancer Registry to obtain information on cases diagnosed between the screening rounds.

During 1996–2004 two screening rounds were completed. The third screening round was started in 2004. A total of 23 320 men (73%) had at least one PSA determination during the study period. A total of 1594 new cases were diagnosed in the screening arm. Of these, 1273 cases were screen detected, whereas 321 were interval cancers. TNM stage was available for 99.6% and Gleason grade in 97.7% of the tumours.

The prescription database of the Social Insurance Institution of Finland (SII) provided detailed information on finasteride and alpha-blocker usage during 1995–2004 for each study participant. SII provides reimbursements for the cost of medicines prescribed by a physician (with the exception of hospital inpatients) to each Finnish citizen as part of the national public health insurance (Martikainen and Rajaniemi, 2002). All reimbursements for purchased prescription drugs approved as reimbursable by the SII are recorded in the reimbursement database.

All drugs in clinical use for treatment of BPH in Finland are reimbursable and available only through a physician's prescription. During the study period, these included 5α-reductase inhibitor, finasteride, and alpha-blockers, tamsulosin (since 1996) and alfuzosin (since 1997). Finasteride prescribed for treatment of androgenic alopecia was not reimbursable and thus not recorded by the prescription database.

Amount of medication use was defined as daily doses in treatment of BPH: finasteride 5 mg, tamsulosin 0.4 mg and alfuzosin 10 mg per day. The cumulative number of daily doses during the study period was calculated for each person based on dosage, package size and number of packages bought each year. Cumulative amounts of tamsulosin and alfuzosin use were summed to obtain total usage of alpha-blockers.

Statistical analysis

Cox proportional hazards regression was used to estimate hazard ratios and their 95% confidence intervals (CIs) for prostate cancer by medication usage. Men who used neither finasteride nor alpha-blockers were used as the reference group in all analyses on risk.

Each man in the study population contributed person time from the date of the first screening test until date of diagnosis, emigration from the study area, death or end of study period (31 December 2004), whichever came first.

Time-dependent Cox regression model with adjustment for age (continuous time-dependent covariate; $P<0.001$ in the model), family history (father, brother or son diagnosed with prostate cancer; $P=0.916$), simultaneous use of the other group of BPH drugs ($P=0.07$ for finasteride or $P=0.847$ for alpha-blockers), number of PSA screens attended (continuous time-dependent covariate; $P<0.001$) and the calendar period of screening test (before or after year 2000; $P=0.209$) was used for analyses. Additional adjustment for BMI ($P=0.854$) and prostate volume (as measured by a urologist in a transrectal ultrasound examination; $P=0.047$) was used in subgroup analyses of men with this information available (3130 men attending the third screening round in 2004). Age was the single most influential covariate in the model.

Each man, who was not a medication user at randomisation, contributed person time in the analysis as a non-user until the first medication reimbursement. After a period of 6 months without reimbursements, the men were reclassified as medication non-users. Exposure status was allowed to change as often as necessary. If the man had simultaneously used both finasteride and alpha-blockers, he contributed person time (and potentially events) in both categories, that is, as a finasteride user and as an alpha-blocker user.

Amount (daily doses) and duration (in years) of medication use were analysed as time-dependent covariates. In analyses stratified by cumulative amount/duration of medication use, the users contributed person time in lower stratum until reaching the cut-point for upper stratum.

Trends in incidence by amount or duration of medication use were tested by adding these indicators into Cox regression model as continuous covariates.

The proportional hazards assumption was tested by adding the interaction term for finasteride or alpha-blocker use and person time to the model. The term was not statistically significant by the likelihood ratio test, confirming the assumption.

All analyses were performed using SPSS 15.0 statistical software.

RESULTS

Of the 23 320 men in the cohort, 1754 (7.5%) had used finasteride and 3848 (16.5%) had used either tamsulosin or alfuzosin. Prevalence of medication use increased with age at start of follow-up. Family history was comparable in the two groups (Table 1). The age-standardised median PSA was higher among BPH medication users compared with non-users (Table 1). Both finasteride and alpha-blocker use was associated with a decreased proportion of free PSA, the effect again being stronger in finasteride users. Among the men attending the third screening round, average prostate volumes and the median BMI were higher among medication users than non-users (Table 1).

Overall, finasteride use was not significantly associated with risk (HR 0.87, 95% CI 0.63–1.19; Table 2). However, the risk of low-grade (Gleason 2–6) tumours was decreased among finasteride users (HR 0.59; 95% CI 0.38–0.91) and further diminished in relation to the cumulative amount and duration of medication usage (P for trend 0.009 and 0.019, respectively; Table 2). Generally, incidence of high-grade, organ-confined or advanced stage tumours was not affected by finasteride usage (Table 2). However, among long-term finasteride users, increased incidence of high-grade tumours was observed (HR 2.49; 95% CI 1.27–4.89 for men who had used at least 1087 doses of finasteride). Overall risk did not differ between alpha-blocker users and non-users. However, lowered incidence of high-grade tumours was observed (HR 0.55; 95% CI 0.31–0.96), with a decreasing trend in risk with cumulative duration of alpha-blocker use (Table 3).

In an analysis stratified by serum PSA concentration, prostate cancer risk was decreased in finasteride and alpha-blocker users with PSA $\geqslant 4$ ng ml^{-1} (the cut-off value for screen-positive test, i.e., indication for prostate biopsy; Table 4). The point estimate was lower among finasteride users, but the confidence intervals overlap. The decreased risk was driven by the lower incidence of screen-detected tumours among these men. Risk of interval cancers, that is, tumours diagnosed between the screening rounds, was not significantly affected in finasteride users. However, among alpha-blocker users with PSA below 4 ng ml^{-1}, the risk of interval cancer was increased (HR 2.46; 95% CI 1.21–5.00).

DISCUSSION

In our cohort study within the screening arm of the Finnish Prostate Cancer Screening Trial we found a reduced risk of low-grade prostate cancer among finasteride users, among whom an increased risk of high-grade cancers was seen among long-term users. These findings confirm previous findings on this topic, but provide wider generalisability than the Prostate Cancer Prevention Trial, and improved internal validity compared with non-randomised studies due to comprehensive and systematic case ascertainment. Alpha-blocker usage generally did not affect incidence, but some evidence for a decreased risk of high-grade tumours was observed.

