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EERIK SANTALA

The Association Between Antihypertensive Drug Use and Risk of Cancer Death in Finland

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ABSTRACT

Antihypertensive drugs (anti-HT drugs) are very commonly used drugs. They include several different drug molecules with different mechanisms of action. Based on their mechanism of action, they can be categorized into five main groups: angiotensin converting enzyme (ACE) inhibitors, angiotensin-receptor (ATR) blockers, beta-blockers, calcium-channel blockers, and diuretics. These drugs are used in also other conditions than hypertension such as in the treatment of coronary artery disease and heart failure; the loop diuretic compound, furosemide, is mainly used in the treatment of oedema.

Since antihypertensive drugs are so widely prescribed, it would be important to know whether they would affect also other diseases; one can speculate that the mechanism of action of some antihypertensive drug groups may have relevance in non-cardiovascular diseases e.g., cancer. Although there are some indications that the drugs affecting the renin-angiotensin aldosterone (RAA) system (ACE-inhibitors and ATR-blockers) might affect cancer cell growth and improve prognosis of some cancer types, like prostate cancer, the published results have been conflicting.

The purpose of this thesis is to evaluate the association between antihypertensive drug use in general as well as subdivided according to the drugs' mechanism of action and the risk of cancer death from prostate (PCa), urothelial (UC), breast (BCa) and ovarian (OC) cancer. The study was conducted by obtaining the information on cancer diagnoses from The Finnish Cancer Registry during 1995-2013 and combining this with information on drug purchases from the national prescription database. Drug use was evaluated separately before and after cancer diagnosis as well as the amount of use by calculating drug-specific Defined Daily Dose (DDD) for each participant. Cox regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the risk of cancer death after the diagnosis of each cancer type.

Anti-HT drug use before diagnosis was analysed as a time-fixed variable taking into account the duration and cumulative dose of use occurring between 1995 and the year of cancer diagnosis. Post-diagnostic use was analyzed as a time-dependent variable to minimize immortal time bias. Time-dependent variables were formed by updating medication user status as well as estimating the cumulative amount, duration, and intensity of use separately for each follow-up year after the cancer diagnosis. Dose dependence was evaluated by stratifying medication users by tertiles of DDD amount, duration and intensity of use based on the level reached on each follow-up year.

The simultaneous use of multiple anti-HT drug groups was modelled by forming separate time-dependent variables for use of each drug group with these variables included in a Cox- regression model. The long-term association between anti-HT drug use and the risk of cancer death was investigated in lag time analyses where the exposure was lagged forward in the follow-up time and analyzing medication use that occurred before that event. Analyses were adjusted for several confounders such as primary treatment, tumor extent, comorbidities, and simultaneous use of other drugs like statins and antidiabetic medication.

In prostate cancer, the use of ATR-blockers was associated with a decreased risk of cancer death. The risk decrease was dose-dependent and concerned usage both before and after diagnosis. The risk decrease remained for five years after usage. In contrast, use of beta-blockers was associated with an increased PCa death risk with both pre-and post-diagnostic use.

Similarly, the post-diagnostic use of ATR-blockers was dose-dependently associated with a reduced risk of cancer death also in bladder (BC) cancer. In BCa, ATR-blockers but also beta-blockers and calcium-channel blockers displayed a dose-dependent association with a reduced BCa death risk in post-diagnostic use. In ovarian cancer, ACE-inhibitors were associated with a decreased cancer death risk but only with very long follow-up periods exceeding 10 years.

ATR-blockers, unlike any other anti-HT drug group, were associated with decreased risk of cancer death in PCa, BC and BCa and furthermore in these three cancer types, the risk decrease was dose-dependent. This

indicates that the association was causal. RAA- inhibition may confer benefits in preventing the progression of cancer. However, similar results were not observed for ACE-inhibitors even though they also inhibit RAA-system but in a different way. The role of the RAA- system in cancer progression warrants further study.

In BCa, decreased risk associations were observed for multiple anti-HT drug groups after cancer diagnosis. This suggests that the control of hypertension may be more important in this cancer type than any given mechanism of action. However, ATR-blockers were the only drug group also in this cancer type in which the pre-diagnostic use was associated with a decreased BCa death risk and furthermore in a dose-dependent manner.

In conclusion, the use of ATR-blockers is associated with improved cancer-specific survival in multiple cancer types. ATR- blockers differ in this regard from all other anti-HT drug groups, even ACE-inhibitors. Our studies suggest a possible prognostic role of ATR- inhibition in cancer. It would be enlightening to clarify the underlying biological mechanisms to explain why the blockade of the ATR- receptor can exert this potential anti-cancer effect.

TIIVISTELMÄ

Verenpainelääkkeet on hyvin yleisesti käytetty lääkeryhmä. Niihin kuuluu useita lääkeaineita, jotka toimivat eri vaikutusmekanismeilla. Vaikutusmekanismin mukaan ne jaetaan viiteen pääryhmään: angiotensiinia konvertoivan entsyymin (ACE) estäjiin, angiotensiinireseptorin (ATR) salpaajiin, beetasalpaajiin, kalsiumkanavan salpaajiin ja diureetteihin. Nimestään huolimatta verenpainelääkkeitä käytetään verenpainetaudin lisäksi myös sepelvaltimotaudin ja sydämen vajaatoiminnan hoidossa. Furosemidia, joka kuuluu diureetteihin, käytetään lähinnä turvotusten ja sydämen vajaatoiminnan hoidossa.

Koska verenpainelääkkeet ovat paljon käytettyjä, on hyvä tietää niiden vaikutuksesta myös mahdollisiin muihin sairauksiin kuten syöpiin. Joillakin verenpainelääkkeillä saattaa olla vaikutusta myös syöpäsoluihin vaikutusmekanisminsa kautta. Eräiden tutkimusten mukaan reniini-angiotensiini-aldosteronijärjestelmään (RAA) vaikuttavilla lääkkeillä saattaa olla vaikutusta syöpäsolujen kasvuun ja syövän ennusteeseen esimerkiksi eturauhassyövässä. Tulokset ovat kuitenkin ristiriitaisia.

Tämän väitöskirjan tarkoitus on arvioida verenpainelääkkeiden käytön ja syöpäkuoleman välistä riskiä eturauhassyöpä-, uroteelisyöpä-, rintasyöpä- ja munasarjasyöpäpotilailla. Tutkimusaineisto muodostettiin keräämällä Suomen Syöpärekisteristä tiedot syöpädiagnooseista, jotka tehtiin Suomessa vuosina 1995–2013 ja aineistoon yhdistettiin tiedot reseptilääkkeiden käytöstä Kelan lääkekorvaustietokannasta. Lääkeostoja arvioitiin ennen ja jälkeen syöpädiagnoosin ja myös käytön voimakkuutta arvioitiin laskemalla vuosikohtainen suositeltu päiväannos (DDD) jokaiselle osallistujalle. Riskitiheyssuhteet (HRs) ja luottamusvälit (95 % CIs) syöpäkuolemalle laskettiin Cox- regressiolla.

Syöpädiagnoosia edeltävään verenpainelääkkeiden käyttöön huomioitiin kaikki ostot vuoden 1995 ja syöpädiagnoosin välillä. Diagnoosin jälkeistä käyttöä arvioitaessa käytettiin aikariippuvaa analyysiä kuolemattomuusharhan minimoimiseksi. Riskiyhteyksien annosriippuvuutta arvioitiin käytön intensiteetin mukaan. Jokaiselle verenpainelääkeryhmälle luotiin oma muuttuja ja ne lisättiin samaan analyysimalliin yhtäaikaisen käytön mallintamiseksi. Analyysissa vakioitiin useita potentiaalisia sekoittavia tekijöitä kuten primaarivaiheen hoito, syövän levinneisyys, liitännäissairaudet ja statiinien sekä diabeteslääkkeiden samanaikainen käyttö.

Eturauhassyöpäpotilailla ATR-salpaajien käyttö oli yhteydessä pienempään syöpäkuoleman riskiin. Riskin alenema oli annosriippuvainen sekä ennen että jälkeen diagnoosin. Riskinalenema oli nähtävissä vielä viisi vuotta käytön jälkeenkin. Sen sijaan beetasalpaajien käyttö oli yhteydessä suurentuneeseen eturauhassyöpäkuoleman riskiin ennen ja jälkeen diagnoosin. Samaan tapaan ATR-salpaajien käyttö oli annosriippuvaisesti yhteydessä myös pienempään rakkosyöpäkuoleman riskiin. Rintasyövässäkin ATR-salpaajien ja lisäksi myös beetasalpaajien ja kalsiumkanavan salpaajien käyttö oli annosriippuvaisesti yhteydessä alentuneeseen rintasyöpäkuoleman riskiin. Munasarjasyövässä ainoastaan ACE-estäjien käyttö oli yhteydessä alentuneeseen syöpäkuoleman riskiin mutta vain pitkän yli 10 vuoden seuranta-ajan yhteydessä.

ATR-salpaajien käyttö toisin kuin muiden verenpainelääkkeiden käyttö oli yhteydessä alentuneeseen syöpäkuoleman riskiin useassa eri syöpätyypissä. Kaikissa näissä syövissä yhteys oli annosriippuvainen mikä tukee kausaalista yhteyttä. AT-reseptorin lääkkeellinen salpaaminen saattaa siis vaikuttaa syövän ennusteeseen. Samanlaisia tuloksia ei kuitenkaan havaittu ACE-estäjillä, vaikka nekin vaikuttavat RAA-järjestelmään eri mekanismilla. RAA-järjestelmän rooli syövän kasvussa vaatii lisätutkimuksia.

CONTENTS

ABBREVIATIONS

ACE-inhibitor	Angiotensin-converting enzyme inhibitor
ADT	Androgen-deprivation therapy
ATR-blocker	Angiotensin-receptor blocker
BC	Bladder cancer
BCa	Breast cancer
BRCA	Breast cancer gene
CCI	Charlson comorbidity index
CI	Confidence interval
COX	Cyclo-oxygenase
DDD	Defined daily dose
DM2	Type 2 diabetes
EGF	Epidermal growth factor
GnRH	Gonadotropin-releasing hormone
GS	Gleason score
HR	Hazard ratio
IGF	Insulin-like growth factor
OC	Ovarian cancer
PCa	Prostate cancer
RAA-system	Renin-angiotensin aldosterone system
UC	Urothelial cancer
UTUC	Upper tract urothelial carcinoma

ORIGINAL PUBLICATIONS

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Santala, E. E., Murto, M. O., Artama, M., Pukkala, E., Visvanathan, K., & Murtola, T. J. (2020). Angiotensin Receptor Blockers Associated with Improved Breast Cancer Survival—A Nationwide Cohort Study from Finland. *Cancer Epidemiology and Prevention Biomarkers*, *29*(11), 2376-2382.

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AUTHOR´S CONTRIBUTION

The author designed the analyses together with the supervisor. The analyses were conducted by the author with help from the supervisor. The results were interpreted by the author and supervisor. The author wrote the first drafts of manuscripts and also final versions with help of supervisor and co-authors.

1 INTRODUCTION

Antihypertensive drugs (anti-HT drugs) are commonly used drugs in treatment of several conditions like hypertension and coronary artery disease. Anti-HT drugs include different drug molecules with different mechanisms of action. Based on their mechanism of action, they are categorized into five main groups: angiotensin converting enzyme (ACE) inhibitors, angiotensin-receptor (ATR) blockers, beta-blockers, calcium-channel blockers, and diuretics.

As antihypertensive drugs are commonly used, it is essential to know whether they also affect prognosis of other diseases like cancer. Moreover, some anti-HT drug groups target mechanisms such as the renin-angiotensin aldosterone (RAA) system that may be relevant in cancer. Although there is some evidence of the drugs affecting RAA-system decreasing cancer cell growth and improving prognosis of some cancer types, like prostate cancer, not all studies agree (Gardwell CR et al. 2014). Epidemiological associations between drugs affecting RAA-system and cancer outcomes are unknown.

The aim of this thesis is to evaluate the association between antihypertensive drug use in general as well as subdivided according to the drugs' mechanism of action and the risk of cancer death from prostate (PCa), urothelial (UC), breast (BCa) and ovarian (OC) cancer.

2 CANCER EPIDEMIOLOGY

2.1 Incidence

2.1.1 Prostate cancer

Prostate cancer (PCa) is the most common cancer among men in Finland and in global terms, the second most common malignancy in males (Cancer in Finland 2018, Finnish Cancer Registry) (Pernar CH et al. 2018). While local PCa may be totally asymptomatic, urinary urgency, hesitation, or difficulties in emptying the bladder are the most common symptoms in localized disease (Mansson J et al. 1999). These symptoms are however not specific for PCa; in fact, they are more often caused by benign prostatic hyperplasia (BPH) rather than PCa (Cicione A et al. 2017). This leads to difficulties in early detection of potentially fatal PCa cases among the huge number of BPH patients with similar symptoms. In its advanced stage, PCa may cause other symptoms such as bone pain due to metastases and weight loss (Smith JA et al. 1999). The most common histological type of PCa is adenocarcinoma (Grignon DJ 2004).

The incidence of PCa has been continuously increasing from the end of 1990s. In 2018, a total of 5,016 new PCa cases were diagnosed in Finland with an age-standardized incidence of 165.7 / 100,000 person years in Finland (Cancer in Finland 2018). Worldwide, a total of around 1,276,000 new PCa cases were diagnosed in 2018, with the highest incidence being in men over 65 years old (Bray F Globocan 2018). In Finland, the incidence of PCa is at its highest at 80 years age (Cancer in Finland 2018). Evidently, the incidence of PCa seems to increase with age; the ten-year incidence rate among 60–70-year-old men was 6.41% compared to 2.31% among men between 50-60 years in 2013 (Perdana NR et al 2016) (SEER Cancer Statistics Review, 1975-2013). The incidence of PCa is increasing worldwide and this is also occurring among younger men (Zhai Z et al. 2020).

There are also national differences in PCa incidence rates; in Europe, PCa comprised 24% of all new cancer diagnoses among men in 2018 but only 9.5% in the USA (Epidemiology of prostate cancer in Europe. European Commission, 2015, Cancer Stat Facts: Prostate Cancer 2018). Differences in diagnostic testing may be one factor behind the differences in PCa incidence worldwide. A significant number i.e., 20-40%, of new PCa diagnoses in both USA and Europe are estimated to be due to over diagnostics of localized low-risk PCa attributed to active prostate-specific antigen (PSA) testing as a screening measure (Draisma G et al. 2009). PSA-testing has a strong effect on PCa incidence. In the early part of this century when the PSA-test was introduced into clinical practice, an increase in PCa incidence was observed in Finland (Cancer in Finland 2018). Conversely, under diagnostics of high-risk cancer may also occur especially in the less developed nations where PSA-testing is not available (Graif T et al. 2007). It is also important to consider that a normal level of PSA does not rule out the existence of prostate cancer (Thompson IA et al. 2004). While PSA-testing may lead to over diagnostics of low-risk PCa, nonetheless it also identifies advanced cancers (Etzioni R et al. 2002) (Buzzoni C et al. 2015). In the Prostate, Lung, Colorectal and Ovary (PLCO) trial conducted in the United States, PSA-testing increased PCa incidence but did not affect the number of PCa deaths (Andriole GL et al. 2012). In the European Randomized Study of Screening for Prostate Cancer, PSA-testing was associated with a 20% reduction in PCa mortality. However due to over diagnostics, this indicates that 1,410 men need to be screened and 48 additional PCa cases would have to be treated to prevent one death from PCa (Schröder FH et al. 2009). These numbers reveal that PSA-testing is better at finding low-risk cases rather than those at high-risk. Furthermore, in the data of 7- and 10-years' follow-up rates, there were no differences in the numbers of PCA deaths between the screening and control arms (Schröder FH et al. 2009).

2.1.2 Urinary tract cancers

Urinary tract cancers (UC) occur in the bladder, ureters or in renal pelvis. Urothelial carcinomas arise from the urothelial epithelium lining the urinary tract and are the most common histological type of urinary tract cancers. There are also other categories of urinary tract cancers e.g., squamous cell carcinoma and adenocarcinoma. Although the histology of urothelial carcinoma is rather similar regardless of tumor location in the urinary tract, some differences are found in the genetics such as in microsatellite instability and in epigenetic mechanisms like methylation (Yates DR et al. 2013). UTUC has also specific genetic hereditary non-polyposis colorectal cancer associated risk factors compared to BC. For anatomical reasons, tumors in different locations in urinary tract are treated in different ways. However, 90-95% of malignant tumors in the urinary tract occur in the bladder (Taari K et al. 2013).

Bladder cancers (BCs) are a heterogenous group of cancers. The most common histology is urothelial carcinoma (90-95%) with the rest consisting of squamous cell carcinomas, adenocarcinomas, and sarcomas (Taari K et al. 2013). Most BCs (75%) are diagnosed as locally restricted to the bladder epithelium (non-muscle invasive bladder cancer NMIBC). Patients with NMIBC have only 5-20% lower survival as compared to the healthy population in 5 years´ follow-up. On the contrary when BC is found at the muscle invasive stage in which it has already infiltrated into the bladder's muscle layer under the urothelial epithelium, only every second patient will be alive after 5 years despite radical treatment (Taari K et al. 2013). Unfortunately, NMIBC has a high recurrence rate; according to one study, 68.6% of NMIBC cases suffered a relapse during the 5 years' follow-up (Lu M et al. 2019). Due to the high recurrence rate and the high proportion of NMIBC, BC is associated with the highest lifetime costs per patient compared to all other cancers: yearly costs in Europe are estimated to total 5 billion euros (Leal J et al. 2016).

Urinary tract cancers (UC) as a group are the fourth most common cancer type among men in Finland. Bladder cancer and other urinary tract cancers are categorized as one group in Finnish Cancer Registry Statistics. In 2018, a total of 1,940 UC cases were diagnosed in Finland. The incidence of UC in women has not changed after the 1990s, while there was an initial decline in the incidence in men, but values started to increase again after the 1990s (Cancer in Finland 2018).

BC is worldwide the 9th most common cancer; in 2018, the prevalence of BC was 1,650,000 cases (Ferlay et al. 2018). In the area of the European Union, approximately 110,500 men and 70,000 women are diagnosed with BC every year and 38,200 people die from BC (Miyazaki J et al. 2017). The highest incidence rates are found in Southern and Western Europe as well as in North America (Wong MCS et al. 2018). Previously the incidence of BC was high in East Africa due to infection with Schistosoma haematobium, a risk factor for BC (el-Mawla NG et al. 2001). In Egypt, health efforts aiming at the eradication of Schistosoma led to a decrease in the incidence of squamous cell BC (Salem S et al. 2011).

2.1.3 Breast cancer

Breast cancer (BCa) is the most common malignancy suffered by women in Finland as approximately 5,000 new cases are diagnosed yearly. Despite its relatively good prognosis (5- year survival) in comparison with many other cancers, it still is the most common cause of female cancer death in Finland (Cancer in Finland 2018).

In Finland, the incidence of BCa has been increasing since the 1970s. During the years 2014-2018, the incidence of BCa increased by 5% as compared to 2009-2013. In 2018, 4,934 new BCas were diagnosed in Finland with an age-standardized incidence of 165.7 per 100,000 life years (Cancer in Finland 2018). BCa is rare among men: in 2013 only 33 BCa cases were diagnosed in Finnish men (Mattson et al. 2016).

Mammography, an X-ray imaging procedure, is used to screen for BCa in Finland at the population level with all 50-69 years old women being invited to a free screening every second year. In the USA, mammography has been claimed to have decreased BCa mortality by approximately 20-35% among 50-69 years old women with 14 years' follow-up (Elmore JG et al. 2005). According to a Finnish cohort study, the results are in the same direction i.e., mammography reduced BCa mortality by 22% among 50-69 women (RR 0.78, 95% CI: 0.70–0.87) (Sarkeala T et al. 2008). Screening causes also over diagnostics i.e., identifying 15 to 25% of clinically non-significant cases (cases that would not have affected the woman's life if she had not attended the screening) (Kalager M et al. 2012).

In Europe, a total of 523,000 new BCa cases were diagnosed in 2018 and 138,000 women died from BCa (Ferlay J et al. 2018). Worldwide BCa is the most common invasive cancer found in women, each year accounting for 25% of all new cancers in women (Choncheh M et al. 2016) (McGuire A et al. 2015). The age-standardized incidence has also been increasing worldwide: from 39.2 / 100,000 women in 1990-2017 up to 45.9 / 100,000 new cases yearly in 2018. In 2012 a total of 1.7 million new BCa diagnoses were made worldwide, and 522,000 women died of BCa (Dumais V et al. 2017). In 2015, there were 2.4 million new BCa cases worldwide and 523,000 BCa deaths (Fitzmaurice C et al. 2017). Thus, the incidence of BCa increased by 700,000 new cases in the time frame 2012-2015 while the numbers of BCa deaths increased by only 1,000. In global terms with a longer time period, there is also evidence that an increase in BCa mortality has occurred during the last 25 years (an additional 0.7 per 100 000 women during 1995-2015) which may be due to increased incidence and prevalence (Azamjah M et al. 2019). The main causes behind the increased incidence may be aging and lifestyle factors such as obesity, a known risk factor for BCa (McPherson K et al. 2000). However, treatment methods for BCa have improved during recent years explaining at least partly the rather stable mortality values despite the increased incidence. In addition, earlier diagnostics may account for the improvement in survival as nowadays BCas may be found at an earlier stage at which curative treatment is possible (Narod SA et al. 2015).

The highest BCa incidence is observed in the developed countries and there is a large difference between the developing and developed nations; the BCa incidence among white women in the USA was 97/ 100,000 compared to 27/100,000 among women in Asia (Althuis MD et al. 2005). However, some declines in the incidence have also been observed in the developed countries such as in the USA and United Kingdom (Chen Z et al. 2020). Both incidence and survival in BCa are associated with the financial income level (purchase parity level) (Dafni U et al. 2019). In Europe, purchase parity is highest in the Northern countries. Concordantly, the highest incidence but also the highest BCa survival rates within Europe are observed in the North.

2.1.4 Ovarian cancer

Ovarian cancer (OC) is the eighth most common cancer and the second most common gynecological cancer among women in Finland (Cancer in Finland 2018) and globally OC is the 7th most commonly diagnosed cancer and the 8th most common cause of cancer death among women (Torre LA et al. 2018). Worldwide, OC accounts for 2.5% of malignancies among women, but is responsible for 5% of all cancer deaths (Howlader N et al. 2017). Unfortunately, most OC are diagnosed at an advanced stage when they display a poor prognosis. Most patients with malignant ovarian tumors are non-symptomatic and thus the diagnosis is often made by ultrasound imaging by coincidence. In its advanced stage, OC causes non-specific symptoms with the most common being swelling of the stomach caused by the collection of fluid in the abdominal cavity, ascites, but also mild gastro-intestinal symptoms like constipation or abdominal pain may occur (Goff BA et al. 2004). Because the symptoms are not specific for OC but rather common in many benign gastro-intestinal conditions, the diagnosis of OC is also often delayed and made only when the disease is in an advanced stage. There are no effective screening methods for OC. Early detection is the

most important prognostic factor as if OC can be diagnosed at localized stage, it has an excellent 5-year survival rate of 93% (Howlader N et al. 2017).

There was 549 new OC diagnosed in Finland in the year 2018, with an age-standardized incidence of 17.8 per 100,000 life years. In Finland, the OC incidence has been decreasing: 2014-2018 by 7% compared to 2009-2013 (Cancer in Finland 2018). Worldwide, it has been calculated that the life-time risk of developing OC is 1.3 % (Torre LA et al. 2018). In 2012, it was estimated that yearly there were 239,000 new global OC cases (Ferlay et al 2012 Globacan). While the highest total number of new OC cases and deaths is found in China (Chen W et al. 2016), the highest age-adjusted incidence is seen in the Western countries with the lowest in Asia and Africa (Ferlay et al. 2012 Globacan). This may be partly explained by environmental and lifestyle risk factors as it has been shown that the risk increases among women who migrate from a lower risk nation to a higher risk country (Herrinton LJ et al. 1994). The incidence of OC has been declining also worldwide since the 1990s (Bray F et al. 2005). In the USA, the OC incidence rate fell from 16.6 per 100,000 in 1985 to 11.8 per 100,000 in 2014 i.e., a reduction of 29% (Torre LA et al. 2018).

2.2 Cancer prognosis and mortality

2.2.1 Prostate cancer

In Finland, 55% of PCas are diagnosed at a localized stage and 23% at an advanced stage (Prostate cancer care guideline 2014). At the end of 2018, there were 55,118 men wih PCa in Finland. In fact, PCa is the second most common cause of cancer death after lung cancer in Finland: in 2018 PCa caused 914 deaths (lung cancer killing 1,473 Finns) but this is mainly based on the high prevalence of PCa. In general, PCa is a cancer with relatively good prognosis with a total 5-year survival of 93% in Finland in 2018. Prognosis has also improved during the last 15 years (Cancer in Finland 2018). However, survival rates highly depend on both the extent and grade of the disease. Among men with a well differentiated local disease, the 10-year survival is 90-94% but among men with advanced disease 5-year survival is only 33% (Prostate cancer guideline 2014).

In 2018, PCa caused 359,000 deaths worldwide which was only 3.8% of all male cancer deaths (Ferlay J et al. 2019). The highest mortality rates were found in Central America (10.7 per 100,000), Australia (10.2 per 100,000), New Zealand (10.2 per 100,000) and Western Europe (10.1 per 100,000) with the lowest in Asia (South-Central Asia 3.3 per 100,000) (Ferlay J et al. 2019). Approximately every second i.e., 55%, of all PCa deaths occurred among over 65-year-old men (Ferlay et al. 2019). The disease burden of PCa has decreased over time and prognosis has improved during the period 1990-2017 since most PCas are now found at a local stage (Zhai Z et al. 2020). Even though there are relatively good survival rates, PCa is the second most common cause of male cancer death also in the USA (Prostate Cancer Survival Rates, 2018).

2.2.2 Urinary tract cancer

In 2018, there were a total of 480 deaths due to UC in Finland and the total 5-year survival was 75% among men and 70% among women with UC according to the Finnish Cancer Registry. Age seems to affect prognosis also in UC: the combined 5-year survival for both genders among under 54-year-old was 87%, while it was only 67% among over 75-year-old in 2018. The UC mortality in Finland decreased by 14% during 2014-2018 compared to 2009-2013 and has been decreasing since 1970s in both genders. (Cancer in Finland 2018)

When considering only BC, in Europe the 5-year survival among BC patients was 70% according to EUROCARE-5 study but varied widely depending on the nation (between 60% and 80%) (Marcos-Gragera R et al. 2015). Globally BC mortality rates are highest in Northern Africa and Asia (Wong MCS et al. 2018). In 2018, approximately 200,000 people died of BC worldwide (Ferlay et al. 2018). For unknown reasons, survival rates among women with BC are lower than in men. The difference is not explained by stage as it has also been observed in stage-adjusted analyses (Mun DH et al. 2019).

2.2.3 Breast cancer

At the end of 2018, there were 74,001 women with BCa alive in Finland. In the same year, BCa was responsible for 873 deaths (Cancer in Finland 2018). The total 5-year survival in BCa was 91% in Finland in 2018 but survival differences between young (under 54-year-old) and older (over 75-year-old) age groups are not high in BCa; the difference in 5-year survival is approximately 10 percentage points. During the time period 2014-2018, BCa mortality has decreased by 5% even although there has been a similar increase in BCa incidence in the same period. Therefore, the total number of yearly BCa deaths has remained approximately unchanged. (Cancer in Finland 2018)

BCa mortality increased until 1990s (Althuis MD et al. 2005) but has since decreased by 19% from 1986 to 2006 in Europe (Autier P et al. 2010). BCa mortality rate in Europe has decreased from 21.3 / 100,000 in 1990 to 16.7/100,000 in 2007 (Bosetti C et al. 2012). The 5-year survival rates in Europe vary between 81-84% except for Eastern Europe where the 5-year survival is lower, 69% (Allemani C et al. 2013) (Allemani C et al. 2018). Though BCa survival has been improving, rather few improvements have been seen among women diagnosed with advanced disease or among women over 70-year-old (Allemani C et al. 2013) (Sant M et al. 2015).

In the USA, the 5-year survival of BCa is also good with approximately 90% of patients alive 5-years after diagnosis in 2015 (American Cancer Society); for localized BCa it was 99%, 86% for locally advanced and 27% for advanced disease among women diagnosed between 2009-2015 (American Cancer Society).

2.2.4 Ovarian cancer

In Finland, both the OC incidence and prevalence increased until the 1990s but subsequently have been declining. In 2018, 549 new OC cases were diagnosed in Finland. It is recognized that the incidence is highly dependent on age: OC incidence among 20-69-year-old women was 16.4/100,000 person years but 54.2 / 100,000 person years among women over 70-years old. (Cancer in Finland 2018)

Total 5-year survival in OC was 44% at the end of 2018. Among over 75-year-old women, 5-year survival seemed to decline to only 25% percent. In contrast, the 5-year survival in the age group of under 54-years old was as high as 70%. At the end of 2018, there were 5,525 women with OC alive in Finland and OC was responsible for 361 deaths. (Cancer in Finland 2018)

OC is the fourth most common cause of cancer death in the world among women and about 152,000 OC deaths occur yearly (Ferlay et al. 2012 Globacan). In Europe, OC mortality has decreased since 1990 (Bray F et al. 2005). In less developed nations, both OC mortality and incidence have however been increasing (Malvezzi M et al. 2016). In the USA, mortality rate in OC has declined between 1976 (10.0 per 100,000) and 2015 (6.7 per 100,000) due to decreased incidence and improved OC treatments (SEER 2017).

3 CANCER RISK FACTORS

3.1 Prostate cancer

The most important risk factors for PCa are age as well as genetics and family history of PCa; other risk factors are not so well established.

Age is clearly a risk factor for PCa (Crawford E 2003); the proportion of high-risk PCas increases with age and PCa survival is poorer among over 75- years old men compared to younger men (Bechis SK et al. 2011). As life-expectancy among men increases worldwide and PSA-screening becomes more common, it is expected that the number of new PCa diagnoses will increase. In the future, due to the increasing number of PCa patients, it is estimated that PCa will be responsible for a total of 740,000 deaths worldwide in 2040 which means that the number of PCa deaths will almost double since 2018 (Ferlay et al. 2019).

Race and genetics may also have a role in PCa risk e.g., African-Americans have the highest incidence of PCa while lowest incidence is seen in Asia. Reasons for the differing incidence have been sought. African-Americans harbor more often genetic variants which are associated with increased risk of PCa (Chang BL et al. 2005) (Okobia MN et al. 2011). Recently, mutations in DNA-repair genes have been associated with an increased risk of metastatic PCa (Pritchard CC et al. 2016) (Leongamornlert D et al. 2014). BRCA2 (breast cancer gene 2) mutations are also associated with an increased risk of high-grade PCa (Agalliu I et al. 2009). However only as few as 5 % of the total PCa risk may be caused by an inherited predisposition (Sridhar G et al. 2010). A known risk factor for PCa commonly evaluated in clinical practice is the number of first-degree relatives with PCa (Randazzo M et al. 2016).

Metabolic syndrome is associated with an elevated overall PCa and especially high-grade PCa risk and men with the metabolic syndrome have also poorer prognosis than healthy men (Xiang Y et al. 2013) (Hammarsten J et al. 2018). In addition, a weak association has been observed between obesity alone and incidence of PCa e.g., obesity has been associated with high-grade disease (De Nunzio C et al. 2016) (Allot EH et al. 2013). Another study also supported the fact that obesity was associated with an increased risk for high-grade PCa but a decreased risk for low-risk PCa (Gong Z et al. 2006). According to the Prostate Cancer Prevention Trial, diabetes has been associated with a decreased risk of both low- and high-risk PCa (Gong Z et al. 2006) (Leitzmann MF et al. 2008). However, there is a suggestion for an elevated risk among obese diabetic men (Wu C et al. 2011). These findings suggest that obesity and diabetes should be considered as different risk factors for PCa.

Modifiable risk factors are also important, e.g., dietary, and other lifestyle factors such as physical activity and obesity may also explain the differing incidence rates in different countries. For example, a high intake of fat is associated with an increased PCa risk (Aronson WJ et al. 2010). A high calcium intake is also associated with an elevated PCa risk (Gao X et al. 2005). The results on the association between red meat consumption and PCa risk are controversial but it has been claimed that at least processed meat may be associated with an elevated risk of PCa (Rohrmann S et al. 2015). Instead, a vegetarian and low-fat containing diet has been associated with lower testosterone levels which at least partly could explain the decreased PCa risk among men consuming these foodstuffs (Fleshner N et al. 2007). Studies investigating the link between vegetable consumption, alcohol drinking and smoking as PCa risk factors have not been conclusive. As a single vegetable, tomatoes and and their ingredient lycopene were associated with a decreased risk of PCa (Giovannucci E et al. 2007). There is a report that physical exercise may protect against PCa (De Nunzio C et al. 2016).

3.2 Urinary tract cancers

The most important risk factors for BC are age, smoking and repeated urinary tract infections; the role of other risk factors is not as well established.

Age is an important risk factor also for BC. It is estimated to be the main reason why the incidence of BC will grow worldwide (Shariat SF et al. 2010). The lifetime risk of developing BC among men is 1.1% and women 0.27% (Ferlay J et al. 2018).

Smoking and other exogenous carcinogens are the most important environmental risk factors for BC and other urinary tract cancers (Masaoka H et al. 2016). Smoking is estimated to cause approximately every second case of BC (Miyazaki J et al. 2017) and second-hand smoking has also been claimed to increase the risk (Yan H et al. 2018). There seem to be some other environmental risk factors for BC e.g., certain chemicals like arsenic and chronic urinary tract infection caused by Schistosoma haematobium which both are common in the developing nations (Cassell A et al. 2019).

A high dietary intake of fat may be associated with an increased risk of BC according to a meta-analysis (Wang J et al. 2019). A low vitamin-D level in serum was associated with an increased risk of BC (Dunn JA et al. 2019). In contrast, dietary fiber intake was not associated with the BC risk (Luo J et al. 2019). The consumption of vegetables and milk has been associated with a decreased risk of BC and stewed or roasted meat with an increased risk of BC diagnosis (Di Maso M et al. 2019) (Bermejo LM et al. 2019). According to a meta-analysis, alcohol consumption was not associated with an increased risk of BC (Vartolomei MD et al. 2019). In a Swiss meta-analysis, vitamin E, which is an antioxidative agent, was dose-dependently inversely associated with the BC risk (Lin JH et al. 2019).

In a Danish cohort study, frequent urinary-tract infections were risk factor for squamous-cell BC (Pottegard A et al. 2020). A high BMI and waist circumference were also associated with an increased BC risk (Choi JB et al. 2019). According to a meta-analysis, people with diabetes may be at increased risk for developing BC (Larsson SC et al. 2006). In one study, untreated hypertension was associated with a decreased risk of BC (Jiang X et al. 2010). However, another large cohort study reported an increase in the BC risk among hypertensive women and a borderline significant increase among men with elevated blood pressure (Kok VC et al. 2018).

Smoking is also an important risk factor for UC (Zeegers MPA et al. 2000). Coffee consumption has been associated with an increased risk of urinary tract cancer, but no such similar association has been observed for tea consumption (Zeegers MPA et al. 2001). Recurrent primary superficial BC also seems to be a risk factor for upper urinary tract cancer (Millan-Rodriguez F et al. 2000). Urinary tract infections are also a risk factor for upper urinary tract cancers (Sun LM et al. 2013). Vegetable consumption may decrease the risk for UC (Negri E et al. 1991). According to one meta-analysis, alcohol consumption may increase the risk for UC (Zeegers MPA et al. 1999).

3.3 Breast cancer

The most important risk factors for BCa are age, estrogen exposure, obesity, smoking and alcohol consumption. The role of other lifestyle factors in the risk for developing BCa is uncertain.

Age is a clear risk factor also for BCa: the risk of BCa is doubled every ten years until menopause after which the increase in incidence becomes remarkably reduced (McPherson K et al. 2000).

There is also inherited risk for BCa; if a woman has a first-degree family history of BCa, this at least doubles her risk for developing BCa. The highest risk is encountered in women with BCa who have a first degree relative diagnosed before 50 years age or earlier. Up to 10% of cases of BCa in Western countries are estimated to be due to a genetic predisposition (McPherson K et al. 2000). Genetics may explain part of an individual's BCa risk. Two genes, BRCA1 and BRCA2, account for 90% of hereditary BCa but only 5% of all BCas (Mahdavi M et al. 2019) (Van der Groep P et al. 2011). BRCA1 and 2 are associated with BCa at a younger age and with a more aggressive cancer at diagnosis (Loi M et al. 2018). Prophylactic mastectomy reduces the risk for BCa among women carrying these mutations (Honold F et al. 2018) (Peled AW et al. 2014). The removal of ovaries among BRCA1 and 2 carriers also decreases the risk for BCa by approximately 50% (Eisen A et al. 2005).

Estrogen is associated with an elevated BCa risk and therefore factors leading to increased exposure for endogenous or exogenous estrogens are associated with an increased BCa risk (Travis RC et al. 2003). Postmenopausal hormone replacement therapy has been associated with an increased risk of BCa (Santen RJ et al. 2020) and also the use of oral contraceptives may be associated with slightly increased BCa risk (OR 1.5 95% CI 1.3-1.9) (Beaber EF et al. 2014) (Kahlenborn C et al. 2006). Pregnancy seems to protect against BCa while the effect of abortion and infertility treatments on BCa risk is controversial (Britt K et al. 2007) (Reeves GK et al. 2006) (Salhab M et al. 2005). In addition, an early menarche has been associated with an increased risk of BCa whereas breastfeeding is thought to reduce the risk (Unar-Munquia M et al. 2017). The BCa risk also increases along with the mother´s age at the time she experiences labour (Wohlfahrt J et al. 2001).

Alcohol consumption has been associated with an increased BCa risk as compared to non-users (OR = 1.26 95% CI 1.01- 1.59) and the association even seems to be dose-dependent (Rainey L et al. 2019). In addition, smoking in general and particularly before the first labour was associated with an increased BCa risk (HR = 1.45 95% CI = 1.21- 1.74) (Gaudet MM et al. 2013) but also passive smoking may increase the risk (Gao CM et al. 2013). High intakes of sugar, saturated and trans-saturated fats have been claimed to increase the BCa risk (Seiler A et al. 2018). It was reported that physical activity reduced the BCa risk (Guo W et al. 2020). In contrast, the consumption of vegetables did not seem to be associated with the BCa risk (Van Gils Chet al. 2005) (Smith-Warner SA et al. 2001).

Obesity is associated with an increased risk of BCa in both pre-and postmenopausal women and it also impairs the prognosis (Seiler A et al. 2018) (Harvie M et al. 2003) (Neuhouser ML et al. 2015). In addition, treated hypertension has been associated with an increased BCa risk among obese women (Largent JA et al. 2006). Diabetes was linked with an increased risk of BCa among post-menopausal but not among pre-menopausal women (La Vecchia C et al. 2011) (Boyle P et al. 2012). According to a meta-analysis, hypertension was associated with an increased BCa risk among postmenopausal but not among premenopausal women (Han H et al. 2017).

3.4 Ovarian cancer

The risk factors for OC are not as well established as risk factors for prostate, urinary tract, and breast cancer.

Age alone does not seem to be a clear risk factor for OC. Instead, factors related to age like early age at menarche and late age at menopause have been claimed to associate with an elevated risk for OC (Reid BM et al. 2017). There is also a hereditary risk for OC, since if OC has been diagnosed in first-degree relatives, this represents a clear risk factor (Nguyen HN et al. 1994). Mutations in the BRCA1 and 2 genes greatly

increase the lifetime risk for OC and are responsible for up to 15% of familiar OC risk (Malander S et al. 2004) (Pal T et al. 2005).

There is a theory suggesting that the number of lifetime ovarian cycles may be associated with an elevated risk of gene mutations and therefore this would be reflected in the increased OC risk (Casagrande JT et al. 1979) (Moorman PG et al. 2002). Concordantly factors inhibiting the natural ovarian cycle like breastfeeding, pregnancy and hormonal contraceptives have been demonstrated to reduce the risk for OC (Wu ML et al. 1988) (Cramer DW et al. 1983) (Cramer DW et al. 1983) (Risch HA et al. 1994). According to a meta-analysis, endometriosis has been linked with an increased risk of some OC subtypes such as endometrial OC (Sayasneh A et al. 2011). Obesity has been associated with an elevated epithelial OC risk (Olsen CM et al. 2007) whereas a high intake of vegetables as well as physical activity may confer protection (Schulz M et al. 2004) (Olsen CM et al. 2007). Smoking does not seem to be a clear OC risk factor (Franks AL et al. 1987) (Smith EM et al. 1984) and there is no consensus whether alcohol consumption is an OC risk factor (Modugno F et al. 2003) (Goodman MT et al. 2003).