Table 1 Characteristics of users and non-users of finasteride and alpha-blockers in the Finnish Prostate Cancer Screening Trial

	Finasteride usage		**Alpha-blocker usage[a]**	
	Yes	**No**	**Yes**	**No**
Characteristics:				
Participants (*n*)	1754	21 566	3848	19 472
Age at randomisation (years)	No. of men (% of total)		No. of men (% of total)	
55	261 (3.5)	7295 (96.5)	790 (10.5)	6766 (89.5)
59	427 (6.9)	5804 (93.1)	998 (16.0)	5233 (84.0)
63	476 (9.2)	4674 (90.8)	1025 (19.9)	4125 (80.1)
67	590 (13.5)	3793 (86.5)	1035 (23.6)	3348 (76.4)
Prevalence of family history of prostate cancer (%)[b]	0.3	0.3	0.4	0.3
Mean no. of screening rounds attended	2.0	1.9	2.0	1.9
Geometric mean of PSA (95% CI)[c]	1.58 (0.24–11.05)	1.22 (0.27–7.72)	1.60 (0.28–9.46)	1.22 (0.26–7.67)
	$P<0.001$[d]		$P<0.001$	
Cumulative amount of medication use[e]	Non-users	1.22 (0.27–7.72)	Non-users	1.22 (0.26–7.67)
1st quartile	1.95 (0.31–12.94)	—	1.54 (0.26–8.64)	—
2nd quartile	1.72 (0.19–9.56)	—	1.66 (0.19–9.07)	—
3rd quartile	1.49 (0.23–8.94)	—	1.58 (0.29–9.58)	—
4th quartile	1.31 (0.17–1.25)	—	1.80 (0.36–11.66)	—
Geometric mean of % free PSA (95% CI)[c]	22.37 (9.49–48.36)	26.48 (10.40–52.80)	25.26 (10.56–50.96)	26.43 (10.30–52.80)
	$P<0.001$		$P<0.001$	
Cumulative amount of medication use[e]	Non-users	1.22 (0.27–7.72)	Non-users	1.22 (0.26–7.67)
1st quartile	22.87 (10.96–45.40)	—	25.26 (10.50–50.99)	—
2nd quartile	22.67 (9.13–47.26)	—	24.66 (9.90–47.47)	—
3rd quartile	21.22 (9.35–48.59)	—	25.36 (10.85–54.85)	—
4th quartile	21.12 (7.75–43.57)	—	25.76 (10.76–52.53)	—
Men attending the third screening round (N = 3130)				
Median body mass index	26.7	26.2	26.6	26.2
	$P=0.032$		$P=0.035$	
Median prostate volume (ml)[f]	49	36	42	36
	$P<0.001$		$P<0.001$	

[a]Includes users of tamsulosin and alfuzosin. [b]Father, brother or son diagnosed with prostate cancer prior to initiation of the Finnish Prostate Cancer Screening Trial. [c]Age-standardised values. [d]*P* estimated using Man–Whitney *U*-test. [e]Quartiles for finasteride users : 28–180 doses (1st quartile), 181–398 doses (2nd quartile), 399–1086 doses (3rd quartile), 1087 doses or more (4th quartile); for alpha-blockers: 10–60 doses (1st quartile), 61–180 doses (2nd quartile), 181–629 doses (3rd quartile) and 630 doses or more (4th quartile). [f]As measured by a urologist on a transrectal ultrasound examination.

Availability of comprehensive and detailed information on medication purchases from the SII prescription database allowed us to evaluate BPH medication usage accurately and in an unbiased fashion. Finasteride, tamsulosin and alfuzosin were available in Finland only through the physician's prescription during the study period, so their purchase is comprehensively documented by the prescription database.

Our finding of a decreased risk of low-grade tumours among finasteride users is similar with the results from the Prostate Cancer Prevention Trial (Thompson *et al*, 2003). However, a major limitation of our study in comparison to PCPT is that this is a non-experimental study without any intervention related to BPH medication, whereas PCPT was a randomised clinical trial. Due to lack of random allocation, our results are, therefore, more prone to systematic differences between men with or without BPH. In our study, finasteride was prescribed for treatment of symptomatic BPH, whereas men eligible for PCPT were free of LUTS and had PSA of 3 ng ml^{-1} or less (Thompson *et al*, 2003). Therefore, our study population was more representative of the general population with BPH in terms of prostate volume and PSA.

The PCPT study protocol included offering an end-of-study prostate biopsy for all willing participants regardless of symptoms or PSA level, resulting in high prostate tumour incidence with obvious potential for overdiagnosis of indolent tumours but also reducing possibility of detection bias (Thompson *et al*, 2003). In our study, all men were screened and only screen-positive men (PSA 4 ng ml^{-1} or higher or PSA between 3 and 4 ng ml^{-1} and proportion of free PSA below 16%) underwent biopsy. Thus, our study shows that the protective effect also applies to men using finasteride for treatment of BPH and attending standard urological care, a conclusion supported by a previous case–control study (Irani *et al*, 2002). Unlike PCPT, we did not observe a significant decrease in overall risk among finasteride users, although the relative risk reduction in our study (22%) was close to that reported in the PCPT (25%). However, among the biopsied (screen-positive) men, the overall risk decrease was also significant in our study. It should be noted that the average duration and cumulative amount of finasteride usage was lower in our study than in the PCPT.

In this study, finasteride users had symptomatic BPH, and confounding by indication could affect the results, if BPH affects the risk of prostate cancer or additional testing in the clinical setting would affect prostate cancer detection. In this case, a positive association between BPH and prostate cancer and further PSA tests would be expected to increase detection. In our study, the contrary was observed, so BPH as indication for finasteride use cannot account for our findings. Unlike the PCPT trial (Thompson *et al*, 2003), we did not observe overall risk increase for high-grade prostate tumours among finasteride users. However, the risk was increased among long-term users, although no dose dependence between cumulative dose or duration of finasteride use and risk of high-grade cancer was observed. Later analyses of the PCPT results

Table 2 Hazard ratio for prostate cancer by amount and duration of use of finasteride and by prostate cancer stage and grade, Finnish Prostate Cancer Screening Trial

	Overall		Gleason ⩽6		Gleason 7–10		Organ-confined tumours[a]		Advanced tumours[b]	
Quantity/ duration of medication use	**No. of cases**	**HR (95% CI)[c]**	**No. of cases**	**HR (95% CI)**	**No. of cases**	**HR (95% CI)**	**No. of cases**	**HR (95% CI)**	**No. of cases**	**HR (95% CI)**
Finasteride										
Non-users	1507	Reference	1139	Reference	338	Reference	1364	Reference	143	Reference
All users	87	0.87 (0.63–1.19)	55	0.59 (0.38–0.91)	26	1.33 (0.77–2.30)	81	0.89 (0.65–1.24)	6	0.55 (0.14–2.24)
Cumulative quantity of finasteride use (daily doses)[d]										
28–180	34	1.34 (0.74–2.42)	24	0.80 (0.33–1.92)	6	1.17 (0.29–4.74)	32	1.32 (0.70–2.46)	2	1.48 (0.21–10.68)
181–398	21	0.91 (0.50–1.65)	14	0.76 (0.36–1.60)	5	0.79 (0.20–3.20)	19	1.00 (0.55–1.81)	2	—
399–1086	17	0.57 (0.27–1.19)	13	0.64 (0.29–1.43)	4	0.37 (0.05–2.68)	17	0.61 (0.29–1.28)	0	—
⩾1087	15	0.82 (0.47–1.46)	4	0.28 (0.09–0.87)	11	2.49 (1.27–4.89)	13	0.81 (0.45–1.48)	2	0.96 (0.13–6.94)
P_{trend}[e]		0.204		0.009		0.114		0.275		0.415
Years of finasteride use[d]										
1	41	0.89 (0.5–1.48)	30	0.62 (0.31–1.24)	7	0.57 (0.14–2.32)	39	0.91 (0.53–1.54)	2	0.66 (0.09–4.71)
2	19	0.96 (0.50–1.85)	13	0.84 (0.38–1.88)	5	1.02 (0.25–4.13)	19	1.03 (0.53–1.99)	0	—
3–4	11	0.72 (0.39–1.35)	7	0.48 (0.20–1.16)	4	1.60 (0.66–3.91)	10	0.70 (0.36–1.34)	2	1.10 (0.15–7.94)
>4	16	1.00 (0.47–2.11)	5	0.40 (0.10–1.61)	10	2.61 (1.06–6.45)	13	1.07 (0.51–2.28)	2	—
P_{trend}		0.411		0.019		0.057		0.524		0.429

[a]Men with $T_1N_{0/X}M_{0/X}$ and $T_2N_{0/X}M_{0/X}$ tumours combined. [b]Men with stage $T_3N_{0/X}M_{0/X}$, $T_4N_{0/X}M_{0/X}$, $T_{1-4}N1M0$ or $T_{1-4}N_{0-1}M1$ tumours combined. [c]From Cox proportional hazard regression adjusted for age, family history of prostate cancer, use of alpha-blockers, number of PSA screens and time period of screening (before or after year 2000). [d]Stratification in quartiles of cumulative quantity/duration of finasteride use. [e]Estimated by including cumulative dose (DDDs) or duration (years) of medication use into Cox regression model as a continuous covariate. All statistical trends are inverse, i.e., indicating a decreased risk with larger amount of medication use.

Table 3 Hazard ratio for prostate cancer by amount and duration of use of alpha-blockers and by prostate cancer stage and grade, Finnish Prostate Cancer Screening Trial

	Overall		Gleason ⩽6		Gleason 7–10		Organ-confined tumours[a]		Advanced tumours[b]	
Quantity/ duration of medication use	**No. of cases**	**HR (95% CI)[c]**	**No. of cases**	**HR (95% CI)**	**No. of cases**	**HR (95% CI)**	**No. of cases**	**HR (95% CI)**	**No. of cases**	**HR (95% CI)**
Alpha-blockers										
Non-users	1399	Reference	1041	Reference	330	Reference	1262	Reference	137	Reference
All users	195	1.05 (0.85–1.31)	153	1.20 (0.94–1.52)	34	0.55 (0.31–0.96)	183	1.09 (0.87–1.36)	12	0.70 (0.28–1.73)
Cumulative quantity of alpha-blockers use (daily doses)[d]										
10–60	77	1.25 (0.83–1.87)	62	1.65 (1.09–2.49)	12	0.21 (0.03–1.52)	70	1.27 (0.83–1.93)	7	1.17 (0.29–4.72)
61–180	46	1.00 (0.64–1.56)	35	0.84 (0.48–1.49)	8	0.95 (0.39–2.30)	44	0.99 (0.62–1.58)	2	1.14 (0.28–4.64)
181–629	39	1.11 (0.75–1.64)	30	1.21 (0.77–1.88)	8	0.64 (0.24–1.72)	37	1.16 (0.78–1.73)	2	0.54 (0.08–3.86)
⩾630	33	0.89 (0.59–1.36)	26	1.12 (0.72–1.75)	6	0.40 (0.13–1.25)	32	0.96 (0.64–1.46)	1	—
P_{trend}[e]		0.975		0.345		0.053		0.700		0.230
Years of alpha-blockers use[d]										
1	111	1.00 (0.73–1.38)	86	1.08 (0.75–1.55)	19	0.60 (0.27–1.35)	102	1.00 (0.72–1.39)	9	1.10 (0.41–2.99)
2	43	1.46 (1.00–2.15)	36	1.67 (1.09–2.56)	5	0.60 (0.19–1.89)	42	1.53 (1.03–2.26)	2	0.70 (0.10–5.01)
3–4	23	0.87 (0.55–1.37)	15	1.04 (0.63–1.70)	8	0.48 (0.15–1.52)	21	0.93 (0.59–1.47)	1	—
>4	18	0.88 (0.42–1.86)	16	1.15 (0.51–2.60)	2	0.38 (0.05–2.73)	18	0.96 (0.45–2.03)	0	—
P_{trend}		0.858		0.186		0.044		0.580		0.208

[a]Men with $T_1N_{0/X}M_{0/X}$ and $T_2N_{0/X}M_{0/X}$ tumours combined. [b]Men with stage $T_3N_{0/X}M_{0/X}$, $T_4N_{0/X}M_{0/X}$, $T_{1-4}N1M0$ or $T_{1-4}N_{0-1}M1$ tumours combined. [c]From Cox proportional hazard regression adjusted for age, family history of prostate cancer, use of alpha-blockers, number of PSA screens and time period of screening (before or after year 2000). [d]Stratification in quartiles of cumulative quantity/duration of alpha-blocker use. [e]Estimated by including cumulative dose (DDDs) or duration (years) of medication use into Cox regression model as a continuous covariate. All statistical trends are inverse, i.e., indicating a decreased risk with larger amount of medication use.

have shown that the observed higher proportion of high-grade cancers in finasteride-treated men is due to detection bias caused by decreased prostate volume, increased sensitivity of PSA to detect prostate cancer and altered tumour grading in finasteride users (Thompson *et al*, 2006; Lucia *et al*, 2007; Pinsky *et al*, 2008). This effect could also have caused the slightly increased incidence of high-grade tumours in our study.