All the individual components of the metabolic syndrome have not been associated with OC risk, but obesity was associated with a poorer OC survival among over 50-year-old women (Björge T et al. 2011). In a Chinese case-control study, the presence of the metabolic syndrome was associated with an elevated epithelial ovarian cancer risk and also with more advanced disease at diagnosis and poorer survival (Chen Y et al. 2017). On the other hand, in an American study, women with metabolic syndrome had a decreased OC risk compared to women not meeting the diagnostic criteria for metabolic syndrome (Michels KA et al. 2019).

In one trial, elevated fasting glucose levels were not associated with the OC risk even though they were linked with increased risks for BCa and endometrial cancer (Lambe M et al. 2011). However according to a meta-analysis of 19 trials, women with diabetes did seem to display a moderately increased risk for OC (RR 1.16 95% CI 1.01–1.33) (Lee JY et al. 2013).

4 COMMONLY USED DRUGS AND CANCER RISK

4.1 Statins

The mechanism of action of statins is the inhibition of the enzyme, HMG-CoA-reductase (3-hydroxy-3-methyl-glutaryl-co-enzyme A) leading to a reduced production of cholesterol in hepatocytes. This in turn increases the amount of low-density lipoprotein (LDL) receptors on the cell membranes of hepatocytes decreasing the level of LDL in plasma (Sirtori CR. 2014). For example, cholesterol is an important precursor of testosterone and testosterone metabolism is active in PCa (Gao F et al. 2018) (Dillard PR et al. 2008). Testosterone in turn plays an important role in advanced PCa, in fact one commonly used treatment is androgen-deprivation therapy (ADT) where the goal is to minimize the effect of testosterone on PCa cells (Perlmutter MA et al. 2007). This role of cholesterol in PCa metabolism has sparked an interest towards using cholesterol lowering drugs, statins. In a Finnish cohort study, statin use was not associated with the total PCa risk but men using statins had a decreased risk for advanced PCa as compared to non-users (Murtola TJ et al. 2007). In another Finnish study, a decreased overall risk of PCa diagnosis was observed among statin users (Murtola TJ et al. 2010). When men were screened for PCa annually with PSA-testing, no association between statin use and PCa risk was observed (PLatz EA et al. 2014). One trial even reported an increased risk of PCa among men using statins (Chang CC et al. 2011).

Statins have not been associated with an increased risk of urothelial cancer (Zhang X et al. 2013) nor have these drugs been shown to alter the BCa risk (Boudreau DM et al. 2007) (Pocobelli G et al. 2008) but in OC, some association has been reported. In a Danish cohort study, statin use was not associated with the epithelial OC risk as compared to non-users (Baandrup L et al. 2015). In contrast, in an English cohort study, statin use was associated with a decreased risk for both serous and non-serous EOC and mucinous EOC (Akinwunmi B et al. 2019). According to one meta-analysis, statin use is associated with a decreased OC risk (RR 0.79 95% CI 0.64–0.98) (Liu Y et al. 2014).

4.2 Non-steroidal anti-inflammatory drugs and aspirin

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit enzymes called cyclo-oxygenases (COX: s). There are two subtypes of COX: s but the COX-2 subtype is the most important in inflammation. NSAIDs non-selectively block both COX subtypes. Aspirin is also classified as an NSAID but nowadays it is primarily used to inhibit arterial thrombosis, for example in coronary artery disease rather than in pain management due to its higher affinity for COX-1 (which is needed in the formation of blood clots and thus important in arterial thrombosis). (Ruskoaho H et al. 2018). NSAID use may be associated with a decreased PCa risk compared to non-users (Nelson JE et al. 2000). In a Finnish cohort study, aspirin, but not other NSAIDs, was associated with a decreased risk of PCa (Veitonmäki T et al. 2013). According to meta-analyses, there is slightly reduced risk of PCa associated with both aspirin and NSAID use (Mahmud SM et al. 2010 and 2004, Wang X et al. 2014).

In UC, the use of NSAIDs and aspirin has been associated with a decreased BC risk (Castelao JE et al. 2000) (Fortuny J et al. 2007) and furthermore the combination of an NSAID and metformin, a drug used to treat type 2 diabetes, has been linked with a decreased BCa risk as compared to non-users (Cotterchio M et al. 2001) (Col NF et al. 2012) (Bodmer M et al. 2010).

Neither NSAIDs nor aspirin use were associated with the OC risk in one trial when compared to non-users (Lacey JV et al. 2004). However, another study reported a decreased OC risk among NSAID (OR 0.74 95% CI 0.52–1.05) and aspirin users (OR 0.56 95% CI 0.35–0.92) while acetaminophen (paracetamol) did not seem to change the OC risk (Peres LC et al. 2016). According to a pooled analysis of 12 case-control studies, aspirin seemed to decrease the risk for OC by a value between 20% to 34% with the risk decline being strongest with low dose (<100mg) aspirin use (OR 0.66 95% CI 0.53-0.83) although high dose (≥500mg) use of other NSAIDs was also associated with decreased risk for OC as compared to non-users (OR 0.76 95% CI 0.64-0.91) (Trabert B et al. 2014).

4.3 Antidiabetic drugs

There are several antidiabetic drugs with different mechanisms of action. According to Finnish treatment guidelines, metformin is the first line drug in treatment of type 2 diabetes (Diabetes care guideline 2020). Metformin acts by decreasing insulin resistance in tissues as well as helping in weight control. There are also other drugs used in the treatment of type 2 diabetes: glitazones which promote the effects of insulin in tissues, glucagon-like-peptide-1 (GLP-1) agonists which increase the secretion of insulin from the pancreas, sodium-glucose transport protein 2 (SGLT-2) inhibitors increasing glucose secretion into urine, dipeptidyl peptidase 4 (DPP4) inhibitors which promote the release of insulin from pancreas and of course the many forms of insulin. (Ruskoaho H et al. 2018)

In a Finnish case-control study, the use of antidiabetic drugs was also associated with a decreased risk of PCa diagnosis when compared to non-users. The risk decrease was observed for multiple antidiabetic drug groups so that diabetes itself might explain the results: diabetes has been associated with a reduced PCa risk (Murtola TJ et al. 2008). As an individual antidiabetic drug, metformin was associated with a decreased PCa risk in two trials (Haring A et al. 2017) (Preston MA et al. 2014) but this result was not confirmed by others (Azoulay L et al. 2011).

According to a meta-analysis, diabetic patients treated with pioglitazone were at a slightly increased BC risk as compared to the healthy population (Ferwana M et al. 2013). In one trial, the consumption of metformin did not alter the BC risk as compared to non-users (Huj et al. 2018). In contrast, long-time metformin use (over 30 prescriptions) among diabetic patients was associated with a lowered risk for OC (OR 0.61 95% CI 0.30–1.25) while long-time insulin use (over 40 prescriptions) was claimed to slightly elevate the risk (OR 2.29 95% CI 1.13–4.65) as compared to non-users (Bodmer M et al. 2011). In a Taiwanian cohort study, metformin use among diabetic patients seemed to decrease the OC risk (Tseng CH et al. 2015). Therefore, according to a meta-analysis, metformin use seems to be associated with a decreased OC risk and with improved prognosis among diabetic women as compared to non-users (Shi J et al. 2019).

4.4 Finasteride and dutasteride

Finasteride and dutasteride are inhibitors of 5-alpha-reductase, an enzyme involved in the production of dihydrotestosterone (DHT) from testosterone. DHT is a biologically active compound which mediates the effects of testosterone in prostate. Both finasteride and dutasteride decrease prostate levels of DHT. (Ruskoaho H et al. 2018). According to one study, finasteride use was associated with a decreased PCa risk (Irani J et al. 2002). In contrast, the results from a clinical trial, indicated that finasteride use was associated with an elevated high-grade PCa risk as compared to non-users. However, this may be partly explained by the lower proportion of low-risk cases in the finasteride group and thus more high-risk cases receiving this

treatment (Ford LG et al. 2007). The consumption of dutasteride has also been associated with a decreased PCa risk (Andriole G et al. 2004).

4.5 Antihypertensive drugs

There are several groups of anti-HT medications which will be discussed more closely later in the thesis.

The use of antihypertensive medication in general and especially calcium-channel blockers have been associated with a decreased PCa risk compared to non-users (Fitzpatrick AL et al. 2001). In another trial, antihypertensive drug use was not associated with the risk of PCa diagnosis (Pai PY et al. 2015). Beta-blockers as well as ATR-blockers have been associated with a decreased PCa risk in one study (Perron L et al. 2004). However, in another study, ATR-blockers were instead claimed to increase the risk of PCa (Bhaskaran K et al. 2012). As a single drug, captopril, but not other ACE-inhibitors, has been linked with a decreased PCa risk (Ronquist G et al. 2004). In a Finnish cohort study, the use of ACE-inhibitors, beta-blockers and diuretics was associated with an elevated risk for PCa diagnosis as compared to non-users (Siltari A et al. 2018). According to a meta-analysis, no clear relationship between ACE-inhibitors, ATR-blockers, beta-blockers, diuretics, and risk of PCa diagnosis could be identified although calcium-channel blockers may be associated with an increased risk of PCa diagnosis as compared to non-users (Cao L et al. 2018).

In one meta-analysis, when compared to non-users, ATR-blocker therapy, but not other antihypertensive drugs, was associated with a slightly increased risk of BC diagnosis (RR 1.07 95% CI 1.03-1.11) (Xie Y et al. 2020).

It has been postulated that antihypertensive drugs in general may be associated with an increased BCa risk (Largent JA et al. 2010). When analysed, separately calcium-channel blockers were associated with an increased risk of BCa while beta-blockers, diuretics and ATR-blockers did not seem to modify the BCa risk (Li CI et al. 2013) (Saltzman BS et al. 2013). In other studies where antihypertensive drugs were analysed as one group, no association was observed between BCa risk and antihypertensive drug use (Fryzek JP et al. 2006) (Devore EE et al. 2015).

As a single drug group, thiazides were associated with an increased OC risk whereas this did not extend to other antihypertensives (Huang T et al. 2016). Thiazides have also been associated with increased risk of skin cancer including melanoma (Shao SC et al 2022).

5 DIAGNOSIS AND SCREENING

5.1 Prostate cancer

An enlarged prostate and possible protuberances within the tissue may be found in a digital rectal examination (DRE) conducted by physician and together with PSA (prostate-specific antigen)-testing, it may serve as a guide in the PCa diagnosis (Catalona WJ et al. 2017). A suspicion of PCa due to a high PSA level or an abnormal finding in DRE in primary health care will lead to referral to a urological clinic in a secondary care hospital. Often in cases where there is a suspicious PSA- level, prostate MRI is used as a further examination. If the suspicion of PCa is confirmed in MRI, then a transrectal ultrasound may be performed and routine biopsies from prostate taken to set a definitive diagnosis. Prostate biopsies can be targeted to collect specimens on lesions that appear to be suspicious of PCa in the prostate MRI.

5.1.1 Screening

Methods for PCa screening have been actively searched as PCa is an expensive and common disease causing many cancer deaths among men (Globocan cancer statistics 2018). PSA is a protein almost exclusively produced in prostate cells. It is found in low circulatory levels in the serum. PSA levels in serum may increase in several conditions like benign prostate hyperplasia (BPH), prostatitis and after catheterization but also in PCa (Liotta RF et al. 2008) (Torricelli FC et al. 2011). In PCa-screening, PSA is the only marker that has been studied extensively as a screening tool and although other biomarkers are being developed, they are not in clinical use (Saini S et al. 2016). In addition to serum total PSA, also the amount of free PSA (not bound to carrier proteins) is calculated and the level of free PSA is divided with total PSA to obtain the PSA-ratio. This increases the test's sensitivity of finding high-grade PCa cases which would be missed using only the total PSA- concentration (Rowe EW et al. 2005).

The main problem in PCa diagnostics is the inability to differentiate between high-grade, potentially fatal PCa and low-grade slow growing cancers which will not metastasize. It is estimated that 70-80% of PCa diagnosed in over 80-year-old men are latent and only 10% of them will develop into a clinically significant form of PCa (Prostate cancer guideline 2014). PSA-testing increases the incidence of latent low-grade PCa, causing overtreatment as these tumors often would not progress to cause problems even if left untreated. These facts and the false positive results (for example due to prostatitis, BPH) limit the ability to use PSA-testing for PCa screening alone at an asymptomatic population level.

The European Randomised Study of Screening for Prostate Cancer (ERSPC) detected an increase among PCa incidence due to PSA-testing (RR 1.63 95% CI 1.57-1.69) but also an improvement in the risk of PCa death after 11 years of follow-up (RR 0.79 95% CI 0.68-0.91) (Schroder FH et al. 2014). It was also concluded that to avoid one PCa death after follow-up of 11 years a total of 38 men should be diagnosed with PCa.

In The Prostate, Lung, Colorectal and Ovarian (PLCO) screening trial, also an increase in PCa incidence was observed (RR 1.12 95% CI 1.07-1.17) but this was less extensive than in ERSPC. However, after 13 years, no PCa survival benefit was observed with PSA-testing in PLCO (RR 1.09 95% CI 0.87-1.36). (Andriole GL et al. 2012). There are also some other studies which also have not detected any survival benefits in screening at the population level (Andriole GL et al. 2009) (Sandblom G et al. 2011). These

differences between mortality outcomes are likely caused by differences in opportunistic screening activity outside of trial protocols and different lengths of screening intervention.

According to a meta-analysis, PSA-testing should be considered on an individual basis evaluating the possible advantages and disadvantages of a PCa diagnosis. When an elevation in PSA is observed, the need for needle biopsy should be re-considered and when a new PCa diagnosis is set, conservative treatment options as far as possible should be used (Hayes JH et al. 2014). According to the newest meta-analysis, the harms from screening outweigh its benefits (Ilic D et al. 2018).

In clinical practice, attitudes toward PSA testing vary between physicians. Urologists use the test more easily in asymptomatic men than general practioners (Pogodin-Hannolainen et al. 2011). However, PSA testing is an important tool in the differential diagnostics of men exhibiting symptoms in their urinary system.

5.2 Urinary tract cancer

The vast majority, 90%, of BCs are urothelial carcinomas with the rest being squamous cell carcinomas, adenocarcinomas, and sarcomas (Taari K et al. 2013).

Macroscopic painless hematuria is one of the most common symptoms experienced by individuals with BC: 67-85% of patients have had macroscopic hematuria before the BC diagnosis (Sell V et al. 2019) (Wakui M et al. 2000). However, hematuria is not specific for BC: only 28% of patients with macroscopic hematuria are diagnosed with BCa (Kirkali Z et al. 2005). The presence of hematuria correlates neither with tumor size nor with infiltration depth (Wawroschek F et al. 2003). In addition to macroscopic hematuria, also microscopic hematuria can occur in BC, but it is more common in nephrological diseases like nephritis. In one study, only 1.2% of participants with microscopic hematuria were diagnosed with BC. None of the BCs diagnosed in patients with asymptomatic microhematuria were found in persons younger than 50 years (Gonzalez AN et al. 2019). Partial or total urinary retention can also be a symptom of BC or UTUC when the tumor causes constriction of the ureter or bladder at the upper part of the urethra. Difficulties in emptying the bladder or pain during urination alone are rarely symptoms of BC: according to one study, only 4.1% of BC patients reported symptoms from their lower urinary tract region (hesitation, urgency, difficulties in emptying the bladder) before diagnosis (Dobbs RW et al. 2014).

Macroscopic hematuria is an indication requiring a referral to a urological clinic in secondary care hospital. Before invasive investigations, patients are examined for urinary tract infections with urine bacterium culture and urine cells. In addition, urine cytology is performed to detect the presence of cells which are atypical or suspicious for cancer. The sensitivity of cell cytology in BC diagnostics is as high as 94% but the specificity is only up to 26% depending on values from different investigators. It has been claimed that the sensitivity of cell cytology for high-grade BC is better (51%) compared to low-grade (18%) but specificity for both is approximately the same at 26% (Abdullah LS et al. 2013). The Paris system established in 2015 is a standardized international system for reporting urine cytology (VandenBussche CJ 2016).

Normal cytology does not rule out BC with most tumors being detected macroscopically and in unclear cases, biopsies can be taken. In the case of macroscopic hematuria, there is also a need for imaging of the upper urinary tract for possible upper tract urothelial carcinomas or cancer metastases. Today´s imaging method of choice is CT (computed tomography) but alternatively ultrasound can be used to detect kidney tumors as the reason for the hematuria. The sensitivity of CT in small T3-T4 BC tumors is only 60-80% (Taari K et al. 2013) and the likelihood of a false negative result is as high as 40% for nodes under 1cm and distant metastases. Magnetic resonance imaging (MRI) has been examined in evaluating BC infiltration depth and due to its higher sensitivity than CT, it may be helpful in staging BC already before surgery

(Ghafoori M et al. 2013). The Vesical Imaging-Reporting and Data System (VI-RADS) is used to standardize imaging and report BC staging with MRI (Pecoraro M et al. 2020).

The final diagnosis of BC is usually conducted with TURB (transurethral resection of bladder) which is done either under general anesthesia with local relaxation or with spinal anesthesia. Tissue samples removed in TURB ensure the diagnosis and make possible the TNM-classification. The most important part of the classification is to evaluate infiltration depth and grade as these affect the likelihood of disease progression to advanced disease. There are some other factors that predict disease progression i.e., tumor size, multifocality of tumor and the presence of carcinoma in-situ. If the presence of muscle invasion remains unclear after the first TURB or in the case of high-grade tumors, TURB must be conducted again within one month to check for the presence of possible residual tumor (second look TURB). (Taari K et al. 2013)

There are no screening methods for BC at the population level and there are no biomarkers in clinical use. The only way to decrease prevalence and incidence of BC and UTUC is to decrease the prevalence of smoking which is the most important risk factor for both cancers. Another important factor affecting disease prognosis is the delay in the patient´s access to secondary health care. According to a Finnish study, the median delay before first health care contact was 7 days after symptoms started followed by a median delay from primary health care to urological clinic of 8 days. Total median time before operative treatment was 78 days. Ex-smokers and current smokers seemed to obtain access to the health care system more rapidly than never-smokers (Sell V et al. 2019).

5.3 Breast cancer

Most BCas emerge from the epithelium of ducts or lobules and therefore are called ductal or lobular carcinomas. The most common symptom of BCa is a lump palpable in the breast. Other symptoms include eczema in breast skin and in advanced disease there may be bone pain and swollen lymph nodes. When a suspicion of BCa arises, breast ultrasound and X-ray imaging should be undertaken. A biopsy from the tumor is taken for pathological diagnosis with or without ultrasound control. The primary treatment in local BCa is surgical removal of tumor. (Leppäniemi A et al. 2010)

Before surgery, axillary ultrasound imaging is carried out to evaluate the status of local lymph nodes with a biopsy being taken from the most suspicious node when required (Nori J et al. 2007) (Diepstraten SC et al. 2014). The proportion of false negative results in ultrasound imaging is as high as 25% and it does not exclude lymph node metastases: sentinel lymph nodes are therefore collected during surgery for subsequent pathological analyses (Diepstraten SC et al. 2014).

The sentinel lymph node is the first node in the lymphatic system in the route from breast into axilla and towards the lymphatic system. Therefore, if the sentinel lymph node contains no cancer cells, it is estimated that there is no nodal spread, and a complete axillary lymph node dissection is not needed. According to one study, the rate of false negative results in sentinel node biopsy was only 1.4% i.e., it is a very sensitive procedure (Chung MA et al. 2002). Sentinel lymph node analysis has also been proved to be accurate and safe in the detection of lymph node metastases as compared to total axillary dissection which was generally used before sentinel lymph node dissection was discovered (Veronesi U et al. 2003) (Nano MT et al. 2002). If nodal involvement is observed, neoadjuvant and adjuvant therapies like cytostatics, radiation therapy and hormonal treatments are used to prevent progression to metastatic disease.

5.3.1 Screening

One way to screen for BCa is clinical breast examination by the patient herself or her doctor. The focus is to find palpable masses which could be tumors in the breast. This is not part of any screening program but is highly recommended for patients and can be conducted also by a doctor in health care if there is a suspicion of BCa. However, self-examination conducted by non-symptomatic women themselves has not been associated with a decreased risk of BCa death (Hackshaw AK et al. 2003) while examination conducted by physician may be associated with improved BCa survival (Weiss NS et al. 2003). Breast self-examination is therefore not routinely recommended in all countries.

In Finland, all 50-69-year-old women are invited to come for breast X-ray imaging, i.e., mammography, every second year to screen for BCa. The screening program was started in 1978 (Sarkeala T et al. 2008). There has been discussion whether mammography would be effective also among under 50-year-old women: at least according to a Japanese case-control study, it could be cost effective also among 40–49-year-old women (Morimoto T et al. 2000). Another older study had the same results claiming that mammography was as accurate among pre- and post-menopausal women (Davies RJ et al. 1993). MRI is more sensitive than mammography and can be used in specific cases such as among women with a high hereditary risk for BCa (Narayan AK et al. 2016). Mammography screening has been proved to improve BCa survival (Kaplan HG et al. 2015) (Zielonke N et al. 2020) and in a Finnish study, it improved BCa survival also among women in whom there was local spread into regional lymph nodes (Klemi PJ et al. 2003). The costs of screening rise in association with the reduction in BCa mortality, depending on number of lifetime screens per women and procedures performed due to mammography findings (Mittmann N et al. 2018). Therefore, the protocol of screening and the whole pathway from a positive finding in X-ray to BCa treatment must be planned carefully. Mammography may also lead to over diagnostics and has especially raised the incidence of DCIS (carcinoma in-situ) which are seldom found by clinical examination only (Heinävaara S et al. 2014).

5.4 Ovarian cancer

Approximately 1-2% of women will be diagnosed with OC during their lifetime with about 400 new OC being diagnosed in Finland every year. Epithelial ovarian cancer is the most common subtype of ovarian cancer accounting for 90% of OC in Western countries (Jayson GC et al. 2014) (Sankaranarayanan R et al. 2006). OC is responsible for 30% of gynecological cancers but causes 50% of gynecological cancer deaths (Jayson GC et al. 2014) (Sankaranarayanan R et al. 2006). Five-year survival in OC is only 44% in Finland (Cancer in Finland 2018). In general, OC is not a disease of young women; in global terms, the median age at time of OC diagnosis is over 60 years (DeSantis CE et al. 2014). The dismal prognosis is due to difficulties in early diagnosis; for example, high-grade serous cancer (the most common subtype of epithelial cancer, HGSC) is diagnosed in an advanced stage (stage III-IV) in almost 90% of cases (Tapanainen J et al. 2019). The dismal prognosis is due to difficulties in early diagnosis; for example, high-grade serous cancer (the most common subtype of epithelial cancer, HGSC) is diagnosed in an advanced stage (stage III-IV) in almost 90% of cases (Tapanainen J et al. 2019).

As mentioned, both local benign and malignant ovarian tumors can be totally asymptomatic. When there are symptoms, they tend to be non-specific like slight or moderate abdominal pain, palpable abdominal mass, fatigue, or loss of appetite (Ebell MH et al. 2016). The three most common symptoms are swelling of abdomen, abdominal pain and other symptoms linked with gastrointestinal irritation. It is not known whether OC could be identified when it is still in the local stage if it could be found at the appearance of the first non-specific symptoms (Friedman GD et al. 2005). Weight loss and fever may occur especially in the

advanced stage when there may also be symptoms occurring from other organs like urinary urgency, hesitation, constipation, lower abdominal pain, or dyspareunia due to metastases (Behtash N et al. 2008). Sometimes bleeding from uterus may occur outside of the menstrual period if the tumor has spread into uteral mucosa or produces estrogen (Khan A et al. 2010) (Bankhead CR et al. 2008). Symptoms are non-specific for OC and common also in other conditions managed in primary health care which makes early diagnostics of OC very difficult (Hamilton W et al. 2009) (Goff BA et al. 2004). Swelling of stomach caused by ascites is one common symptom which may lead to contact with health care personnel. Pain from almost any abdominal organ can occur in advanced disease. Sometimes even pleural effusion and dyspnea are present in advanced OC (Kim KW et al. 2010). Typically, OC spreads also to a non-symptomatic stage inside the abdominal cavity and peritoneum; this is thought to be due to ovarian cancer cells spreading along with vessel and diaphragm movements (Wang E et al. 2005) (Pickel H et al. 1989). In addition, spreading may occur via the lymphatic system with typical findings being metastatic nodules in the pelvis and the para-aortal region (Bogani G et al. 2017) (Pickel H et al. 1989) (Ebell MH et al. 2016).

A suspicion of OC may arise due to symptoms or may become apparent in imaging. Tender resistance next to the uterus may be found in gynecological manual palpation. However, a malignant ovarian tumor may also be soft and mobile. Ascites may be noticed in abdominal palpation and nodal enlargements in the groins may also be palpable. Vaginal ultrasound may be able to detect a hyper vascular tumor (Moro F et al. 2018).

The levels of cancer antigen 125, CA-125 are elevated in most OC cases but this is not specific for OC and not sensitive enough for screening (Scholler N et al. 2007). For example, individuals suffering from endometriosis, colon carcinoma and pelvic inflammatory disease may have elevated levels of the marker, leading to a false positive finding (Mol BW et al. 1998). Furthermore, the CA-125 level is elevated at diagnosis only in every second woman with local epithelial cancer. In an advanced stage, it is elevated in up to 80% of women. The levels are highest in poorly differentiated serous OC. CA-125 can be used in follow-up after treatment if it was elevated at the time of diagnosis (Salminen L et al. 2019) (Guo N et al. 2017). Human epididymis protein 4, HE4 is more specific for OC than CA-125 and may help to differentiate OC from other conditions elevating CA-125 (Yucel E et al. 2017). Granulosa cell tumors arising from sex-cord stromal cells sometimes produce inhibin and anti-Mullerian hormone (AMH) which may be used both in diagnostics and follow-up (Tapanainen J et al. 2019) (Scholler N et al. 2007). The levels of carcinoembryonic antigen, CEA are often elevated in colon carcinoma and stomach cancer and thus it can be used in differential diagnostics when OC has become metastatic. Granulosa cell tumors arising from sex-cord stromal cells sometimes produce inhibin and anti-mullerian hormone (AMH) which may be used in diagnostics and follow-up. (Tapanainen J et al. 2019)

Vaginal ultrasound is the main imaging method in diagnostics of OC. It is often diagnostic and can even be used to differentiate between benign versus malignant ovarian tumors. Benign tumors are often cystic while malignant are cystic-solid. Malignant tumors are also often bilateral and sometimes ascites may be observed in the abdominal cavity. Computed tomography (CT) is the method of choice to evaluate the extent of disease progression. There are no screening methods for OC which can be applied at the population level. (Tapanainen J et al. 2019)

6 PROGNOSTIC FACTORS

6.1 Prostate cancer

The most common histopathology of PCa is adenocarcinoma which accounts for over 90% of all PCas. Some PCas like small cell adenocarcinoma or carcinoid tumors may have neuroendocrine properties, producing hormones but atypical adenocarcinoma variants such as mucinous and ductal adenocarcinoma may be also found whereas squamous cell carcinomas and sarcomas are rare. Sometimes a systemic malignancy such as leukemia or lymphoma can manifest in the prostate; other solid cancers rarely metastasize to the prostate (Pathology of prostatic neoplasia in: Walsh PC: 3025-3037).

Prognostic factors in PCa can be categorized into those predicting disease recurrence after primary treatment and those predicting metastatic disease and PCa death with both predicted by tumor extent, the primary level of PSA and the Gleason score (GS) which is a grading system for PCa. The total blood PSA-level at diagnosis is the most important prognostic marker in the evaluation of risk for PCa death in local disease. In advanced disease, the most important factors are GS and cell nuclear morphology (Buhmeida A et al. 2006). The Finnish Prostate Cancer Screening Trial was a case-control study which evaluated factors affecting the risk of PCa death; PSA levels between 6 and 10 were associated with a poorer prognosis than levels below 6 and GS points were associated with the risk of PCa death in the screening arm. Comorbidities were also associated with an increased risk of PCa death in the control arm. Age was associated with an increased PCa death risk. (Neupane S et al. 2018). Poorly differentiated cancer, invasion into seminal vesicles, lymph node metastases as well as all forms of extra prostatic spread have been associated with an increased risk of PCa death after radical prostatectomy (Eggener SE et al. 2011).

Factors associated with risk of disease recurrence after primary treatment are high tumor volume, remaining surgical margin after prostatectomy and high Ki-67 proliferation index after prostatectomy. Ki-67 is a cellular marker of tumor proliferation.

6.1.1 Gleason Score (GS)

The Gleason Score (GS), created in the 1960-70s, is used to estimate the aggressiveness of PCa and to choose the most appropriate treatment methods (Chen N et al. 2016) (Table 1). It has good prognostic value in evaluating the prognosis of PCa (Helpap B et al. 2016). The scale of GS is between 1 and 5 and it is determined by the histological appearance of the tumor. PCa consists often of cells with different histological appearances and thus the total Gleason Score is formed by the two main types of cells (Chen N et al. 2016). Scores of the largest and the second largest area of cancer are added together to form a total GS. Thus, the maximum total Gleason Score is 5+5=10 and minimum 1+1=2. Gleason 10 describes the most poorly differentiated tumor having the worst prognosis while GS 2 is the best differentiated with the best prognosis (Chen N et al. 2016). GS has good prognostic value in evaluating the prognosis of PCa (Helpap B et al. 2016). The scale of GS is between 1 and 5 and it is determined by the histological appearance of the tumor. PCa consists often of cells with different histological appearances and thus the total Gleason Score is formed by the two main type of cells (Chen N et al. 2016). Scores of the largest and the second largest area of cancer are added together to form the total GS. Thus, maximum of total Gleason Score is 5+5=10 and minimum 1+1=2. Gleason 10 describes the most poorly differentiated tumor having the worst prognosis while GS 2 is the most well-differentiated with the best prognosis.

The ISUP-classification (grade group) is a modified version of GS which was generated in 2005 by the International Society of Urological Pathology (ISUP). It is claimed to be better than GS especially in the estimation of follow-up strategies in men in the low-grade stage. (Erickson A et al. 2018).

Table 1: International Society of Urological Pathology 2014 grade (group) system

Gleason score	**ISUP grade**
2-6	1
7 (3+4)	2
7 (4+3)	3
8 (4+4 or 3+5 or 5+3)	4
9-10	5

From EAU prostate cancer guidelines 2021

6.1.2 TNM- classification

Tumor-node-metastasis (TNM)-classification is used to describe the anatomic extent of the disease (Table 2). The Union for International Cancer Control (UICC) publishes and maintains internationally accepted TNM-classifications for malignant tumors. It contains information of the local extent at primary site (T), regional nodal spread (N) and metastatic spread (M).

Table 2: Clinical Tumour Node Metastasis (TNM) classification of PCa

T - Primary Tumour (stage based on digital rectal examination [DRE] only)		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
T1	Clinically inapparent tumour that is not palpable	
	T1a	Tumour incidental histological finding in 5% or less of tissue resected
	T1b	Tumour incidental histological finding in more than 5% of tissue resected
	T1c	Tumour identified by needle biopsy (e.g., because of elevated prostate-specific antigen [PSA])
T2	Tumour that is palpable and confined within the prostate	
	T2a	Tumour involves one half of one lobe or less
	T2b	Tumour involves more than half of one lobe, but not both lobes
	T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule	
	T3a	Extracapsular extension (unilateral or bilateral)
	T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall	
N - Regional (pelvic) Lymph Nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
M - Distant Metastasis		
M0	No distant metastasis	
M1	Distant metastasis	
	M1a Non-regional lymph node(s)	
	M1b Bone(s)	
	M1c Other site(s)	

From EAU prostate cancer guidelines

6.1.3 Risk classification

Risk classification is used in local (T1–2c, N0, M0) PCa to decide primary treatment (surgery, radiation, other) and to estimate the risk for recurrence (Table 3). According to Finnish PCa guidelines, PCa risk groups are low risk, moderate risk, high risk and very high risk while in the EAU guidelines the high and very high-risk groups are included in the same category. Low risk PCa is clinically T1–T2a, N0, M0 and GSS<7 and PSA-level < 10microg/l. The moderate risk group contains PCa with one of the following criteria: T2b or GSS=7 or PSA 10-20 microg/l. The high-risk group is designated as those with T2c-T3a or GSS 7 or 8-10 or PSA> 20microg/l. The very high-risk group includes men with clinical T3b-T4 or whichever T class but N1. Moderate and high-risk groups have some overlapping features as PCa with GSS value 7 is included in both classifications.

Table 3: EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

Definition			
Low-risk	**Intermediate-risk**	**High-risk**	
PSA < 10 ng/mL and GS < 7 (ISUP grade 1) and cT1-2a	PSA 10-20 ng/mL or GS 7 (ISUP grade 2/3) or cT2b	PSA > 20 ng/mL or GS > 7 (ISUP grade 4/5) or cT2c	any PSA any GS (any ISUP grade) cT3-4 or cN+
Localised			**Locally advanced**

GS = Gleason score; ISUP = International Society for Urological Pathology; PSA = prostate-specific antigen

From EAU prostate cancer quidelines

6.2 Urinary tract cancer

Urothelial carcinoma is the most common bladder cancer histology and accounts for 90% of all BCs, followed by squamous cell carcinoma, adenocarcinoma, neuroendocrine and some other tumors. The urothelial epithelium in the bladder contains many cell layers under which is the basement membrane. Tumors not penetrating through the basement membrane (growing only inside the bladder) are called non-

muscle invasive bladder cancer (NMIBC). BC is called muscle invasive (MIBC) when it penetrates to lamina propria and when it may send distant metastases (Hansel DE et al. 2013).

Prognostic factors are categorized in those predicting NMIBC recurrence after surgical resection and those predicting tumor invasion and distant spread. Carcinoma in-situ is a risk factor for distant spread. Tumor size, multifocal tumors and grade are risk factors for both NMIBC recurrence and distant spread, and finally nodal involvement is a risk factor for distant spread.

Risk factors for NMIBC recurrence are female gender, smoking, tumor size, multifocal tumors and high grade (Lu M et al. 2019) (Ozbir S et al. 2014) although not all investigators agree about the role of gender (Ozbir S et al. 2014). Stage affects the risk of BC recurrence as the more advanced stage at time of cystectomy, the greater is the risk for local and distant recurrences. Local recurrences can occur at the site of the removed bladder. (Hernandez-Fernandez C et al. 2017) (Boc A et al. 2018)

According to WHO, bladder cancers are divided into three classes in terms of tumor differentiation: grade 1 (well differentiated), grade 2 (moderately differentiated) and grade 3 (poorly differentiated) (Mostofi FK et al. 1974). WHO has revised the classification in 2004 and the new names are low grade (grade 2), high grade (grade 3) and papillary urothelial neoplasm of low malignant potential (PUNLMP) (grade 1) (Montironi R et al. 2005) (Table 4). However, the European Association of Urology recommends the use of both classification systems in parallel because most studies utilized the old classification, and the new classification is still based on quite a low number of BC cases.

Table 4: WHO classification in 1973 and in 2004/2016

1973 WHO classification system
Grade 1: well differentiated Grade 2: moderately differentiated Grade 3: poorly differentiated
2004/2016 WHO classification system (papillary lesions)
Papillary urothelial neoplasm of low malignant potential (PUNLMP) Low-grade (LG) papillary urothelial carcinoma High-grade (HG) papillary urothelial carcinoma

From EAU Non-muscle invasive bladder cancer quidelines

6.2.1 TNM-classification

The TNM-staging is also used in BC classification as in the classification of other cancers (Table 5). In it, BCa is classified into different groups based on tumor extent and tumor invasivity. At diagnosis, 70-80% of

BCa are present at the Tis, Ta or T1 stage when they have not grown through the basement membrane (NMIBC). (Taari K et al. 2013)

Table 5: 2017 TNM classification of urinary bladder cancer

T - Primary tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Ta	Non-invasive papillary carcinoma	
Tis	Carcinoma *in situ*: 'flat tumour'	
T1	Tumour invades subepithelial connective tissue	
T2	Tumour invades muscle	
	T2a	Tumour invades superficial muscle (inner half)
	T2b	Tumour invades deep muscle (outer half)
T3	Tumour invades perivesical tissue	
	T3a	Microscopically
	T3b	Macroscopically (extravesical mass)
T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall	
	T4a	Tumour invades prostate stroma, seminal vesicles, uterus or vagina
	T4b	Tumour invades pelvic wall or abdominal wall
N – Regional lymph nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in common iliac lymph node(s)	
M - Distant metastasis		
M0	No distant metastasis	
	M1a	Non-regional lymph nodes
	M1b	Other distant metastases

From EAU Non-muscle invasive bladder cancer quidelines

The classification and morphology of UTUC and bladder carcinoma are similar (Table 6).

Table 6: TNM classification 2017 for upper tract urothelial cell carcinoma UTUC

T - Primary tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
	Ta	Non-invasive papillary carcinoma
	Tis	Carcinoma *in situ*
T1	Tumour invades subepithelial connective tissue	
T2	Tumour invades muscularis	
T3	(Renal pelvis) Tumour invades beyond muscularis into peripelvic fat or renal parenchyma (Ureter) Tumour invades beyond muscularis into periureteric fat	
T4	Tumour invades adjacent organs or through the kidney into perinephric fat	
N - Regional lymph nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Metastasis in a single lymph node 2 cm or less in the greatest dimension	
N2	Metastasis in a single lymph node more than 2 cm, or multiple lymph nodes	
M - Distant metastasis		
M0	No distant metastasis	
M1	Distant metastasis	

TNM = Tumour, Node, Metastasis (classification)

From EAU UTUC Guidelines

6.2.2 Risk classification

Non-muscle invasive bladder cancer (NMIBC) is also stratified by the likelihood for disease recurrence and progression (Table 7). The categories are low risk, intermediate risk and high risk and there are several factors affecting the risk of recurrence i.e., number of tumors, size of tumors, whether there is a recurrence during 3 months, earlier frequent recurrences, T-classification, grade of tumor and whether it has been found concomitant with a papillary tumor. In muscle invasive disease, the most important factors for risk of recurrence are deepness of tumor infiltration into the muscle layer, whether patient has node metastases, patient's age, and general condition. (Taari K et al. 2013)

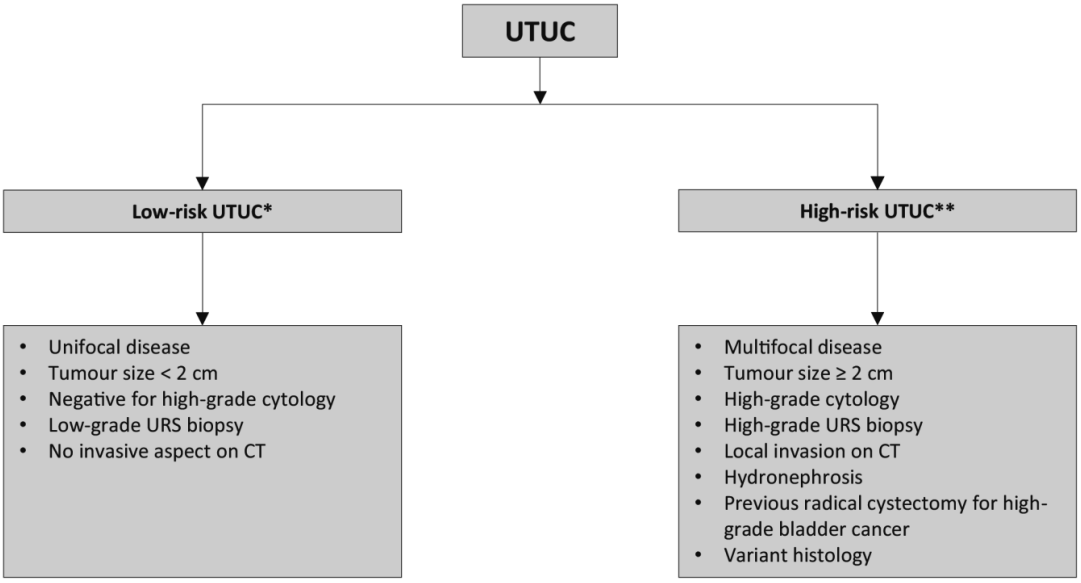
Table 7. Clinical composition of the new EAU NMIBC prognostic factor risk groups based on the WHO 2004/2016 or the WHO 1973 grading classification systems

Risk group	
Low Risk	A primary, single, Ta/T1 LG/G1 tumour < 3 cm in diameter without CIS in a patient < 70 years
	A primary Ta LG/G1 tumour without CIS with at most ONE of the additional clinical risk factors (see above*)
Intermediate Risk	Patients without CIS who are not included in either the low, high or very high-risk groups
High Risk	All T1 HG/G3 without CIS, EXCEPT those included in the very high-risk group All CIS patients, EXCEPT those included in the very high-risk group
	Stage, grade with additional clinical risk factors: Ta LG/G2 or T1 G1, no CIS with all 3 risk factors Ta HG/G3 or T1 LG, no CIS with at least 2 risk factors T1 G2 no CIS with at least 1 risk factor
Very High Risk	**Stage, grade with additional clinical risk factors:** Ta HG/G3 and CIS with all 3 risk factors T1 G2 and CIS with at least 2 risk factors T1 HG/G3 and CIS with at least 1 risk factor T1 HG/G3 no CIS with all 3 risk factors

From EAU UTUC quidelines

Risk stratification of UTUC is described below (Figure 1).