Use of alpha-blockers tamsulosin and alfuzosin had no effect on overall risk, but there was some indication of a reduced risk of high-grade tumours. Previously, quinazoline-derived alpha-

Table 4 Hazard ratio for screen-detected and interval prostate cancer among finasteride and alpha-blocker users, stratified by serum PSA level and serum PSA, Finnish Prostate Cancer Screening Trial

	Overall		Screen-detected cancer		Interval cancer	
Quantity/duration of medication use	**No. of cases (users/non-users)**	**HR (95% CI)[a]**	**No. of cases**	**HR (95% CI)**	**No. of cases**	**HR (95% CI)**
Finasteride						
Serum PSA < 4	19/214	0.87 (0.43–1.76)	5/134	0.64 (0.23–1.79)	14/80	1.26 (0.48–3.31)
Serum PSA ⩾ 4	68/1293	0.62 (0.46–0.83)	46/1084	0.61 (0.44–0.84)	22/209	0.49 (0.23–1.06)
Alpha-blockers						
Serum PSA < 4	48/185	1.75 (1.08–2.82)	20/119	1.40 (0.73–2.68)	28/66	2.46 (1.21–5.00)
Serum PSA ⩾ 4	147/1214	0.72 (0.58–0.90)	97/1033	0.66 (0.51–0.84)	50/181	1.06 (0.64–1.73)

[a]From Cox proportional hazard regression adjusted for age, family history of prostate cancer, finasteride or alpha-blocker use, number of PSA screens and time period of screening (before or after year 2000).

blockers, terazosin and doxazosin, have been reported to inhibit prostate cancer cell growth and reduce incidence (Kyprianou and Benning, 2000; Benning and Kyprianou, 2002; Harris *et al*, 2007). Our results suggest that tamsulosin and alfuzosin could have similar effects but this aspect needs further research.

PCPT reported decreased serum PSA concentrations in finasteride users as compared with non-users (Etzioni *et al*, 2005). In our study, instead, serum PSA was increased in both finasteride and alpha-blocker users. Odds of having serum PSA exceeding the prostate biopsy cut-point ($4\,ng\,ml^{-1}$) was not decreased, but conversely increased in finasteride users (OR 2.37; 95% CI 2.13–2.64). This is due to the fact that in our study these medications were used for BPH treatment and men using them are not comparable with non-users. Therefore, these differences reflect the effect of BPH, and not medications. However, the PSA concentration tended to decrease with increasing cumulative amount of finasteride use, although the geometric mean PSA remained above non-users even among men in the highest quartile of finasteride use (1087 doses or more), though the confidence intervals were wide (Table 1). A similar association was observed with increasing duration of finasteride use (results not shown). For alpha-blockers, the geometric mean PSA was constantly higher among users than non-users with no decrease by duration or amount of use. The decrease in the proportion of free PSA was more pronounced in finasteride users and increased in relation with amount and duration of medication use, probably reflecting its effect on proportion of free PSA in long-term use, as such relation was not observed in alpha-blocker users.

Both finasteride and alpha-blocker use was associated with a decreased risk of screen-detected tumours among screen-positive men. As the risk decrease was observed among users of both drug groups, it may be due to the underlying disease, BPH. PSA elevation in men with LUTS (medication users) is often caused by prostate enlargement, whereas in men with no such symptoms (medication non-users) PSA increase is more commonly caused by a prostate cancer. Alpha-blocker users, whose PSA was below $4\,ng\,ml^{-1}$, were at increased risk between the screening rounds. This finding is consistent with our results from the previous case–control study (Murtola *et al*, 2007) and may reflect a similar mechanism. The Finnish guideline for clinical management of BPH recommends using alpha-blockers if a man has significant LUTS but no prostate enlargement (Finnish Medical Society Duodecim). Symptoms lead to clinical examinations and thus possibly to diagnosis despite the negative screening test. Additionally, men with significant LUTS may undergo transurethral resection of the prostate, in which incidental prostate cancer is a common finding (Merrill and Wiggins, 2002). This would lead to a bias of greater cancer detection in alpha-blocker users but not in finasteride users, as finasteride reduces the need for surgical management of BPH (Roehrborn *et al*, 2004).

We were able to control the confounding caused by age and familial predisposition (Crawford, 2003) in the analysis. Confounding by ethnicity (Crawford, 2003) is likely minimal due to the homogeneity of the Finnish population with over 98 percent of the population being of Finnish ancestry (Statistics Finland). Additionally, we had information on prostate volume and BMI for a proportion of our study population. Adjustment for these variables did not materially affect the results.

Our study has some limitations. The number of stage T_3, stage T_4, lymph node-positive or metastatic tumours was small in our study population of screened men, limiting our inference concerning the risk of advanced cancer. Similarly, we could not analyse mortality among finasteride users due to the small number of deaths.

We did not have information on less established prostate cancer risk factors such as dietary patterns or nutrient intake (such as selenium or vitamin E). Medication users may be more health conscious than non-users, and follow a healthier diet, which could have reduced the incidence in medication users.

Some exposure misclassification was likely caused by the fact that the cohort follow-up started in 1996 at the earliest, though finasteride was licensed in Finland in 1992. Additionally, SII does not reimburse finasteride prescribed for treatment of androgenic alopecia, and thus we did not have information on finasteride use for this indication. Therefore, some of the finasteride users likely have longer history of use than appeared in our study, a bias that may have weakened the observed association with prostate cancer risk.

The decreased risk among finasteride users in a cohort of men participating in the Finnish Prostate Cancer Screening Trial suggest that finasteride has a clinically significant preventive effect against low-grade tumours also when used for treatment of symptomatic benign prostatic hyperplasia. Future research should aim to evaluate whether finasteride can reduce mortality.

ACKNOWLEDGEMENTS

This study was supported by grants from Academy of Finland (205 862); Sigrid Juselius Foundation; the Finnish Cancer Society; Pirkanmaa Regional Fund of the Finnish Cultural Foundation; Medical Research Fund of Tampere University Hospital; the Finnish Cancer Organisations. The work of TJ Murtola has also been supported by Competitive Research Funding of Central Finland Central Hospital District, The Finnish Medical Society Duodecim and non-restricted grants from Astellas, Pfizer, Coloplast, research foundation of Orion Pharma and Abbott Pharma. We thank Dr Roger Rittmaster for his helpful comments during preparation of this article.

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American Journal of Epidemiology Advance Access published August 11, 2008

American Journal of Epidemiology

Doi:10.1093/aje/kwn190

Original Contribution

Antidiabetic Medication and Prostate Cancer Risk: A Population-based Case-Control Study

Teemu J. Murtola, Teuvo L. J. Tammela, Jorma Lahtela, and Anssi Auvinen

Received for publication January 30, 2008; accepted for publication May 30, 2008.