Figure 1: Risk stratification of non-metastatic UTUC.



CT = computed tomography; URS = ureteroscopy; UTUC = upper urinary tract urothelial carcinoma.

* All these factors need to be present.

**Any of these factors need to be present

From EAU UTUC Guidelines

6.3 Breast cancer

Breast cancers can be divided into many subtypes according to their histology. Ductal carcinoma in situ (DCIS) is a non-invasive cancer growing in the ductal epithelium. It does not penetrate the basement membrane and thus does not send metastases (Wellings SR et al. 1973). Curative treatment of DCIS is surgery (Leppäniemi A et al. 2010). The use of mammography has increased the number of DCIS detected as they are most commonly found in X-ray imaging (Statbite 2011) (Ernster VL et al. 1997) and it is a rare occurrence that DCIS can be found by physical examination of the breast. DCIS can further be divided into several subtypes. (Leppäniemi A et al. 2010)

Invasive breast cancers are divided into two categories: ductal and lobular carcinomas which in turn can be divided into subgroups. They differ not only in their growth pattern but also genetically. The term invasive means that BCa has invaded through the basement membrane. The molecular classification of BCa divides it into luminal-A, luminal-B, HER2 and basal BCa. Luminal-A has the best prognosis as it is often well differentiated, estrogen-positive and HER2-negative. Luminal-B has a poorer prognosis. The worst

prognosis is in women with basal BCa which is often poorly differentiated, estrogen-negative, and HER2-negative. (Leppäniemi A et al. 2010)

Ductal carcinoma accounts for the majority, even up to 75-90% of breast cancers with invasive lobular carcinoma as the second most common (10-15%). The epidemiology as well as the prognosis of different cancer types and tumor characteristics depend on age: young (under 40-year-old) women may have a worse prognosis compared to older women (Yazdani-Charati R et al. 2019) (Kong Y et al. 2013) (Tsuchiya SI et al. 2016) (Leppäniemi A et al. 2010)

There is also another subtype of BCa. Inflammatory BCa is rare and typically causes swelling and redness of the breast. It is seldom found in mammography or by physical examination (Molckovsky A et al. 2009). This cancer may be found accidentally in a skin biopsy taken from the involved skin area. Unfortunately, due to symptoms, patients with inflammatory BCa may have been treated with several antibiotics before BCa diagnosis: therefore, inflammatory BCa should be considered always when a non-breast-feeding woman has symptoms of mastitis (Tsuchiya SI et al. 2016). The inflammation in inflammatory BCa is mediated by various markers such as interleukin-6 and COX-2 which are inflammatory cytokines in normal physiological inflammation (Fouad TM et al. 2014). Inflammation parameters like CRP levels and leukocyte numbers can also be elevated. (Leppäniemi A et al. 2010)

Paget´s disease is another rare subtype of BCa; an adenocarcinoma in the nipple or areola with diagnosis being made by a skin biopsy. The most common symptom of Paget´s disease is a red plaque or a rash in the nipple or areola. Paget's disease is often accompanied with DCIS or invasive carcinoma. Treatment involves removal of the areola, nipple and possibly the invasive tumor in the breast. Prognosis is good with 5-year survival of 75-95%. (Morris CR et al. 2020) (Leppäniemi A et al. 2010)

Grade is a classification describing how well BCa cells are differentiated as compared to normal breast tissue. There are three categories for grade which are low-grade (cells well differentiated), intermediate grade (moderately differentiated) and high-grade (poorly differentiated) (Leppäniemi A et al. 2010). High-grade breast cancer has the worst prognosis (Talman ML et al. 2007) (Schneeweiss A et al. 2004) (Zhang T et al. 1998).

6.3.1 TNM-classification

The TNM-classification is used also in BCa as in other cancers, but the classification is modified according to the cancer type (Table 8). Stage describes tumor extent. There are three main stages: 0-1 which includes carcinoma in-situ and Paget´s disease. Stages 1-3 refer to an invasive cancer in breast tissue and/or in regional lymph nodes. Stage 4 includes metastatic cancer which has the poorest prognosis as compared to the others (Sawaki M et al. 2019) (Hortobagyi GN et al. 2018).

Table 8. TNM-classification of BCa according to WHO

Tis	Cancer in situ
T1	≤ 2 cm (T1a ≤0.5 cm, T1b >0.5-1 cm, T1c >1-2 cm)
T2	>2 cm-5 cm
T3	>5 cm
T4a	Involvement of chest wall
T4b	Involvement of skin (includes ulceration, direct infiltration, and satellite nodules)
T4c	T4a and T4b together
T4d	Inflammatory cancer
N0	No regional node metastases
N1	Palpable mobile involved ipsilateral axillary nodes
N2	Fixed involved ipsilateral axillary nodes
N3	Ipsilateral internal mammary node involvement (rarely clinically detectable)
M0	No evidence of metastasis
M1	Distant metastasis (includes ipsilateral supraclavicular nodes)

Breast cancer cells and also normal breast tissue cells have receptors for hormones and growth factors on their cell membranes (Lamb CA et al. 2019). Thus, BCa can be classified into different subgroups also by receptor-status: expression/non-expression of estrogen-, progesterone- and HER2-receptors. If cells express a certain receptor on their cell membrane, they are called receptor positive (estrogen receptor positive ER+, progesterone receptor positive, PR+, human epidermal growth factor- 2 positive, HER2+) and without receptor expression receptor negative (ER-, PR-, HER2-). BCa cells that do not express any of above mentioned three types are called triple negative. This cancer type has the poorest prognosis of all forms of BCa (Navratil J et al. 2015).

6.4 Ovarian cancer

Histologically, the ovaries are composed of germ cells, sex-cord stromal cells and epithelium and mesothelium of the ovarian surface and both benign and malignant ovarian tumors arise from these tissues. Ovarian tumors are histologically classified into three main categories by their origin: epithelial tumors, germ cell tumors and sex cord-stromal tumors. Epithelial carcinomas are the most common type accounting for as many as 90% of all OC cases (Sankaranarayanan R et al. 2006). Sex cord-stromal tumors account for 5-6% and germ cell tumors only 2-3% of malignant ovarian tumors (Prat J et al. 2012). Epithelial carcinomas are subdivided into high-grade serous, endometrioid, clear cell, mucinous and low-grade serous subtypes. The classification includes also borderline tumors which do not fulfil the criteria of a malignant tumor but are not totally benign. Less than 10% of ovarian tumors are metastases from other cancers.

WHO published a histogenesis-based classification for ovarian tumors in 1973; this was summarized in 1998 by International Agency for Research on Cancer (IARC) into a more compact form for clinical use (Table 9).

Table 9. IARC Histologic Groups of Ovarian Tumors according to International Agency for Research on Cancer

Histologic type	**WHO ICD-O morphology code**
1. Carcinoma	8010–8570, 9014–9015, 9110
1.1 Serous carcinomac	8441–8462, 9014
1.2 Mucinous carcinomac	8470–8490, 9015
1.3 Endometrioid carcinoma	8380–8381, 8560, 8570
1.4 Clear cell carcinoma	8310–8313, 9110
1.5 Adenocarcinoma NOS	8140–8190, 8211–8231, 8260, 8440
1.6 Other specified carcinomas	
1.7 Unspecified carcinoma	8010–8034
2. Sex cord-stromal tumors	8590–8671
3. Germ cell tumors	8240–8245, 9060–9102
4. Other specified cancers (including malignant Brenner tumor, müllerian mixed tumor, and carcinosarcoma)	
5. Unspecified cancer	8000–8004

IARC: International Agency for Research on Cancer; WHO: World Health Organization; ICD-O: International Classification of Diseases for Oncology; NOS: not otherwise specified

6.4.1 TNM-classification

Stage (tumor extent) of epithelial-stromal tumors is based on the FIGO classification of (International Federation of Gynecology and Obstetrics) from year 2014 (Table 10). Staging is based on findings in surgical excision and radiological evaluation.

Table 10. Ovarian Surface Epithelial-Stromal Tumor Staging Protocols: AJCC TNM System and FIGO Staging System

TX		Primary tumor cannot be assessed.
T0		No evidence of primary tumor.
T1	I	Tumor limited to ovaries (one or both).
T1a	IA	Tumor limited to one ovary; capsule intact, no tumor on ovarian surface. No malignant cells in ascites[c] or peritoneal washings.
T1b	IB	Tumor limited to both ovaries; capsules intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings.
T1c	IC	Tumor limited to one or both ovaries, with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings.
T2	II	Tumor involves one or both ovaries with pelvic extension.
T2a	IIA	Extension and/or implants on uterus and/or tube(s). No malignant cells in ascites or peritoneal washings.
T2b	IIB	Extension to other pelvic tissues. No malignant cells in ascites or peritoneal washings.
T2c	IIC	Pelvic extension (2a/IIA or 2b/IIB) with malignant cells in ascites or peritoneal washings.
T3 and/or N1	III	Tumor involves one or both ovaries, with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph node metastasis.
T3a	IIIA	Microscopic peritoneal metastasis beyond pelvis.
T3b	IIIB	Macroscopic peritoneal metastasis (2 cm or less in greatest dimension) beyond pelvis.
T3c and/or N1	IIIC	Peritoneal metastasis (more than 2 cm in greatest dimension) beyond pelvis and/or regional lymph node metastasis.
M1	IV	Distant metastasis (excludes peritoneal metastasis).

AJCC: American Joint Committee on Cancer, FIGO: International federation of Gynecology and Obstetrics.

The histological examination of tumor involves a determination of the histological subtype, extent of the disease and also differentiation of the tumor. Differentiation is defined by how closely the tumor resembles normal ovarian tissue. Ovarian tumors are graded as well-differentiated, moderately differentiated, poorly differentiated and undifferentiated. Surface-epithelial tumors may also be classified by the degree of borderline malignancy. Prognostic factors are best known in surface epithelial-stromal tumors: stage and residual disease after surgical excision are the most important (Fleming ID et al. 1997). It is difficult to constitute a grading system which would include all histological variations of OC and thus the importance of histological typing in OC prognosis is still unknown. Grading of sex-cord stromal tumors lacks a grading system; for example, there are no criteria for malignant and benign tumors, and these may vary by subtype. For germ cell tumors, stage at diagnosis is the most important prognostic factor and grading between histological subtypes is not in clinical use. (Chen VW et al. 2003)

7 CANCER TREATMENT

7.1 Prostate cancer

7.1.1 Passive following

In PCa patients with local disease, total-PSA <20 microg/l and total Gleason score < 7 and expected life-expectancy maximum 10 years, the disease can be passively followed without active treatment or active follow-up. In this group overall survival without active treatment might not be shortened or is only shortened slightly in this group (Adolfsson J et al. 1991) (Rice KR et al. 2013). The only relevant treatment modality in this group is often endocrine hormonal therapy which merely slows disease progression and spread (Damber JE 2005). Disease following in this group is not active which means that only if disease starts to cause symptoms (like pain or urinary problems) or cancer progression is some other way recognized for example in imaging, will endocrine hormonal therapy be initiated.

7.1.2 Active surveillance

Among patients with local T1a-T2a PCa with total Gleason score < 7 and total-PSA-level < 10 microg/l, active surveillance can be chosen (Prostate cancer guideline 2014). Active surveillance is an option instead of radical curative treatment in low and intermediate risk PCa cases and the prognosis among those men does not differ from men treated with curative intent immediately after diagnosis (Klotz L 2020) (Klotz L et al. 2015). The aim of active surveillance is to avoid complications (like sexual and bowel dysfunction) that may be caused by active treatments (Prostate cancer guideline 2014). An individual's suitability for active following is still evaluated on a patient-by-patient basis considering life-expectancy, other comorbidities, and the patient's opinion. Active surveillance is conducted by a program containing repeated PSA-measurements, clinical examination, and follow-up biopsies (Prostate cancer guideline 2014). There are local differences in how the follow-up program is scheduled. If clinical characteristics of disease change (PSA rises or histology of tumor changes into a higher grade) during active surveillance, active treatments are initiated e.g., radical prostatectomy or radical radiation therapy is conducted to avoid further spread. If there is an increase in the free to total-PSA- ratio, this seems to predict the need for radical treatment later (van AS NJ et al. 2008).

7.1.3 Radical prostatectomy

Radical prostatectomy is used to treat local PCa and it is the only treatment that has been proved to improve PCa survival compared to passive following (Prostate cancer guideline 2014). Radical prostatectomy is used only among patients with an expected life-expectancy over 10 years. In moderate and high risk PCa, radical prostatectomy seems to improve survival but does not appear to have the same effect in low risk PCa (Prostate cancer guideline 2014). Radical prostatectomy includes removing of the prostate, its capsule and seminal vesicles. If PSA is over 10 microg/l or Gleason > 7 (moderate and high-risk patients) then the regional pelvic lymph nodes will also be removed for pathological analyses to evaluate possible spread (Prostate cancer guideline 2014). The number of affected nodes serves as a prognostic

factor: in 10 years´ follow-up patients with 1-2 nodes involved with cancer had a recurrence-free survival of 70% while patients having 5 or more nodes involved had recurrence-free survival of only 49% (Daneshmand S et al. 2004). Prostatectomy can be conducted with open surgery, laparoscopic surgery or robotic-associated laparoscopic surgery (RALP) (Prostate cancer guideline 2014). Laparoscopic surgery causes less complications than open surgery and is preferred (Martinez-Holguin E et al. 2020). The newest trend for surgery is RALP which has been proved to be safer with a shorter operation time than laparoscopic prostatectomy: it has as good oncological results as laparoscopic prostatectomy and therefore is the most commonly used technique today (Prostate cancer guideline 2014). The 10-year survival results in men treated with radical prostatectomy are excellent: 94.2 % are still alive (Prostate cancer guideline 2014). Factors predicting PCa recurrence after radical prostatectomy are the plasma level of total PSA before prostatectomy, Gleason score, pT-classification and number of nodes involved (Prostate cancer guideline 2014). The histology of the removed tumor and nodes are examined after prostatectomy to estimate any possible spread of disease. In local disease, the PSA-level will decrease into a non-measurable level after radical surgery and this phenomenon is used in follow-up after surgery: a rise in PSA-level after radical prostatectomy indicates a recurrence of disease and need for radiation therapy (Freedland SJ et al. 2003) (Forman JD et al. 1998). When local disease is seen in histological analysis of prostate (cancer has not penetrated through the capsule of prostate) and PSA level decreases to a level lower than 0.05 microg/l, prostatectomy alone may be sufficient.

The acute risks of prostatectomy include blood loss, urine leak and need for re-operation (Novara G et al. 2012). RALP is associated with decreased risk for perioperative complications as compared to laparoscopic prostatectomy (Hu JC et al. 2006). According to one study, the proportion of patients reporting urinary incontinence needing protection at least 6 months after surgery was 33% and self-reported impotence was reported by 88.4%. However, 77.5% of patients would select radical surgery again (Kao TC et al. 2000). These complications caused by radical prostatectomy will at least partly recover during the next two years after treatment (Manfredi M et al. 2019) (Litwin MS et al. 2001).

7.1.4 Radiation therapy

Radiation therapy can be used instead of radical surgery in local and locally advanced PCa (Prostate cancer guideline 2014). Radical prostatectomy and radiation therapy have equal oncological outcomes in local PCa (Hamdy FC et al. 2016). Radiation therapy can be used if the patient prefers this form of therapy or if he is not suitable for surgery, for example considering anesthetic risks.

Adjuvant radiation therapy is used after radical surgery to minimize the risk for disease recurrence when the risk of recurrence is estimated to be at least moderate (Leibovich BC et al. 2000). Radiation therapy can also be used for other indications than curative intent: radiation into bone metastases is used to alleviate pain in metastatic PCa (Pinski J et al. 2005). There are some side effects of prostate radiation therapy including rectal bleeding and irritative bladder symptoms (Budaus L et al. 2012).

One option for radiation therapy is high-dose brachytherapy. In this setting, needles are inserted into the prostate under general anesthesia. Radiation is delivered to the prostate from the needles after which the needles are removed. Large doses of radiation can be given at one treatment. Often high-dose brachytherapy is supplemented with a short course of external beam radiation therapy. High-dose brachytherapy is used for high-risk PCa cases as primary treatment and also as salvage therapy in recurrent disease. (Strouthos I et al. 2021)

7.1.5 Medical therapy

The treatment in advanced disease is based on systemic drug therapy i.e., hormonal therapy in which the effects of androgen on PCa cells are eliminated; as advanced PCa is often dependent on androgen-stimulation, this leads to destruction of cancer cells (Dreicer R 2000) (Heinlein Ca et al. 2004). Hormonal therapy can be conducted with physical castration by removal of testicles but more commonly by androgen-deprivation therapy with gonadotropin-releasing hormone (GnRH) agonists and antagonists (Weckermann D et al. 2004) (Perlmutter MA et al. 2007). Antihormonal therapy in advanced PCa is recommended to be started immediately after diagnosis of advanced or recurrent PCa (Tenenholz TC et al. 2007) (Messing E 2003). A good immediate response is often achieved if no previous hormone therapy has been in use (Tammela TL 2012). Antihormonal therapy may cause flushes, sweating, redness in the face, impotence, anemia, osteoporosis, and loss of muscle mass which are all climacteric symptoms (Greenspan SL et al. 2005) (Basaria S et al. 2002) (Saylor PJ et al. 2013).

If PCa during anti-hormonal therapy continues to spread even if testosterone level in serum is < 1.73 mmol/l, the disease is called castration resistant (Prostate cancer guideline 2014). In this stage, the treatment aims are to ease symptoms and improve the quality of life. Drug treatment may include chemotherapy with docetaxel or cabacitaxel, androgen-signaling inhibitors enzalutamide, darolutamide or apalutamide, abiraterone or radium-223 and more recently, lutetium-PSMA- treatment. Patients with mild symptoms may be treated by prednisolone alone. Palliative treatment is necessary when all treatment options have been used or the patient does not tolerate any other treatment. Median survival in castration resistant metastatic disease is limited.

7.2. Urinary tract cancer

7.2.1 Bladder cancer

BC is a very heterogenous disease and thus treatment choice is based on TNM-classification, tumor grade, presence of carcinoma in situ and the patient's general condition. Localized low-grade BC can often be managed endoscopically but often recurs and therefore close follow-up is needed. High-grade BC often develops into a muscle invasive disease, which has a poor prognosis and requires major surgery when feasible.

Trans-urethral resection of the bladder (TURB) is used to treat superficial Ta-T1 BC (non-muscle invasive bladder cancer, NMIBC). It can also be used instead of radical cystectomy in muscle invasive or high-grade disease among patients not eligible for major surgery due to several comorbidities and a frail general condition. In the latter cases, TURB is often supplemented with radiation therapy to the bladder. However, in that case, there is a higher risk for recurrence and disease progression compared to cystectomy. Advantages and surgical risks must be evaluated individually for each patient.

Bladder irrigation therapies are combined with TURB if the patient has previously had recurrences or is at a high risk for disease progression (Taari K et al. 2013). For example, carcinoma in situ (CIS) is an aggressive carcinoma in which the whole inner surface of the bladder is often involved; management of CIS includes BCG (Bacillus-Calmette Guerin) instillations to trigger a local immune response in the bladder. Immediately after TURB, chemotherapy may be initiated to prevent cells detaching from the primary tumor and spreading to another location in the bladder mucosa. Irrigation therapies have been proved to inhibit local recurrences even if used once after TURB. BCG is the most effective in preventing recurrences of

carcinoma in situ. There is no evidence for what would represent an optimal frequency of irrigation therapy and there are variations in treatment protocols. (Taari K et al. 2013)

NMIBC and CIS have a high recurrence rate as 50-70% of patients will suffer a recurrence (Sylvester RJ et al. 2006). Recurring disease often stays NMIBC, but 10-20% of patients may develop muscle-invasive disease during repeated recurrences over time (Fernendez-Gomez J et al. 2009). The highest risk for recurrence is encountered with a carcinoma in which there are in situ changes and in poorly differentiated tumors.

Regular follow-up constitutes most of the financial costs that BC imposes on the health care budget as patients with NMIBC are regularly subjected to cystoscopy. The first cystoscopy is conducted three months after diagnosis and has an important prognostic effect. Low risk BC is followed up to five years after diagnosis if recurrences are not observed. Moderate and high-risk patients are followed by cystoscopies for the rest of their lives. In addition, second look TURB may be used instead of cystoscopy in these cases. If a recurrence is seen, the follow-up program starts from the beginning. Urine cytology is used as a part of follow-up among moderate and high-risk patients. (Taari K et al. 2013)

Approximately 25% of people with BC have muscle invasive disease at the time of diagnosis. About 10-15 % of patients have distant metastases at the primary diagnosis (Kamat AM et al. 2013). Treatment of advanced BC consists of chemotherapy and immune checkpoint inhibitors. (Taari K et al. 2013)

In locally advanced BC, T2–4aN0M0, radical cystectomy is used. In men, the prostate and occasionally the penile urethra are also removed; in women, the uterus, urethra, and upper part of vagina are removed. Lymphadenectomy is part of the procedure in both genders. When the bladder is removed, its function must be replaced by urinary diversion or with an orthotopic neobladder. Mortality in radical cystectomy is 2% during the next 3 months. Despite undergoing radical surgery, every second BC patient will die of BC during the next five years (Taari K et al. 2013). The main reason for the high mortality is likely to be micro metastases outside the operative area leading to disease recurrence. Neoadjuvant platinum-based chemotherapy can be used before cystectomy to decrease the size of the tumor before surgery and also to destroy micro metastases. After radical surgery, adjuvant therapy may be provided to improve surgical outcomes when radical surgery was not completely successful, or metastases have been identified in the removed nodes. Both neoadjuvant and adjuvant therapies are commonly conducted with chemotherapy with immune checkpoint inhibitors being actively studied for these indications. Radiation therapy is not an established option in BC; it can be used in patients not eligible or unwilling to undergo radical cystectomy. The efficacy of radiotherapy can be increased by a combination with chemotherapy, but it is still not as effective as radical surgery. (Taari K et al. 2013)

Locally advanced disease is followed by urologists. Most of recurrences are seen during the first 24 months, the majority occur during five years of follow-up. Five-year survival in locally advanced BC is poor even with radical therapies as every second patient will die of BC. Invasive BC is considered as local BC but is in fact a systemic disease with 20-40% of cases having micro metastases at the time of diagnosis causing later recurrences (Kurahashi T et al. 2005) (Raimondi C et al. 2014).

In the metastatic stage, i.e., if nodes are involved and the patient is classified as T4b, surgery is no longer an option. Only if there are difficult disturbing symptoms such as bleeding from the bladder can its removal be considered as a part of palliative care. Radiation therapy may be used to alleviate symptoms caused by obstruction of the ureters and to treat hematuria and bone pain in advanced disease.

7.2.2 Upper tract urothelial carcinomas (UTUC)

The ureter, renal pelvis and calyx are lined with urothelial epithelium, like the arrangement in the bladder. Upper tract carcinomas constitute only 10% of all urothelial carcinomas. One third of them are located in the ureter and two thirds in renal pelvis. Men have a higher incidence of UTUC than women. About half of UTUC patients exhibit disease also in the bladder. On the contrary, only 2-4% of patients with BC have urothelial carcinoma in the upper tract. Risk factors for UTUC are the same as for BC with smoking and chemical exposures being the most important. Most tumors in renal pelvis and ureters are urothelial carcinomas while squamous cell carcinomas and adenocarcinomas are rare. (Taari K et al. 2013)

The most common symptoms in UTUC are macroscopic hematuria and pain felt in the back or side. CT is the most important tool for diagnostics to help the physician conduct a differential diagnosis and to evaluate the spread of the disease. Diagnostics can also be conducted via cystoscopy in cases where BC is suspected. The ureters and renal pelvises can be further imaged with retro-grade pyelography i.e., a catheter is placed into the ureter or renal pelvis to infuse contrast medium and then the X-ray may reveal filling defects when contrast medium spreads in the urinary tract. Urine cytology is used in diagnostics and follow-up also in UTUC and it can also be applied to monitor moderately or poorly differentiated carcinomas. (Taari K et al. 2013)

Nephroureterectomy is the most common treatment in both carcinoma of renal pelvis and ureters in which the kidney, ureter and bladder surrounding the ureter are removed. If the patient has only one kidney or has a well differentiated single tumor, some form of more conservative surgery may be used. Follow-up after surgery includes cystoscopy, urine cytology and urography if needed. Among patients with moderately or well-differentiated carcinoma five-year survival is as high as 80-100% but only 20-30% among patients with a poorly differentiated cancer. (Taari K et al. 2013)

7.3 Breast cancer

7.3.1 Surgery

Surgical treatment in BCa has developed into a more conservative direction during recent decades. Until the 1970s, radical mastectomy was the main surgical intervention in which the whole breast and underlying minor and major pectoralis muscles, lymph nodes and lymph ducts were totally removed as one item. During the 1970s, it was observed that even with more restricted and an individually evaluated surgical operation as good cancer survival could be achieved compared to mastectomy. Since that time, the minor and major pectoralis muscles are no longer removed and also removal of axillary lymph nodes is individually evaluated. Today surgical treatment aims to be as conservative as possible with partial mastectomies being performed when feasible. At the same time, it needs to be considered whether BCa might have spread outside the breast already at the time of diagnosis and before surgery and thus whether prognosis could be improved with adjuvant therapies. This means that nowadays BCa treatment is a combination of surgery and adjuvant therapies. (Leppäniemi A et al. 2010)

Surgery is planned individually as are the possible neoadjuvant and adjuvant therapies. CT-images and ultrasound images are used to evaluate the extent of tumor growth in the breast. Whenever possible, breast conserving surgery is applied but it is important to be able to remove the tumor along with healthy skin tissue marginals. In almost all cases, adjuvant radiation therapy is initiated after conservative surgery as it has been proved to decrease the risk for local recurrence in the operated breast (Lanitis S et al. 2010) (Ye JC et

al. 2015). If radiation therapy cannot be used, total mastectomy must be considered as the risk for local recurrence is otherwise elevated (Abner AL et al. 1993). Among under 35-year-old women and women with hereditary BCa, the risk for local recurrence is higher compared to over 35-year-old and women without a hereditary risk but still mastectomy is not routinely recommended (van den Broek AJ et al. 2019) (Huang J et al. 2018). However about 40% of all BCa patients in Europe will undergo mastectomy (Fancellu A et al. 2018) (Garcia-Etienne CA et al. 2012). Mastectomy and removal of axillary lymph nodes have been associated with an increased risk of developing lymph oedema after surgery and thus to avoid this possibility, conservative surgery is preferred whenever possible (Clark B et al. 2005). If mastectomy is used, a new breast is reconstructed during the same operation or in a new operation later (Leppäniemi A et al. 2010)

7.3.2 Sentinel lymph nodes and evacuation of axillary nodes

The spread of BCa into regional lymph nodes is the most important prognostic factor. Tumor spread into the axillary lymph nodes is categorized into three groups: tumor cells found in lymph nodes, micro metastases found in lymph nodes and macro metastases found in lymph nodes. A macro metastasis is a tumor with a size greater than 2mm and a micro metastasis is over 0.2mm but under 2mm. Tumor cells means that single tumor cells are found and the area they constitute is under 0.2mm. The worst prognosis is in macro metastatic disease and number of macro metastatic nodes is a prognostic factor. Lymphatic spread is evaluated before surgery by carrying out ultrasound of the axillary region with a needle biopsy being taken in the most suspicious nodes.

The evaluation of BCa spread by examining sentinel lymph node has replaced the evacuation of the axillary lymph nodes. If no spread into lymph nodes is observed with ultrasound before surgery, a sentinel lymph node investigation is carried out; the only exception is inflammatory BCa and locally advanced BCa where axillary evacuation is used. The sentinel lymph node is the first lymph node where lymphatic fluid and within it tumor cells from the breast drain to other parts of the lymphatic system. Multiple nodes can serve as sentinel nodes. If no spread is found in the sentinel lymph node, it is anticipated that also other nodes will be healthy and thus the woman will not gain any benefit from axillary evacuation (Castelo M et al. 2020). There are about 8% false negative results in sentinel node investigation but disease recurrence in axilla is however found only among 0.3% of patients not treated with axillary evacuation: this could be explained by adjuvant therapies destroying tumor cells not observed in sentinel lymph investigation in axilla. (Leppäniemi A et al. 2010)

7.3.3 Neoadjuvant therapy

Neoadjuvant therapy may be used to decrease the size of the primary tumor to be able to conduct surgical treatment (Miller E et al. 2014). A sentinel lymph node investigation can be conducted after neoadjuvant therapy among patients that were node negative before adjuvant therapy (Leppäniemi A et al. 2010).

7.3.4 Treatment after surgery

Further procedures and investigations after surgery are decided in multiprofessional meetings. Nowadays, it seems that BCa has metastasized only among 10% of women at diagnosis. Investigations such as computed

tomography are conducted routinely only in patients with locally advanced disease or metastases in multiple axillary nodes as well as in a patient who has symptoms indicating a spread or a local recurrence.

The aim of follow-up is to observe local recurrences and also to diagnose new BCa in the other healthy breast. Follow-up consists of mammography and clinical breast examination by a doctor. The patient is asked if she has symptoms indicative of advanced disease such as cough, dyspnea, or bone pain. Psychological support and information on disease are also provided. Metastases attributable to hematologic spread are however typically noticed by symptoms between the follow-up visits and their prognosis could not be improved with earlier detection. It seems that mammography is the most important follow-up tool and routine outpatient visits during follow-up have become less common. (Leppäniemi A et al. 2010) (Joensuu H et al. 2013)

7.3.5 Adjuvant therapies

Despite distant metastases being uncommon at BCa diagnosis, micro metastases have often spread outside of breast and the regional lymph nodes even if they cannot be detected. Therefore, most BCa patients will receive adjuvant therapies after surgery (Hsieh MC et al. 2019). Adjuvant therapies are likely the most common reason for improved BCa survival and prognosis during the last decades as they significantly improve BCa survival, especially in cases of metastatic disease (Rossi L et al. 2015). Adjuvant therapies may consist of chemotherapy, antihormonal therapies or highly specific drugs such as antibodies. These agents are selected according to the hormonal status of the tumor cells, patient's age, the evaluated risk for recurrence, HER2-expression, and the patient's general appearance. Antihormonal therapy includes the antiestrogen tamoxifen and aromatase inhibitors like letrozole (Kiang DT et al. 1977) (Thurlimann B et al. 2005). Antihormonal therapy should not be provided if tumor cells do not express estrogen or progesterone receptors (Ariazi EA et al. 2006) (Awan A et al. 2018); in these cases, chemotherapy is an alternative as it is considered to improve prognosis among estrogen-negative but also in estrogen-positive pre-and postmenopausal women. If HER2 is expressed, then its antibody trastuzumab can be administered (Maximiano S et al. 2016) (Joensuu H et al 2013).

7.3.6 Relapses in breast cancer

According to one study, 10.4% of all BCa cases relapse during 5 years after BCa diagnosis (Colleoni M et al. 2016) with 60% of relapses occurring during the next 5 years after BCa diagnosis (Joensuu H et al 2013). Tumor subtype affects the risk for recurrence as high grade, HER2 positivity, young age, lack of estrogen and progesterone receptors and large tumor size increase the risk (Ess SM et al. 2018). BCa may relapse even as long as 20 years after its diagnosis (Pan H et al. 2017). If the tumor recurrence is local in breast, it is treated with total mastectomy and adjuvant therapies (Wapnir IL et al. 2019). If recurrence is observed elsewhere this implies that there is metastatic disease. The most common form of recurrence is a recurrence into an advanced stage. Instead, recurrence in the other breast indicates often a new primary BCa and is treated like a new disease.

7.3.7 Advanced breast cancer

There is no curative treatment for advanced BCa but disease remission can be achieved and progression be delayed. Treatment will aim to improve the quality of life and also to slow disease prognosis. According to a meta-analysis, median survival after metastases have been diagnosed was 38 months in the year 2010 (Caswell-Jin JL et al. 2018). If hormone-receptors are expressed, treatment is often started with antihormonal therapy with a response being seen in most patients who are either ER and/or PR positive (Jordan C et al. 2002). Tamoxifen is the most commonly used antihormonal therapy but in premenopausal women, removal of ovaries can also be used to reach a hypoestrogenic stage (Conte CC et al. 1989).

When the response to antihormonal therapy is no longer evident and the disease continues to progress, cytostatics are often started; these compounds are used alone or combined. Chemotherapy may stop disease progression for months or even years. Trastuzumab may be used also in advanced BCa if cells highly express HER2. Surgery may be used to cure symptoms, but it has been claimed that removal of the primary tumor in advanced disease does not improve the disease prognosis (Shibasaki S et al. 2011). Radiation therapy is also used but only to cure symptoms like pain caused by bone metastases (Joensuu H et al 2013).

7.4 Ovarian cancer

7.4.1 Surgery

Surgery has an important role not only in OC diagnosis but also in treatment as surgical treatment is conducted in almost every OC patient. During the surgical procedure, histological samples are taken to characterize the OC. Depending on disease spread, in addition to the ovaries, specimens may also be removed from both adnexes, part of omentum and also pelvic and para-aortal nodes (Di Re F et al. 1996). It has been proved that the less remaining residue tumor size, the better the OC prognosis (Polterauer S et al. 2012). If ascites is observed, fluid samples will be taken: if not, the peritoneum will be flushed to obtain samples. However, OC often spreads widely in the abdominal cavity and thus surgical removal is often incomplete.

Among fertile women being treated for local OC, the ovaries and especially uterus are not removed. This fertility sparing surgery is a safe treatment option, but removal of the ovaries and uterus is recommended in some cases after completion of childbearing (Wright JD et al. 2009) (Borgfeldt C et al. 2007) (Mutch DG et al. 2002). However, fertility-sparing surgery is seldom needed as epithelial ovarian cancer is rarely encountered in women younger than 40 years. Instead, sparing surgery is more often used among women having borderline tumors as these patients tend to be younger than women with malignant tumors.

In advanced stage both surgery and chemotherapy are used. In this stage, surgery is called debulking in which the goal is to remove all visible tumor mass. This may indicate resection of vessel or removal of carcinoma metastases in peritoneum or removal of the spleen. Surgery is combined with neoadjuvant cytostatics as it has been proved that neoadjuvant therapy combined with interval debulking surgery leads to a better prognosis and less morbidity in stage IV OC as compared to primary debulking surgery alone (Rauh-Hain JA et al. 2012) (Rosen B et al. 2014). Surgery is the most important form of treatment (Schorge JO et al. 2010).

Almost invariably, cytostatic drugs are used after surgery; only if the patient has local well differentiated (stage 1, gradus 1) OC with a good prognosis then no additional benefit is achieved with adjuvant cytostatic

compounds. In the treatment of borderline tumors, cytostatic drugs are not used. The most common combination of cytostatics is paclitaxel with carboplatin.

Bevacizumab was the first biological medicine used in the treatment of OC; it is a monoclonal antibody binding to vascular endothelial growth factor, VEGF. The highest benefits are achieved among OC patients with stage IV or stage III and over 1cm residual tumor. Bevacizumab is used together with carboplatin and paclitaxel and after that on its own as maintenance therapy. (Burger RA et al. 2011) (Coleman RL et al. 2017)

7.4.2 Treatment in recurrent ovarian cancer

Approximately 80% of patients with stage II-IV OC will relapse and at this stage, curative treatment is no longer possible. Relapses are often treated with cytostatics but curative treatment is seldom possible. If the response to the primary treatment has lasted over six months, then the disease is called chemo-sensitive, and recurrence treated with the same chemotherapy as in adjuvant treatment. Up to 30% of patients enjoy a response from this treatment (Tapanainen J et al. 2019).

If the disease progresses during primary treatment or recurrence is seen during the first six months after primary treatment, then the disease called is chemo resistant. This group consists 25% of OC and has the worst prognosis. In this case, bevasitsumab may be combined with cytostatics and some effects in disease progression may be observed. (Tapanainen J et al. 2019)

The newest trend in the treatment of recurrent OC are PARP-inhibitors. PARP-enzymes are responsible for repairing DNA. PARP-inhibitors have been proved to be beneficial in cytostatic sensitive recurrent OC with the BRCA-mutation. Many clinical trials on PARP-inhibitors as first line therapy of OC are ongoing. Cytopenia is the most common adverse effect of PARP-inhibitors. (Tapanainen J et al. 2019)

Sometimes surgery can be conducted again in recurrent OC aiming to remove visible tumor. Factors favoring re-surgery are single metastasis, over 12 months' remission before and the patient's good general condition. Since OC spreads widely in the abdominal cavity, radiation therapy seldom can be delivered but a local recurrence in pelvis may be treated with radiation therapy as a part of palliative care (Fujiwara K et al. 2002) (May LF et al. 1990) (Tapanainen J et al. 2019).

8 DRUGS AND CANCER PROGRESSION

8.1 Non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin

Non-steroidal anti-inflammatory drugs (NSAIDs) are used in pain and fever management. They act by inhibiting COX-1 and- 2 enzymes which leads to an inhibition of the formation of prostanoids which are important mediators in inflammation and pain. The COX-2 selective NSAIDS, coxibs, selectively inhibit COX-2 but do not affect COX-1. COX-1 is an important enzyme in several physiological processes like regeneration of gastric mucosa and the risk of gastric ulcer is less likely during coxib use compared to use of other NSAIDs. However, the risk of heart attack is increased as compared to other NSAIDs. (Ruskoaho H et al. 2014). There is some evidence that NSAIDs might have anticancer effects, but they also have many clinically significant disadvantages such as increased risk of ulcer and heart attack which limits their administration to experimental use. They restore apoptosis in cancer cells and may also inhibit angiogenesis. Attempts have been made to create possible derivatives from these COX-1 and COX-2 enzymes inhibiting agents to avoid the disadvantages caused by direct inhibition of these enzymes. (Michael J et al. 2002) Lately inflammation has been strongly linked with carcinogenesis via angiogenesis, DNA mutations and cell invasion and it has been postulated that several anti-inflammatory agents could act as antitumor agents (Zappavigna, S et al. 2020). Aspirin, which acts as an irreversible inhibitor of COX-1 and is not an NSAID since it lacks a steroid structure, has also been claimed to possess antitumor efficacy. For example, the epidermal growth factor, EGF, pathway may be modulated by aspirin which causes internalisation of EGF-receptors as a possible anticancer effect (Bashir AI et al. 2019).

NSAID use before and after PCa diagnosis has been associated with an increased risk of PCa death in a Finnish cohort study (HR 1.30 95%CI 1.07–1.58 for before diagnosis use and HR 2.09 95%CI 1.75–2.50 for after diagnosis use). The study included 6,537 men and found that the association between the use of NSAIDs and the risk of PCa death was dose dependent. However, when the last three years before PCa death were excluded, the association was transformed to the protective level (HR 0.42 95% CI 0.34–0.51 for before and HR 0.30 95% CI 0.24–0.39 for after diagnosis use). Aspirin use was not associated with the PCa death risk. The results might be explained by treating metastatic bone pain in an advanced stage of PCa with NSAIDs: this may account for the increased risk of PCa death during the last years of life. Aspirin is used in the prevention of cardiovascular events rather than pain management; no such similar risk association was observed in aspirin users. (Veitonmäki T et al. 2015). An American study reported that any self-reported NSAID use after radical prostatectomy (RP) or radiation therapy (RT) was associated with decreased risk of all-cause mortality (HR 0.47 95% CI 0.30–0.75 after RP) and (HR 0.39 95% CI 0.25–0.59) after RT. (Katz MS et al. 2010). Unfortunately, the results are not comparable as the end point variable was not disease specific death. Medication use in the second study was also self-reported while in the first study, medication use was based on information from national prescription database which diminishes the possibilities for information recall bias.