Decreased risk of prostate cancer in diabetic men has been reported. The authors evaluated the association between antidiabetic medication use and prostate cancer at the population level. All incident prostate cancer cases in Finland during 1995–2002 were identified from the Finnish Cancer Registry. Matched controls were provided by the Population Register Center (24,723 case-control pairs). Information on medication use was obtained from a comprehensive prescription database. Multivariable-adjusted odds ratios were computed by using conditional logistic regression. The authors found that prostate cancer risk was decreased for antidiabetic medication users (odds ratio = 0.87, 95% confidence interval: 0.82, 0.92). The decrease was observed for most drug groups. The odds ratio decreased in a dose-dependent fashion by quantity of use. Duration of antidiabetic treatment was inversely associated with overall prostate cancer risk and risk of advanced cancer. Similar risk reduction for users of different antidiabetic drugs suggests that diabetes, instead of the medication itself, is behind the association. This finding is unlikely to be secondary because of differential uptake of the prostate-specific antigen test or different prostate-specific antigen levels between medication users and nonusers; prevalence of testing in Finland is low. Dose and time dependency of the relation probably indicates that duration of diabetes is negatively associated with risk.

case-control studies; diabetes mellitus; drug therapy; Finland; incidence; population; prostatic neoplasms

Abbreviations: DDD, defined daily dose; PSA, prostate-specific antigen.

Type 2 (adult-type) diabetes is a condition currently affecting a substantial proportion of the Western population. Its development is often linked with obesity and resulting insensitivity to endogenous insulin, leading to impaired glucose balance. Type 1 (juvenile) diabetes is characterized by complete absence of endogenous insulin production and is not associated with obesity (1).

Medical therapy for adult-type diabetes is often started with oral drugs that improve glucose tolerance or increase insulin production, later possibly combined with injectable insulin treatment. Therapy for juvenile diabetes involves insulin when treatment begins.

Recent studies have reported a decreased prostate cancer risk for diabetic men, although the evidence is controversial (2). An inverse association of prostate cancer with metabolic syndrome has also been described, of which adult-type diabetes is an integral part (3, 4).

It is currently unclear whether use of antidiabetic medication affects the association between diabetes and prostate cancer. One study has reported that adjustment for antidiabetic medication did not affect the negative association between diabetes and prostate cancer (5); another study suggested that the risk reduction for diabetic men could be restricted to users of sulfonylureas and insulin only (6).

Biologic effects of oral antidiabetic drugs in prostate cancer cells are not well known, whereas the effect of insulin metabolism on prostate cancer growth has been studied more extensively (7). To our knowledge, only 1 study has reported growth reduction via cell cycle arrest in prostate cancer cells and xenografts after metformin treatment (8). However, all types of antidiabetic drugs affect insulin metabolism, providing a possible indirect mechanism for the effect on prostate cancer.

Correspondence to Dr. Teemu J. Murtola, School of Public Health, University of Tampere, Medisiinarinkatu 3, 33520 Tampere, Finland (e-mail: teemu.murtola@uta.fi).

In the current study, we evaluated prostate cancer risk for users of antidiabetic medication in a population-based setting.

MATERIALS AND METHODS

Study design

The Finnish Cancer Registry identified all newly diagnosed prostate cancer cases in Finland during 1995–2002, a total of 25,029 men. The registry collects data through mandatory notifications of all cancer diagnoses made by the Finnish health care units. Thus, it is a nationwide register covering more than 99% of all cancer patients in Finland (9). The register information includes the primary site of cancer, histology, date, and method of diagnosis, but the register does not record differentiation, such as Gleason score, or serum prostate-specific antigen (PSA) values.

Practically all cases were histologically confirmed (99.3%). In addition, cases whose diagnosis was based solely on clinical (0.4%), radiologic (0.3%), or specific laboratory (0.02%) findings were included. A total of 185 cases (0.7%) for whom method of diagnosis was unknown were excluded.

Information on the stage of prostate cancer was available for 55% of the cases ($n = 13{,}616$). Of these, 73% of the cancers were localized. Median age did not substantially differ between cases with or without information on stage (68 years vs. 69 years). The yearly number of new cases and the proportion of cases without information on stage of disease tended to rise during the study period—from 2,328 new cases (34% without stage information) in 1995 to 3,840 new cases (64%) in 2002.

Controls were individually matched to cases by age and residential area at the time (month and year) of the corresponding case's prostate cancer diagnosis. The Population Register Center of Finland randomly selected 24,723 male controls. A total of 963 men were considered twice in the analysis, first as a control and later as a case in another case-control pair after being subsequently diagnosed with prostate cancer later in the study period. Matched controls could not be found from the same municipality for 121 cases in the oldest age group, resulting in their exclusion. A total of 24,723 case-control pairs were included in the analyses.

Approval was received from the ethics committee of the Pirkanmaa health care district, Finland (Pirkanmaa University Hospital ethics committee license code ETL R03290). However, obtaining informed consent from the study population was not required because of the large size of the population and the fact that some of the subjects could not be contacted (because of death or emigration) by the time the study began.

Information on antidiabetic medication purchased by the study population and for which the cost was reimbursed by the Social Insurance Institution of Finland during 1995–2002 was obtained from the comprehensive nationwide prescription database of this institution. The prescription database (10) and the reimbursement system (11) have been described in detail previously. In short, the Social Insurance Institution of Finland reimburses the cost of medication for each physician-prescribed drug approved as reimbursable. Reimbursement is available for all Finnish residents. The amount and dose of the drug, as well as the date of each reimbursed purchase, are recorded in the prescription database. All antidiabetic drugs in clinical use in Finland during the study period were reimbursable and were available through a physician's prescription only, thus comprehensively documented by the registry.

The database provided detailed information on the quantity and time of medication purchases for each person in the study population for a maximum of 8 years. The drugs available for the entire study period were human insulin, metformin, guar gum, and the sulfonylureas glibenclamide and glipizide. Glimepiride was available beginning in 1997, rosiglitazone in 2002, insulin aspart in 2001, and insulin lispro in 1996.

Medication use was followed until the diagnosis date (cases) or index date (corresponding controls), ensuring identical exposure time within each case-control pair. The defined daily doses (DDDs) recommended by the World Health Organization (12) were used to quantify the amount of use of antidiabetic drugs. For each year during the study period, cumulative usage (in milligrams or international units for insulin) for each drug was calculated based on all purchases reimbursed that year. Yearly usage was divided by the quantity corresponding to 1 DDD. The total number of DDDs used for each drug during the study period was obtained as the sum of yearly DDDs. Total DDDs for all separate drugs in the sulfonylurea or insulin categories were combined to obtain the overall amount of sulfonylurea or insulin use during the study period. For the subjects with multiple prescriptions, for example, metformin initially and insulin subsequently, the cumulative quantity was calculated for each drug and the subject was considered both a metformin and an insulin user.