One study investigated whether the use of parecoxib (a COX-2 enzyme selectively inhibiting NSAID) during operative treatment would improve BC survival. Parecoxib was not associated with BC survival or cancer recurrence after radical cystectomy (Mao S et al. 2020). No other studies have been conducted investigating if there is a link between NSAIDs use and BC progression.

Cronin-Fenton DP et al. conducted a cohort study of 34,188 women diagnosed with BCa in the years 1996-2008 in Denmark. They reported an association between pre-diagnostic use of aspirin, NSAIDs and COX2-inhibitors and a decreased risk for BCa recurrence after curative surgery (HR 0.92 95% CI 0.82-1.0 for aspirin; HR 0.86 95% CI 0.81-0.91 for NSAIDs; HR 0.88 95% CI 0.83-0.95 for COX2-inhibitors). Instead, post-diagnostic use was not associated with the BCa recurrence risk (Cronin-Fenton DP et al. 2016). Li Y et

al. studied the association between NSAID, or aspirin use and BCa survival but did not detect any association (Li Y et al. 2012). On the contrary, Blari CK et al. described improved BCa and overall survival among women with self-reported NSAID use after diagnosis (HR 0.64 95% CI 0.39–1.05 for BCa death and 0.57 95% CI 0.40–0.81 for overall death). The results were however not dose dependent. (Blair CK et al. 2007). A meta-analysis of 16 cohort and case-control studies indicated that after diagnosis, the use of NSAIDs was associated with a decreased risk of BCa and overall death (HR 0.65 95 % CI 0.48–0.89 for BCa death, HR 0.73 95 % CI 0.57–0.92 for overall death). (Huang XZ et al. 2015)

A retrospective cohort of 77 women diagnosed with clear cell ovarian carcinoma diagnosed from 1995 to 2010 was examined to see if there was an association between aspirin use and OC prognosis. All patients were treated with primary cytoreductive surgery and platinum-based chemotherapy. Patients were considered as aspirin users if either 81 mg or 325 mg use of medication was documented in at least two distinct medical records six months apart. Post-diagnosis aspirin use among clear cell OC was associated with improved overall survival (HR 0.13 95% CI 0.02-0.95) and longer disease-free survival (HR 0.13 95% CI 0.13-0.83) compared to non-users with age, stage, and result of cytoreductive surgery being taken into account (Wield AM et al. 2018).

However not all studies agree; a case-control study of 1,305 Australian women with invasive epithelial OC evaluated pre-diagnostic use of aspirin, NSAIDs and paracetamol and OC prognosis with use being defined as any use of these drugs during the last five years before OC diagnosis. There was no association between drug use and the risk of OC or overall death, and no dose-response was observed. In a subgroup analysis, results were not modified by stage, age at diagnosis or histological subtype (Nagle CM et al. 2015). In a Danish cohort, low-dose aspirin use after diagnosis was not associated with OC or other cause mortality. The cohort included all women diagnosed with epithelial OC between 2000 and 2012 i.e., a total of 4,117 women. Information on drug use was obtained from a national database and there was adjustment for confounding factors such as comorbidities. (Verdoodt F et al. 2018)

A Danish study examined a cohort of 4,117 women diagnosed with primary OC during 2000-2012. Post-diagnostic use was evaluated and information on drug usage was obtained from a prescription database. Non-aspirin NSAID use was not associated with OC mortality, but high cumulative dose and intensity use were associated with improved OC survival in serous OC (HR 0.87 95% CI 0.77–0.99) furthermore in cases of non-serous OC, it was associated with an increased OC mortality risk (Verdoodt F et al. 2018)

Bar D et al. conducted a study of OC prognosis and aspirin and metformin use. The study included 143 OC patients diagnosed in the time period 2000-2012 and treated with debulking surgery and platinum-based chemotherapy. In the multivariable adjusted analysis, post-diagnostic use of aspirin (HR 0.52 95% CI 0.30–0.89 p = 0.02) and metformin (HR 0.37 95% CI 0.14–0.97 p = 0.04) were associated with a prolonged recurrence-free survival compared to non-users. Overall survival was also longer among aspirin users as compared to non-users. When analysing only patients being disease-free after 12 months, use of statins was associated with improved recurrence-free survival (HR 0.34 95% CI 0.19–0.61 p = 0.001) compared to non-users. (Bar D et al. 2016)

8.2 Metformin

Metformin is a drug used as the first line treatment of diabetic patients alone or combined with other drugs. Several theories of its possible anticancer mechanism have been postulated. In vitro, metformin has been shown to inhibit BCa cell proliferation (Zhang T et al. 2013). It has also been suggested that the anticancer effect of metformin could be mediated via decreased insulin and insulin-like growth factor 1 (IGF-1) levels in plasma. IGF-1 is produced mainly in liver by growth-hormone stimulation and both IGF-1 and insulin

have been demonstrated to be involved in cancer development. IGF-1 mediates the normal anabolic and the growth-promoting effects of growth hormone. (Kasznicki, J et al. 2014) (Laron Z et al. 2001)

Several investigators have examined the association between metformin use and PCa prognosis. Patel T et al. reported that diabetes was associated with an increased risk of PCa biochemical recurrence after radical prostatectomy (HR 1.55 95% CI 1.03-2.33 p = 0.034) and the use of metformin did not confer any benefit (HR 0.94 95% CI 0.6-1.5 p = 0.817) (Patel T et al. 2010). Another cohort study also evaluated the use of metformin and the risk of PCa progression. All the examined men had localized PCa treated with external-beam radiotherapy or brachytherapy, and some had also received androgen-deprivation drugs as adjuvant therapy. Metformin users had a lower risk for biochemical recurrence as compared to non-users, but risk estimates attenuated to the non-significant level when the analyses were adjusted with the tumor's characteristics. When evaluating overall survival, diabetic men using metformin had improved survival as compared to non-users (HR 0.5 95% CI 0.26-0.86 p = 0.01) (Taussky et al. 2018). Metformin use during androgen-deprivation therapy has also been associated with a decreased risk of overall and PCa death when compared to diabetic men without metformin use (HR 0.82 95% CI 0.78–0.86 for overall and HR 0.70 95% CI 0.64–0.77 for PCa death). (Richards KA et al. 2018)

There is also one meta-analysis examining metformin use and PCa incidence and prognosis. A total of 30 cohort studies (consisting of 1,660,795 men) were included. Men with diabetes using metformin were compared to diabetic men not using metformin. Metformin use was associated with improved overall, cancer-specific, and relapse-free survival (HR 0.72 95% CI 0.59–0.88 p = 0.001; HR 0.78 95% CI 0.64–0.94, p = 0.009; and HR 0.60 95% CI 0.42–0.87 p = 0.006). The criteria for metformin use may vary in different studies which may have affected the results. (He K et al. 2019). As a conclusion based on the above literature, it does seem that metformin use is associated with improved PCa survival.

BC survival has been also estimated in conjunction with metformin use. Nine retrospective cohort studies were included in a meta-analysis of 1,270,179 patients. Use of metformin was associated with longer recurrence-free survival (HR0.55 95% CI0.35–0.88) and longer BC-specific survival (HR0.57 95% CI0.40–0.81) in diabetic BC patients as compared to diabetic patients not using metformin. Metformin was however not associated with decreased incidence of BC or longer all-cause survival (HR0.83 95% CI0.47–1.44 for all-cause survival) (Hu J et al. 2018). According to Heidari F et al., metformin might also be able to delay cancer recurrences but did not affect the total recurrence rate (Heidari F et al. 2016). Rieken M et al. found also benefits for metformin use among diabetic patients with NMIBC. The cohort included 1,117 participants diagnosed between 1996 and 2007. Diabetic patients not taking metformin were at a higher risk for disease recurrence (HR 1.45 95% CI 1.09–1.94) and disease progression into a higher grade (HR 2.38 95% CI 1.40-4.06) as compared to users. Furthermore, diabetic subjects treated with metformin displayed a decreased risk of disease recurrence (HR 0.50 95% CI 0.27–0.94). (Rieken M et al. 2013). Nayan M et al. reported similar results for metformin use at the time of radical cystectomy i.e., a decreased risk for disease recurrence (HR 0.38 95% CI 0.20–0.72) and BC death (HR 0.57 95% CI 0.35–0.91) (Nayan M et al. 2015). In contrast, Ahn J et al. reported conflicting results; use of metformin among diabetic patients had no impact on BC progression or the risk of recurrence (Ahn J et al. 2016).

Treatment with metformin in breast cancer patients has been studied in prospective clinical trials as neoadjuvant therapy but no benefits were detected (Pimentel I et al. 2019) (Oppong BA et al. 2014). Among triple negative BCa patients, the use of metformin among non-diabetic patients during adjuvant chemotherapy was not associated with improved BCa or overall survival (Bayraktar S et al. 2012).

According to a systematic review, metformin use may decrease the risk of all-cause death among diabetic patients (HR 0.55 95% CI 0.44–0.70) but this is not associated with the BCa death risk (Tang GH et al. 2018). Yang T et al. conducted their meta-analysis and reported similar results i.e., the risk for all-cause death was decreased among metformin users (RR 0.65 95% CI 0.49-0.87 p=0.004) (Yang T et al. 2015). In their meta-analysis, Xu H et al. described also improved BCa survival (HR 0.89 95% CI 0.79-1.00) in

addition to improved all-cause survival (HR 0.53 95% CI 0.39-0.71) among diabetic patients using metformin as compared to non-users (Xu H et al. 2015).

Another study reported improved BCa and overall survival among diabetic HER2-positive BCa patients using metformin during chemotherapy and endocrine therapy as compared to non-users (HR for disease free survival 2.14 95 % CI 1.14-4.04). No association was found among diabetics treated with other medications and furthermore the improvement in survival was also not observed among HER2-negative patients (Kim HJ et al. 2015). Another study reported results in the the same direction i.e., metformin was associated with improved BCa survival among diabetic women (HR 0.47 95% CI 0.24-0.90 p= 0.023). Another antidiabetic drug, pioglitazone, was also associated with improved BCa survival (HR 0.42 95% CI 0.18-0.98 p = 0.044). (He X et al. 2012). Peeters PJ et al. concluded that long duration use of metformin may be associated with better BCa survival compared to non-users though the risk estimates were statistically non-significant (HR 0.88 95% CI 0.59-1.29) but became significant after stratification according to the cumulative number of prescriptions. Metformin use at diagnosis associated also with a decreased risk of all-cause death. (HR 0.74 95% CI 0.58-0.96) (Peeters PJ et al. 2013). However, there are also conflicting results of metformin use and outcomes in BCa (Lega IC et al. 2013).

Metformin use has been associated with better OC survival and metformin therapy was a predictor of survival (HR 2.2 95% CI 1.2-3.8). (Kumar S et al. 2013). According to a systematic review containing 4 studies, metformin may have a beneficial effect on overall, disease-specific, and progression-free survival as compared to non-users (Dilokthornsaul P et al. 2013). Another larger review also confirmed that metformin use was associated with a better prognosis of OC compared to non-users (OR 0.55 95% CI 0.36-0.84) (Shi J et al. 2019).

In summary, studies on metformin and cancer progression are partly discordant and the role of metformin as a possible anticancer agent is still unclear. Metformin users may have a better prognosis than diabetic patients not using metformin because metformin is used as a first-line therapy in diabetes. Therefore, comparisons between diabetic patients with or without metformin use may essentially be a comparison between early stage and late-stage diabetes.

8.3 Statins

Statins decrease the levels of low-density lipoprotein (LDL) in serum by inhibiting the HMG-CoA-reductase enzyme in liver which in turn increases the number of LDL-receptors on the surface of liver evoking a decrease in LDL levels in the circulation. Statins are used in cholesterol-lowering purpose in arteriosclerosis or to decrease the risk of cardiovascular events among high-risk patients without heart and cardiovascular diseases (Ruskoaho H et al. 2014). Statin use has been associated with a decreased risk of dying from cancer in one study (Nielsen et al. 2012). However, a meta-analysis failed to show any benefits of adding statins to cancer treatment in solid tumors (Jang HJ et al. 2018). Lovastatin and simvastatin have been proved to induce apoptosis and arrest cell growth in prostate cancer cells in vitro (Hoque A et al. 2008). Despite promising anticancer effect in vitro, the role of statins in cancer prognosis is still uncertain and more clinical studies are needed.

In prostate cancer, Katz MS et al. also analysed statin use and the risk of PCa death in a cohort study in participants who had been treated with radical surgery or radiotherapy during 1990-2003. Statin use was based on self-reported use after diagnosis and was associated with a decreased risk of all-cause mortality after radical prostatectomy (HR 0.35 95% CI 0.21–0.58) and after radiation therapy (HR 0.59 CI 0.37–0.94) (Katz MS et al. 2010).

With respect to pre-diagnostic use, statins have been associated with improved PCa survival and decreased risk for starting androgen-deprivation therapy (ADT) in a large Finnish cohort study (HR 0.70 95% CI 0.52-0.95). The study consisted of 14,424 men treated with radical prostatectomy. The association found that statins' effect was dose-dependent with the risk of PCa death lowest at highest dose of statin use. Post-diagnostic statin use was associated with a decreased risk of PCa death in the age-adjusted analysis (HR 0.76 95% CI 0.62-0.93) but not in the multivariable adjusted analysis. In the lag-time analysis, which minimizes the healthy user bias, the risk decrease was seen clearest for statin use that occurred 5 years earlier (HR 0.71 95% CI 0.55-0.92). Both pre-and post-diagnostic statin use were also associated with a decreased risk of starting ADT which was applied as an estimation for disease recurrence (HR 0.72 95% CI 0.65-0.80 for pre-diagnostic use and HR 0.73 95% CI 0.67-0.80 for post-diagnostic use) (Joentausta RM et al. 2019). Another Finnish cohort study has evaluated whether disease or treatment characteristics explain the improved PCa survival among statin users. The study included a total of 6,537 men from the Randomized Study of Screening for Prostate Cancer in Finland conducted in the period 1996-2012. After adjustment for different treatment methods and also tumor characteristics, pre-diagnostic statin use not associated with the risk of PCa death (HR 0.95 95% CI 0.75–1.12). In contrast, post-diagnostic statin use was associated with a decreased risk of PCa death (HR 0.80 95% CI 0.65–0.98) and this association was dose-dependent. The risk decrease was however statistically significant for only men treated with androgen-deprivation therapy (not for surgery or radiotherapy as the primary treatment) which highlights the importance of adjustments with primary treatment and tumor characteristics (Murtola TJ et al. 2017).

In a cohort study from Taiwan, pre-diagnostic simvastatin and lovastatin use was associated with a reduction in the PCa death risk (HR 0.84 95% CI = 0.73-0.97) as compared to non-users. The analyses were adjusted for comorbidities but not for the use of other drugs, cancer treatments or tumor characteristics. (Chen YA et al. 2018)

Nickels S et al. investigated the association between statin use and BCa prognosis. The study utilized a German database in which women over 50 years old had been diagnosed with BCa between 2001 and 2005 and a total of 3,189 women were included. Self- reported statin use at the time of study recruitment was defined as use. The results seemed to be dependent on tumor characteristics; when stage IV was excluded in the analysis, statins were associated with a non-significant improvement in the BCa recurrence risk and BCa survival (HR 0.83 95% CI 0.54–1.24 for BCa recurrence and for breast cancer-specific mortality HR 0.89 95% CI 0.52–1.49). (Nickels S et al. 2013). On the contrary, a Swedish study reported no association between statin use and the risk of BCa death. Both pre-diagnostic, post-diagnostic and ever-statin use was evaluated (Bjarnadottir O et al. 2020). Another larger Swedish nationwide cohort study investigating 20,559 women diagnosed with BCa during 2005-2008 did detect a decreased risk association of BCa death with both pre-and post-diagnostic statin use as compared to non-users (HR 0.77 95% CI 0.63–0.95 p = 0.014 for pre-diagnostic use and HR 0.83 95% CI 0.75–0.93 p = 0.001 for post-diagnostic use) (Borgquist S et al. 2019).

On the contrary, Shaitelman SF et al. reported that among triple-negative BCa women, statin use after diagnosis was associated with improved overall survival (HR 0.10 95% CI 0.01-0.76) but not significantly with distant metastasis-free survival (HR 0.14 95% CI 0.01-1.40) or local-regional-recurrence free survival (HR 0.10 95% CI 0.00-3.51). The study examined 869 women diagnosed with non-metastatic BCa during 1997-2012 with use being defined as statin use at any time before treatment (Shaitelman SF et al. 2017). According to an Irish study conducted by Smith A et al., pre-diagnostic use of statins was associated with a decreased risk of BCa death (HR 0.81 95% CI 0.68-0.96) and all-cause death (HR 0.78 95% CI 0.69-0.89) with the association being strongest among estrogen-receptor positive patients (HR 0.69 95% CI 0.55-0.85). The study consisted of 6,314 women with stage I-III BCa with the information on statin use being obtained from a national database (Smith A et al. 2017). A Scottish nationwide cohort also reported a marginally improved BCa survival among patients with pre-diagnostic statin use while risk estimates for post-diagnostic use were statistically non-significant (HR 0.85 95 % CI 0.74- 0.98 for pre-diagnostic use). This retrospective

cohort included 15,140 BCa patients diagnosed from 2009 to 2012 (Mc Menamin UC et al. 2016). On the contrary, Smith et al. did not detect any association between post-diagnostic use of statins and an improved BCa or overall survival (Smith A et al. 2016).

In a large nationwide Finnish cohort study, Murtola TJ et al. reported an improved BCa survival associated with pre-and post-diagnostic use of statin users (HR 0.46 95% CI 0.38–0.55 for pre-diagnostic and HR 0.54 95% CI 0.44–0.67 for post-diagnostic use) and furthermore the risk estimates in pre-diagnostic analyses were dose-dependent. The cohort consisted of 31,236 BCa cases diagnosed in Finland in the period 1995-2003 obtained from Cancer Registry. Information on statin use was obtained from the National Prescription Database. While the investigators suggested that the post-diagnostic results were likely to be affected by a healthy-user bias, the pre-diagnostic dose-dependent results did provide support for a causal link (Murtola TJ et al. 2014).

Another study reported a weak association between post-diagnostic statin use and decreased BCa and overall mortality risk (HR 0.84 95% CI 0.68–1.04 for BCa death and HR 0.84 CI 0.72–0.97 for all cause death). Risk estimates were lowest for post-diagnostic simvastatin use (HR 0.79 CI 0.63–1.00 for BCa death and HR 0.81 CI 0.70–0.95 for all cause death) (Gardwell CR et al. 2015). Statins have also been associated with a decreased recurrence risk after diagnosis (RR 0.67 95% CI 0.39–1.13) (Kwan ML et al. 2008).

Leiter A et al. conducted a study comparing black and white women diagnosed with BCa and their pre-diagnostic statin use; it included 487 women of whom 100 were black. LDL levels did not differ between the groups. Overall black women had a worse BCa prognosis compared to their white counterparts. Black women were however more likely to have been treated with statins. Statin use was not associated with the BCa prognosis in either group (Leiter A et al. 2018).

Ovarian cancer was examined in a Finnish cohort study examining the pre-diagnostic use of statins; it reported improved OC survival in women with type 2 diabetes (DM2). Before diagnosis use of metformin or other oral antidiabetic medications was not associated with OC survival. The study consisted of 471 OC patients diagnosed with DM2 between 1998 and 2011. Drug use was defined as any use three years before OC diagnosis. (Urpilainen E et al. 2018)

As a conclusion, there is no consensus if there is an association between statin use and BCa survival and prognosis although there seems that there are more studies showing benefits for statin use than those not reporting benefits. It is important to adjust for primary treatment as in a Finnish cohort study, the reduction in the PCa death risk was only observed among men with androgen-deprivation therapy for PCa. The role of modifying the cholesterol level needs to be clarified as this may help explain the association between statins and cancer mortality.

8.4 Antihypertensive drugs

8.4.1 Angiotensin-converting enzyme inhibitors

There are several angiotensin-converting enzyme inhibitors (ACE-inhibitors) on the market e.g., enalapril, captopril, lisinopril, perindopril, quinapril, zofenopril and ramipril. Of them enalapril, lisinopril, perindopril, quinapril and ramipril were available in Finnish health care in the year 2019. Captopril was invented in the 1970s and other ACE-inhibitors during 1980-90s (Christen 1991)

ACE-inhibitors affect renin-angiotensin-aldosterone system (RAA-system). Renin is an enzyme produced by the kidneys. Its production is controlled by sodium balance, blood pressure level and the sympathetic

nervous system. When there are decreases in the concentration of sodium in distal tubules of glomerulus, macula densa-cells located in distal tubules are stimulated to increase the release of renin into circulation. Renin production is activated also when the perfusion pressure decreases in afferent artery of the glomerulus i.e., its production is activated by decreased intra-arterial pressure. The third mechanism for renin production is increased sympathetic activity. Noradrenaline, the neurotransmitter of sympathetic nervous system, activates AT_1-receptors in juxtaglomerular cells in glomerulus which promotes the production of renin. There are some other minor agents that can affect renin production e.g., natriuretic peptides produced mainly by ventricles of heart and antidiuretic hormone (ADH) produced in the pituitary gland when blood pressure increases. In addition, angiotensin II produced by RAA-system exerts a form of negative feedback control to inhibit renin production. (Ruskoaho H et al. 2014)

Renin is a proteolytic enzyme which converts angiotensinogen into angiotensin I. Angiotensinogen is found in the circulation and is mainly produced by liver. Its formation is promoted by for example estrogen, inflammation, and glucocorticoids. The biological half-time of renin is very short 10-15 min, to avoid overactivation of the pathway.

Angiotensin I is a weak vasoconstrictive agent, but it is converted into a more powerful vasoconstrictor, angiotensin II, by angiotensin-converting enzyme. Angiotensin I is located in the endothelial cells in alveolar vessels in the lungs. Angiotensin II is converted further to angiotensin III which is also a vasoconstrictor. (Ruskoaho H et al. 2014)

In addition to constricting blood vessels, angiotensins II and III also promote the release of aldosterone from adrenal cortex via AT_1-receptors. Aldosterone in turn increases sodium re-uptake in distal tubulus of glomerulus via the Na, K-ATPase-channel. As sodium re-uptake also increases the re-uptake of water increases leading to an elevation of blood pressure and subsequently there is increased secretion of potassium and protons into urine. (Ruskoaho H et al. 2014)

The action of angiotensin II is mediated mainly by two receptors: AT_1- and AT_2-receptor. For example, AT_2-receptors are known to inhibit cell proliferation in heart muscle cells and thus they inhibit hypertrophy of heart muscle. They may also cause dilatation of vessels acting in the opposite way to the AT_1-receptor. The AT_1-receptor is a G-protein-coupled receptor which mediates contraction of smooth muscle in vessels, and it also promotes the formation of growth factors that mediate cell proliferation. (Ruskoaho H et al. 2014)

The mechanism of action of all ACE-inhibitors is inhibition of the formation of angiotensin II from angiotensin I. This inhibition leads to dilatation of arteries; veins also become dilated but to a lesser extent. Administration of ACE-inhibitors decreases both systolic and diastolic blood pressure. ACE-inhibitors also inhibit cell hypertrophy and are therefore part of routine care in chronic heart failure. They are used as first line treatment of hypertension alone or combined with other anti-HT drugs. (Ruskoaho H et al. 2014)

Adverse effects of ACE-inhibitors include vertigo, hypotension, high potassium levels, cough, kidney toxicity and a rare condition called angio-oedema. Vertigo and hypotension are caused by the lowered blood pressure. Cough is a general side-effect which is observed in 5-20% of users, at least at the beginning of use. The mechanism for cough is thought to be caused by inhibition of bradykinin breakdown. High potassium levels might be problematic especially in patients with kidney failure which is a condition associated with high potassium levels. The mechanism of action of ACE-inhibitors is potassium sparing as they inhibit the formation of aldosterone. Thus, if the function of kidneys is already depressed, this might cause a rise in potassium levels. Acute kidney toxicity might be seen among patients diagnosed with renal artery stenosis where the circulation in the glomerular arteries depends on angiotensin II. When ACE-inhibitors inhibit formation of angiotensin II, hypotension might occur and lead to a collapsed circulation in the kidneys. Angioneurotic oedema is a rare condition presenting as oedema of the face, lips, nose, arms and in certain

situations also in the larynx. ACE-inhibitors are also teratogenic drugs, and they must be avoided in pregnant women. (Ruskoaho H et al. 2014)

8.4.2 Angiotensin-receptor blockers

Angiotensin-receptor blockers (ATR-blockers) include losartan, candesartan, olmesartan, telmisatan, valsartan, eprosartan, irbesartan and azilsartan. Losartan was the first ATR-blocker, and it received a trading licence in Finland in 1995. It had been developed in Sweden one year previously. The effect of ATR-blockers on the RAA-system is similar to the ACE-inhibitors but they act on a different part of the pathway. Since ATR-blockers are newer, no generic variants were available in the 90s making ATR-blockers more expensive than ACE-inhibitors. (Ruskoaho H et al. 2014)

The mechanism of action of ATR-blockers is selective blockade of the AT_1-receptor; they do not have any effect on AT_2-receptors. The affinity of ATR-blockers for the AT_1-receptor varies; candesartan is the compound with the highest affinity. Due to inhibition of the negative feedback of angiotensin II on renin production, the secretion of renin and the formation of angiotensin II are increased during the therapy. The effects of angiotensin II are thus targeted to the AT_2-receptor since AT_1-receptors are inhibited. The clinical significance of this phenomenon is still unknown. (Ruskoaho H et al. 2014)

The most important clinical effect of ATR-blockers in the management of hypertension is dilatation of blood vessels because the actions of angiotensin II are inhibited. ATR-blockers also inhibit aldosterone secretion by blocking AT_1-receptors also in adrenal cortex.

ATR-blockers are well tolerated drugs and have fewer negative side effects than ACE-inhibitors. They do not cause the cough typically encountered with ACE-inhibitors. Nonetheless, they may cause hypotension and high potassium levels by the same mechanism as the ACE-inhibitors, and they are also teratogenic just like the ACE-inhibitors. (Ruskoaho H et al. 2014)

ATR-blockers inhibit ventricular hypertrophy in chronic heart failure and are therefore part of routine care and an alternative to ACE-inhibitors. ATR-blockers may be used for hypertension treatment alone or combined with different anti-HT drugs other than ACE-inhibitors because they share a similar mechanism of action with these drugs. ATR-blockers have also been proved to decrease protein secretion into urine among hypertensive patients and are therefore used in nephrotic syndrome. (Ruskoaho H et al. 2014)

8.4.3 Calcium-channel blockers

The cellular calcium concentration regulates the contraction of smooth muscle and heart muscle cells. Calcium ions flow into cells via L-type voltage-dependent channels on the cell membrane. Thus, blockade of these channels leads to a relaxation of smooth muscle cells, for example in the walls of blood vessels. (Ruskoaho H et al. 2014)

Calcium-channel blockers can be divided into two groups according to their chemical structure. The first group consists of the dihydropyridines i.e., amlodipine, felodipine, isradipine, lercanidipine, nifedipine, nilvadipine, nimodipine and nisoldipine. The second group non-dihydropyridines include for example verapamil and diltiazem. They are very rarely used in treatment of hypertension.

Calcium ion levels outside cells are much higher compared to the amounts inside with the difference maintained by ion pumps. When calcium flows into cell through calcium-gated channels, it releases also

more calcium-ions from endoplasmic reticulum inside the cell. In addition to L-type voltage-dependent channels, there are also ligand-dependent channels in cell membrane which are regulated by different hormones. (Ruskoaho H et al. 2014)

The effects of calcium-channel blockers are seen mainly in heart muscle cells and blood vessels due to the higher concentration of L-type channels in these tissues. Calcium inflow leads to depolarization of muscle cell which triggers muscle contraction. Smooth muscle is found mainly in the walls of arteries and to a lesser extent in veins. Thus calcium-channel blockers relax arteries and decrease blood pressure. They also relax smooth muscle and increase blood flow in coronary arteries.

In addition to acting on smooth muscle in blood vessels, verapamil and diltiazem also exert effects on atrio-ventricular conduction and thus act like antiarrhythmic drugs. They increase the time period that calcium-channels in the heart need to recover after the action potential leading to a decrease in heart rate. Recovery time is the time when calcium-ion concentrations are returned to the original levels in and outside the cells before the cell can generate a new action potential and a subsequent muscle contraction. By prolonging this time, conduction in heart is also slowed down because the transmittance of the action potential in the heart happens along specialized conductance cells. (Ruskoaho H et al. 2014)

Calcium-channel blockers are well tolerated. The most common side effects are hypotension and vertigo caused by the excessively low blood pressure. This may also cause a compensatory increase in heart rate which in turn may cause a sudden lack of oxygen in heart muscle triggering chest pain symptoms like angina pectoris. Sometimes vasodilation of vessels may cause oedema in legs, ankles and fingers, facial flushes, headache, and nausea. Oedema in ankles is experienced by 2-10% of patients and is a dose-dependent side effect. Since verapamil and diltiazem have their own distinct effect on cardiac conduction, they may cause bradycardia and conduction blockades. Other possible side effects for calcium-channel blockers include constipation, rash, cough, and shortness of breathing. They may also have interactions with other drugs since their metabolism takes place via the CYP3A4-enzyme in liver. Consumption of grapefruit juice may increase the concentration of calcium-channel blockers in the circulation due to their reduced catabolism in liver and gut. (Ruskoaho H et al. 2014)

Dihydropyrimidines are first line treatments of hypertension alone or combined with other anti-HT drugs. Verapamil and diltiatzem are also used as antiarrhythmic drugs.

8.4.4 Beta-blockers

B-receptors are found in different organs and the expression of each receptor subtype varies organ by organ. The main subtypes of B -receptors are B_1 which is the main subtype in heart and kidneys, the B_2-receptor found mainly in blood vessels and bronchus and B_3-receptors found in fat tissue, bladder, and heart. All B-receptors are G-protein receptors which are activated by the two catecholamines, noradrenaline and adrenaline. (Ruskoaho H et al. 2014)

Heart expresses all three subtypes of B-receptors. The sympathetic nervous stimulation releases noradrenaline from synapses which activates mainly B_1-receptors. Adrenaline is secreted in times of stress from adrenal medulla, and it stimulates both B_1- and B_2-receptors. Activation of B_1-receptor increases the heart rate and the power of contraction. The significance of B_3-receptors in heart is unknown. In the bladder, the B_3-receptor is responsible for mediating the feeling of a full bladder. Its agonist, mirabegron, is used in the treatment of overactive bladder. (Chapple et al. 2014)

In clinical use, beta-blockers are divided into two groups based on their selectivity to B_1-and B_2-receptors. Selective beta-blockers acetabulol, atenolol, betaxolol, bisoprolol, esmolol, landiolol, metoprolol, nebivolol

and seliprolol are mainly B_1-receptor blocking drugs and their affinity for the B_2-receptor is low in normal doses. There are some non-selective beta-blockers e.g., pindolol, propranolol, sotalol and timolol which are not selective for receptor subtype and have affinity for B_2-receptor also in clinical doses. (Ruskoaho H et al. 2014)

The blood pressure lowering effect of beta-blockers is based on B_1-receptor blockade. In the resting state, noradrenaline stimulation of the B_1-receptor is minimal and thus B_1-receptor blockade emerges more clearly in times of stress and physical activity. The main mechanisms behind blood pressure lowering are decreases in both heart rate and minute volume. However, with a longer duration of use, also peripheral resistance in vessels is lowered, leading to decreased blood pressure. Beta-blockers also inhibit renin secretion by blocking B_1-receptors in the kidneys, leading to an inhibition of the RAA-system. (Ruskoaho H et al. 2014)

With large doses beta-blockers may cause bradycardia. A rebound syndrome is possible if the medication is stopped abruptly and thus the dose must be decreased in small steps. Non-selective beta-blockers have clinically significant affinity also for B_2-receptors which may cause contraction of the smooth muscle in bronchus among patients with asthma or chronic obstructive pulmonary disease. Beta-blockers may locally cause peripheral constriction of arteries which may cause claudication and Raynaud´s syndrome. Beta-blockers also have effects on carbohydrate and fat metabolism which may be potentially serious among diabetic or pre-diabetic patients. Their heart rate decreasing properties may represent a contraindication when treating hypertension in athletic patients. (Ruskoaho H et al. 2014)

Beta-blockers on their own are no longer first line treatments of hypertension. They are primarily used in coronary artery disease and in the treatment of arrhythmias and heart failure. Labetalol can be used alone in the treatment of hypertension during pregnancy.

8.4.5 Diuretics

Diuretics include thiazides, loop-diuretics (furosemide, which is discussed more closely in the next section) and potassium-sparing diuretics. The thiazides used in Finland include hydrochlorothiazide and indapamide. The potassium-sparing diuretics include spironolactone, eplerenone, amiloride and triamterene. Their common mechanism of action is increasing sodium secretion in glomerular tubulus which leads to water removal from the body. Plasma volume and thus minute volume of the heart decreases, leading to a reduction of the blood pressure. Plasma volume remains decreased during treatment, but heart minute volume recovers to the normal level because of compensatory effects. However, after a couple of weeks of therapy, peripheral resistance decreases which is the main cause of the decline in blood pressure. Vasodilation is caused by a reduced intracellular calcium-concentration caused by the decreased sodium-concentration in smooth muscle where diuretics also have their target ion-channels. (Ruskoaho H et al. 2014)

Thiazides inhibit the NaCl-symporter at the beginning of the distal tubule in the glomerulus leading to increased secretions of sodium, chloride, and water into urine. They also decrease the secretion of uric acid which may lead to a gout attack among sensitive patients.

Spironolactone and eplerenone are mineralocorticoid-receptor antagonists. Aldosterone is the most important mineralocorticoid regulating blood pressure. The mineralocorticoid antagonists block the aldosterone receptor leading to decreased potassium secretion and increased sodium re-uptake from urine. (Ruskoaho H et al. 2014)

Amiloride and triamterene are both weak diuretics and are therefore used combined with other diuretics. They block the Na-channel in distal tubule of glomerulus leading to sodium secretion into urine, which indirectly changes the voltage between cell membranes leading to decreased secretion of potassium.

The side effects of diuretics, especially the thiazides, are disturbances in potassium and sodium balance, hyperuricemia, and also metabolic disturbances. Thiazides act as diabetogenic agents causing an increase in the blood glucose level. They may also decrease levels of HDL and increase levels of LDL cholesterol. Thiazides may cause impotence more often than other anti-HT drugs. Spironolactone has affinity also for estrogen receptors and thus can cause gynecomastia in men. (Ruskoaho H et al. 2014)

Diuretics are often used combined with other drugs in the management of hypertension. When hypertension is complicated with heart failure, diuretics are a good option because of their water removing properties. By the same mechanism, diuretics may also activate the RAA-system which in turn leads to a better treatment response when combined with ACE-inhibitors or ATR-blockers. Blood pressure decreasing effect of diuretics is also based on other mechanisms than water removing like vasodilation of vessels (Duarte JD et al 2010). (Ruskoaho H et al. 2014)

8.4.6 Furosemide

Furosemide is included in group of loop-diuretics due to its mechanism of action. Furosemide is not used for hypertension management. It however is a powerful diuretic drug and the only loop-diuretic used in Finland.

The name loop-diuretic is based on furosemide's mechanism of action since the drug blocks the action of Na, K, 2Cl-symporter in the ascending part of the distal tubulus which is called the loop of Henle. Furosemide inhibits re-uptake of sodium and chloride leading to their increased secretion. It also indirectly increases the secretion of magnesium and calcium into urine. (Ruskoaho H et al. 2014)

The elevated secretion of sodium leads to a decrease in blood pressure. However, because of the intense fluid removing capacity, furosemide is not used for primary hypertension treatment but for example to treat oedema in kidney and heart failure. Its short duration of action also limits its utility in the management of hypertension. Instead, it may be used in the treatment of oedema in cases of heart failure and ascites.

Furosemide has some serious side effects e.g., disturbances in electrolyte balance, hypovolemic conditions, and ototoxicity with large doses and since it increases directly or indirectly the secretion of many electrolytes, it can evoke a severe loss of sodium, potassium, magnesium, chloride, and calcium. Furthermore, it has such a powerful water removing effect that a hypovolemic state can also occur (Ruskoaho H et al. 2014)

9 METABOLIC CONDITIONS AND CANCER PROGNOSIS

Hypertension and other metabolic conditions such as diabetes may exert an influence on both the cancer risk and prognosis. Hypertension, hypercholesterolemia, and diabetes are also commonly found together in the same person which makes it difficult to separate the influence of a single condition on cancer prognosis from the others. When studying the effect of these diseases on cancer prognosis, it is important to consider how these conditions have been defined. For example, hypertension may be defined by antihypertensive medication use, self-reported blood pressure levels or self-reported information on diagnosis or by measured blood pressure levels in health care. These factors may have an influence on the reliability of a study and also affect the results. The prognostic effect of hypertension may be negative as described in this section.

9.1 Hypertension

Hypertension and obesity have been associated with an increased risk of biochemical recurrence after radical prostatectomy (HR 1.37 95% CI 0.92–2.09 for hypertension and HR 1.51 95% CI 1.01–2.26 for obesity) without adjustment for use of anti-HT medication (Asmar R et al. 2013). Ohwaki K et al. 2015 reported results in the same direction as hypertension was associated with an increased biochemical PCa recurrence risk (HR 2.08 95% CI 1.09–3.97) (Ohwaki K et al. 2015). However, another study failed to detect any association between obesity and risk of biochemical recurrence in PCa but elevated systolic blood pressure and untreated hypertension were also associated with an increased risk of cancer recurrence in that study (HR 1.04 95% CI 1.02–1.07 for elevated blood pressure, HR 2.45 95% CI 1.06–5.66 for untreated hypertension) (Ohwaki K et al. 2015).

According to a Swedish cohort study, hypertension was associated with an increased risk of BC death among never-smokers (HR 1.10, 95% CI 1.01-1.20) (Teleka S et al. 2021). Only a few studies have reported an increased risk association between hypertension and BC recurrence (Dal Moro F et al. 2015).

In BCa, hypertension was associated with an increased risk of both overall, non-breast cancer death and breast cancer death (HR 1.47 95% CI 1.03–2.09) but estimates were not statistically significant when the use of antihypertensive medications was taken into account (Braithwaite D et al. 2012). In other publications, hypertension has been associated with an increased risk of BCa death (Braithwate D et al. 2008) (Braithwate D et al. 2012). However, Braithwate D et al. 2012 reported that the risk association in BCa became attenuated to a non-significant level after adjustment for the use of anti-HT medication. Diabetes and hypertension have been associated with a decreased overall survival and recurrence-free time also in OC. (Bar D et al. 2016) (Bakhru A et al. 2011) (Akhavan S et al. 2018).

9.2 Other metabolic conditions

According to a meta-analysis of 17 cohort studies, diabetes was associated with 29 % increase in prostate cancer-specific mortality (RR 1.29 95 % CI 1.22–1.38) and with 37 % increase in all-cause mortality (RR 1.37 95 % CI 1.29–1.45) (Lee J et al. 2016). Another meta-analysis reported results in the same direction (Cai H et al. 2015).

Diabetes may worsen BC prognosis especially among young individuals whereas data on hypertension and BC prognosis is controversal (Tseng CH et al. 2009) (Cantiello F et al. 2015). Patients with metabolic syndrome have worse disease-free survival compared to healthy patients; a high BMI was associated with a higher risk for disease recurrence and progression (HR 2.94 95% CI 1.43–6.03) (Lenis AT et al. 2018). According to a meta-analysis examining the link between metabolic syndrome and the risk of BC diagnosis and BC progression, no clear conclusions can be made between components of metabolic syndrome and BC progression. The only correlation may be diabetes which negatively affected the prognosis of BC (Cantiello F et al. 2014).