Statistical analysis

All medication reimbursements between January 1, 1995, and the month of diagnosis were included in the analyses, regardless of length of use. For controls, the month of diagnosis of their matched case was used as the reference month for medication use, serving as the end of the exposure period.

Conditional logistic regression was used to estimate the odds ratios and likelihood-based 95% confidence intervals for the odds ratios of prostate cancer related to medication use in Stata 8.2 software (Stata Corporation, College Station, Texas). All reported P values are 2 sided.

Age-adjusted and multivariable-adjusted odds ratios were calculated. The multivariable-adjusted model included age, place of residence (municipality), and use of drugs commonly combined with antidiabetic drugs (aspirin, cholesterol-lowering drugs, and antihypertensive drugs) as covariates.

To estimate dose dependence between antidiabetic medication use and prostate cancer risk, users were stratified into quartiles by amount of DDDs, and the risk was analyzed separately in each stratum. Similarly, time dependence was analyzed by stratifying users by the length of antidiabetic medication use. Nonusers were considered the reference group in all analyses.

RESULTS

Because of matching, the age distribution was identical between the cases and controls. Median age was 68 years (range, 20–96) for both groups.

The prevalence of oral antidiabetic drug use was 7.5% for cases and 8.4% for controls (Table 1). Similarly, the prevalences of insulin use were 2.5% and 3.0%, respectively. The most commonly used drugs were glibenclamide (5.1% of cases and 5.8% of controls), metformin (3.9% and 4.6%), and human insulin (2.4% and 3.0%). Neither oral antidiabetic drug use (7.6% vs. 8.8%) nor insulin use (2.2% vs. 2.8%) differed substantially between cases for whom information on stage was or was not available.

Overall, ever use of any antidiabetic drugs was associated with a decreased prostate cancer risk (Table 2). The risk decrease was observed for users of metformin, glibenclamide, glipizide, and human insulin. The risk was borderline decreased for users of glimepiride and guar gum (Table 2). Adjustment for multiple covariates compared with only age strengthened the association. We were not able to analyze the risk for users of rosiglitazone or insulin aspart because of the small number of users of these drugs (4 men for each drug).

The overall prostate cancer risk decreased with amount of oral drugs and insulin used (P for trend < 0.001 and P for trend $= 0.009$, respectively) (Table 3). The risk of advanced prostate cancer showed no dose dependence with oral drugs or insulin. However, the risk estimates for advanced cancer were below 1 for all strata, except for the men using the smallest amount ($\leq$228 DDD) of oral antidiabetic drugs (Table 3).

When use of antidiabetic medication was stratified by time since the first drug purchase during the study period, both the overall prostate cancer risk and the risk of advanced cancer showed inverse relations with duration of medical treatment (Table 4). Compared with that for men not using any antidiabetic medications, the overall risk was decreased by 34% for men with 7 years of antidiabetic drug treatment before the diagnosis/reference date, whereas the risk of advanced cancer was decreased by 39% in the same group (P for trend < 0.001 and P for trend $= 0.003$, respectively).

Table 1. Distribution of Medication Use in a Study Population of 24,723 Finnish Prostate Cancer Cases and Matched Controls During 1995–2002

	Cases		Controls	
	No.	%	No.	%
Total	24,723	50	24,723	50
Antidiabetic medication use				
Oral antidiabetic medication	1,852	7.5	2,082	8.4
Insulin	607	2.5	731	3.0
Both oral medication and insulin	422	1.7	521	2.1
Other medication use				
Aspirin	1,943	7.8	2,025	8.2
Cholesterol-lowering drugs[a]	2,960	11.9	2,791	11.3
Antihypertensive drugs[b]	12,765	51.5	11,749	47.5

[a] Includes statins, fibric acid derivatives, bile-acid binding resins, and acipimox.

[b] Includes diuretics, beta-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers.

DISCUSSION

Our study showed a 16% decrease in the odds ratio for prostate cancer among users of antidiabetic drugs. The decrease was observed for users of multiple oral antidiabetic drugs and also for insulin users. This finding suggests that the effect is likely not associated with antidiabetic drug therapy per se but more likely with diabetes, the indication for the medication use. This finding, as well as the magnitude of the risk decrease, is in line with previous studies on this topic (2, 5).

Previous studies have suggested an inverse correlation between prostate cancer risk and time since diagnosis of diabetes, that is, a lower risk for men who have had diabetes for a longer period (13, 14). Our results concur with this finding because length of medical treatment was inversely associated with risk. The risk reduction was also dependent on the amount of medication used, also supporting the importance of treatment duration because use of large quantities of antidiabetic drugs requires a longer time of use. The risk of advanced prostate cancer was inversely associated with duration but not with cumulative amount of medication. However, note that, in most cases, treatment of adult-type diabetes is started with nutritional and lifestyle counseling before initiation of medical therapy. Thus, time since onset of diabetes is longer than it appears to be in the analysis for most men in our study population.

To our knowledge, this study is the first to evaluate the risk for diabetic men by adjusting for other medications commonly prescribed with antidiabetic drugs, namely, aspirin, cholesterol-lowering drugs, and antihypertensive drugs. Each of these drug groups possibly affects prostate cancer risk, thus potentially confounding the effect of diabetes and its treatment (10, 15, 16). Additionally, hypercholesterolemia and hypertension are components of the metabolic syndrome, another condition possibly affecting prostate cancer risk (3, 4). Therefore, adjusting for cholesterol-lowering drugs and antihypertensive drugs enabled us to control for the effect of metabolic syndrome to some degree. Controlling for several covariates strengthened the observed association of lowered prostate cancer risk compared with controlling for age only, confirming the confounding.

This study is thus far the largest single one known to estimate prostate cancer risk for diabetic men. Because of the comprehensive national health care registers in Finland, we were able to carry out a large, population-based case-control study with minimal influence of chance or selection bias.

Detailed exposure information was obtained objectively from a prescription database unaffected by disease status. Thus, recall bias, a common problem in case-control

Table 2. Age-adjusted and Multivariable-adjusted Odds Ratios for Prostate Cancer (With 95% Confidence Intervals) in Users of Antidiabetic Drugs Compared With Nonusers, by Type of Medication Used, Among 24,723 Finnish Prostate Cancer Cases and Matched Controls During 1995–2002

Type of Medication (Ever vs. Never Use)	No. of Discordant Pairs[a]	$OR_{age\ adjusted}$	95% CI	$OR_{multivariable\ adjusted}$[b]	95% CI
Any antidiabetic drug	1,953/2,194	0.89	0.84, 0.94	0.84	0.79, 0.90
Oral drugs	1,812/2,036	0.89	0.84, 0.95	0.85	0.79, 0.91
Metformin	904/1,064	0.85	0.78, 0.93	0.80	0.73, 0.88
Sulfonylureas	1,532/1,781	0.86	0.80, 0.92	0.82	0.77, 0.88
Glibenclamide	1,185/1,362	0.87	0.80, 0.94	0.83	0.77, 0.90
Glimepiride	282/307	0.92	0.78, 1.08	0.88	0.75, 1.04
Glipizide	322/388	0.83	0.72, 0.97	0.80	0.69, 0.93
Guar gum	322/339	0.95	0.82, 1.11	0.89	0.75, 1.04
Any insulin	588/717	0.82	0.74, 0.92	0.78	0.70, 0.87
Human insulin	588/717	0.82	0.74, 0.92	0.78	0.70, 0.87
Insulin lispro	31/29	1.07	0.64, 1.77	1.00	0.60, 1.67

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Number of pairs including an exposed case and unexposed control/number of pairs including an unexposed case and exposed control.

[b] Adjusted for age, place of residence, and simultaneous use of other medications (aspirin, cholesterol-lowering drugs, or antihypertensive drugs).

studies, did not affect our results. The representativeness of the study is demonstrated by the comparative medication use between our study population and the overall Finnish population. In 2003, overall use of metformin, sulfonylureas, and insulin by Finnish men was 14.07 DDD, 23.44 DDD, and 20.16 DDD per 1,000 persons per day (17), respectively. In our study population, the respective observed use in 2002 was 12.42 DDD, 22.61 DDD, and 20.36 DDD per 1,000 persons per day, which is highly consistent with the population estimates. All antidiabetic drugs in Finland during the study period were available through a physician's prescription only. Therefore, medication purchases were comprehensively documented by the prescription database. However, we did not have information on actual intake of medication because men used their own discretion. The main limitation of the Social Insurance Institution of Finland database is lack of information on medication for institutionalized patients.

Some exposure misclassification could have been caused by the fact that information on medication purchases was available since 1995 only, although metformin, glibenclamide, glipizide, guar gum, and human insulin were licensed in Finland earlier. Thus, some information on actual medication use was probably missing, likely to result in underestimation of exposure. For instance, some subjects may have had a longer history of use than found in our study. Because antidiabetic medication is not curative, it is rarely discontinued, decreasing the probability of misclassifying past users as nonusers. Information on medication use was obtained in a similar fashion for cases and controls; therefore, nondifferential misclassification is likely to result, which may dilute the observed association. However, the distortion is likely to be small because the risk estimates were not systematically different for cases diagnosed during the early period (with less complete coverage of recent use) versus later.

A limitation of our study is the missing information on serum PSA testing within the study population. The prevalence of latent prostate cancer, already high among men in their forties, increases with age (18, 19). Introduction of serum PSA testing in prostate cancer diagnostics and as a screening tool has led to detection of many prostate tumors in their latent, clinically nondetectable phase and an increase in incidence rates of prostate cancer (20). The benefits of prostate cancer screening with the PSA test are yet to be proven, and systematic screening is not officially recommended in most countries (21). Nevertheless, opportunistic screening occurs, although the prevalence is low in Finland—less than 20% annually (22).

Clinical management of diabetes includes frequent control of blood glucose balance and serum cholesterol level. It is plausible that PSA testing is more frequent among diabetic men than among nondiabetic men, who probably use health services less often. Thus, there could be more opportunistic prostate cancer screening of diabetic men than nondiabetic men, causing a positive detection bias, that is, increasing the probability of prostate cancer diagnosis. However, the lack of mass screening for prostate cancer and the low prevalence of opportunistic screening in Finland (22) is another strength of our study, decreasing the likelihood of such bias. Furthermore, such bias would not jeopardize our conclusions because we observed a lower risk for diabetic men.

Table 3. Odds Ratios for Risk of Any Prostate Cancer and Advanced Prostate Cancer (With 95% Confidence Intervals), by Amount of Antidiabetic Medication Use, Among 24,723 Finnish Prostate Cancer Cases and Matched Controls During 1995–2002

Total Amount of Medication for Which Subjects Were Reimbursed, DDD[a]	No. of Discordant Pairs[b]	Overall Cancer		Advanced Cancer[c]	
		OR[d]	95% CI	OR	95% CI
Oral drugs					
≤228	598/604	0.99	0.88, 1.11	1.06	0.79, 1.42
229–700	575/632	0.91	0.81, 1.02	0.73	0.53, 0.99
701–1,650	559/621	0.90	0.80, 1.01	0.81	0.59, 1.11
≥1,651	509/688	0.74	0.66, 0.84	0.80	0.56, 1.14
		P for trend < 0.001[e]		*P* for trend = 0.294	
Insulin					
≤288	148/172	0.86	0.69, 1.08	0.49	0.27, 0.87
289–744	142/290	0.70	0.56, 0.86	0.65	0.37, 1.14
745–1,707	142/192	0.74	0.60, 0.93	0.74	0.40, 1.35
≥1,708	156/184	0.85	0.68, 1.05	0.63	0.35, 1.16
		P for trend = 0.009		*P* for trend = 0.129	

Abbreviations: CI, confidence interval; DDD, defined daily dose; OR, odds ratio.

[a] Medication users were stratified by quartiles of reimbursements.

[b] Number of pairs including an exposed case and unexposed control/number of pairs including an unexposed case and exposed control.

[c] Locally or regionally invasive and metastatic prostate cancer.

[d] Adjusted for age, place of residence, and simultaneous use of other medications (aspirin, cholesterol-lowering drugs, or antihypertensive drugs).

[e] *P* values for trend were computed by including the cumulative total quantity of medication purchases in the multivariable-adjusted logistic regression model as a continuous covariate.

On the other hand, serum PSA level has been reported to be 21.6% lower in diabetic men compared with nondiabetic men, not depending on antidiabetic medication use (23). This difference could cause a negative detection bias, that is, fewer prostate cancers being diagnosed in diabetic men because fewer prostate biopsies are being performed based

Table 4. Odds Ratios for Prostate Cancer Overall and for Advanced Prostate Cancer (With 95% Confidence Intervals), by Time Since Onset of Antidiabetic Medication Use, in a Study Population of 24,723 Finnish Prostate Cancer Cases and Matched Controls During 1995–2002

Time Since Start of Treatment, years	No. of Discordant Pairs[a]	Overall Cancer		Advanced Cancer[b]	
		OR[c]	95% CI	OR	95% CI
≤1	606/631	0.96	0.85, 1.07	0.96	0.74, 1.25
2	312/359	0.87	0.74, 1.01	0.61	0.42, 0.90
3	268/353	0.76	0.65, 0.89	1.12	0.70, 1.79
4	250/281	0.89	0.75, 1.06	0.79	0.49, 1.27
5	209/268	0.78	0.65, 0.94	0.64	0.37, 1.11
6	171/225	0.76	0.62, 0.92	0.62	0.34, 1.13
7	137/208	0.66	0.53, 0.83	0.61	0.28, 1.34
		P for trend < 0.001[d]		*P* for trend = 0.003	

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Number of pairs including an exposed case and unexposed control/number of pairs including an unexposed case and exposed control.