Metabolic syndrome is an important prognostic factor in BCa as women with metabolic syndrome have a higher risk for recurrence (OR 2.17 CI 1.31–3.60). In addition, low HDL-levels and high triglyceride levels have been associated with an increased risk of recurrence (OR 1.83 CI 1.24–2.70 for low HDL and OR 1.58 CI 1.01–2.46 for high triglycerides) (Berrino F et al. 2014) (Emaus A et al. 2010). Metabolic syndrome has been associated with an increased risk of BCa death, at least among over 60-year-old women (RR 1.23 95% CI 1.04-1.45). A high blood pressure and elevated blood glucose levels were also associated with increased BCa death risk (Björge T et al. 2010). Diabetes combined with hypertension has been associated with an elevated BCa death risk while this was not the case for either diabetes or hypertension alone (HR 2.29 95 % CI 1.91-2.74 for combination) (Nelson SH et al. 2016).

In OC, diabetes has been associated with an increased risk of overall mortality (HR 1.12 95% CI 1.01–1.25) but not with the OC death risk and this was also the case for either hypertension or other cardiovascular diseases (Minlikeeva AN et al. 2017). Obesity has been linked with lower overall survival and shorter recurrence-free time among women with advanced OC as compared to healthy women (Pavelka JC et al. 2006).

In summary, according to currently published studies, both hypertension and diabetes are associated with a poor cancer prognosis. Most studies have defined the prevalence of hypertension by use of anti-HT medication.

10 ANTIHYPERTENSIVE MEDICATION USE AND CANCER PROGNOSIS

10.1 RAA-system affecting drugs and cancer progression

It has been proved in vitro that components of RAA-system are found in many cancer-prone tissues (like prostate, ovarian, breast and ovaries) and this has sparked interest towards clarifying the role of the RAA-system in cancer prognosis (Chow L et al. 2009) (De Paepe B et al. 2001) (Ino K et al. 2006). The RAA-system also may influence cancer prognosis and patient survival: for example, AT_1-receptor expression in OC cells correlates with a poor prognosis and shorter OC survival (Ino K et al. 2006). The AT_1-receptor is the target of angiotensin II which is a part of the RAA-system and is known to control angiogenesis and cell proliferation (Escobar E et al. 2004) (Deshayes F et al. 2005) (Uemura H et al. 2008).

ACE-inhibitors and ATR-blockers affect the RAA-system but via different mechanisms. ACE-inhibitors block the whole pathway by inhibiting the formation of angiotensin II which in turn activates angiotensin-receptors (the best known of which are the AT_1- and AT_2-receptors). ATR-blockers selectively block only AT_1-receptor while the AT_2-receptor and other receptors are left free.

There are several in vitro studies which have examined how RAA-system agents affect cancer cells. In one in vitro study in PCa cells, the ATR-blockers losartan, valsartan, eprosartan and fimasartan were associated with cell death and anti-mitotic activity (Woo Y et al. 2017). In mice, administration of losartan inhibited prostate cancer cell growth when the tumor was stimulated with angiotensin II. (Scott-Emuakpor J et al. 2017). In vitro, telmisartan inhibited cell proliferation and induced apoptosis in ovarian cancer cells (Pu Z et al. 2016).

10.2 Prostate cancer prognosis and antihypertensive drug use

There are several investigators that have examined the link between antihypertensive drug use and the risk of PCa diagnosis but there are not so many studies into the association between antihypertensive drug use and PCa prognosis. Since uncontrolled hypertension has been associated with a poorer PCa prognosis, the question has arisen whether antihypertensive drugs would improve PCa survival (Ohwaki et al. 2015).

Antihypertensive medication has been evaluated as a group in one study. All Swedish PCa patients diagnosed with PCa 2007-2013 (n=9,867) and who received GnRH agonists as primary treatment of PCa were included in that study. Any anti-HT drug use at the time on GnRH initiation was defined as use. A weak increase was observed in the risk of prostate cancer death in men who were taking drugs for hypertension or hyperglycemia at the time of starting GnRH- agonists, but it disappeared when the competing risk of cardiovascular death was taken into account. Anti-HT drugs were analysed as one group so that no drug specific results were available. Since the primary treatment was GnRH agonists, these men likely had advanced disease or a decreased general health status prohibiting primary treatment with a curative goal. The increased risk trend among anti-HT drugs may also be explained by the underlying conditions i.e., heart failure or coronary artery disease especially because the association was not seen after taking into account competing causes of death. (Bosco C et al. 2018)

The use of RAA-system affecting drugs (ACE-inhibitors and ATR-blockers) and the risk of PCa death was evaluated in a cohort study examining a total of 6,339 men with PCa. ACE-inhibitors and ATR-blockers

were analysed as separate drug groups. The exposure was defined as use during the time period starting after PCa diagnosis and ending 6 months before PCa death. The use of ATR-blockers was not statistically significantly associated with the risk of PCa death (OR 0.79 95% CI 0.61- 1.03) when compared to non-users. The use of ACE-inhibitors was associated with a reduced risk of PCa death as compared to non-users (OR 0.78 95% CI 0.66- 0.92) (Gardwell CR et al. 2014). However, the risk estimates were identical for both drug groups supporting the decreased risk for drugs affecting the RAA-system.

Alashkham A et al. also evaluated RAA-affecting drugs in a study of 558 men with local or locally advanced PCa treated between 2007 and 2013 who were receiving radical radiotherapy and adjuvant or neoadjuvant antihormonal therapy with only men who were taking ACE-inhibitors or ATR-blockers before, during and after radical PCa treatment included in the assessment. Men who were taking ACE-inhibitors or ATR-blockers combined with any other anti-HT medications or who were also taking statins were excluded. A total of 514 men were finally included in analysis and three groups were formed: hypertensive men using ACE-inhibitors or ATR-blockers, normotensive men with no use of ACE-inhibitors or ATR-blockers and hypertensive men not being treated with either ACE-inhibitors or ATR-blockers. Control groups were normotensive men not using ACE-inhibitors or ATR-blockers. The median follow-up time was only 3.3 years. ACE-inhibitor or ATR-blocker use was associated with a decreased risk of biochemical recurrence (defined as rise in PSA-level) compared to non- users (RR 0.74 95% CI 0.64-0.86 $p < 0.001$) (Alashkham A et al. 2016). Other investigators have not evaluated the risk for biochemical recurrence. As ACE-inhibitors and ATR-blockers were analysed as one single group, no drug specific effects of ACE-inhibitors or ATR-blockers can be deduced. The median follow-up time in this study was also very short as the men in the study had local or locally advanced PCa and since especially local PCa has a good prognosis, it is unlikely that recurrences would have occurred during the follow-up period.

Siltari et al. evaluated both pre-and post-diagnostic antihypertensive use and risk of PCa death in a Finnish cohort study of 8,253 men with PCa. Pre-and post-diagnostic use was analysed separately and also the association between antihypertensive drug use and the risk of starting ADT was evaluated to model disease recurrence. Both pre-and post-diagnostic antihypertensive drug use in general associated with an increased risk of PCa death. Post-diagnostic use of ATR-blockers was associated with a decreased risk of PCa death (HR 0.81 CI 0.67–0.99) while post-diagnostic use of thiazides was associated with an increased risk (HR 1.25 CI 1.05–1.49). The risk of starting ADT was slightly increased among antihypertensive drug users compared to non-users, but no drug specific differences were observed (Siltari et al. 2020).

As a conclusion, there are a couple of reports that post-diagnostic ATR-blocker use is associated with a decreased risk for PCa death, and one study reported results in the same direction for post-diagnostic therapy with ACE-inhibitors.

Assayag J et al. reported that post-diagnostic use of beta-blockers was not associated with the risk of PCa or overall death. The cohort study included 6,270 men diagnosed with local PCa in the years 1998-2009. The follow-up time was quite short, from the year 2009 to 2012 (a mean-follow-up time 3.8 years). Post-diagnostic beta-blocker use was not associated with PCa mortality (HR 0.97 95% CI 0.72-1.31) or all-cause mortality (HR 0.97 95% CI 0.81-1.16). The results were in the same direction for non-selective and selective beta-blockers and for cumulative duration of use (Assayag J et al. 2014). Results in the same direction were seen in Norwegian cohort study where self-reported beta-blocker use at the time of PCa diagnosis was not associated with the risk of PCa death but was instead associated with a decreased PCa mortality risk among men intended to receive ADT. ADT is used in treatment of advanced PCa. (Grytli HH et al. 2013)

Cardwell CR et al. reported results in the same direction; they evaluated post-diagnostic beta-blocker use and the risk of PCa death in a case-control study which included all men diagnosed with PCa in UK during 1998-2006. The follow-up time continued until the year 2011. Beta-blocker users were matched by age and year of diagnosis to non-user men alive at the time of case's death. Beta-blocker use after PCa diagnosis was not associated with the risk of PCa death as compared to non-users (OR 0.94 95% CI 0.81-1.09). (Cardwell

CR et al. 2014). Grytli HH et al. reported contrasting results; in their report, beta-blocker use associated with a reduced PCa mortality risk (HR 0.79 95% CI 0.68–0.91 p= 0.001) but no significant association was observed with all-cause mortality (HR 0.92 95% CI 0.83–1.02). The study included 24,571 men diagnosed with PCa in the period 2004-2009. Information on PCa and other causes of death and medication use was obtained from Cancer Registry of Norway and Norwegian Prescription Database. All men had high-risk or advanced disease at diagnosis. The conflicting results might be explained by the fact that the study population differed from other studies: all men had high risk or advanced disease. It had also previously been reported that men requiring ADT, indicative of advanced disease or a poor general condition, and who had been prescribed beta-blockers had a decreased risk for PCa death (Grytli HH et al. 2013) (Grytli HH et al. 2014).

As a conclusion, beta-blocker use does not seem to be associated with the risk of PCa death except in advanced disease where two studies reported a possibly protective risk association which however may be explained by confounding.

Therapy with calcium-channel blockers and the risk progression-free survival and overall survival in PCa was evaluated in a study among 875 men treated with radical prostatectomy and diagnosed from 1993 to 2010. The use of calcium-channel blockers was not associated with either progression-free survival or overall survival as compared to non-users. Men who received androgen deprivation therapy or radiation therapy prior to radical prostatectomy were excluded from the analyses. Simultaneous use of beta-blockers and ACE-inhibitors was adjusted in the sensitivity analysis, but this did not affect the results. The use antihypertensive drugs was defined as any use at the time of PCa diagnosis (Poch MA et al. 2013). There are also other studies reporting no association with calcium-channel blockers and PCa prognosis (Siltari A et al. 2020).

10.3 Urothelial cancer prognosis and antihypertensive drug use

There are only a few studies examining the association between antihypertensive drugs and urothelial cancer progression. RAA-system inhibiting drugs have been associated with a decreased risk for BC recurrence in subjects with NMIBC. A total of 340 patients treated with TURB were identified from an Institutional Cancer Database; 143 patients had been treated with RAA-inhibiting drugs (ACE-inhibitors or ATR-blockers) at the time of the first TURB which was defined as use. The use of RAA-system inhibiting drugs (HR 0.61 95% CI 0.45-0.84 p = 0.005) and BCG-treatment (HR 0.68 95% CI 0.47-0.87 p = 0.002) was associated with a decreased risk for tumor recurrence. The five-year recurrence-free survival rate was 45.6% in those patients consuming RAA-system inhibiting drugs as compared to non-users in whom the value was 28.1% (p=0.009) (Blute ML et al. 2015).

Yuge K et al. also reported that RAA-inhibiting drugs were associated with a lower risk for NMIBC recurrence but also with improved BC survival after TURB as compared to non-users. RAA-system inhibiting drug use was defined as any use at the time of the first TURB (Yuge K et al. 2012). Bai YJ et al. reported similar results i.e., that RAA-system inhibiting drugs were associated with a reduced risk of NMIBC recurrence (Bai YJ et al. 2018). One meta-analysis of 55 studies evaluated the effect of RAA-inhibiting drugs on recurrence, metastasis, and survival in urothelial cancer patients; it reported improved overall survival among patients with UTUC using ACE-inhibitors or ATR-blockers (HR0.53 95% CI 0.29–0.97 p=0.04) and also for BC (HR0.36 95% CI 0.18–0.72 p=0.004) as compared to non-users. Cancer specific death was not evaluated (Sun H et al. 2017).

There is one report which has examined therapy with RAA-system inhibiting drugs and UTUC outcomes. A total of 279 patients who underwent nephroureterectomy for localized UTUC (pTa-3N0M0) were

evaluated. RAA-system inhibitors were administered to only 48 patients (17.2%). The use of RAA-system inhibiting drugs was associated with improved metastasis-free survival. The five-year metastasis-free survival rate was 93.0% in patients who used RAA-system inhibitors compared to 72.8% in those patients not receiving these drugs (p=0.008) (Tanaka N et al. 2011).

10.4 Breast cancer prognosis and antihypertensive drug use

Chae YK et al. conducted a study of 1,449 women with invasive BCa diagnosed between 1995 and 2007 and who were treated with neoadjuvant chemotherapy; 11% of the women were categorized as users of ACE-inhibitors or ATR-blockers and these formed the exposure group. The use of ACE-inhibitors or ATR-blockers was not significantly associated with the risk of BCa death (HR 0.83 95% CI 0.52-1.31). However, relapse-free survival among users was improved as compared to non-users (82% vs 71% p<0.03) and furthermore, therapy with ATR-blockers alone was associated with a decreased risk of recurrence (HR 0.35 95% CI 0.14-0.86). (Chae YK et al. 2013)

Another study reported improved disease-free survival among women with post-diagnostic use of ACE-inhibitors or ATR-blockers (analysed as one drug group). The study included 703 patients diagnosed with stage II or III BCa in the time frame 1999-2005. Use of a drug group was defined as any use within 6 months after diagnosis and the primary outcome was disease-free survival. Overall survival was secondary outcome. The use of ACE-inhibitors or ATR-blockers associated with improved disease-free survival (HR 0.49 95% CI 0.31-0.76 p = 0.002). The risk association was stronger if ACE-inhibitors or ATR-blockers had been used in combination with statins (HR 0.30 95% CI 0.15-0.61 p = 0.001) (Chae YK et al. 2011).

Therapy with ACE-inhibitors or ATR-blockers was also associated with improved recurrence-free survival in women with lymph node metastases. The study included 218 women diagnosed with N3 positive BCa during 2005-2012. The use of ACE or ATR-blockers was defined as usage within 6 months after diagnosis. The use of either of these drug groups was associated with marginally improved recurrence-free time and overall survival as compared to non-users but risk estimates were not statistically significant (p=0.38 and p=0.24, respectively) (Babacan T et al. 2015).

Ganz PA et al. included 2,269 women diagnosed with BCa during 1997-2000 in a cohort study with the risk of BCa death being compared between post-diagnostic users and non-users of antihypertensive drugs. Therapy with beta-blockers and ACE-inhibitor was not associated with the risk of BCa death. Instead, the combined use of ACE-inhibitors and beta-blockers did seem to increase the risk for all-cause mortality (HR 1.94 95% CI 1.22-3.10 p = 0.01) although in women younger than 70 years, the association was no longer evident. There was no confounding for comorbidities i.e., underlying conditions treated with ACE-inhibitor combined beta-blockers (like heart failure) may account for the increase in all-cause mortality (Ganz PA et al. 2011).

A cohort study of 14,766 women diagnosed stage I or II BCa between 2007-2011 reported an increased risk of BCa death among users of diuretics (HR 1.51 95% CI 1.11–2.04) and beta-blockers (HR 1.41 95% CI 1.07–1.84) as compared to non-users. Post-diagnostic use of diuretics was also associated with an increased risk of BCa recurrence (HR 1.36 95% CI 1.14–1.63). ACE-inhibitors, ATR-blockers and calcium-channel blockers were not associated with a risk of BCa recurrence or BCa death. Drug use was defined as any use after BCa. (Chen L et al. 2017).

Raimondi S et al. conducted a meta-analysis and claimed that beta-blocker use at the time of BCa diagnosis was associated with improved BCa and relapse-free survival compared to non-users. There was no association between ACE-inhibitor or ATR-blocker use and the risk of BCa or overall death. The meta-analysis consisted of 11 retrospective studies and included a total of 46,265 women (Raimondi S et al. 2016).

The third meta-analysis also evaluated beta-blocker use and BCa prognosis with the rates of overall deaths, BCa deaths and recurrences being compared among beta-blocker users and non-users in a total of 18,118 patients. No significant difference in the rate of overall deaths between beta-blocker users and non-users was observed (OR 0.87 95% CI 0.50-1.52 p = 0.49). The difference in risk of BCa death between beta-blocker users and non-users was also non-significant (OR 0.93 95% CI 0.82-1.06 p = 0.29). In addition, therapy with beta-blockers did not affect the incidence of recurrences (OR 0.70 95% CI 0.25-1.95 p = 0.49). (Kim HY et al. 2017).

The fourth meta-analysis evaluated propranolol and other non-selective beta-blockers and the risk of BCa mortality and all-cause mortality. There was no association between post-diagnostic propranolol use and the risk for BCa or all-cause mortality (HR 0.94 95% CI 0.77-1.16 and HR 1.09 95% CI 0.93-1.28) nor was there any association between pre-diagnostic propranolol use and the risk of BCa or all-cause mortality (HR 1.03 95% CI 0.86-1.22 and HR 1.02 95% CI 0.94-1.10). Furthermore, no association was found between the risk of BCa death and the use of non-selective beta-blockers. (Cardwell CR et al. 2016). All these meta-analyses reviewed retrospective studies.

Another study evaluated beta-blocker use and the risk of BCa metastases at diagnosis. The study included 120 participants with BCa. Selective beta-blockers and non-selective beta-blockers were analysed separately and compared to non-users. None of women treated with non-selective beta-blockers had metastasis at diagnosis while women treated with selective-beta-blockers presented with metastases in 30% of cases. Women without beta-blocker therapy had metastases in 70% of cases. However, no conclusions can be made due to this trial's cross-sectional design. (Parada-Huerta E et al. 2016)

Busby J et al. evaluated calcium-channel blocker use and the risk of BCa death in an English population of patients diagnosed in the time period 1998-2012. Cox regression was used to calculate hazard ratios (HRs) comparing BCa and all-cause mortality between post-diagnostic calcium-channel blocker users and non-users. The cohort included 23,669 breast cancer patients 5,141 of whom had been prescribed calcium-channel blockers. A total of 3,053 women died of breast cancer during the median follow-up of 5.5 years but the risk of BCa death did not differ between calcium-channel blocker users and non-users. (Busby J et al. 2018)

Michels KB et al. also evaluated self-reported calcium-channel blocker use and the risk of BCa diagnosis and mortality. A total of 18,635 female nurses self-reported regularly taking at least one antihypertensive medication in 1988: diuretics, beta-blockers, calcium channel blockers or ACE-inhibitors. In this trial, users of a single drug group were compared to women using the other classes of antihypertensive drugs. No significant difference in the risk of dying of BCa was observed among women with self-reported use of calcium channel blockers as compared to women treated with other antihypertensive drugs (HR 1.25 95% CI 0.91-1.72) (Michels KB et al. 2000)

10.5 Ovarian cancer prognosis and antihypertensive drug use

One cohort study with a minimum follow-up of 4 years evaluated the association between pre- (n=899) and post-diagnostic (n=683) use of antihypertensive medications and OC survival. Pre-diagnostic use of calcium-channel blockers was associated with an increased OC mortality risk (HR 1.52 95% CI 1.15-2.00) whereas a decreased OC mortality risk was observed for post-diagnostic use of ACE-inhibitors (HR 0.64 95% CI 0.44- 0.93). Post-diagnostic use of beta-blockers was non-significantly associated with improved OC mortality (HR 0.76 95% CI 0.58-1.01). In another report, hypertension was not associated with OC mortality (HR 0.99 95% CI 0.83-1.17) but risk associations between antihypertensive drugs and risk of OC mortality were stronger among women with a history of hypertension (Huang T et al. 2018).

Other studies on the association of antihypertensive drugs use and risk of OC death have tended to focus on beta-blockers, generally the evidence of beta-blockers and OC survival is conflicting.

One meta-analysis of 11 cohort studies (20,274 patients) evaluated post-diagnostic beta-blocker use and OC prognosis; no association was found between post-diagnostic beta-blocker use and the risk of cancer-specific death (HR 1.22 95% CI 0.89–1.67), overall mortality (HR 1.08 95% CI 0.92–1.27) or progression-free survival (HR 0.88 95% CI 0.75–1.05). (Wen Z et al. 2021)

A Korean cohort study evaluated beta-blocker use and survival outcome in OC with 866 OC patients identified from The Korean Health Insurance Service. There was no survival difference between beta-blocker users and non-users. When patients were grouped according to the duration of medication, patients with over one year's duration of beta-blocker use showed better survival outcomes (HR 0.31 95% CI 0.19-0.50 $p < 0.001$) when compared to non-users. Furthermore, beta-blocker use among women over 60-years old was linked with better all-cause survival compared to use by younger patients (HR 0.58 95% CI 0.41-0.82 $p = 0.002$) i.e., in patients over 60-years old, medication use lasting longer than 720 days was associated with better survival (HR 0.27 95% CI 0.14-0.51 $p < 0.001$). Both selective and non-selective beta blockers conferred survival benefits. (Park JY et al. 2017)

An Irish study evaluated the association between pre-and post-diagnostic use of beta-blockers and OC survival. All women diagnosed with invasive ovarian cancer from 2001 to 2011 were included in this assessment. The use of beta-blockers before diagnosis was not associated with OC death (HR 1.08 CI 0.93 - 1.23) or other cause of death (HR 1.39 CI 0.92-2.09). Post-diagnostic use with a 6-month lag time was marginally associated with the risk of OC death (HR 0.80 95% CI 0.65-0.99) but not with other causes of death (HR 1.61 95% CI 0.85-3.03) (Brown C et al. 2015)

11 AIMS OF THE STUDY

Antihypertensive drugs are commonly used drugs and previous studies have evaluated the association between certain anti-HT drugs and cancer risk. Rather few investigators have evaluated the association with either the simultaneous use of multiple anti-HT drug groups or these drugs used separately and cancer survival.

The aims of this thesis are:

1. To evaluate the association between the use of different groups of anti-HT drugs and prostate cancer (PCa) survival in prostate cancer patients (cohort 1)

2. To assess the association between anti-HT drug use and the risk of bladder cancer (BC) death and upper tract urothelial carcinoma (UTUC) death in urothelial cancer patients (cohort 2)

3. To determine the association between anti-HT drug use and risk of breast cancer (BCa) death in breast cancer patients (cohort 3)

4. To evaluate the association between anti-HT drug use and the risk of ovarian cancer (OC) death in ovarian cancer patients (cohort 4)

12 METHODS

12.1 Data Sources

12.1.1 Finnish Cancer Registry

The Finnish Cancer Registry maintains a database including all cancer cases diagnosed in Finland after 1953. It is a national research institute in cancer statistics and epidemiology. It has been compulsory for health care units to send notifications of new cancer diagnoses to Cancer Registry since 1961 (Cancer Registry). Most commonly, the information comes from pathology units and therefore information on clinical factors is not as complete as information on histological diagnosis. The Cancer Registry provides information on cancer burden and prognosis as well as cancer incidence and prevalence predictions for healthcare professionals and decision makers. It acts as an information institute giving information on cancer epidemiology to the media and every Finnish citizen. It supports researchers in collection of data and in statistical analyses. The delay in reporting cancer diagnoses to Cancer Registry is 0.5-0.9 years in all cancers other than pancreatic cancer in which the delay is greater, approximately 3.2 years. The accuracy of the Cancer Registry database is high and rates of false-negative between 2.2%- 5.4 % and false-positive between 2.4%-10.7%. (Korhonen P et al. 2002)

12.1.2 Social Insurance Institution of Finland Prescription Register

Social Insurance Institution (SII) provides reimbursements on prescribed medicines for every Finnish citizen. Pharmaceuticals Pricing Board (HILA) subordinated to the Ministry of Social Affairs and Health determines which drugs are included within the reimbursement program. It also sets wholesale prices for these drugs and other medical products. (HILA). In 2016, SII renewed criteria of paying reimbursements: reimbursements are paid only after a yearly 50 euros deductible is exceeded (KELA Reimbursements for drugs). For most of our study period, this deductible was not in use and reimbursements were available for all purchases of drugs approved by HILA. The deductible is not applied for persons under 19 years of age. There are different levels of reimbursements i.e., the basic rate is 40% of the medicine's price. In some specific diseases or with specific criteria, the reimbursements are higher i.e., 65% and 100%. For example, the reimbursement rate of antihypertensive drugs is 40% in the management of non-complicated hypertension (with no end-point organ failure) but with complicated hypertension fulfilling diagnostic criteria (if there is at least one end-point organ failure) then the higher 65% reimbursement rate is available. The same drug may also have a different reimbursement rate when used for different indications. For example, rivaroxaban is reimbursed at 40% in the treatment of deep vein thrombosis but at 65% in the treatment of atrial fibrillation. At every purchase, SII provides reimbursements for drugs to cover 3 months use at a time. (KELA Reimbursements for drugs)

In 2021, yearly maximum deductible is 579.78 euros after which a citizen pays only 2.5 euros deductible for every purchased drug. The yearly maximum deductible is 50 euros from the start of the calendar year (KELA Reimbursements for drugs).

Not all medicines are included in reimbursement program. It is up to HILA to decide which new medicines are included into the program; for example, not all new expensive cancer medicines are included when they first come on the market. Reimbursements are also paid only for prescribed medicines in an outpatient

setting: over-the-counter drugs and drugs used in an in-patient setting in health care units are not included. SII maintains a database of prescribed drugs in which purchases are recorded with different drugs categorized according to the drug specific Anatomical Therapeutic Chemical codes (ATC-codes). The information of every purchase includes details of package size, number of packages bought, dose and the date of purchase (Klaukka T 2001). All antihypertensive drugs in Finland are available only by prescription and are thus recorded by the prescription database.

12.1.3 Care Register for Health Care

The Finnish Institute for Health and Welfare (THL) maintains Care Register for Health Care (HILMO). Nowadays it contains information from in- and outpatient settings in both public and private health care units. The register collects information on the use of health care services, acceptance into health care system, diseases in population, epidemics, and division of work between professionals (HILMO). The register collects data only in special health care. The oldest information in this register dates to 1969. Since 1998, the register has collected information from also hospital outpatient clinics in addition to inpatient settings. The register provides information on medical procedures and diagnoses for example for decision makers and medical researchers.

12.1.4 Digital and Population Data Services Agency

The Digital and Population Data Services Agency maintains information on each Finnish citizen as well as foreign citizens permanently living in Finland. Information contains a citizen's unique identification number, date of birth, name, address, native language, where the citizen is living and possible date of death. The agency was founded in Jan 2021 and replaced the Population Register Center.

12.1.5 Statistics Finland

Statistics Finland founded in 1865 is an authority specialized solely in statistics. It provides approximately 160 many kinds of statistics: from salaries and cost of living data extending to health and population information. For example, statistics on the population contain information on deaths (age at death, nationality, number of children), births, family size and adoptions. Information contains specific causes of death categorized according to International Classification of Diseases (ICD-10).

12.2 Study settings for cohorts I-IV

In cohort I, participants were identified from The Cancer Registry database. All men with PCa diagnosed 1995-2013 and treated with radical prostatectomy were included into our study cohort: a total number of 14,442 PCa cases. Information on anti-HT medication use from the prescription database between 1995-2015 was combined in the cohort using unique identification numbers. Anti-HT drugs were categorized into six groups based on their mechanism of action: ACE-inhibitors, ATR-blockers, beta-blockers, calcium-channel blockers, diuretics (also containing furosemide) and other anti-HT drugs. Anti-HT drugs were

identified from the prescription data according to their drug specific ATC-codes (Table S1). Also, information was obtained on purchases of GnRH-agonists and antagonists as well as antiandrogens.

Cohort II consisted of two sub cohorts in which 14,065 BC cases and 1,080 UTUC cases were obtained from the Cancer Registry. All cases in both cohorts were diagnosed from 1995 to 2012. Both cohorts contained information on the primary site of cancer, tumor extent at diagnosis (localized, locally advanced, advanced, unknown), date and method of diagnosis, primary treatment method (surgery, radical cystectomy, cytostatic drugs, chemotherapy, antihormonal therapy) and date and cause of death. Like cohort I, these cohorts were also linked to the national prescription database to obtain information on anti-HT drug use. In this cohort, only five groups of anti-HT drugs were used: ACE-inhibitors, ATR-blockers, beta-blockers, calcium-channel blockers, and diuretics.

Cohort III consisted of 73,170 women diagnosed with BCa between 1995-2013 identified from the Cancer Registry. Data contained information on date and method of diagnosis, tumor extent at diagnosis (recorded in the registry as local, advanced into regional lymph nodes, advanced to distant organs, no information), information on participation in national mammography screening program, tumor histology (ductal, lobular, other, unknown) and primary breast cancer treatment (surgery, other). The data also included dates and causes of cancer death as well as all-cause deaths until the end of 2015. Information on hormone-receptor status of tumor was obtained from pathology databases of the university hospitals in Tampere and Turku. Information on estrogen receptor (ER), progesterone receptor (PR), and HER2 expression was obtained from these databases. Information on HER2 status was available for 8,617 patients, ER for 7,283, and PR for 7,288 participants. The cohort was linked to the national prescription database to collect information on anti-HT drug use. Information was also obtained on therapies with statins, antidiabetic medication, anticoagulant drugs, and hormone-receptor antagonists. Anti-HT drugs were categorized into six groups based on their mechanism of action: ACE-inhibitors, ATR-blockers, beta-blockers, calcium-channel blockers, diuretics, and furosemide. In this cohort, furosemide was analysed separately as it is not primarily used to treat hypertension.

In cohort IV, anti-HT drug use and risk of OC death was analysed by obtaining 12,122 women diagnosed with OC between 1995-2013 from the Cancer Registry. The data contained information on the date of OC diagnosis, tumor extent at diagnosis (categorized as localized, locally advanced, distally advanced, advanced to unknown extent, unknown), primary cancer treatment as well as date and cause of death. The number of 1st degree female relatives was also obtained from Statistics Finland. Information on relatives was linked to the Cancer Registry database to obtain OC and breast cancer (BCa) cases among them to determine if there was a family history of cancer. The cohort was linked to the national prescription database to obtain information on anti-HT drug, statin and antidiabetics use in the time frame 1995-2013. Anti-HT drugs were categorized into six groups based on their mechanism of action similar to cohort III.

Table S1. Drug spesific ATC-codes for antihypertensive drugs

Drug	**ATC-code**
Enalapril	C09AA0, C09BA02, C09BB02
Imidapril	C09AA16
Captopril	C09AA01, C09AB01
Cinapril	C09AA06, C09BA06
Lisinopril	C09AA0, C09BA03
Perindopril	C09AA04, C09BA04, C09BB04
Ramipril	C09AA05, C09BA05, C09BB05
Trandolapril	C09AA10, C09BB10
Other ACE-inhibitors	C09AA08, C09BA08, C09AA07, C09BA07, C09AA09, C09BA09, C09AA11, C09AA12, C09BA12, C09BB12, C09AA13, C09BA13, C09AA14, C09AA15, C09BA15
Eprosartan	C09CA02, C09DA02
Candesartan	C09CA06, C09DA06
Losartan	C09CA01, C09DA01
Olmesartan	C09CA08, C09DA08, C09DB02
Telmisartan	C09CA07, C09DA07
Valsartan	C09CA03, C09DA03, C09DB01, C09DX01
Irbesartan	C09CA04, C09DA04
Other sartans	C09CA05
Clonidine	C02AC01, C02LC01, C02LC51
Moxonidine	C02AC05, C02LC05
Rauwolfia-alkaloids	C02AA01, C02AA02, C02AA03, C02AA04, C02AA05, C02AA06, C02AA07, C02AA52, C02AA53, C02AA57
Other antagonists of imidatsoline receptor	C02AC02, C02AC04, C02AC06
Antiadrenergics	C02BA01, C02BB01
Prazosine	C02CA01, C02LE01
Other alfa-blocking antihypertensives	C02CA02, C02CA03, C02CA04, C02CA06
Guanidiines	C02CC01, C02CC02, C02CC03, C02CC04, C02CC05, C02CC06, C02CC07, C02LF01
Smooth muscle relaxants	C02DA01, C02DB01, C02DB02, C02DB03, C02DB04, C02DD01, C02DG01

Other antihypertensives	C02KA01, C02KB01, C02KC01, C02KD01
Acebutolol	C07AB04, C07BB04
Atenolol	C07AB03, C07BB03, C07CB03, C07CB53, C07DB01, C07FB03
Betaksolol	C07AB05
Bisoprolol	C07AB07, C07BB07
Carvedilol	C07AG02
Labetalol	C07AG01, C07BG01, C07CG01
Metoprolol	C07AB02, C07AB52, C07BB02, C07BB52, C07CB02, C07FB02
Pindolol	C07AA03, C07CA03
Propranolol	C07AA05, C07BA05, C07FA05
Seliprolol	C07AB08
Timolol	C07AA06, C07BA06, C07DA06
Nebivolol	C07AB12
Other beta-blockers	C07AA01, C07AA12, C07AA14, C07AA15, C07AA16, C07AA17, C07AA19, C07AA23, C07AA27, C07AB01, C07AB06, C07AB09, C07AB10. C07AB11, C07AB13, C07BA12, C07BA68, C07BB06, C07CA17, C07CA23
Amiloride	C03DB01, C03EA01
Furosemide	C03CA01, C03CB01, C03EB01
Hydrochlorothiazide	C03AA03, C03AB03, C03AX01, C02LB01, C02LC01, C02LC05, C02LC51, C02LE01, C07BA02, C07BA05, C07BA06, C07BA07, C07BA12, C07BA68, C07BB02 C07BB03, C07BB04, C07BB06, C07BB07, C07BB52, C07BG01, C07DA06, C07DB01 C08GA01, C09BA01, C09BA02, C09BA03, C09BA05, C09BA06, C09BA07, C09BA08, C09BA09, C09BA12, C09BA13, C09BA15, C09DA01, C09DA02, C09DA03 C09DA04, C09DA06, C09DA07 C09DA08, C03EA01
Indapamide	C03BA11, C09BA04
Spironolaktone	C03DA01
Triamteren	C03DB02, C03EA02, C03EA03, C03EA04, C03EA05, C03EA06, C03EA07, C03EA12, C03EA13, C03EA14,

	C03EB01, C03EB02
Trichloromethiazide	C03AA06, C03AB06, C03EA02
Other diuretics	C03AA01, C03AA02, C03AA04, C03AA05, C03AA07, C03AA08, C03AA09, C03AA13, C03AB01, C03AB02, C03AB04, C03AB05, C03AB07, C03AB08, C03AH01, C03AH02, C03BA02, C03BA03, C03BA04, C03BA07, C03BA09, C03BA10, C03BA12, C03BA13, C03BA82, C03BB02, C03BB03, C03BB04, C03BB07, C03BC01, C03BD01, C03BX03, C03CA03, C03CA04, C03CC01, C03CC02, C03CD01, C03CX01, C03DA02, C03DA03, C03DA04, C03EA03, C03EA04, C03EA05, C03EA06, C03EA07, C03EA13, C03EA14, C03XA01, C03XA02
Amlodipine	C08CA01, C09DB01, C09DB02, C09DX01, C09BB04
Diltiazem	C08DB01
Felodipine	C08CA02, C09BB05, C07FB02
Isradipine	C08CA03
Lerkanidipine	C08CA13, C09BB02
Nifedipine	C08CA05, C08CA55, C08GA01, C07FB03
Nilvadipine	C08CA10
Nimodipine	C08CA06
Nisoldipine	C08CA07
Verapamil	C08DA01, C08DA51, C09BB10
Other calcium-channel blockers	C08CA04, C08CA08, C08CA09, C08CA11, C08CA12, C08CA14, C08CA15, C08CX01, C08DA02, C08EA01, C08EA02, C08EX01, C08EX02, C09BB12

12.3 Statistical methods cohort I-IV

Detailed information on each purchased package size and dose was obtained by specific production numbers of each anti-HT drug. The total amount of yearly used anti-HT drug group was calculated by adding together size of packages multiplied with dose included in one package. This was calculated for every package size which was then added together to estimate the total yearly milligram (mg)-amount. Total mg-amounts between different drugs are not directly comparable because different medicines are used with different mg- amounts in normal use. Thus, dosing was standardized between drugs by dividing mg-amounts with defined daily dose (DDD) specific for each drug. Drug-specific DDDs are reported in the

WHO website and describe average consumed daily amount of each drug in normal use (WHO: Defined Daily Doses for drugs)

Duration of use was also calculated by using information on yearly anti-HT drug use. Each year with any use was recorded as a usage year regardless of the amount purchased. Participants remained in the user category after discontinuation of use to minimize selection bias due to the clinical practice of minimizing medication use in the terminal stage of cancer.

The intensity of use was evaluated by forming an intensity variable dividing the cumulative amount of DDDs by the number of usage years. Participants were then stratified into three groups based on amount, duration, and intensity of use. Anti-HT drug use in general as well as cumulative use were evaluated both for pre-and post-diagnostic use. Pre-diagnostic use (anti-HT drug use before cancer diagnosis) was analysed as a time-fixed variable. The use before diagnosis was defined as any use between 1995 and the year of PCa diagnosis.

Post-diagnostic use (anti-HT drug use after cancer diagnosis) was analysed with time-dependent variables using logistic Cox regression to minimize immortal time bias. Post-diagnostic use was defined as use between PCa diagnosis- closing date 31st Dec 2013 or emigration or death, whichever came first. Separate time-dependent variables were formed for each anti-HT drug group to model same time use of multiple drugs. Participants who used multiple anti-HT drug groups during the same year were recorded as users for each purchased drug group. Long-term association was analysed with lag-time analyses in which the exposure (anti-HT drug use) was lagged forward for one, three and five years to estimate use that had occurred years earlier. In this way, also the last years before cancer death were excluded from the analysis and we also controlled for a possible healthy user bias due to finishing anti-HT drug use in terminal stage cancer.

12.3.1 Cohort I, Prostate cancer

In cohort I, post-diagnostic Cox regression was also used to analyse the association between anti-HT drug use and the risk for starting ADT. Androgen-deprivation therapy is used to treat advanced PCa and was therefore used as an estimate for recurrence because all men had primarily been treated with radical surgery. The cohort was also linked to HILMO to obtain information on conducted orchiectomies. This information was combined with GnRH-agonist, -antagonist and antiandrogen use to estimate ADT usage. Pre-diagnostic and post-diagnostic analyses were adjusted for age at diagnosis, tumor extent at diagnosis (local, locally advanced, advanced, unknown), Charlson comorbidity index (CCI, a calculated index that is used to control other comorbidities) and statin use (Koppie T et al. 2008). The Charlson co-morbidity index was calculated based on information on comorbidities in HILMO.

Sensitivity analyses were stratified by time of PCa diagnosis (1995–1999, 2000–2009, 2010 or later) to estimate the role of evolving criteria for operative management in the risk association by anti-HT drug use over the course of time. Year of diagnosis was also added as an adjusted covariate into the Cox regression analysis. In sensitivity analyses, also the association between anti-HT drug use and risk of all-cause mortality was evaluated. Sensitivity analyses were performed excluding telmisartan and captopril from the analysis: captopril had previously been associated with a decreased PCa diagnosis risk and a possible prognostic effect was excluded in this way (Ronquist G et al. 2004). Telmisartan had been proved to cause apoptosis in PCa cells in vitro and by excluding its use, we tested that the risk trend among ATR-blockers was not due to telmisartan use (Matsuyama M et al. 2010). The analyses were also run among men using only ATR-blockers (simultaneous use of other anti-HT drugs excluded).

12.3.2 Cohort II, Urothelial cancer

In cohort II, the analyses were adjusted for age at diagnosis, year of diagnosis, tumor extent (local or advanced), surgery, cytostatic drugs, kidney failure, COPD, Charlson comorbidity index and use of statins, antidiabetic medication, non-steroidal anti-inflammatory drugs, and aspirin during the follow-up. Also in this study, the long-term association was evaluated with lag-time analyses. In the sensitivity analyses, post-diagnostic analyses were run separately in four subgroups stratified by potential confounding factors: age at diagnosis (73-year-old or older), tumor extent at diagnosis (localized, locally advanced, advanced), comorbidities (CCI value) and COPD separately and use of statins (use/no use). COPD was analysed separately as it is associated with smoking as well as the risk for death. In addition, COPD might limit the possibilities for surgery in BC introducing a potential bias.

12.3.3 Cohort III, Breast cancer

In cohort III, pre-and post-diagnostic analyses were adjusted for age at diagnosis, tumor extent at diagnosis, primary treatment of breast cancer (surgery, other), obesity, CCI, participation in national breast cancer screening program and use of hormone-receptor antagonist therapy after breast cancer diagnosis. All anti-HT drug groups were added into the analysis simultaneously to model simultaneous use: also, simultaneous therapies with statins, antidiabetic drugs and anticoagulative drugs were added into the analysis as time-dependent variables and not as time-fixed covariates as in cohorts I and II.

In the subgroup analyses, the risk association between anti-HT drug use and risk of BCa death was analysed stratified by hormone-receptor status, age at diagnosis (over and under 60-year-old), detection method (screening-detected vs cases detected outside the screening program) and median CCI score. Sensitivity analyses were performed including only those women who had used a single anti-HT drug group. In addition, anti-HT drug use and risk of all-cause mortality was evaluated in sensitivity analyses as was the association between anti-HT drug use at the time of BCa diagnosis and the risk of BCa death to help comparability with some previous studies where the exposure has been defined as use at time of BCa diagnosis. In one analysis, selective and non-selective beta-blockers were analysed as separate drug groups.

12.3.4 Cohort IV, Ovarian cancer

In cohort IV, the analyses were adjusted for year of OC diagnosis, age at diagnosis, tumor extent at diagnosis, primary treatments of OC (surgery, cytostatics, radiation or hormonal therapy), number of biological children, age at time of the first labour, number of 1st degree relatives (children, siblings, parents) with OC or breast cancer and use of statins and antidiabetic drugs. All anti-HT drugs were added into the model simultaneously as separate time-dependent variables to evaluate simultaneous use.

Since OC is a disease with a poor prognosis, post-diagnostic analyses were run separately for five, ten and full-time (19 years) follow-up. Any long-time association and any possible protopathic bias were evaluated by lagging the exposure of anti-HT drug use forward for one, three and five years during the follow-up to estimate use that occurred one, three and five years earlier.

In this cohort, the only subgroup analysis was made for competing risk analysis where we evaluated the association between anti-HT drug use and the risk of cardiovascular death.

13 RESULTS

13.1 Antihypertensive drugs and prostate cancer mortality

Antihypertensive drug use was very common in our study population; out of the total of 14,422 men, the majority i.e., 9,799 (67.9%) had used at least one anti-HT drug before or after diagnosis; the remaining 4,625 (32.1%) men had not used any kind of anti-HT medication. During the median follow-up of 9.9 years after the PCa diagnosis, a total of 1,581 men (11 out of every 100 men) died; of these, 424 (3/100) died of PCa. (Santala E et al 2019)

ATR-blockers were associated with a decreased risk of PCa death, and the time of starting ADT compared to non-users of ATR-blockers. On the contrary, both pre-and post-diagnostic therapies with beta-blockers were associated with an increased PCa death risk.

Both pre-and post-diagnostic ATR-blocker use was associated with a decreased risk for PCa death in (HR 0.43 95% CI 0.26-0.72 for pre-diagnostic and HR 0.60 95% CI 0.37-0.97 for post-diagnostic use). The risk decrease was observed even with five years´ time lag (HR 0.55 95% CI 0.30-0.98). The risk of needing to initiate ADT was also decreased (HR 0.81 95% CI 0.71-0.92) among ATR-blocker users as compared to non-users. With respect to post-diagnostic use, the risk of PCa death decreased in an inverse association with cumulative dose, duration and intensity of post-diagnostic ATR-blocker use although risk estimates were not statistically significant in all subgroups in these analyses (Table 11). With respect to ATR-blocker use before PCa diagnosis, no clear dose-dependence was observed. Interestingly, the risk estimates for ACE-inhibitors use were not in the same direction as seen with the ATR-blockers even although both groups of drugs affect the same RAA-system.

Table 11. Risk of prostate cancer death by cumulative amount, duration and average yearly dose of ATR- blocker use after diagnosis.

Amount of use (DDDs)	n of men/PCa deaths	Riski of PCa death HR (95% CI) age-adjusted	Risk of PCa death HR (95% CI) multivariable-adjusted (age-, stage-, CCI-, and statin use-adjusted)
0-1339.32	1351 / 36	1.13 (0.72-1.43)	1.13 (0.80-1.61)
1339.33-4199.99	1392 / 30	0.85 (0.58-1.25)	0.91 (0.62-1.34)
4200.00→	1404 / 11	0.51 (0.25-1.05)	0.54 (0.26-1.10)
Duration of use (years)	n of men/PCa deaths	Riski of PCa death HR (95%CI) age-adjusted	Risk of Pca death HR (95% CI)
0-4	1547 / 44	0.84 (0.62-1.15)	0.91 (0.66-1.24)
4-9	1367/ 24	0.61 (0.40-0.92)	0.64 (0.42-0.97)
9→	1239 / 9	0.03 (0.00-0.08)	0.02 (0.01-0.08)
Average yearly dose (DDDs/year)	n of men/PCa deaths	Riski of PCa death HR (95%CI) age-adjusted	Risk of Pca death HR (95% CI)
0-310.32	1352 / 36	1.19 (0.83-1.67)	1.37 (0.96-1.97)
310.33-536.27	1398 / 24	0.80 (0.52-1.23)	0.86 (0.56-1.33)
536.28→	1403 / 17	0.60 (0.37-0.97)	0.61 (0.38-1.01)

From Santala E et al. 2019.

As ATR-blockers became generic later than other anti-HT drug groups, we evaluated how the timing of diagnosis might modify the risk association. When adjusting analyses with the year of PCa diagnosis risk, estimates for ATR-blocker use remained decreased as compared to non-users although they became attenuated to a statistically non-significant level. In subgroup analyses where participants were divided into three groups based on the year of PCa diagnosis, a decreased PCa death risk was observed only in cases diagnosed in the 1990s. Our follow-up period was 1995-2013 and thus cases diagnosed in the 1990s had had time to reach the primary end point (PCa death) as compared to cases diagnosed later.

Pre-and post-diagnostic use of all other anti-HT drugs except ATR-blockers and diuretics was associated with an increased risk of starting ADT. Beta-blockers were associated with increased risk of PCa death with respect to both pre-diagnostic (HR 1.82 95% CI 1.30–2.56) and post-diagnostic (HR 1.30 95% CI 1.01–

1.67) use. The elevated risk remained even five years after use (HR 1.30 95% CI 0.98–1.73). Pre-diagnostic beta-blocker use was associated with increased risk of starting ADT (HR 1.38 95% CI 1.19–1.61) compared to non-users. Neither pre- nor post-diagnostic therapies with calcium-channel blockers or diuretics were associated with the PCa death risk.

13.2 Antihypertensive drugs and urothelial cancer mortality

Anti-HT drug use was very common in this cohort. Of the 14,065 participants, 10,489 (75 %) had used at least one anti-HT drug before or after diagnosis; 3,576 (25 %) had not used any kind of anti-HT medication. During the median follow-up of 4.1 years after BC diagnosis, a total of 5,550 participants (40/100) died; of these, 2.948 (21/100) died of BC. (Santala E et al. 2019)

ATR-blocker use before BC diagnosis was associated with a decreased BC death risk (HR 0.80 95% CI 0.70-0.92) compared to non-users. In our study, ACE-inhibitors as a single group were not associated with the BC death risk. Only a moderate risk increase was observed between pre-diagnostic ACE-inhibitor use and the risk of UTUC death (HR 1.48 95% CI 1.00-2.21). With respect to pre-diagnostic use, no anti-HT drug group was associated with an increased risk of BC death. Risk estimates between pre- and post-diagnostic use of all anti-HT drugs and risk of UTUC death did not reach statistical significance.

Some evidence of dose-dependence was observed between post-diagnostic ATR-blocker use and the risk of BC death. Risk estimates were lowest with highest intensity (394 DDDs/year) ATR-blocker use (HR 0.65 95% CI 0.50-0.84). A risk decrease among ATR-blockers was observed even after five years´ lagtime (HR 0.72 95% CI 0.61-0.85). In post-diagnostic analyses, the use of diuretics associated with increased BC death risk (HR 1.42 95% CI 1.31-1.54). The highest intensity of post-diagnostic beta-blocker use was associated with a slightly decreased risk of BC death (HR 0.76 95% CI 0.66-0.87). A risk trend in the same direction was also observed for calcium-channel blockers: with high-intensity use, the risk of BC death was decreased (HR 0.67 95% CI 0.52-0.86) for highest-intensity (367 DDDs/year or more) use. In general, therapy with either a beta-blocker or a calcium-channel blocker was not associated with the BC death risk.

Age did not modify the risk association for ATR-blockers: a similar risk decrease was observed in participants under and older than 73 years. Beta-blocker use associated with an increased BC risk among participants under 73 years. No effect modification by age was observed in the UTUC cohort. Beta-blockers were associated with an increased risk of death as compared to non-users among participants diagnosed with localized tumor, whereas no risk association was observed for participants with advanced disease at diagnosis and inclusion of the Charlson comorbidity index did not modify results in our BC cohort. In UTUC, beta-blockers were associated with an increased UTUC death risk only in the presence of a few comorbidities while ATR-blockers associated with decreased risk of UTUC death only with high CCI. When the analyses were restricted to only participants with COPD, risk estimates declined to a non-significant level but risk estimates for ATR-blockers remained decreased as compared to non-users. When excluding participants with COPD, the risk decrease among ATR-blockers became again statistically significant. When stratifying analyses according to the use of statins, an increased BC death risk was observed among beta-blocker users only when these drugs were used together with statins. In the stratified analysis according to the year of diagnosis, therapy with ATR-blockers was associated with improved BC survival only among cases diagnosed in the 1990s.

13.3 Antihypertensive medication use and breast cancer mortality

In our breast cancer cohort, 36,427 (49.8%) women had used at least one group of anti-HT medication during the follow up period. A total of 10,900 women died of BCa during the follow-up of which 4,542 (124/1000) were non-users of anti-HT drugs and 6,358 (175/1000) were receiving anti-HT drug therapy. (Santala E et al. 2020).

The pre-diagnostic use of ATR-blockers was associated with a decreased risk of BCa death in (HR 0.76 95% CI 0.69-0.82) and this association was dose-dependent. Pre-diagnostic use of either furosemide or other diuretics was associated with an increased BCa death risk in (HR 1.26 95% CI 1.17-1.35 for furosemide). With respect to their pre-diagnostic use, neither beta-blockers nor calcium-channel blockers were associated with the BCa death risk.

The post-diagnostic use of ATR-blockers, beta-blockers and calcium-channel blockers was associated with a decreased risk of BCa death as compared to non-users. The reduced risk of BCa death among ATR-blockers was observed after three years´ (HR 0.84 95% CI 0.76–0.93) but not after five years´ lagtime. A decreased risk association for calcium-channel blockers was observed even as long as after five years since their use (HR 0.91 95% CI 0.84–0.99). Furosemide was associated with an elevated risk of BCa death also with respect to post-diagnostic use, but the risk increase attenuated to a non-significant level one year after use.

In the post-diagnostic analyses, the risk of BCa death decreased in an inverse association with increasing intensity of ACE-inhibitor, ATR-blocker, beta-blocker, and calcium-channel blocker use. This kind of decreasing risk associations for multiple anti-HT drug groups with differing mechanisms of action supports the concept that some underlying condition is responsible for the phenomenon.

In the sensitivity analyses subdivided by hormone-receptor status, ACE-inhibitors and calcium-channel blockers were associated with a decreased risk of breast cancer death among HER-negative (cancer does not express HER2) women and ACE-inhibitors also among triple-negative (cancer does not express ER, PR, or HER2) women (Table 12). Other diuretics were associated with a reduced risk among HER-positive (cancer expresses only HER2) women. Age at BCa diagnosis or year of BCa diagnosis did not modify these risk associations. The association of a decreased risk was observed for ATR-blockers both among screen-detected cases and cases detected outside the screening program. Comorbidities modified the risk associations as the decreased BCa death risk among ATR-blockers was observed only among women without comorbidities. When the analyses were limited to only women using one group of anti-HT drug after BCa diagnosis, then ATR-blockers and furosemide were associated with a decreased BCa death risk and the risk estimates were not changed when the primary end point was switched to all-cause death: risk estimates remained decreased for ATR-blocker use before and after BCa diagnosis. When use was defined as use at the time of BCa diagnosis, therapy with ATR-blockers remained associated with a reduced BCa death risk. Neither non-selective nor selective beta-blockers were associated with the risk of BCa death. In these analyses, the results were not modified by tumor receptor status.

Table 12. Risk of BCa death among different antihypertensive drug use based on hormone-receptors.

Antihypertensive drug group	Risk of BCa death by hormone-receptor status (HR, 95% CI)*							
	ER-	ER+	PR-	PR+	HER2-	HER2+	All neg	All pos
ACE-inhibitors	0.60 (0.32-1.02)	0.81 (0.62-1.07)	0.73 (0.49-1.09)	0.81 (0.58-1.12)	0.63 (0.49-0.82)	1.49 (0.89-2.49)	0.45 (0.21-0.97)	1.52 (0.56-4.14)
ATR-blockers	0.60 (0.35-1.00)	0.85 (0.61-1.18)	0.76 (0.51-1.15)	0.89 (0.61-1.31)	0.80 (0.61-1.05)	0.95 (0.48-1.89)	0.53 (0.29-1.00)	0.22 (0.03-1.88)
Beta-blockers	1.18 (0.83-1.68)	0.97 (0.79-1.20)	1.01 (0.78-1.31)	1.06 (0.83-1.35)	1.04 (0.87-1.23)	1.00 (0.66-1.52)	1.07 (0.69-1.67)	0.64 (0.27-1.56)
Calcium-channel blockers	0.97 (0.63-1.49)	0.81 (0.62-1.06)	0.76 (0.55-1.06)	0.85 (0.62-1.16)	0.76 (0.61-0.95)	0.93 (0.56-1.54)	1.13 (0.66-1.95)	1.53 (0.52-4.50)
Furosemide	1.53 (0.91-2.60)	1.48 (1.08-2.04)	1.25 (0.85-1.84)	1.61 (1.10-2.36)	1.49 (1.15-1.93)	2.32 (1.12-4.77)	1.09 (0.58-2.05)	3.26 (0.80-13.30)
Other diuretics	1.11 (0.71-1.73)	0.92 (0.71-1.18)	1.18 (0.86-1.63)	0.88 (0.65-1.20)	0.97 (0.78-1.20)	0.51 (0.28-0.93)	1.37 (0.83-2.28)	0.45 (0.16-1.28)

ER-=estrogen- receptor negative, ER+=estrogen- receptor positive, PR-=progesterone- receptor negative, PR+= progsterone -receptor positive, HER2-= HER2 -negative, HER2+= HER2 -positive, All neg= All three receptors (ER, PR, HER2) negative, All pos= All three receptors positive. ACE= angiotensin-converting enzyme, ATR= angiotensin-receptor, DDD= defined daily dose, HR= hazard ratio, CI= confidence interval. *= calculated cox regression model with adjustments of age at diagnosis, tumor extent charlson-comorbidity index, primary treatment of BCa, obesity, participation in national screening program and use of hormone-receptor antagonists after BCa diagnosis.

From Santala E et al. 2020

13.4 Antihypertensive medication use ovarian cancer mortality

Due to poor prognosis of OC, the median follow-up time in our cohort was short, 3.3 years and varied between 2.8-4.2 years in users of the different anti-HT drug groups. Anti-HT drug use was common since as many as 7,856 ovarian (64.8%) cancer patients had used at least one anti-HT drug group during the follow-up period. (Santala E et al. 2021)

Most OC deaths occur soon after diagnosis. In our study, follow-up time highly modified the risk associations: a decreased risk trend for anti-HT drug use was observed only with the full 19 years' follow-up

time and therefore we ran the analysis separately for 5, 10 and full 19 years follow-up. It is likely that women with OC alive after 19 years have different tumor characteristics compared to women who had succumbed to OC earlier. This means that possible prognostic effect of a single drug group should be seen earlier. Because the associations in our study were seen only with the longer follow-up time, it is possible that selection bias was responsible for the apparent effect.

Pre-diagnostic use of furosemide was associated with an increased risk of OC death regardless of the length of follow-up time. In contrast, ACE-inhibitor use was associated with a decreased 10-year OC mortality (HR 0.92 95% CI 0.87-0.98) compared to non-users. Both 5- and 10-year OC mortality declined dose-dependently when the intensity of ACE-inhibitor use increased, being smallest for the highest intensity of ACE-inhibitor use (HR 0.84 95% CI 0.77-0.92 at 10 years). However, risk estimates for 5-year mortality were not statistically significant. No such similar risk decrease or dose-dependence in the risk associations was observed for any other anti-HT drug group. When we examined the full follow-up time (maximum 19 years), high-dose, long duration, and high-intensity therapies with either a beta-blocker or a calcium-channel blocker were associated with an increased risk of OC death.

The post-diagnostic use of ACE-inhibitors was associated with a decreased OC death risk but only with the full follow-up time (HR 0.81 95% CI 0.71-0.93). The use of ATR-blockers was only associated with decreased 10-year OC mortality (HR 0.90 95% CI 0.84-0.98). In contrast, neither beta-blocker nor calcium-channel blocker use was associated with the OC death risk. However, dose-dependent decreased risk associations were observed between all anti-HT drugs and risk of OC death for full follow-up post-diagnostic use. (Table 13) Therapies with furosemide and other diuretics were associated with an increased OC death risk in all follow-up times. In lag time analyses, a decreased risk of OC death was seen in the ACE-inhibitor group even with a 5- year lag time. When cardiovascular diseases were taken into account as competing causes of death, then ACE-inhibitors remained to be associated with a decreased risk for OC death when we examined the data from the full follow-up (HR 0.73 95% CI 0.58-0.91).

Furosemide was analysed separately as it is not primarily used in the treatment of hypertension. There are no previous studies that would have evaluated the link between furosemide and the risk of OC death. The increased risk trend for furosemide and other diuretics are likely affected by underlying causes such as the treatment of oedema caused by advanced cancer or severe cardiac insufficiency.

Table 13. Risk of OC death by antihypertensive drug use after OC diagnosis. Risk estimates by cumulative dose, duration, and intensity of anti-HT drug use.

	Antihypertensive drug groups, HR (95% CI)*					
Amount of use DDDs	ACE-inhibitors	ATR-blockers	Beta-blockers	Calcium-channel blockers	Furosemide	Other diuretics
1st tertile	0.95 (0.83-1.09)	0.76 (0.65-0.88)	1.16 (1.06-1.27)	1.04 (0.92-1.18)	2.55 (2.31-2.83)	1.63 (1.48-1.79)
2nd tertile	0.71 (0.62-0.83)	0.83 (0.68-1.02)	0.83 (0.74-0.94)	0.88 (0.75-1.02)	1.79 (1.59-2.02)	0.98 (0.86-1.11)
3rd tertile	0.38 (0.25-0.58)	0.26 (0.12-0.58)	0.92 (0.69-1.22)	0.60 (0.41-0.89)	1.27 (1.05-1.54)	0.93 (0.75-1.15)
Duration of use (years)	ACE-inhibitors	ATR-blockers	Beta-blockers	Calcium-channel blockers	Furosemide	Other diuretics
1st tertile	0.84 (0.73-0.97)	0.71 (0.61-0.82)	1.07 (0.98-1.17)	0.95 (0.85-1.05)	2.23 (2.03-2.44)	1.51 (1.37-1.66)
2nd tertile	0.75 (0.64-0.87)	0.98 (0.80-1.20)	0.89 (0.78-1.03)	1.01 (0.82-1.24)	1.82 (1.53-2.16)	1.09 (0.96-1.23)
3rd tertile	0.67 (0.48-0.93)	0.45 (0.27-0.75)	1.02 (0.82-1.26)	0.52 (0.29-0.95)	1.38 (1.14-1.68)	0.97 (0.78-1.21)
Intensity of use,(DDDs/year)	ACE-inhibitors	ATR-blockers	Beta-blockers	Calcium-channel blockers	Furosemide	Other diuretics
1st tertile	0.94 (0.83-1.06)	0.90 (0.78-1.05)	1.22 (1.11-1.34)	1.19 (1.04-1.37)	2.52 (2.27-2.78)	1.58 (1.44-1.74)
2nd tertile	0.67 (0.57-0.79)	0.62 (0.51-0.76)	0.85 (0.76-0.95)	0.83 (0.73-0.96)	1.78 (1.57-2.03)	1.00 (0.88-1.14)
3rd tertile	0.18 (0.08-0.37)	0.42 (0.26-0.68)	0.64 (0.47-0.88)	0.67 (0.50-0.90)	1.32 (1.10-1.57)	0.95 (0.77-1.17)

OC= ovarian cancer, ACE= angiotensin-converting enzyme, ATR= angiotensin-receptor, DDD= defined daily dose, HR= hazard ratio, CI= confidence interval. *= calculated cox regression model with adjustments of age at diagnosis, year of OC diagnosis, tumor extent, surgery, chemotherapy, antihormonal therapy and radiation therapy. From Santala E et al. 2021

14 DISCUSSION

14.1 Antihypertensive drug use and the risk of prostate cancer death

ATR-blockers were the only anti-HT drug group that was associated with a decreased risk of PCa death. This supports the possibility that ATR-inhibition may represent a promising mechanism of inhibition of cancer growth. None of the other anti-HT drugs was associated with a decreased PCa death risk, suggesting that hypertension treatment in general probably has no prognostic role. Not even ACE-inhibitors demonstrated a similar risk decreasing association as ATR-blockers despite affecting the same RAA-system. Therefore, one can speculate that segments of the RAA-system targeted only by ATR-blockers may affect prostate cancer. Thus, the role of the RAA-system in PCa requires further clarification in in vitro, in vivo studies and possibly even in clinical trials.

Concordantly Siltari et al. 2020 reported that post-diagnostic ATR-blocker use was associated with a slightly decreased risk for PCa death and Gardwell CR et al. 2014 reported a risk association in the same direction for post-diagnostic use of ACE-inhibitors. Therefore, epidemiological studies support a prognostic role of targeting the RAA-system in PCa. All studies have not separated the use of ACE-inhibitors and ATR-blockers from each other and thus in these reports it was not possible to evaluate their independent risk associations (Alashkham A et al. 2016).

Siltari et al. also reported that thiazides were associated with an increased risk of PCa death. We analysed all diuretics as one group containing thiazides, potassium-sparing diuretics, furosemide and other rarely used diuretic agents. The risk of PCa death was not increased in the group treated with diuretics. This difference may be explained by differences in the study population as we had only men treated with radical prostatectomy whereas the study cohort of Siltari et al. included PCa cases regardless of primary treatment. Thus, the distribution of clinical characteristics is probably different between the studies.

Previous studies have not detected evidence of an elevated PCa death risk among beta-blocker users as found here. Assayag J et al. conducted a study of beta-blocker use among men with local PCa. Treatment options in local PCa are radical prostatectomy and radiation therapy. Our study included only men treated with radical prostatectomy. It is likely that individuals undergoing radical surgery may be healthier or in some other way in better general condition compared to men treated with radiation therapy. This selection bias may partly explain the differing results. In addition, the methods of gathering information on beta-blocker exposure differed between our study and previously published ones. Grytli HH et al. 2013 analysed only self-reported beta-blocker use at the time of PCa diagnosis. We obtained information on medication use from the national prescription database. It is evident that self-reported medication use is prone to recall bias. However, it must be admitted that we had no information if the prescribed medications were actually consumed. Grytli HH et al. 2014 found evidence for a decreased PCa death risk among men with high-risk or advanced disease and beta-blocker use after diagnosis. Results in the same direction were reported also in a previous study conducted in 2013 among men intended to receive ADT. In a study from 2014, medical information was obtained from a national database. It is unclear which factors would explain the decreasing risk trend among beta-blockers in advanced PCa. However, one factor that should be evaluated is competing causes of death: if men with advanced PCa have higher other cause mortality, then PCa mortality may be lower because these men die from these other causes. However, our results do not support the theory that beta-blockers have a protecting property.

Poch MA et al. 2013 found no association between calcium-channel blocker use and the risk of PCa death among men treated with radical prostatectomy. Our results were similar as calcium-channel blockers were not associated with the PCa death risk.

All men in our cohort were primarily managed with radical prostatectomy which makes the cohort very homogenous. All these men had been evaluated as being suitable for radical surgery at diagnosis and tumor extent had been local or locally advanced as prostatectomy is not performed in cases of advanced disease.

14.2 Antihypertensive drug use and the risk of urothelial cancer death

We detected evidence for a decreased BC death risk among ATR-blocker users but results in the same direction were not seen among ACE-inhibitor users. In previous studies, ATR-blockers and ACE-inhibitors have been analysed as a single group and therefore it was not possible in these reports to differentiate possible differences in risk estimates between these two drug groups. Two previous studies have reported improved BC disease-free and overall survival among users of ATR-blockers or ACE-inhibitors (Song T et al. 2017) (Yoshida T et al. 2017). Many studies have evaluated anti-HT drug use and the risk of BC recurrence which is not comparable to the risk of BC death. According to our results, it is possible that the decreased BC death risk associations observed in previous studies among users of drugs affecting the RAA-system are attributable only to therapy with ATR-blockers.

The elevated risk associations observed among diuretics are likely due to underlying conditions treated with diuretics. For example, heart failure and oedema in advanced cancer may be treated with these types of drugs. Therefore, it is quite probable that heart failure itself has a negative effect on BC prognosis, by limiting treatment options and this may explain why there was an association with increased BC mortality. On the other hand, if diuretics are used in the management of oedema caused by terminal stage cancer, reverse causation is likely, i.e., it is the cancer, not the drug, which is responsible for these elevated risk associations. It may also be possible that terminal stage cancer causes acute worsening of heart failure leading to an increasing need for diuretics. There is no biological rationale by which diuretics would adversely affect BC prognosis. Thus, the risk association observed here is not likely to be causal. Previous studies have not evaluated the role of different anti-HT drug groups other than RAA-affecting drugs in BC survival.

14.3 Antihypertensive drug use and the risk of breast cancer death

We detected a decreased BCa death risk for ATR-blockers in pre-and post-diagnostic use and also for beta- and calcium-channel blockers with respect to post-diagnostic use and the association was dose-dependent in all of those groups. In contrast, therapy with diuretics and furosemide was associated with an increased BCa death risk compared to non-users with respect to both pre-and post-diagnostic use.

Holmes et al. 2013 reported an increased risk of BCa death among ACE-inhibitor or ATR-blocker users when these drugs were analysed as one group. However, several other investigators have reported a reduced risk for BCa death among users of ACE-inhibitors/ ATR-blockers and thus our study is concordant as we reported decreased risk associations with ATR-blockers, ACE-inhibitors, and beta-blockers.

Unlike in other cancer types, in the BCa cohort we observed an inverse association between post-diagnostic beta-blocker use and BCa survival. In agreement, multiple previous studies have reported a decreased risk of BCa death among beta-blocker users (Botteri et al. 2012) (Barron et al. 2011). We evaluated beta-blockers as one group so that we were not able to differentiate the individual effect of non-selective beta-blockers on the BCa death risk.

Unlike in our study, in previous reports, calcium-channel blockers have not been associated with a decreased BCa death risk. However, it is most likely that our positive risk associations are due to underlying confounding. We observed similar risk associations for multiple drug groups with a variety of mechanisms of action. Therefore, the observed associations are probably not due to the biological effects of the drugs. We took into account simultaneous use of every anti-HT drug group but also statins, antidiabetic and anticoagulative medications. We also adjusted in the analysis for primary treatment, comorbidities, tumor extent at diagnosis and use of post-diagnostic antihormonal therapy, all of which should serve as confounding factors. For example, most previous studies had not been adjusted for the simultaneous use of different medications which may have influenced the results. Nevertheless, residual confounding is still possible.

14.4 Antihypertensive drug use and the risk of ovarian cancer death

Therapy with ACE-inhibitors was associated with a decreased OC death risk in the 10-year follow-up. With the full 19- year follow-up, also high-intensity therapy with either beta-blockers or calcium-channel blockers was associated with a decreased BCa death risk. Furosemide was associated with an increased OC death risk with all levels of use regardless of follow-up time.

OC generally has a short time prognosis, and it is probable that OC patients alive 10 years after diagnosis may have had differing tumor characteristics compared to women succumbing within 5 years after diagnosis. For example, they may have had a more local disease or better possibilities to undergo cytoreductive surgery. This may at least partly explain the differing results with longer and shorter follow-up periods.

Most previous investigators have examined only long-term OC survival. For example, Harding BN et al. 2019 had a minimum follow-up time of 12 years and they reported decreased OC death risk associations for post-diagnostic therapy with ACE-inhibitors, thiazide, and non-selective beta-blockers. We also detected a decreased risk trend for post-diagnostic ACE-inhibitors when the follow-up time was a minimum of 10 years: no association was found with any drug group with shorter follow-up times. In agreement with our study, Huang T et al. in 2018 reported a decreased risk trend for post-diagnostic ACE-inhibitor use and the risk of OC death. Thus, drugs affecting RAA-system do seem to be associated with improved survival in all of the four cancer types studied in this thesis.

Unlike our study, previous investigators have reported decreased risk associations for beta-blockers and especially non-selective beta-blocker use (Baek MH et al. 2018) (Watkins JL et al. 2015). We evaluated beta-blockers as one group and did not differentiate between those with different B-receptor selectivities.

15 METHODOLOGICAL CONSIDERATIONS

We utilized data from the Finnish Cancer Registry which covers almost all cancer diagnoses via mandatory reports from health care units. These cohorts represent all such cases diagnosed in Finland during the time period. In cohort I, there were 14,422 Finnish men diagnosed with PCa between 1995-2013 and treated with radical prostatectomy. Cohort II included 14,065 BC and 1,080 UTUC patients both diagnosed in the time period 1995-2012 in Finland. Cohort III included 73,170 women diagnosed with BCa in Finland from 1995 to 2013. Finally, cohort IV examined a total of 12,122 women with OC diagnosed in 1995-2013. For all cancers, the data contained information on date of diagnosis, tumor extent at diagnosis (categorized as localized, locally advanced, distally advanced, advanced to unknown extent, unknown), primary cancer treatment as well as date and cause of death allowing us to adjust for date of diagnosis, treatment, and tumor extent.

All cohorts were obtained from the Cancer Registry so that recall bias and misclassification bias are minimal (Pukkala E et al. 2018). All cohorts except the UTUC cohort were large and had high statistical power. Nevertheless, even with nationally representative data, statistical power can be reduced for rare cancer types. In the UTUC cohort, the CI values were wide, and thus no statistically significant results were observed. However, in some subgroup analyses, CI values also were wide even for common cancer types. For example, this was observed in the BCa and BC cohorts when we conducted the sensitivity analyses.

Information from the prescription database was combined with the cancer information. The prescription database covers all drugs prescribed in an out-patient setting and is free from recall bias. All anti-HT drugs are available only by prescription in Finland and thus are included in the database (Klaukka T 2001). Information on comorbidities was obtained from the national registry (HILMO) allowing us to control for confounding by adjusting the analyses.

Medication user status was updated every follow-up year and post-diagnostic use was evaluated as a time-dependent variable to control for immortal time bias. The immortal time bias refers to the time period during which outcome (in this case, cancer death) cannot occur and is a common bias in pharmacoepidemiologic studies (Suissa S et al. 2011). For example, if a medication user had a 5- year follow-up time but had used the medication only during the final year of the follow-up, it would create a bias favoring medication users if this was unaccounted for. By using the time-dependent exposure variables, we were able to divide the follow-up time to non-exposed and exposed periods based on registered purchases.

We ran different sensitivity analyses to test for the role of possible confounders. In the PCa and BCa cohorts, the risk for all-cause death was analysed but observed associations between it and anti-HT drug use were in the same direction to the risk of cancer death. In the OC cohort, we ran competing risk analyses excluding deaths due to cardiovascular causes. This was conducted to evaluate confounding caused by competing causes of death because it would have been likely that anti-HT users have higher cardiovascular mortality as compared to non-users. However, this did not modify the results. We also used CCI to adjust for comorbidities (including cardiovascular comorbidities) in the PCa, BC and BCa cohorts. In OC, we did not have information on comorbidities so that their role was indirectly evaluated in sensitivity analyses by excluding cardiovascular deaths as a competing cause of death, but this did not affect the results.

Another important form of confounding is confounding by indication. This means that the observed association between exposure and outcome is in fact caused by a factor that is related to exposure. In our case, hypertension might cause confounding by indication: antihypertensive drugs are mostly used to treat hypertension. The possible effect of hypertension on cancer mortality risk is seen in each anti-HT drug group. This is also in the way with which we controlled for this confounding: the effect of hypertension should be seen in all anti-HT drug groups in the same direction because they are all used to treat

hypertension. When a single anti-HT drug group has a differing risk association than the others, this discrepancy is not explained by confounding by indication but rather another mechanism such as the drug's pharmacology. For example, ATR-blockers had differing risk associations as compared to the other types of anti-HT compounds which is support for a causal explanation and not confounding by indication. However, this takes into account only the role of hypertension as a confounder: there may also be other confounding factors. For example, beta-blockers and RAA-affecting drugs are used in the management of heart failure in addition to hypertension. The effect of heart failure on the risk of cancer death might be seen in all these drug groups. However, this was controlled for with CCI. Moreover, the risk associations observed for ACE-inhibitors and ATR-blockers were not in the same direction which does not support this theory. Dose-dependent associations between certain anti-HT drug groups and the risk of cancer death is also supportive of a causal explanation. This dose-dependence was seen in many anti-HT drug groups in BCa which indicates that the treatment of hypertension may have a prognostic benefit in this cancer type. On the other hand, in PCa, dose-dependence was observed for only ATR-blockers which suggests that the mechanism of action for this particular drug group may have prognostic relevance.

By updating users' status each year, it was possible also to control for any bias caused by selective discontinuation of use. Users did not move back to the non-user category even if use of anti-HT medication had been discontinued. Selective discontinuation refers to a situation where drugs used for reasons other than palliative care of cancer or cancer treatment are discontinued. This means that the use of statins, antihypertensive and antidiabetic drugs is often discontinued (Smith A et al. 2017). This may favor users as cancer deaths are recorded among non-users if selective continuation is not taken into account. We also controlled for this bias by conducting lag time analyses: we lagged the exposure forward for one, three and five years in each cohort. It is likely that bias caused by terminal stage of cancer would have been eliminated after one to three years´ lag time.

Protopathic bias is a form of bias that indicates that drugs are used to treat undiagnosed conditions (Horwitz RI et al 1980). A general example in cancer epidemiology are pain killers that have been associated with an increased risk of advanced PCa (Veitonmäki T et al. 2014). This is not caused by the medication itself but rather an underlying non-diagnosed cancer progression that causes metastatic pain and the requirement for pain relief. Protopathic bias is unlikely in these analyses as, except for diuretics, anti-HT drugs are not used for the treatment of any cancer symptoms. Lag time analyses were used to evaluate the possible role of any protopathic bias.

There are also several limitations in our studies. Even if information on drug purchases was obtained from a reliable national database, we did not have information on whether the drugs were actually consumed. Furthermore, drugs used in in-patient setting like hospitals were not included which may have meant that real cumulative dose and intensity of use could have been higher than estimated in our analyses. Over-the-counter drugs were not included in database, but this does not cause bias as anti-HT drugs are available only by prescription. We had medical information only from the same time as the follow-up: this means that all medication use before the follow-up time was not recorded. This should however cause the same direction bias for all anti-HT drugs and not affect our results.

The yearly deductible before obtaining reimbursements in purchases of prescribed medicines has been 50€ since the year 2016 which is after our follow-up ended so that it could not have affected our results. Nowadays, purchases that do not exceed the yearly deductible are not recorded in prescription database but are recorded in a separate database. We did not have information on environmental factors such as smoking and diet which might cause bias. Then again it is possible that non-users have a healthier diet and lifestyle habits than users and actually do not need anti-HT medication. It might be possible that participants using anti-HT drugs systematically differ from non-users in these kinds of factors: this is called healthy user bias meaning that people using anti-HT drugs may more actively see a physician and participate in cancer screening programs as compared to non-users. We did not have information on medical care contacts.

Active seeking into medical care might result in finding cancer while it is still in a more local stage favoring radical treatment, leading to a better prognosis. However, we were able to control for this bias in our analyses by including data on tumor extent and primary treatment.

ATR-blockers are a rather new group of antihypertensive drugs, and their use was not common until the 1990s. In the early 21st century, they were also more expensive compared to other anti-HT drugs. This may have caused a selection bias because participants using ATR-blockers might systematically differ from users of other anti-HT drugs, for example by socioeconomical factors which might also affect cancer prognosis since these better-off individuals might be more likely to seek medical care when the cancer was still at an early stage. People with high socioeconomical status may also seek medical help in private health care leading to cancer diagnosis and treatment earlier compared to them with lower socioeconomical status. High socioeconomical status may also lead to more active use of anti-HT medication and better lifestyle habits compared to low socioeconomical status which might affect cancer prognosis.

16 FUTURE CONSIDERATIONS

The benefits of ATR-blockers observed here are biologically plausible. These drugs cause apoptosis in prostate cancer cells and decrease cell mitosis (Matsuyama et al 2010). We detected evidence of improved survival among ATR-blocker users in patients with prostate, bladder and breast cancer at the population level which supports the hypothesis that ATR-inhibition could represent a putative way to influence cancer prognosis. However similar results were not observed for ACE-inhibitors, thus RAA-inhibition in general is probably not enough to gain this kind of beneficial effect. Clearly the effects of the RAA-system in cancer requires further characterization.

17 CONCLUSION

Therapy with ATR-blockers was associated with a decreased risk of cancer death in PCa, BC and BCa. In OC, a risk decrease in OC death was observed for ACE-inhibitors but only with over 10 years' follow-up time. The risk decrease among ATR-blockers was dose-dependent in three of this thesis's publications. This supports the possibility that there is causality in this linkage. It is however interesting that results in the same direction were not observed for ACE-inhibitors even although these drugs affect the same RAA-system but in a different way. The reasons that would explain this difference are unclear; one possibility is that only some components of the RAA-system have prognostic relevance.

In BCa, decreased risk associations were observed for multiple anti-HT drug groups after cancer diagnosis. When all results point in the same direction for many drug groups with totally different mechanisms of action, this suggests that there is a non-causal explanation i.e., hypertension control. However, ATR-blockers were the only drug group that was associated with a decreased BCa death risk in pre-diagnostic use in a dose-dependent manner. Also elevated risk estimates for single drug groups like calcium-channel blockers were observed without dose-dependence in some analysis supporting the role of underlying hypertension as a possible prognostic agent also in cancer.

ATR-blockers seemed to differ from ACE-inhibitors and other anti-HT medications when one examines the association between anti-HT drug use and the risk of cancer death. These studies support a possible prognostic role of ATR-blockers in hindering cancer progression. More research is needed in this area to clarify this phenomenon.

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PUBLICATION I

Antihypertensive drugs and prostate cancer survival after radical prostatectomy in Finland—A nationwide cohort study

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Antihypertensive drugs and prostate cancer survival after radical prostatectomy in Finland—A nationwide cohort study

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Antihypertensive (anti-HT) drugs targeting renin-angiotensin-aldosterone (RAA)- system have been associated with improved prostate cancer (PCa)-specific survival. Challenge is that often multiple drugs are used simultaneously. We evaluated the association between use of anti-HT drugs and PCa survival among 14,422 surgically treated Finnish PCa patients. Information on drug purchases was obtained from a national prescription database. We used Cox regression to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for risk of PCa death and initiation of androgen deprivation therapy (ADT) with adjustment for age, tumor extent, use of statins and for Charlson Comorbidity Index. Angiotensin-converting enzyme (ACE)-inhibitors, angiotensin- receptor (ATR)-blockers, diuretics, calcium-channel blockers, beta-blockers and other anti-HT drugs were analyzed as separate time-dependent variables to model simultaneous use. Overall anti-HT drugs were associated with an increased risk of PCa death. Conversely use of ATR-blockers was associated with decreased risk of PCa death (HR: 0.43, 95% CI: 0.26–0.72 and HR: 0.60, 95% CI 0.37–0.97 for pre- and post-diagnostic use). Similar risk decrease was not observed in other drug groups. Anti-HT drugs were also associated with an increased risk of starting ADT, with the exception of ATR-blockers (HR: 0.81 CI:0.71–0.92). ATR- blockers differ from other anti-HT drugs as the survival is better in users of this drug group. The result partly supports the role of RAA system in PCa progression. Nevertheless, the risk decrease was not observed in ACE-inhibitor users. Further research is needed to elucidate the molecular mechanism for the potential anticancer effect of ATR- blockers.