[b] Locally or regionally invasive and metastatic prostate cancer.

[c] Adjusted for age, place of residence, and simultaneous use of other medications (aspirin, cholesterol-lowering drugs, or antihypertensive drugs).

[d] *P* values for trend were computed by including the cumulative total quantity of medication purchases in the multivariable-adjusted logistic regression model as a continuous covariate.

on elevated PSA levels. Lower PSA levels could explain some of the observed risk decrease in our study and in previous studies on this subject. An inverse detection bias is also supported by the fact that prostate cancer risk for diabetic men has been consistently lower in studies performed after the introduction of the PSA test compared with the studies conducted in the pre-PSA era (2). However, the pre-PSA studies have also reported lower prostate cancer risk for diabetic men (2).

A 25% decrease in average PSA (e.g., from 4 ng/mL to 3 ng/mL) can decrease the prostate cancer detection rate by 36% (24). Thus, our results need to be confirmed in further studies with adjustment for PSA level.

Information on prostate cancer stage was available for only slightly more than half of the cases, which impeded our analyses of advanced cancer. There were no substantial differences in age between the cases for whom information on stage was or was not available. However, the proportion of cases without stage information steadily increased throughout the study period, from 7.0% in 1995 to 21.8% in 2002. The largest increase occurred between 1999 and 2000, from 11.6% to 17.1%, which could reflect an increasing prevalence of opportunistic PSA screening in Finland, with a larger proportion of early cancers. For these cancers, complete staging is not routine. However, the most prominent short-term effect of screening is an increase in early cancer. Thus, more common screening in men with diabetes would most likely lead to a decrease or reversal in protective effect regarding early prostate cancer. When the results were analyzed separately by using cases diagnosed before and after 2000, there was no difference in overall prostate cancer risk but some indication of a decrease in risk of advanced cancer. Therefore, it is unlikely that detection bias by opportunistic PSA testing would substantially explain the observed lower odds ratio of prostate cancer among antidiabetic medication users.

Overall prevalence of antidiabetic drug use was slightly lower in cases for whom stage information was available (8.3% vs. 9.4% for cases without such information), which, on the other hand, could have diminished the observed association with advanced cancer.

Age and ethnicity are established risk factors for prostate cancer (25). We controlled the confounding effect of age by individual matching of cases and controls. No significant effect modification by age was observed. We did not have information on the race of our study subjects. However, more than 98% of the Finnish population is Caucasian, minimizing potential for confounding by ethnicity in our study population (26). We could not control for study subjects' family history of prostate cancer. An inherited predisposition is a strong prostate cancer risk factor. However, hereditary factors have been estimated to account for only a minor proportion of prostate tumors (27), 5%–10% of all Finnish prostate cancers (28). To generate confounding, prostate cancer family history would need to be associated with antidiabetic medication, for which there is little indication.

Furthermore, we did not have data on obesity and a Western-style high-fat diet. These are potential confounding factors because they are frequently associated with adult-type diabetes and possibly affect prostate cancer risk (29, 30) and serum PSA level (31). However, their role as prostate cancer risk factors is debatable.

We could not distinguish between adult-type and juvenile diabetics in our analyses. Thus, we could have missed possible subgroup effects within these 2 groups of diabetics. One might assume that virtually all men using oral drugs have type 2 diabetes mellitus. With more advanced type 2 diabetes, an estimate is that 30%–40% of the patients are using insulin (1). Also given the substantially higher prevalence of type 2 than type 1 diabetes, most patients using insulin are likely to have type 2 diabetes.

The potential mechanism behind decreased prostate cancer risk for diabetic men is currently unclear. Most likely, the changes in endogenous hormone metabolism occurring in diabetes have an important role.

Diabetic men have a lower serum testosterone concentration compared with nondiabetic men (32). Conversely, low serum testosterone is linked with increased risk of developing diabetes (33–35). Because growth of prostate cancer is androgen dependent, changes in serum testosterone in diabetic men could provide a possible explanation for their lowered prostate cancer risk.

Fasting insulin levels (3) or insulin resistance (36) have not been reported to affect prostate cancer risk. However, insulin-like growth factors, overexpression of which is reported to increase prostate cancer risk, are dependent on serum insulin levels (7). Therefore, altered insulin metabolism is another possible explanation for decreased prostate cancer risk for diabetic men.

Our large, population-based study showed decreased prostate cancer risk for users of antidiabetic drugs. A similar decrease was observed for users of metformin, sulfonylureas, and insulin, suggesting an overall lowered risk for diabetic men. The decrease was dose dependent with quantity and length of medication use, suggesting that duration of diabetes is also a determinant of risk. These findings are consistent with recent results in this field. We also showed that the risk of advanced prostate cancer decreases for diabetic men, depending on the length of antidiabetic treatment. Ours is the first study known to demonstrate that the association could not be explained by the medications commonly prescribed along with antidiabetic medication. However, because varying PSA testing activity within the study populations and lower PSA levels in diabetic men can introduce detection bias, future studies that evaluate prostate cancer risk while effectively controlling for serum PSA are needed.

ACKNOWLEDGMENTS

Author affiliations: School of Public Health, University of Tampere, Tampere, Finland (Teemu J. Murtola, Anssi Auvinen); Department of Urology, Tampere University Hospital and Medical School, University of Tampere, Tampere, Finland (Teuvo L. J. Tammela); Department of Internal Medicine, Tampere University Hospital, Tampere, Finland (Jorma Lahtela); and The Finnish Cancer Institute, Helsinki, Finland (Anssi Auvinen).

Funding was received from the Academy of Finland (grant 205 862); the Sigrid Juselius Foundation; the Finnish Cancer Society; the Pirkanmaa Regional Fund of the Finnish Cultural Foundation; the Medical Research Fund of Tampere University Hospital; the Irja Karvonen cancer trust; and the Astellas, Lilly Foundation, Schering Foundation, and research foundation of Orion Pharma (nonrestricted grants to T. J. M.).

Conflict of interest: none declared.

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