Introduction

Prostate cancer is the most common cancer among men in the Western countries. It causes great losses in terms of health- care expenditure and life-years. Nevertheless, etiology of the disease is poorly understood.

It has been suggested that hypertension, by itself or as part of metabolic syndrome, may be a prostate cancer risk factor.[1–4] Furthermore, other factors that associate with hypertension, such as elevated heart rate and obesity, may also be associated with prostate cancer risk.[5,6]

Although hypertension is a putative prostate cancer risk factor, it is unclear whether use of antihypertensive drugs might reduce the risk or improve the prognosis. According to some studies antihypertensive medication can increase the risk of PCa diagnosis.[7] Some classes of antihypertensive drugs, such as angiotensin-receptor blockers and ACE-inhibitors have been associated to better PCa survival and better prognosis.[8,9] Not all studies agree, though.[10,11] Also beta-blockers have been associated with a reduction in PCa risk.[12] In addition to studies estimating antihypertensive drugs as a group, captopril as a single drug may reduce the risk of prostate cancer.[13]

Challenge for epidemiological studies on antihypertensive drugs is that it is common to simultaneously use several different antihypertensive drugs, especially among the elderly. Therefore, when studying the independent effect of one drug or drug group, it is imperative to take into account simultaneous use of other drugs for the same indication.

Here, we evaluated prostate cancer survival and risk of starting androgen-deprivation therapy after radical prostatectomy by anti-HT drug use in a nationally comprehensive cohort while taking into account simultaneous use of multiple drug groups. Our pre-specified hypothesis was that use of ACE-inhibitors, ATR blockers, beta-blockers and calcium-channel blockers would be associated with better survival.

Key words: prostate cancer, survival, antihypertensive drugs, androgen-deprivation therapy
Additional Supporting Information may be found in the online version of this article.
Conflict of interests: Teemu J Murtola: Consultant fees from Astellas and Jansen, Lecture fees from Astellas, Jansen and MSD. Other authors do not have any conflict of interests.
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What's New?

While hypertension is a suspected risk factor for prostate cancer, it remains unclear whether antihypertensive drugs reduce prostate cancer risk or improve prognosis. Moreover, previous studies have identified potentially harmful associations. Along those lines, the authors of the present study found an association between overall antihypertensive drug use and increased risk of prostate cancer death. Investigation of specific drugs, however, suggested that angiotensin-receptor blockers are associated with reduced risks of initiation of androgen-deprivation therapy and prostate cancer death. Survival was also higher among patients who used angiotensin-receptor blockers, compared to other antihypertensive drugs.

Materials and Methods

Study cohort

Our study cohort consisted of 14,422 men with prostate cancer who were treated with radical prostatectomy in Finland during years 1995–2013. The cases were identified from the Finnish Cancer Registry, which covers approximately 95% of cases diagnosed yearly in Finland. Information in the registry is gathered via mandatory reports of all cancer diagnoses made in Finnish health care units.[14] The Registry collects data on the primary site of cancer, histology, date and method of diagnosis, primary treatment method and date and cause of death. Limited information on tumor extent is also available. The registry does not record Gleason score or PSA level at diagnosis.

Information on antihypertensive medication use

The study cohort was linked to a national prescription database for comprehensive information on antihypertensive drug use during 1995–2013. The linkage was done using unique personal identification number.

The national prescription database is maintained by the Finnish Social Insurance Institution (SII). SII provides reimbursements for physician-prescribed drug purchases to all Finnish citizen as part of the national health insurance. Reimbursements are available for all purchases of SII-approved drugs in an outpatient setting. Drugs administered during inpatient periods are not recorded in the database. The information on each purchase includes dose, the date, package size and number of packages bought.

All purchases of anti-HT drugs were identified using drug-specific ATC-codes (Supporting Information Table 1). Antihypertensive drugs were categorized into six separate drug groups: Angiotensin converting enzyme (ACE)-inhibitors, Angiotensin-receptor blockers (ATR-blockers), diuretics, beta-blockers, calcium-channel blockers and other antihypertensive drugs. The diuretics group includes thiazides, loop-diuretics and potassium-sparing diuretics. The Angiotensin-receptor blocker group includes drugs blocking the AT_1 receptor, a receptor for angiotensin 2.

In addition to anti-HT drugs, information on use of statins and antidiabetic drugs was also collected from database as they are often used simultaneously with anti-HT medication. No information on use of other drugs was collected.

Information on androgen deprivation therapy

Information on purchases of GnRH-agonists and -antagonists and antiandrogens were obtained from the prescription database, identified by drug-specific ATC-codes (Supporting Information Table 1).

The cohort was linked to Care Registry (HILMO) maintained by the National Institute For Health And Welfare to collect information on orchiectomies (Nordic Classification of Procedures code KFC00) conducted in study population during 1995–2013. The Registry records all diagnoses and medical procedures from in- and outpatient hospital visits in Finland.

Information on orchiectomies was combined to information on use of GnRH-agonists and -antagonists and antiandrogens to identify men starting androgen deprivation therapy (ADT) after radical prostatectomy. Combined information was used as a proxy for disease recurrence after prostatectomy.

Diagnoses recorded in the HILMO database were also used to calculate Charlson co-morbidity index[15] for each participant. Conditions used in the index calculation are listed in Supporting Information Table 2.

Statistical analysis

Separate analyses were performed for drug usage before and after PCa diagnosis. We compared risk of prostate cancer death between users and nonusers of anti-HT drugs.

The total yearly mg amount of purchases of each anti-HT drug was calculated for each participant based on the dosing, number of packages and package sizes from each purchase. Then, the purchased yearly mg amount was divided with the dose corresponding to drug-specific Defined Daily Dose (DDD)[16] for the total number of DDDs the person had purchased per year. Each year with recorded medication purchases was considered as year of usage regardless of the purchased amount.

Cumulative number of DDDs and years of usage were calculated separately for each year after PCa diagnosis. Yearly dosing was evaluated by forming an intensity variable dividing cumulative number of DDDs with cumulative number of years of usage. Anti-HT medication use before PCa diagnosis was estimated by adding together usage from all years between 1995 and the year of the diagnosis.

Cox regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the risk of prostate cancer death and for starting ADT after diagnosis. Time metric was years and months since PCa diagnosis. In analyses for the risk of death the follow-up continued until death,

emigration or the common closing date December 31, 2013, whichever came first. In analyses for the risk of starting ADT after diagnosis the follow-up continued until first record of any ADT (medical or surgical castration, antiandrogen use), death or the common closing date. Cox regression analyses were adjusted for age at diagnosis, tumor extent (categorized as local, locally advanced, metastatic or unknown), Charlson co-morbidity Charlson co-morbidity index and use of statins during the follow-up. Sensitivity analyses were stratified by time of PCa diagnosis (1995–1999, 2000–2009, 2010 or later) to estimate role of changed criteria for operative management in the risk association by anti-HT drug use over the course of time.

Anti-HT drug use before diagnosis was analyzed as time-fixed variable taking into account the duration and cumulative dose of use occurring between 1995 and year of PCa diagnosis. Post-diagnostic use was analyzed as time-dependent variable to minimize immortal time bias. Time-dependent variables were formed by updating medication user status as well as cumulative amount, duration and intensity of use separately for each follow-up year after PCa diagnosis. Dose dependence was evaluated by stratifying medication users by tertiles of DDD amount, duration and intensity of use based on the level reached on each follow-up year.

Simultaneous use of multiple anti-HT drug groups was modeled by forming separate time-dependent variables for use of each drug group, i.e. ACE-inhibitors, ATR-blockers, beta-blockers, calcium channel blockers, diuretics and other anti-HT drugs not belonging to these groups. These variables were included in the Cox regression model simultaneously. Participants who had purchased more than one anti-HT drug group in a given year were considered as users for each drug group variable of which they had purchases.

Long-term association between anti-HT drug use and risk of prostate cancer death was investigated in lag time analyses where the exposure was lagged forward in the follow-up time; analyzing medication use that occurred 1, 3 or 5 years before.

The data was analyzed using the IBM SPSS statistics 24 program. All reported p-values are two-sided.

Results

Population characteristics

Anti-HT drug use was very common in our study population. Of the 14,422 men 9,799 (67.9%) had used at least one anti-HT drug before or after diagnosis; 4,625 (32.1%) men had not used any kind of anti-HT medication. Compared to nonusers, anti-HT medication users were older at diagnosis (median age 63 years), had more often localized tumor extent and also used more often statins and antidiabetic medication. During the median follow-up of 9.9 years after PCa diagnosis, a total of 1,581 men (11/100 men) died. Of these, 424 (3/100) died of PCa (Table 1). Ten years overall mortality was 7.5/100 men. A total of 2,849 men (20/100 men) started androgen deprivation therapy during the follow-up.

Table 1. Population characteristics.

	Nonusers	ACE-inhibitors	ATR-blockers	Beta-blockers	Calcium-channel blockers	Diuretics	Other anti-HT drugs
n of men	4,624	5,045	4,153	6,367	4,806	5,016	410
median follow time (IQR)	8.08 (5.4–11.6)	10.6 (6.7–14.0)	10 (6.4–13.6)	10.4 (6.7–14.2)	10.3 (6.6–14.0)	10.5 (6.8–14.1)	11.1 (7.3–14.9)
n of Pca deaths (% of users)	85 (1.8%)	131(2.6%)	77 (1.9%)	207 (3.3%)	133 (2.8%)	247 (4.9%)	16 (3.9%)
n (%) of starting ADT	729 (15.8)	1,089(21.6)	792 (19.1)	1,439 (22.6)	1,055 (22.0)	1,239 (24.7)	107 (26.1)
Charlson comorbidity index, median (IQR)	2 (2–4)	2 (2–6)	2 (2–6)	2 (2–6)	2 (2–6)	2 (2–6)	2 (2–4)
Age at diagnosis, median (IQR)	61 (33–91)	63 (40–93)*	62 (40–93)	63 (39–92)*	63 (40–88)*	63 (40–93)*	63 (42–87)
Tumor extent at diagnosis, n(%)							
Localized	3,252 (70.3)	3,626 (71.9)*	3,028 (72.9)*	4,547 (71.4)*	3,447 (71.7)*	3,604 (71.8)*	299 (72.9)
Locally advanced	851 (18.4)	779 (15.4)	637 (15.3)	989 (15.5)	756 (15.7)	779 (15.5)	57 (13.9)
Unknown	522 (11.3)	640 (12.7)	488 (11.8)	831 (13.1)	603 (12.5)	634(12.6)	54 (13.2)
Statin use, n (%)	1,274 (27.5)	3,390 (67.2)*	2,618 (63.0)*	4,164 (65.4)*	3,034 (63.1)*	3,161 (63.0)*	269 (65.6)*
Antidiabetic medication use; n (%)	279 (6.0)	1,370 (27.2)*	1,038 (25.0)*	1,453 (22.8)*	1,227 (25.5)*	1,328(26.5)*	125 (30.5)*

*$p < 0.05$ for difference compared to nonusers

Table 2. Risk of prostate cancer death by antihypertensive drug use before prostate cancer diagnosis.

		Risk of PCa death	
Drug group	***n* of users/PCa deaths**	**HR (95% CI)$_{age\text{-}adjusted}$**	**HR (95% CI)$_{multiavariable\ adjusted}$***
ACE inhibitors	530/28	1.02 (0.66–1.57)	1.10 (0.70–1.72)
ATR-blockers	1,781/15	0.39 (0.23–0.65)	0.43 (0.26–0.72)
Average yearly dose of ATR-blocker (mg/yr)			
0–286.22	592/5	0.34 (0.14–0.81)	0.38 (0.16–0.92)
286.22–460.00	596/6	0.43 (0.19–0.95)	0.50 (0.22–1.11)
460→	593/4	0.40 (0.15–1.09)	0.48 (0.18–1.28)
beta-blocker	670/43	1.54 (1.01–2.14)	1.82 (1.30–2.56)
calcium-channel blocker	448/17	0.77 (0.47–1.27)	0.84 (0.51–1.40)
diuretics	319/22	1.48 (0.89–2.45)	1.62 (0.97–2.70)
other anti-HT drugs	27/5	3.03 (1.24–7.43)	3.90 (1.59–9.62)

*Calculated cox regression model with adjustments of age, tumor extent, CCI and statin use

Antihypertensive drug usage before prostate cancer diagnosis

Compared to nonusers, men who had used ATR- blockers before the diagnosis had a lower risk for prostate cancer death both in the age-adjusted and multivariable adjusted analysis (multivariable adjusted HR: 0.43 CI: 0.26–0.72) (Table 2). When stratified by duration of use also the other anti-HT drug groups, such as ACE inhibitors, calcium channel blockers and beta blockers were associated with lowered risk of PCa death in some strata. However, when stratified by average yearly dose of usage the decreased risk was observed only at low-dose use for drug groups other than ATR-blockers (Table 2). In users of ATR-blockers the risk decrease was observed regardless of yearly dosage.

In contrast, usage of diuretics before the diagnosis was associated with borderline significant increase in risk of PCa death (HR 1.62, 95% CI 0.97–2.70). When stratified by cumulative use, the risk increase was observed only in the strata of lowest cumulative amount (HR: 1.67 CI: 1.10–2.54), but not in longer-term or high-dose use.

Antihypertensive drug use after the diagnosis

Post-diagnosis use of ATR- blockers was associated with better prostate cancer survival compared to nonusers both in the age-adjusted and multivariable-adjusted analyses (Table 3). The risk decrease persisted even with 5 years' lag time.

In contrast, use of any other antihypertensive drugs was associated with an increased risk compared to nonusers (Table 3). When drug groups were analyzed separately, the risk increase was significant only for post-diagnosis use of beta-blockers. The increased risk estimates attenuated within 5 years' lag-time, but remained elevated compared to nonusers for beta-blockers and ACE inhibitors.

Dose-dependence of the risk association between ATR-blocker use and prostate cancer death

The risk of PCa death decreased in inverse association with average annual dose of ATR-blocker use post-diagnosis, although the stratified risk estimates were nonsignificant (Table 4). For ATR-blocker use before PCa diagnosis

Table 3. Risk of prostate cancer death by antihypertensive drug use after prostate cancer diagnosis.

		Risk of PCa death		Lag-time		
Drug group	***n* of users/ PCa deaths**	**HR (95% CI)$_{age\text{-}adjusted}$**	**HR (95% CI)$_{multiavariable\ adjusted}$***	**1 years**	**3 years**	**5 years**
ACE inhibitors	4,515/103	1.16 (0.85–1.58)	1.10 (0.81–1.49)	1.14 (0.84–1.56)	1.14 (0.83–1.56)	1.40(1.00–1.95)
ATR blockers	2,372/62	0.59 (0.36–1.00)	0.60 (0.37–0.97)	0.55 (0.34–0.89)	0.52 (0.31–0.86)	0.55 (0.30–0.98)
Beta-blockers	5,697/164	1.37(1.07–1.75)	1.30 (1.01–1.67)	1.43 (1.11–1.84)	1.40(1.08–1.81)	1.30(0.98–1.73)
Calcium-channel blockers	4,358/116	1.04 (0.77–1.40)	1.01 (0.75–1.37)	1.02 (0.75–1.37)	0.92 (0.67–1.26)	0.97 (0.69–1.37)
Diuretics	4,698/225	1.30(0.93–1.82)	1.32 (0.95–1.85)	1.31 (0.94–1.84)	1.14 (0.80–1.62)	0.94 (0.63–1.40)
Other antihypertensive drugs	383/11	2.18(0.97–4.91)	1.89 (0.84–4.26)	1.96 (0.87–4.43)	2.18(0.96–4.92)	2.34 (0.96–5.71)

*Calculated cox regression model with adjustments of age, tumor extent, CCI and statin use

Table 4. Risk of prostate cancer death by cumulative amount, duration and average yearly dose of ATR- blocker use after diagnosis.

Amount of use (mg)	*n* of men/PCa deaths	Riski of Pca death HR (95%CI) age-adjusted	Risk of Pca death HR (95% CI) $_{\text{multiavariable adjusted}}$*
0–1,339.33	1,351/36	1.13 (0.72–1.43)	1.13 (0.80–1.61)
1,339.33–4,200.00	1,392/30	0.85 (0.58–1.25)	0.91 (0.62–1.34)
4,200.00→	1,404/11	0.51 (0.25–1.05)	0.54 (0.26–1.10)
Duration of use (years)	n of men/PCa deaths	Riski of Pca death HR (95%CI) age-adjusted	Risk of Pca death HR (95% CI)
0–4	1,547/44	0.84 (0.62–1.15)	0.91 (0.66–1.24)
4–9	1,367/24	0.61 (0.40–0.92)	0.64 (0.42–0.97)
9→	1,239/9	0.03 (0.00–0.08)	0.02 (0.01–0.08)
Average yearly dose (mg/yr)	n of men/PCa deaths	Riski of Pca death HR (95%CI) age-adjusted	Risk of Pca death HR (95% CI)
0–310.33	1,352/36	1.19 (0.83–1.67)	1.37 (0.96–1.97)
310.33–536.27	1,398/24	0.80 (0.52–1.23)	0.86 (0.56–1.33)
536.27→	1,403/17	0.60 (0.37–0.97)	0.61 (0.38–1.01)

*Calculated cox regression model with adjustments of age, tumor extent, CCI and statin use

Table 5. Risk of starting androgen deprivation therapy (ADT) by antihypertensive drug use before or after prostate cancer diagnosis

	Anti-HT drug use before diagnosis		
Drug group	*n* of men starting ADT (%)	HR (95% CI)$_{\text{age-adjusted}}$	HR (95% CI)$_{\text{multiavariable adjusted}}$*
ACE inhibitors	162 (30,6)	1.28 (1.08–1.53)	1.32 (1.11–1.58)
ATR-blockers	250 (14,0)	0.81(0.71–0.93)	0.81 (0.71–0.92)
Beta-blockers	211 (31,5)	1.33 (1.14–1.54)	1.38 (1.19–1.61)
Calcium-channel blockers	135 (30,1)	1.21 (1.01–1.45)	1.26 (1.05–1.51)
Diuretics	89 (27,9)	0.89 (0.70–1.13)	0.90 (0.70–1.14)
Other anti-HT drugs	13 (48,1)	1.91 (1.10–3.30)	2.24 (1.29–3.89)
		Anti-HT drug use after diagnosis	
ACE inhibitors	1,089 (24,1)	1.02 (1.03–1.05)	1.01 (0.90–1.13)
ATR-blockers	792 (33,4)	0.80 (0.69–0.92)	0.80 (0.69–0.92)
Beta-blockers	1,439 (25,3)	1.11 (1.00–1.22)	1.09 (0.99–1.21)
Calcium-channel blockers	1,055 (24,2)	1.06 (0.95–1.19)	1.05 (0.94–1.17)
Diuretics	1,239 (26,4)	0.99 (0.87–1.12)	1.00 (0.88–1.14)
Other anti-HT drugs	107 (27,9)	1.43 (0.98–2.10)	1.44 (0.98–2.10)

*Calculated cox regression model with adjustments of age, tumor extent, CCI and statin use

no clear dose-dependence in the risk association was observed.

Anti-HT drug use and risk of starting androgen deprivation therapy (ADT)

Pre-diagnostic use of most anti-HT drug groups was associated with elevated risk of starting ADT after prostatectomy compared to nonusers (Table 5). Only exception was ATR-blockers, which were associated with a reduced risk of starting ADT (HR: 0.81 CI: 0.71–0.92).

For post-diagnostic use, ATR-blockers remained to be associated with lowered risk of starting ADT (HR: 0.80 CI: 0.69–0.92) (Table 5). However, no significant risk difference was observed between users and nonusers of other groups of anti-HT drugs.

Sensitivity analyses

When analyzing all-cause mortality a decreased risk among users of ATR-blockers (HR: 0.73, CI: 0.58–0.92) and increased risk among users of all other anti-HT drug types was observed.

To test whether the risk decrease observed in ATR-blocker users was only due to telmisartan, we re-ran the analysis after exclusion of telmisartan users. ATR blocker use remained associated with lowered risk of PCa death (HR 0.50, 95% CI 0.28–0.88).

We also tested whether captopril had differing risk association compared to ATR-blockers. After excluding captopril the risk of PCa death was lowered in ATR-blocker users compared to nonusers (HR: 0.35 CI: 0.21–0.57). Captopril alone was associated with increased risk of PCa death (HR: 2.09 CI: 0.67–6.58).

Table 6. Risk of prostate cancer death by antihypertensive drug use after prostate cancer diagnosis. Adjusted analyses with year of diagnosis.

Drug group	*n* of users/ PCa deaths	Risk of PCa death		Lag-time		
		HR (95% CI)$_{age\text{-}adjusted}$	HR (95% CI)$_{multivariable\ adjusted\ (*)}$	1 years	3 years	5 years
ACE inhibitors	4,515/103	1.16 (0.85–1.58)	1.28 (0.94–1.74)	1.23 (0.91–1.68)	1.33 (0.97–1.82)	1.45 (1.03–2.04)
ATR blockers	2,372/62	0.59 (0.36–1.00)	1.12 (0.68–1.83)	1.02 (0.63–1.68)	1.03 (0.62–1.73)	0.92 (0.49–1.69)
Beta-blockers	5,697/164	1.37(1.07–1.75)	1.39 (1.08–1.79)	1.34 (1.04–1.73)	1.39 (1.07–1.80)	1.32 (0.99–1.76)
Calcium-channel blockers	4,358/116	1.04 (0.77–1.40)	1.04 (0.77–1.40)	1.01 (0.75–1.36)	0.94 (0.69–1.29)	1.00 (0.71–1.40)
Diuretics	4,698/225	1.30(0.93–1.82)	1.30 (0.94–1.82)	1.29 (0.92–1.80)	1.13 (0.79–1.61)	0.99 (0.67–1.49)
Other antihypertensive drugs	383/11	2.18(0.97–4.91)	1.46 (0.65–4.26)	1.44 (0.64–3.26)	1.69 (0.75–3.82)	2.09 (0.86–5.09)

*Calculated cox regression model with adjustments of age, tumor extent, CCI, statin use and year of PCa diagnosis

After excluding use of all other anti-HT drugs except ATR-blockers the risk decrease was not statistically significant but stayed decreased (HR: 0.64 CI: 0.09–4.65).

To test association of ATR-blockers with PCa survival in different time periods we divided our data in three groups based on year of diagnosis: 1995–1999, 2000–2009 and 2010–2014. We rerun the analyses in those three groups. The risk decrease among ATR-blockers was observed only in group 1995–1999 but not in other groups. The risk associations were not statistically significant as the number of PCa deaths was low. Risk estimates for ATR-blockers in group 1995–1999 (HR: 0.246 CI: 0.034–1.788), in group 2000–2009 (HR: 1.018 CI:0.588–1.762) and in group 2010–2013 (HR: 1.772 CI: 0.134–23.479).

We also tested if year of diagnosis modified the results. Operative management is conducted soon after diagnosis and we supposed that year of surgery was the same as the year of diagnosis. We added year of PCa diagnosis in our multivariable analyses on usage before and after PCa diagnosis. The risk decrease among ATR-blockers became statistically nonsignificant (Table 6). The decreasing association of diuretics and beta-blockers on PCa survival increased (Supporting Information Tables 3 and 4). In analyses of usage before PCa diagnosis some changes in risk estimates were observed but at nonsignificant level (Table 7).

Discussion

In our study antihypertensive drugs are generally associated with increased risk of PCa progression after radical prostatectomy as measured by starting ADT use and prostate cancer death. The risk association was observed for multiple anti-HT drug groups with distinctly different mechanisms of action, like beta-blockers and diuretics. This suggests that the risk increase is caused by underlying common indication for medication use, i.e. hypertension. The risk association was strongest when anti-HT medication use had started before PCa diagnosis, suggesting that hypertensions may be a risk factor for PCa progression in long-term.

In contrast, use of ATR- blockers was associated with lowered risk of starting ADT and improved prostate cancer survival. The risk decrease was significant both for usage before and after PCa diagnosis. No clear dose-dependence was observed for usage before PCa diagnosis, but for postdiagnostic use the risk of PCa death decreased in inverse correlation with the intensity, cumulative amount and years of ATR-blocker use. The differing risk association as compared to other anti-HT drugs and the dose-dependent risk association support causal association between ATR-blocker use and PCa prognosis. The risk of starting ADT after prostatectomy was high also among ATR-blocker users which argues against selection bias of more favorable risk cases among them. However, also noncausal explanations should be considered.

In subgroup analyses where we analyzed the effect of year of diagnosis the risk decrease among ATR-blockers remained decreased. Because of low numbers of PCa deaths the risk

Table 7. Risk of prostate cancer death by antihypertensive drug use before prostate cancer diagnosis. Adjusted analyses with year of diagnosis.

		Risk of PCa death	
Drug group	***n* of users/PCa deaths**	**HR (95% CI)$_{age\text{-}adjusted}$**	**HR (95% CI)$_{multiavariable\ adjusted}$***
ACE inhibitors	530/28	1.02 (0.66–1.57)	1.20 (0.88–1.63)
ATR-blockers	1,781/15	0.39 (0.23–0.65)	0.96 (0.58–1.57)
Average yearly dose of ATR-blocker (mg/yr)			
0–286.22	592/5	0.34 (0.14–0.81)	0.66 (0.27–1.62)
286.22–460.00	596/6	0.43 (0.19–0.95)	0.99 (0.44–2.23)
460→	593/4	0.40 (0.15–1.09)	1.30 (0.48–3.54)
beta-blocker	670/43	1.54 (1.01–2.14)	1.31 (1.02–1.68)
calcium-channel blocker	448/17	0.77 (0.47–1.27)	1.00 (0.74–1.34)
diuretics	319/22	1.48 (0.89–2.45)	1.28 (0.92–1.79)
other anti-HT drugs	27/5	3.03 (1.24–7.43)	1.43 (0.63–3.225)

*Calculated cox regression model with adjustments of age, tumor extent, CCI, statin use and year of PCa diagnosis

decrease was observed only in cases diagnosed in the 90s and which therefore have had sufficient time to reach any significant PCa mortality. There may be selection bias among ATR-blocker users that cause the difference between ATR-users and other anti-HT users. ATR-blocker users may be healthier as we do not have information on therapeutic equilibrium of other diseases. However there are no differences in comorbidity indexes or risk of starting ADT between ATR-users and nonusers.

ACE inhibitors and ATR-blockers both affect renin-angiotensin-aldosterone system (RAA-system), lowering blood pressure. In addition, RAA-system also controls vascular growth by inhibiting cell proliferation and mitosis via AT1 receptor.[17] However, our results do not directly support importance of RAA system in PCa progression as the risk decrease was observed only for users of ATR-blockers, whereas ACE inhibitors were associated even with an increased risk of PCa death.

Thus, the specific mechanism of how ATR-blockers may decrease the risk of PCa death and reduce disease recurrence remains unclear. *In vitro,* telmisartan but not other sartans has been reported to cause apoptosis in prostate cancer cells.[18] However, in sensitivity analyses the survival benefit among ATR-blocker users compared to nonusers remained after exclusion of telmisartan users, confirming that the risk decrease is observed for ATR blockers as a group. Further studies are needed to elucidate the possible mechanism for the risk decrease only among ATR-blocker users.

All anti-HT drugs except beta-blockers are the first line treatment of hypertension in Finland. Beta-blockers are used to treat hypertension combined with coronary artery disease. It is also possible that men using ATR-blockers are systematically different from men using other types of anti-HT drugs, which may cause selection bias to cause the difference compared to other anti-HT drug groups. Nevertheless, selection bias should not be dose-dependent, whereas in our study a dose-dependent inverse risk association between ATR-blocker use and PCa death was observed. This argues against selection bias. Further, all men had been treated with radical prostatectomy at baseline, which presumably makes the study population fairly homogenous. Concordantly, the distribution of measured background characteristics were similar in men using ATR-blockers and those using other types of anti-HT drugs.

The strengths of our study are long follow-up time, detailed information on timing and amount of medication use and a nationwide study cohort, covering all PCa patients managed with prostatectomy in Finland since 1995. We were able to take into account use of other drugs and analyze separately each anti-HT drug group. Our registry-based data on medication use was exceptionally detailed and free of recall bias.

The main limitation of the study is low number of PCa deaths in this cohort of operatively managed PCa patients. This limited statistical power in subgroups analyses. We did not have information on therapeutic equilibrium of the participants' hypertension and we cannot be sure if anti-HT drugs were used to control other diseases than hypertension. Beta-blockers and diuretics are also used to treat coronary artery disease which has been suggested as PCa risk factor.[19,20] Our data on medication use was based on recorded medication purchases, we had no information whether the drugs were actually consumed. Further, we had no information on lifestyle factors such as BMI, smoking, diet or exercise activity which could have served as confounding factors. However, role of these conditions as risk factors for PCa progression or death is unclear.

In conclusion, antihypertensive drugs are associated with increased risk of PCa death and starting of ADT after radical prostatectomy. An exception are ATR-blockers which

are associated with better PCa survival and lowered risk of starting ADT. The risk decrease is observed in inverse association with annual dose of ATR-blocker use. Our results support further studies elucidating the mechanism behind the possible anticancer effect, and ultimately doing clinical trials testing ATR-blockers in men with prostate cancer.

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PUBLICATION II

Risk of urothelial cancer death among people using antihypertensive drugs—a cohort study from Finland

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ARTICLE

Risk of urothelial cancer death among people using antihypertensive drugs—a cohort study from Finland

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ABSTRACT

Background: To analyse the association between antihypertensive (anti-HT) drug use and risk of urothelial cancer (UC) death. UC occurs as bladder cancer (BCa) and upper tract urothelial carcinomas (UTUCs). Hypertension is a suggested risk factor for BCa and may impair disease prognosis. However, it's unclear if use of anti-HT drugs could improve the prognosis of UC.

Materials and methods: This study evaluated the association between use of anti-HT drugs and UC survival among 14,065 participants diagnosed with BCa and 1080 with UTUC during 1995–2012 in Finland. It analyzed data using the multivariable adjusted conditional Cox regression model.

Results: Angiotensin-receptor (ATR) blocker use before BCa diagnosis was associated with slightly decreased risk of BCa death (HR = .81, CI = .71–0.93). The association was dose-dependent and it decreased in association with elevated intensity of ATR-blocker use. Post-diagnostic use of ATR-blockers was similarly associated with better survival compared to non-users (HR = .81, CI = .71–0.92. Interestingly, use of calcium-channel blockers also associated with better survival and the risk of BCa death decreased with increasing intensity of use (HR = .67, CI = .52–0.86 for highest intensity).

Conclusions: This large population-based cohort suggests decreased risk of BCa death among ATR-blocker and calcium-channel blocker users. The risk association among ATR-blockers and calcium-channel blockers was dose-dependent suggesting a causal explanation. Similar risk associations are not observed for other anti-HT drug users, which may suggest a direct effect of ATR blocker or calcium-channel blocker use. Further studies are needed to elucidate the potential anticancer mechanism.

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Introduction

Urothelial cancers (UC) can be divided into bladder cancer (BCa) and upper tract urothelial cancers (UTUCs). BCa is the ninth most common cancer in the world [1]. Low-grade BCa recurs often, requiring intense follow-up, which makes it one of the most expensive cancers in the world. High-grade BCa advances often to fatal stage causing high losses in life expectancy in the Western countries [2]. UTUCs account only for 5–10% of urothelial carcinomas [3]. The yearly incidence of UTUC in the Western countries is estimated to be 2/100,000 [4]. Urothelial cancers are more common in men than women [1]. Smoking is the most important risk factor both for BCa and UTUC [5,6].

Besides smoking, also other possible risk factors for UC have been suggested. Diabetes may increase the risk of BCa and BCa death, as well as increase the risk of disease recurrence in UTUC [7,8]. Hypertension may be a risk factor for BCa and many other cancer types, but studies are few [9], and not all studies agree [10]. Hypertension may also impair disease prognosis [9]. Still it is unknown whether use of antihypertensive drugs (anti-HT drugs) would lower the risk of BCa or improve disease prognosis. A challenge is to separate influence of anti-HT medication from that of the underlying hypertension. Another challenge is to be able to take into account simultaneous use of different drug groups and different treatments when evaluating the possible effect of a single drug group.

Here we analyse BCa and UTUC-specific survival by use of different groups of antihypertensive drugs among participants with urothelial cancer in the bladder or the upper urinary tract.

Materials and methods

Study cohorts

Two study cohorts were identified from the Finnish Cancer Registry (FCR), which registers virtually all cancer diagnoses in Finland through mandatory notifications and pathological reports [11]. Causes of death in the Cancer Registry are obtained from the national mandatory death certificate registry. Causes of death reported by clinicians in death certificates are reviewed by medical authorities and in unclear cases a forensic examination of the cause of death is mandated.

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Supplemental data for this article can be accessed here.

The BCa cohort consisted of 14,065 primary bladder cancer cases from Finland diagnosed during 1995–2012. Data contained information on the primary site of cancer, tumour extent at diagnosis (localized, locally advanced, advanced, unknown), date and method of diagnosis, primary treatment method (surgery, radical cystectomy, cytostatic drugs, chemotherapy, antihormonal therapy) and date and cause of death. Surgery includes radical cystectomies, but also endoscopic operations such as partial removal of bladder and transurethral resection of tumour.

The UTUC cohort consisted of 1080 participants diagnosed with primary cancers in the renal pelvis or the ureter in Finland between 1995 and 2012. The data included the same information as for the BCa cohort (surgery includes radical nephro-ureterectomy but also minor surgical operations). FCR does not record tumour grade, thus it was not available.

Data on either cohort does not include tumour recurrences.

Information on antihypertensive medication use

Both study cohorts were linked to the national prescription database for information on antihypertensive (anti-HT) medication use during 1995–2012. The database is maintained by the Finnish Social Insurance Institution (SII). SII provides reimbursements for physician-prescribed drug purchases for every Finnish citizen in an outpatient setting as a part of the national health insurance. The information on each purchase includes dose, purchase date, package size and number of packages bought.

We identified each anti-HT drug by using drug-specific ATC-code (Supplementary Table S1). Anti-HT drugs were categorized into five groups: angiotensin-converting enzyme (ACE)-inhibitors, angiotensin-receptor (ATR)-blockers, diuretics, beta-blockers and calcium-channel blockers.

Information on co-morbidities

Both cohorts were linked to the Care Registry (HILMO) maintained by the National Institute For Health And Welfare to collect information on diagnoses and procedures conducted in the study population during 1995–2013. The Registry records all diagnoses and medical procedures from in- and outpatient hospital visits in Finland. Diagnoses recorded in HILMO were used to calculate the Charlson co-morbidity index for each participant [12]. Conditions used in the index calculation are listed in Supplementary Table S2. COPD and kidney failure diagnoses were added separately into the analysis as they may serve as potential confounding factors.

Statistical analysis

We performed separate analyses for drug usage before and after UC diagnosis in both study cohorts. We compared the risk of BCa and UTUC death between users and non-users of anti-HT drugs.

The total yearly milligram amount of purchases of each anti-HT drug was calculated for each participant based on the dosing, package sizes and number of packages from each purchase. Total purchased yearly milligram amount was divided by the dose corresponding to the drug specific Defined Daily Dose (DDD) for the total number of DDDs purchased per year [13]. Each year with recorded purchases was considered as the year of usage, regardless of the amount purchased.

The cumulative number of years for usage and DDDs was calculated separately for each year before and after UC diagnosis. Amount of use before the diagnosis was calculated by adding together all usage between 1995 and the year of diagnosis. We evaluated intensity of use by dividing the cumulative amount of DDD with the cumulative number of usage years.

Post-diagnostic use was analysed as a time-dependent variable to minimize immortal time bias. Time-dependent variables were formed by updating medication user status as well as cumulative amount, duration and intensity of use separately for each follow-up year after bladder cancer/UTUC diagnosis according to recorded purchases. Dose-dependence was evaluated by stratifying medication users by tertiles of DDD amount, duration, and intensity of use based on the level reached on each follow-up year. After discontinuation of usage (full calendar year without any anti-HT drug purchases) the participants remained in the user category to minimize bias due to selective discontinuation of preventative medications in the fatal stage of cancer. After discontinuation year cumulative tertiles of DDD amount, duration and intensity of anti-HT drug use remained the same level as before (no cumulative grow up after discontinuation).

Cox regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the risk of cancer-specific death. The time metric used was years and months since BCa or UTUC diagnosis. Follow-up continued until death, emigration or the common closing date of 31 December 2012, whichever came first.

Cox regression analyses were adjusted for age at diagnosis, year of diagnosis, tumour extent (local or advanced), surgery, cytostatic drugs, kidney failure, COPD, Charlson co-morbidity index and use of statins, antidiabetic medication, non-steroidal anti-inflammatory drugs and aspirin during the follow-up.

Simultaneous use of multiple anti-HT drug groups was modelled by forming separate time-dependent variables for use of each drug group, i.e. ACE-inhibitors, ATR-blockers, beta-blockers, calcium channel blockers and diuretics. These variables were included in the Cox regression model together to model simultaneous use.

Delayed association between anti-HT drug use and risk of cancer death was investigated in lag time analyses where the exposure was lagged forward in the follow-up time; analysing medication use that occurred 1, 3 or 5 years before.

The data were analysed using the IBM SPSS statistics 24 program.

Results

Population characteristics

Anti-HT drug use was very common in our bladder cancer cohort. Of the 14,065 participants, 10,489 (75%) had used at least one anti-HT drug before or after diagnosis; and 3576 (25%) had not used any kind of anti-HT medication (Table 1).

Table 1. Population characteristics.

	non-users	ACE-inhibitors	ATR-blockers	beta-blockers	calcium-channel blockers	diuretics
n of participants; (BCa/UTUC)	3578/228	5276/382	2495/240	7544/623	3247/446	7176/516
Men (BCa/UTUC)	2776/148	4123/214	1863/118	5788/352	2451 /229	5235/243
Women (BCa/UTUC)	802/80	1153/168	632/122	1753/271	796/217	1941/273
Median follow-up time (IQR), (BCa/UTUC)	5.2 (0–18.9)/2.5 (0–18.0)	5.8 (0–18.9)/3 (0–18.9)	6.5 (0–18.9)/3.8 (0–18.6)	5.8 (0–18.9)/2.9 (0–18.9)	5.7 (0–18.9)/3.1 (0–18.9)	5.4 (0–18.9)/2.6 (0–18.9)
n of cancer deaths (% of users), (BCa/UTUC)	1013 (28.3)/110 (48.2)	954 (18)/139 (36.4)	355 (14.2)/70 (29.2)	1562 (20.7)/236 (37.9)	646 (19.9)/160 (35.9)	1678 (23.4)/229 (44.4)
Age at diagnosis, median (IQR), (BCa/UTUC)	67.5 (20–102)/66 (29–97)	73.2 (22–102)/75 (44–96)	71.1 (29–98)/74 (44–96)	73.6 (22–102)/75 (44–96)	74.2 (22–101)/76 (44–99)	74.8 (22–104)
Stage, BCa, *n* (%)						
local	2071 (57.9)	3386 (64.2)	1627 (65.2)	4739 (62.8)	2046 (63.0)	4354 (60.7)
advanced	588 (16.4)	534 (10.1)	249 (10.0)	834 (11.1)	329 (10.1)	841 (11.7)
unknown	917 (25.6)	1356 (25.7)	619 (24.8)	1971 (26.1)	872 (26.9)	1981 (27.6)
Stage, UTUC, *n* (%)						
local	86 (37.7)	163 (42.7)	116 (48.3)	260 (41.7)	193 (43.3)	209 (40.5)
advanced	105 (46.0)	138 (36.1)	79 (32.9)	224 (36.0)	149 (33.4)	191 (37.0)
unknown	37 (16.2)	81 (21.2)	45 (18.8)	139 (22.3)	104 (23.3)	116 (22.5)
Primary care of UC, *n* (%)						
surgery in BCa	1739 (48.6)	2717 (51.5)	1336 (53.5)	3817 (50.6)	1622 (50.0)	3443 (48)
radical cystectomy in BCa	528 (14.8)	506 (9.6)	244 (9.8)	699 (9.3)	283 (8.7)	614 (8.6)
other treatment in BCa	1030 (28.8)	1451 (27.5)	623 (25.0)	2164 (28.7)	952 (29.3)	2145 (29.9)
surgery in UTUC	181 (79.4)	288 (75.4)	189 (78.8)	476 (76.4)	341 (76.5)	385 (74.6)
radical nephro-ureterectomy in UTUC	138 (60.5)	243 (63.6)	159 (66.3)	394 (63.2)	283 (63.5)	302 (58.5)
other treatment in UTUC	64 (28.0)	81 (21.2)	41 (17.1)	135 (21.7)	97 (21.7)	114 (22.1)
Statin use, *n* (%) (BCa/UTUC)	535 (15)/37 (16)	2934 (55.6)/234 (61.3)	1494 (59.9)/150 (62.5)	3943 (52.3)/333 (53.5)	1699 (52.3)/238 (53.4)	3211 (44.7)/227 (44.0)
Antidiabetic medication use, *n* (%) (BCa/UTUC)	237 (6.6)/10 (4.4)	1810 (34.3)/116 (30.4)	816 (32.7)/71 (29.6)	2031 (26.9)/135 (21.7)	933 (28.7)/104 (23.3)	2025 (28.2)/121 (23.4)
Radiotherapy (*n*; no information)	444 (835)	566 (1161)	230 (560)	867 (1641)	362 (711)	890 (1671)
Chemotherapy (*n*; no information)	746 (777)	1089 (1054)	521 (509)	1511 (1494)	624 (649)	1417 (1512)

BCa: Bladder cancer; UTUC: Upper tract urothelial carcinoma; UC: urothelial cancer; IQR: interquartile range.

Compared to non-users, anti-HT medication users were older at diagnosis (median age 73 years) and also used more often statins and antidiabetic medication. During the median follow-up of 4.1 years after BCa diagnosis, a total of 5550 participants (40/100) died. Of these, 2948 (21/100) died of BCa.

Among the UTUC cohort use of anti-HT drugs was also common: of 1080 participants, 852 (79%) had used anti-HT drugs, while only 228 (21%) had not used any anti-HT medication during the follow-up. Anti-HT users were older at the time of cancer diagnosis and they used statins and antidiabetic medication more often. During the follow-up, a total of 713 (66/100) participants died, of which 458 (42/100) were by UTUC. The headline other treatment in Table 1 includes all other treatment methods except surgery in both BCa or UTUC (cytostatic drugs, chemotherapy, antihormonal therapy).

Antihypertensive drug usage before UC diagnosis

Angiotensin-receptor (ATR) blocker use before BCa diagnosis was associated with a slightly decreased risk of BCa death (HR = .80, 95% CI = .70–0.92) (Table 2). In the intensity analyses highest intensity of ATR-blocker use was associated with most reduction in BCa death risk (HR = .65, 95% CI = .50–0.84). Long-time (5 years or more) use of ATR-blockers was associated with statistically significant reduction in BCa death risk (HR = .63, 95% CI = .50–0.79). On the contrary, among users of diuretics, the risk increase for BCa death was observed in all sub-group analyses being highest with strongest intensity of use (HR = 1.28, 95% CI = 1.13–1.44). Diuretics were associated with increased risk of BCa death also in lag-time analyses.

In analysis stratified by gender, beta-blockers were associated with slightly increased risk of BCa death in men (p for interaction = .003, Table 3). ATR-blockers were associated with decreased risk only among women (p for interaction = .046). Diuretics associated with increased risk of BCa death risk in both genders.

Pre-diagnostic use of ATR-blockers and calcium-channel blockers were associated with slightly decreased risk of UTUC death, although the risk differences were not statistically significant (Table 2). In lag-time analyses no clear delayed risk associations between any anti-HT drug group and UTUC death was found (Table 4).

Table 2. Risk of urothelial cancer death by antihypertensive drug use before diagnosis of UC.

		Risk of BCa death			Risk of UTUC death	
Drug group	*n* of users/BCa deaths	HR (95% CI)$_{age\text{-}adjusted}$	HR (95% CI)$_{multivariable\ adjusted}$*	*n* of users/ UTUC deaths	HR (95% CI)$_{age\text{-}adjusted}$	HR (95% CI)$_{multivariable\ adjusted}$*
ACE inhibitors	3450/ 751	0.89 (0.81–0.97)	1.03 (0.94–1.13)	267/123	1.14 (0.90–1.43)	1.48 (1.00–2.21)
ATR-blockers	1409/258	0.76 (0.67–0.87)	0.80 (0.70–0.92)	144/52	0.78 (0.58–1.06)	0.87 (0.54–1.39)
Average yearly dose of ATR-blocker (DDDs/year)						
0–245	475/111	0.97 (0.80–1.18)	0.92 (0.76–1.12)	49/20	1.02 (0.65–1.62)	1.36 (0.63–2.95)
245–392	465/83	0.71 (0.57–0.89)	0.80 (0.64–1.00)	47/16	0.67 (0.40–1.11)	1.13 (0.50–2.58)
392+	467/63	0.58 (0.45–0.75)	0.65 (0.50–0.84)	48/16	0.69 (0.41–1.15)	0.63 (0.33–1.19)
Beta-blockers	5327/1211	0.85 (0.78–0.91)	1.03 (0.95–1.12)	448/189	0.91 (0.73–1.12)	1.15 (0.76–1.75)
Calcium-channel blockers	754/180	0.87 (0.79–0.96)	0.98 (0.88–1.08)	281/116	0.86 (0.68–1.09)	0.77 (0.52–1.15)
Diuretics	4426/1121	1.20 (1.10–1.31)	1.13 (1.04–1.24)	311/149	1.30 (1.04–1.63)	1.20 (0.78–1.83)

*Calculated Cox regression model with adjustments of age, radical surgery, tumor extent, CCI, year of diagnosis, statin, NSAID, aspirin and antidiabetic medication use, kidney failure, COPD and cytostatic drugs.
UC: Urothelial cancer; BCa: Bladder cancer; UTUC: Upper tract urothelial carcinoma; DDD: Defined Daily Dose.

Table 3. Risk of UC death before and after diagnosis by antihypertensive drug use. Separated analyses by gender (men/women).

	Men				Women			
	Before diagnosis		After diagnosis		Before diagnosis		After diagnosis	
Drug group used	HR (95% CI)$_{age\text{-}adjusted}$	HR (95% CI)$_{multivariable\ adjusted}$*	HR (95% CI)$_{age\text{-}adjusted}$	HR (95% CI)$_{multivariable\ adjusted}$*	HR (95% CI)$_{age\text{-}adjusted}$	HR (95% CI)$_{multivariable\ adjusted}$*	HR (95% CI)$_{age\text{-}adjusted}$	HR (95% CI)$_{multivariable\ adjusted}$*
Risk of BCa death								
ACE inhibitors	0.94 (0.84–1.05)	1.13 (1.01–1.27)	0.81 (0.72–0.90)	1.00 (0.90–1.12)	0.85 (0.71–1.00)	0.87 (0.74–1.04)	0.81 (0.67–0.96)	0.92 (0.77–1.10)
ATR blockers	0.76 (0.65–0.90)	0.84 (0.71–1.00)	0.67 (0.57–0.78)	0.79 (0.67–0.93)	0.76 (0.60–0.95)	0.76 (0.60–0.96)	0.74 (0.59–0.93)	0.82 (0.66–1.04)
Beta-blockers	0.91 (0.83–1.00)	1.18 (1.07–1.30)	0.93 (0.85–1.02)	1.14 (1.04–1.25)	0.74 (0.64–0.85)	0.80 (0.69–0.92)	0.81 (0.71–0.93)	0.89 (0.78–1.03)
Calcium-channel blockers	0.82 (0.73–0.93)	0.96 (0.85–1.09)	0.81 (0.71–0.93)	0.91 (0.80–1.05)	0.98 (0.83–1.16)	1.01 (0.85–1.19)	0.93 (0.77–1.12)	1.05 (0.86–1.27)
Diuretics	1.14 (1.02–1.27)	1.05 (0.94–1.17)	1.67 (1.51–1.84)	1.54 (1.40–1.71)	1.19 (1.03–1.37)	1.19 (1.03–1.38)	1.21 (1.05–1.39)	1.18 (1.03–1.36)
Risk of UTUC death								
ACE inhibitors	1.14 (0.83–1.57)	1.66 (0.90–3.06)	0.86 (0.60–1.22)	1.49 (0.79–2.81)	1.16 (0.83–1.62)	1.55 (0.82–2.93)	0.86 (0.58–1.27)	1.06 (0.56–1.99)
ATR blockers	0.94 (0.61–1.45)	0.83 (0.40–1.72)	0.78 (0.50–1.24)	0.91 (0.43–1.93)	0.69 (0.45–1.06)	0.92 (0.46–1.84)	0.85 (0.56–1.29)	1.30 (0.67–2.54)
Beta-blockers	0.69 (0.52–0.92)	1.98 (1.05–3.73)	0.82 (0.62–1.09)	1.14 (0.63–2.06)	1.25 (0.91–1.73)	0.75 (0.39–1.45)	1.14 (0.83–1.56)	1.19 (0.64–2.24)
Calcium-channel blockers	0.91 (0.65–1.26)	0.65 (0.35–1.21)	1.05 (0.77–1.45)	0.74 (0.40–1.38)	0.75 (0.53–1.06)	1.01 (0.55–1.85)	0.97 (0.70–1.34)	1.12 (0.62–2.04)
Diuretics	1.51 (1.10–2.08)	1.78 (0.96–3.30)	1.59 (1.17–2.18)	1.51 (0.75–3.04)	1.14 (0.82–1.59)	0.93 (0.49–1.76)	1.36 (0.98–1.90)	1.23 (0.64–2.34)

*Calculated Cox regression model with adjustments of age, radical surgery, tumor extent, CCI, year of diagnosis, statin, NSAID, aspirin and antidiabetic medication use, kidney failure, COPD and cytostatic drugs.
UC: Urothelial cancer; BCa: Bladder cancer; UTUC: Upper tract urothelial carcinoma; DDD: Defined Daily Dose.

Table 4. Risk of UC death by antihypertensive drug use after UC diagnosis.

		Risk of BCa death		Lag-time		
Drug group	*n* of users/BCa deaths	HR (95% CI)$_{age\text{-}adjusted}$	HR (95% CI)$_{multivariable\ adjusted}$*	1 year	3 years	5 years
BCa						
ACE inhibitors	377/19	0.80 (0.73–0.88)	0.99 (0.90–1.08)	1.06 (0.96–1.17)	0.99 (0.88–1.00)	0.99 (0.88–1.10)
ATR blockers	177/ 4	0.70 (0.61–0.79)	0.81 (0.71–0.92)	0.82 (0.71–0.93)	0.72 (0.61–0.85)	0.72 (0.61–0.85)
Beta-blockers	500/20	0.89 (0.82–0.96)	1.05 (0.97–1.13)	1.09 (1.01–1.18)	1.08 (0.99–1.19)	1.08 (1.00–1.19)
Calcium-channel blockers	127/ 3	0.85 (0.76–0.95)	0.95 (0.85–1.06)	0.93 (0.83–1.05)	0.92 (0.81–1.05)	0.92 (0.81–1.05)
Diuretics	490/30	1.53 (1.41–1.66)	1.42 (1.31–1.54)	1.24 (1.14–1.35)	1.21 (1.10–1.34)	1.21 (1.10–1.34)
UTUC						
ACE inhibitors	179/74	0.87 (0.67–1.12)	1.20 (0.79–1.85)	1.23 (0.81–1.87)	1.39 (0.92–2.12)	1.45 (0.95–2.11)
ATR blockers	130/49	0.81 (0.60–1.11)	1.03 (0.65–1.65)	1.07 (0.66–1.74)	1.08 (0.62–1.87)	0.88 (0.41–1.88)
Beta-blockers	410/178	0.96 (0.78–1.18)	1.06 (0.70–1.59)	1.06 (0.71–1.59)	1.02 (0.70–1.49)	1.09 (0.74–1.59)
Calcium-channel blockers	238/104	1.00 (0.80–1.25)	0.93 (0.62–1.40)	0.93 (0.62–1.40)	0.90 (0.59–1.39)	1.05 (0.66–1.68)
Diuretics	285/146	1.46 (1.17–1.83)	1.47 (0.95–2.28)	1.28 (0.82–2.02)	1.44 (0.91–2.29)	1.32 (0.81–2.15)

*Calculated Cox regression model with adjustments of age, radical surgery, tumor extent, CCI, year of diagnosis, statin, NSAID, aspirin and antidiabetic medication use, kidney failure, COPD and cytostatic drugs.
UC: Urothelial cancer; BCa: Bladder cancer; UTUC: Upper tract urothelial carcinoma; DDD: Defined Daily Dose.

Table 5. Risk of bladder cancer death by cumulative amount, duration and average yearly dose of ATR-blocker use after diagnosis.

	n of users/BCa deaths	Risk of BCa death HR (95% CI)age-adjusted	Risk of BCa death HR (95% CI)$_{multivariable\ adjusted}$*
Amount of use (DDDs)			
0–490	641/148	0.82 (0.70–0.97)	0.90 (0.76–1.06)
490–1764	641/91	0.59 (0.47–0.73)	0.73 (0.59–0.91)
1764+	657/23	0.51 (0.33–0.78)	0.60 (0.39–0.91)
Duration of use (years)			
0–2	601/153	0.69 (0.60–0.80)	0.80 (0.69–0.93)
2–4	245/25	0.71 (0.51–1.00)	0.85 (0.60–1.18)
4+	566/24	0.74 (0.49–1.3)	0.80 (0.52–1.22)
Average yearly dose (DDDs/year)			
0–259	634/135	1.04 (0.87–1.24)	1.04 (0.87–1.24)
259–504	630/98	0.67 (0.54–0.82)	0.79 (0.64–0.97)
504+	632/34	0.35 (0.26–0.48)	0.48 (0.35–0.65)

*Calculated Cox regression model with adjustments of age, radical surgery, tumor extent, CCI, year of diagnosis, statin, NSAID, aspirin and antidiabetic medication use, kidney failure, COPD and cytostatic drugs.
UC: Urothelial cancer; BCa: Bladder cancer; UTUC: Upper tract urothelial carcinoma; DDD: Defined Daily Dose.

Antihypertensive drug use after the UC diagnosis

Post-diagnostic use of ATR-blockers was similarly associated with better BCa survival compared to non-users, and the risk decreased in inverse association with cumulative dose and intensity of use (Table 5). When analysed by gender, ATR-blockers associated with decreased risk of BCa death only among men (p for interaction = .004, Table 3). Also calcium-channel blockers were associated with reduced risk of BCa death as the intensity of use increased (HR = .67, 95% CI = .52–0.86 for 367 DDDs/year or more). However, such risk trend was not found for the duration of calcium-channel blocker use (Table 6). Increased risk of BCa death by diuretics use was observed among both genders (Table 3).

The highest intensity of post-diagnostic beta-blocker use was associated with slightly decreased risk of BCa death (HR = .76, 95% CI = .66–0.87). Diuretics associated with increased risk of BCa death in all intensity analyses, but the risk was highest in lowest intensity of use (HR = 1.64, 95% CI = 1.48–1.81). Risk declined to non-significant level when intensity of use increased.

In UTUC analyses most of the risk differences by anti-HT drug use were not statistically significant. Similar to BCa, high dose as well as high-intensity use of diuretics associated with worse UTUC survival compared to non-users.

Sub-group analyses

We analysed separately the association between post-diagnostic anti-HT drug use on UC death in four sub-groups stratified by potential confounding factors. The analysis was stratified by age at diagnosis, tumour extent at diagnosis, comorbidities and COPD separately, and use of statins. Subgroup analyses in BCa cohort are shown in Figures 1–5.

No effect modification by age was observed for ATR-blocker use, the risk decrease was similar among participants younger than 73 or older. The risk of BCa death among beta-blocker users, however, appeared to be modified by age; the risk was increased in the younger age group only (p for interaction < 0.001). No significant effect modification by age was observed in the UTUC cohort.

Tumour extent at diagnosis modified the association between beta-blocker use and cancer deaths in both study cohorts. Users of beta-blockers had increased risk of death compared to non-users among participants diagnosed with localized tumour, whereas no risk association was observed for participants with advanced disease at diagnosis (p for interaction < 0.001 for BCa and UTUC cohorts, respectively).

Charlson comorbidity index did not modify the risk associations in the BCa cohort. In the UTUC cohort, however, beta-blockers were associated with increased risk of cancer death only among participants with little or no co-morbidities

Table 6. Risk of BCa death by cumulative amount, duration and average yearly dose of calcium-channel blocker use after diagnosis.

	n of users/BCa deaths	Risk of BCa death HR (95%CI)age-adjusted	Risk of BCa death HR (95% CI)$_{multivariable\ adjusted}$*
Amount of use (DDDs)			
0–333	690/210	1.04 (0.90–1.21)	1.14 (0.99–1.33)
333–1200	687/127	0.67 (0.55–0.82)	0.82 (0.67–1.00)
1200+	691/37	0.48 (0.28–0.81)	0.56 (0.33–0.94)
Duration of use (years)			
0–1	686/207	0.83 (0.72–0.95)	0.93 (0.81–1.07)
1–4	814/146	0.93 (0.78–1.12)	1.03 (0.86–1.23)
4+	537/21	0.69 (0.45–1.08)	0.73 (0.47–1.13)
Average yearly dose (DDDs/year)			
0–196	667/155	1.20 (1.02–1.41)	1.26 (1.06–1.48)
196–367	624/113	0.69 (0.56–0.85)	0.91 (0.73–1.13)
367+	678/78	0.61 (0.48–0.78)	0.67 (0.52–0.86)

*Calculated Cox regression model with adjustments of age, radical surgery, tumor extent, CCI, year of diagnosis, statin, NSAID, aspirin and antidiabetic medication use, kidney failure, COPD and cytostatic drugs.
UC: Urothelial cancer; BCa: Bladder cancer; UTUC: Upper tract urothelial carcinoma; DDD: Defined Daily Dose.

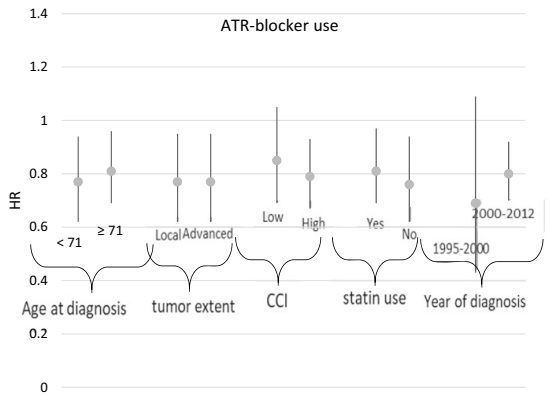

Figure 1. Risk of BCa death among ACE-inhibitor users. Stratified analyses with age at diagnosis, tumor extent, CCI, statin use, and year of BCa diagnosis.

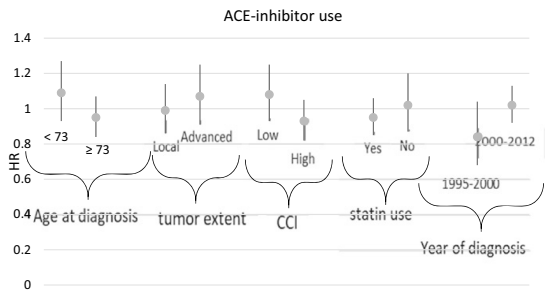

Figure 2. Risk of BCa death among ATR-blocker users. Stratified analyses with age at diagnosis, tumor extent, CCI, statin use, and year of BCa diagnosis.

(p for interaction = .005). On the contrary, ATR-blocker users had a decreased risk of BCa death among participants with high CCI-value (p for interaction < 0.001). No effect modification by CCI was observed in the BCa cohort.

When analysed only among COPD-diagnosed participants the risk estimates for BCa death declined to a non-significant level, but risk estimates among ATR-blocker users stayed decreased compared to non-users. When excluding COPD-participants the risk decrease among ATR-blocker users became statistically significant (HR = .81, 95% CI = .70–0.93).

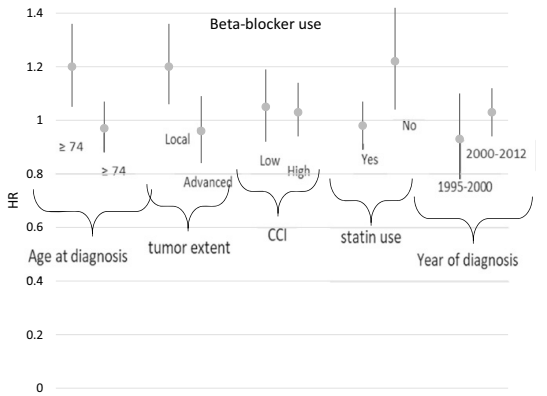

Figure 3. Risk of BCa death among beta-blocker users. Stratified analyses with age at diagnosis, tumor extent, CCI, statin use, and year of BCa diagnosis.

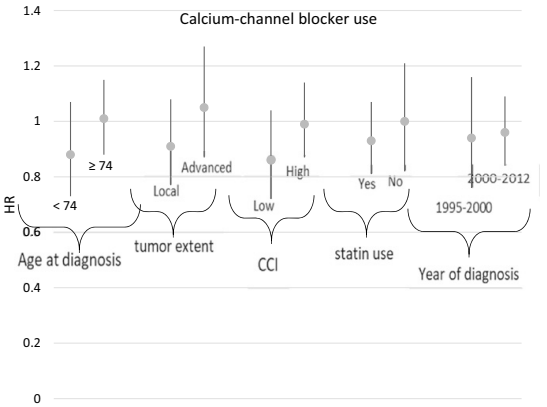

Figure 4. Risk of BCa death among calcium-channel blocker users. Stratified analyses with age at diagnosis, tumor extent, CCI, statin use, and year of BCa diagnosis.

The risk of BCa death was increased in beta-blocker users only among participants also using statins ($p < 0.001$). No effect modification by statin use was observed in the UTUC cohort.

When stratified by year of UC diagnosis, ATR-blockers were associated with better BCa survival only among cases

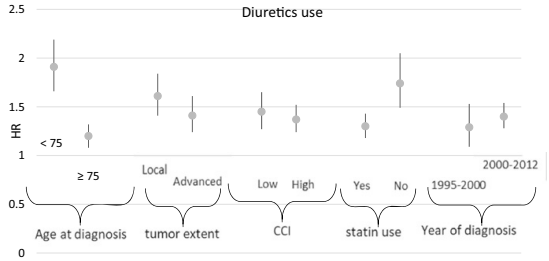

Figure 5. Risk of BCa death among diuretic users. Stratified analyses with age at diagnosis, tumor extent, CCI, statin use, and year of BCa diagnosis.

diagnosed in the 1990s ($p < 0.001$). In the UTUC cohort effect modification by diagnosis year could not be evaluated.

Discussion

To our knowledge this is the first study to compare risk of death due to urothelial cancer by different groups of antihypertensive drugs.

In our BCa cohort post-diagnostic ATR-blocker use generally was associated with better BCa-specific survival compared to non-users. The association was observed in both genders, but when stratified by gender among females for pre-diagnosis usage and among males for post-diagnosis usage. The risk decrease was dose-dependent, being inversely associated with the intensity (yearly dose) of ATR-blocker use. The same dose-dependence was also observed among calcium-channel blocker users. Similar risk trend for multiple groups of antihypertensive drugs with differing mechanisms of action suggests that the common indication, treatment of hypertension, may have a prognostic role in BCa patients. Diuretics instead associated with increased risk of BCa death in all analyses. This is likely affected by diuretics being used also for other causes besides controlling hypertension, such as oedema common in advanced cancer.

Similar risk differences were not observed in the UTUC-cohort. It has to be noted that UTUC is frequently managed with nephroureterectomy, which often leads to renal insufficiency limiting medication use, for example of drugs affecting the RAA-system. Therefore, UTUC patients may not be able to use drugs affecting the RAA-system, which could explain more subtle risk associations compared to the BCa cohort. However, our analyses were adjusted with kidney failure so that there must be another explanation.

All anti-HT drugs except beta-blockers and some diuretics such as furosemide are first-line treatments of hypertension in Finland. Thus, it́s not likely that patients using different groups of anti-HT drugs differ from each other by difficulty of hypertension. On the contrary anti-HT drugs are also used to treat other diseases than hypertension, like coronary artery disease and kidney and heart failure, which may have a confounding effect on results, particularly among beta-blocker and diuretic users. Nevertheless, adjustment for CCI did not remove the risk increase observed among users of diuretics and beta-blockers.

The strengths of our study are long follow-up time and large BCa-cohort consisting of all bladder cancers diagnosed in Finland between 1995 and 2012. Our registry-based data on medication use was exceptionally detailed and free of recall bias. We were able to take into account simultaneous use of different anti-HT drug groups and statins, NSAIDs, aspirin and antidiabetic medication and to adjust the analysis for primary treatment, as anti-HT drug users likely had more comorbidities limiting possibilities for curative-intent surgery. We also adjusted our analyses with year of diagnosis as cancer management has changed over time, possibly modifying the survival associations with anti-HT drug use.

We didn't have information on blood pressure level, i.e. on how well hypertension was managed, which may affect results if hypertension indeed was a prognostic factor. We also didn't know whether anti-HT drugs purchased were actually consumed. Our information on medication use starts in 1995, which likely causes under-estimation of pre-diagnostic medication use. Also low number of BCa and UTUC deaths in our data must be considered because it limits the statistical power in sub-group analyses increasing probability for type 2 error. We didn't have information on tumour grade, which may have caused confounding if anti-HT medication was associated with grade. We didn't have information on socioeconomical or lifestyle factors such as physical activity or smoking, which could have served as confounders depending on their association with antihypertensive medication use and urothelial cancer survival. These factors may partly explain the differing results among ATR-blocker and calcium-channel blocker users compared to other anti-HT drug groups. Nevertheless, selection bias shouldn't be dose-dependent.

In conclusion, ATR-blocker use was associated with better BCa survival both in pre- and post-diagnostic use. The association was dose-dependent. Also high-intensity use of beta-blockers and calcium-channel blockers associated with reduced BCa death risk, which may be partly explained with better control of hypertension. Our study supports further studies on the association between ATR-blockers and BCa progression.

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Disclosure statement

No potential conflict of interest was reported by any of the authors.

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PUBLICATION III

Angiotensin Receptor Blockers Associated with Improved Breast Cancer Survival—A Nationwide Cohort Study from Finland

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Angiotensin receptor blockers associated with improved breast cancer survival- a nationwide cohort study from Finland

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ABSTRACT

Introduction: Breast cancer (BCa) has been associated with hypertension which might adversely affect disease prognosis. It is however unclear whether use of antihypertensive drugs would improve BCa prognosis.

Materials and Methods: A cohort of 73,170 women diagnosed BCa during 1995-2013 identified from the Finnish Cancer Registry and information on anti-HT drug use based on national prescription database during the same time period was combined. Antihypertensive drug use was analysed separately by drug use before and after BCa diagnosis. Analyses were performed using time-dependent usage variables for six antihypertensive drug group, statins, antidiabetic drugs and anticoagulative drugs to model for simultaneous use of multiple drugs. Association between cumulative dose, duration and intensity of antihypertensive drug use and risk of BCa death was evaluated.

Results: In pre-diagnostic use only ATR-blockers associated with decreased risk of BCa death compared to non-users (HR: 0.76 95% CI: 0.69-0.82) and risk decreased in inverse association with cumulative dose and duration of use. Diuretics and furosemide associated with statistically significant increase in BCa death risk.

In post-diagnostic analyses ATR-blockers and also ACE-inhibitors, beta-blockers and calcium-channel blockers were associated with better BCa survival compared to non users. The results were dose-dependent in all mentioned drug groups. The risk decrease was however highest among users of ATR-blockers (HR: 0.69 95% CI: 0.63-0.75).

Conclusions: ATR-blockers were the only antihypertensive drug group associated with improved BCa survival in both pre- and post-diagnostic use. The association was dose-dependent and supported by biological rationale which suggests a direct, causal explanation. However, for post-diagnostic use similar lowering was found also for other antihypertensive groups which also supports prognostic role of hypertension control. Risk estimates for post-diagnostic ATR-blocker use were however lower compared to others drug groups. Inhibiting angiotensin receptor could be a promising novel way to affect risk of breast cancer progression.

INTRODUCTION

Breast cancer (BCa) is the most common cancer among women worldwide and it causes huge losses in life-expectancy. BCa is mainly a women´s disease but few new cases are diagnosed also among men yearly(1).

Many modifiable risk factors for BCa diagnosis have been observed such as smoking and use of oral contraceptives (2) (3) (4) . Metabolic factors such as hypertension, high blood glucose and abdominal obesity are also linked with higher BCa risk and impaired prognosis (5) (6), whereas physical exercise may decrease risk of BCa death (7). Hypertension is very common among breast cancer patients (8). It is unclear whether use of antihypertensive medication could decrease the risk of BCa diagnosis or improve disease prognosis. One study has reported higher BCa incidence among women using calcium-channel blockers (9) and another study for antihypertensive drug use in general (10) . Many studies have found no association between antihypertensive drug use and BCa incidence (11) (12) (13) .

To our knowledge only few previous studies have explored antihypertensive drug use as risk factor for BCa death. Beta-blocker use has been associated with better BCa survival compared to non-users (14) but not all studies agree (15). No clear association has been found with other antihypertensive drugs and risk of BCa death (16) (17). A big challenge is to take into account simultaneous use of multiple drug groups and comorbidities as these are common in antihypertensive drug users. It is also important to try to separate the direct influence of a drug from the indirect influence of underlying conditions such as obesity among hypertensive participants.

Here we analyse the association between antihypertensive drug use and BCa death among Finnish women in a large nationwide cohort taking into account these challenges.

MATERIALS AND METHODS

Study cohort

The study cohort was identified from the Finnish Cancer Registry (FCR) which registers new cancer diagnoses in Finland by obligatory reports from all health care units (18).

A total of 73,170 new BCa cases among women were obtained from the database. Cases were diagnosed between 1995-2013. Data contained information on date and method of diagnosis, tumor extent at diagnosis (recorded in the registry as local, advanced into regional lymph nodes, advanced, no information), information on participation in national mammography screening program, histology of tumor (ductal, lobular,other, unknown) and primary treatment (surgery, other). The data also included dates and causes of cancer death as well as all-cause deaths until the end of 2015. In Finnish national mammography screening program every 50-69 year old women is invited to free breast x-ray imaging study every second year to screen for BCa.

Information on antihypertensive medication use

The cohort was linked to national prescription database maintained by the Finnish Social Insurance Institution (SII) for information on anti-HT drug use during 1995-2013. It provides reinbursements for drug purchases in outpatient setting for every Finnish citizen. Drugs used in hospitals are not recorded. The information on each purchase includes the date, package size, number of packages and dose for each purchase.

Antihypertensive drugs were identified using unique ATC-codes (Table S1). They were divided into six different groups based on the mechanism of action: angiotensin- converting enzyme (ACE) inhibitors, angiotensin- receptor (ATR) blockers, furosemide, other diuretics, beta-blockers and calcium- channel blockers. The other diuretics group includes thiazides and potassium-sparing diuretics but not furosemide as it is mostly used for management of oedema rather than hypertension.

Information on co-morbidities

The cohort was linked to nationwide Care Registry (HILMO) which is maintained by the Finnish Institute for Health and Welfare (THL) for information on diagnoses and procedures in the cohort population during 1995-2013. The Registry records all diagnoses and medical procedures from in- and outpatient hospital visits in Finland. Diagnoses recorded in HILMO were used to calculate

Charlson co-morbidity index for each participant (19). Conditions used in the index calculation are listed in Table S2.

Information on hormone receptor status

Information on tumor pathological characteristics was supplemented from archives of pathology departments of university hospitals in Tampere and Turku, two of the largest cities in Finland. Information on estrogen-receptor (ER), progesterone-receptor (PR) and human epidermal growth factor- receptor 2 (HER2) status was obtained from the databases. These were used in subgroup analyses to evaluate possible effect modification by hormone receptor status.

Statistical analyses

Analyses were run separately for drug use before and after BCa diagnosis. Risk of BCa death was compared between antihypertensive drugs users and non-users in a model including all antihypertensive drug groups simultaneously.

The total yearly mg amount of each antihypertensive drug was calculated for each participant based on the dosing, package size and number of packages from each purchase. Total purchased yearly mg amount was divided by the dose corresponding to the drug specific Defined Daily Dose (DDD) for total number of DDDs purchased per year (20). Each year with any recorded purchase was considered as year of usage regardless of the purchased amount.

Cumulative number of usage years and DDDs was calculated separately for each year before and after BCa diagnosis. Amount of use before the diagnosis was calculated by adding together all usage between 1995 and the year of BCa diagnosis. Intensity (DDDs/year of use) was evaluated by dividing cumulative amount of DDDs with cumulative number of usage years.

Post-diagnostic use was analysed as time-dependent variable to control for immortal time bias. Time-dependent variables were formed by updating medication user status as well as cumulative amount, duration and intensity of use separately for each follow-up year after BCa diagnosis according to recorded purchases. Dose-dependence was evaluated by categorizing medication users in three groups (tertiles) by DDD amount, duration and intensity of use based on the level reached on each follow-up year. It´s important to notice that after discontinuation of usage the participants remained in the user category to minimize error based on selective discontinuation of medication for example in advanced stage of BCa.

Cox regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the risk of BCa-specific death. Time metric was years since BCa diagnosis. Follow up continued until death, emigration or the closing date Dec 31st, 2015. Cox regression analyses were adjusted for age at diagnosis, tumor extent at diagnosis, primary treatment of BCa (surgery, other), obesity, CCI, participation in national BCa screening program and use of hormone-antagonist therapy after BCa diagnosis.

Simultaneous use of multiple antihypertensive drug groups was modelled forming separate time-dependent variables for every six antihypertensive drug group as also for possible confounders statins, antidiabetic and anticoagulative drugs use in post-dg analyses. These variables were included in the Cox regression model together to model simultaneous usage.

Latency of the risk association between antihypertensive drug use and BCa death was evaluated in lag time analyses where the exposure was lagged forward in the follow-up time analysing medication use that occurred one, three or five years earlier as the exposure.

The data were analysed using the IBM SPSS statistics 25 program.

RESULTS

Population characteristics

Antihypertensive drug use was very common in our breast cancer cohort as 36,427 (49.8%) women had used at least one groups of antihypertensive medication during the follow up (Table 1). Only total of 11,258 (15.4%) BCa had been found in BCa screening program. Antihypertensive drug users were older at diagnosis and also at time of BCa death and they also used more statins and antidiabetic drugs compared to non-users. A total of 10,900 women died of BCa during the follow-up of which 4542 (124/1000) among non-users and 6358 (175/1000) among antihypertensive drug users.

Antihypertensive drug usage before BCa diagnosis

In pre-diagnostic age-adjusted analysis use of ACE-inhibitors, ATR-blockers and beta-blockers was associated with statistically significant reduction in BCa death risk (Table 2). However in multivariable adjusted analysis only use of ATR-blockers remained associated with reduced risk of BCa death (HR: 0.76 95% CI: 0.69-0.82). When analyzing the amount of use among ATR-blockers, risk of BCa death decreased in association with increasing amount of dose, duration and intensity

of ATR-blocker use (Table 2). Similar results were not seen with other antihypertensive drug groups. Only low intensity of beta-blocker use associated with better BCa survival (HR: 0.86 95% CI: 0.79-0.93). Furosemide and other diuretics use associated with increased risk of BCa death in high intensity of use.

Antihypertensive drug use after the BCa diagnosis

Use of all antihypertensive drugs except furosemide and other diuretics was associated with decreased risk of BCa death in age-adjusted analyses. Also in multivariable-adjusted analysis use of ATR-blockers, beta-blockers and calcium-channel blockers associated with better BCa survival compared to non-users (Table 3). The risk estimates were lowest among ATR-blocker users (HR: 0.77 95% CI: 0.71-0.84). Furosemide associated with statistically significant increase in BCa death risk. When analyzing cumulative dose and intensity of antihypertensive drug use ACE-inhibitors, ATR-blockers, beta-blockers and calcium-channel blockers associated with statistically significant decrease in BCa death risk (Table 4). The risk decrease was dose-dependent among ACE-inhibitors, beta-and calcium-channel blockers and decreased in inverse association with increasing dose and intensity of use. Furosemide associated with increased risk of BCa death and the risk estimates were highest for lowest dose and intensity and shortest duration of use; risk decreased in association with dose, intensity and duration but stayed elevated in all groups (Table 4). The same direction results were observed also for other diuretics. When analyzing duration of antihypertensive drug use the same direction results were seen in all drug groups; the risk of BCa death was lowest with longest duration of use in all six antihypertensive drug groups.

In lag-time analyses a decreased risk of BCa death among ATR-blocker users persisted after time lag of one and three years but not longer (Table 3). Calcium-channel blockers associated with reduced BCa death risk after three and five years´ lag-time. Use of furosemide associated with increased BCa death risk in one years´ lag-time. Other antihypertensive drugs did not have effect on BCa survival in lag-time analyses.

Subgroup analyses

We evaluated the association between post-diagnostic antihypertensive drug use and risk of BCa death also stratified by hormone-receptor status. The groups and results are shown in Table 5. ACE-inhibitors and calcium-channel blockers were associated with decreased risk of BCa death among HER-negative (cancer cells do not express HER2) women and ACE-inhibitors also among

triple negative (cancer cells do not express ER, PR or HER2) women. Other diuretics associated with reduced risk among HER-positive (cancer cells express only HER2) women.

DISCUSSION

ATR-blockers differ from other antihypertensive drugs as they were associated with dose-dependent improvement in BCa survival both in pre-and post-diagnostic use compared to non-users. That could indicate a causal risk association, supporting prognostic role of angiotensin-receptor inhibiton.

ACE-inhibitors and ATR-blockers both inhibit renin-angiotensin aldosterone system (RAA-system). However ATR-blockers block selectively only AT_1-receptor (angiotensin-receptor subtype 1) and leave others (for example angiotensin-receptor subtype 2) free while ACE-inhibitors block the whole pathway by inhibiting formation of angiotensin. Mechanism of action in ATR-blockers thus leads to angiotensin activating only AT_2-receptors which in turn has been proved to induce apoptosis for example in heart endocardial endothelial cells (24).

In post-diagnostic analyses also beta-blockers and calcium-channel blockers were associated with better BCa survival compared to non users. The same direction results were seen also among ACE-inhibitors. The results among cumulative use, duration and intensity of use were dose-dependent and statistically significant in all antihypertensive drugs with different mechanisms of action. This may indicate that the underlying condition i.e. hypertension partly explains the results and better control of hypertension might improve BCa prognosis.

Use of furosemide and other diuretics associated with elevated risk of BCa death. The risk of BCa death decreased with increasing intensity of furosemide and diuretics use. Furosemide is not primarily used to control hypertension but to treat oedema or heart failure for example. Conditions like oedema are frequent in terminal BCa which could explain the result. Other diuretics are also used to treat i.e. heart failure and are not recommended as first-line treatment for hypertension alone. The dose-dependence can be explained by lowering dose of furosemide in advanced stage of heart failure or cancer when any response for drug is not achieved. Time period of furosemide use is also short in advanced cancer compared to chronic heart failure for example which might explain better survival when duration of use increases.

There are only a few previous studies on the association between antihypertensive drugs and risk of BCa death. Our results are partly same direction as beta-blockers associated with better BCa

survival in this study as in previous studies also (14, 21, 22, 23). However we evaluated separately association in pre-and post-diagnostic use while previous studies have concentrated on antihypertensive drug use general (use or not use) or only pre-diagnostic use during the follow-up. Previous studies have also not reported better BCa survival among ATR-blockers or ACE-inhibitor users even when evaluated separately.

The strength of our study was our reliable registry-based data on drug use which was detailed and free of bias (18) (25). We also had a long follow-up time and large national cohort consisting of all BCas diagnosed in Finland between 1995-2013. We were able to take into account simultaneous use of different antihypertensive drugs, statins, anticoagulative drugs and antidiabetic drugs, thus controlling for possible confounding. We were also able to adjust the analysis for primary treatment as antihypertensive drug users likely had more comorbidities limiting possibilities for curative surgery. However we managed to evaluate comorbidities also with CCI.

We didn´t have information on blood pressure levels which may affect results if hypertension is a prognostic factor. However we take into account simultaneous use of different antihypertensive drug groups so that role of hypertension should be seen in all groups. We did not have information if drugs purchased were actually consumed. We didn´t have information on socioeconomical or lifestyle factors such as physical activity, smoking, BMI or nutrition which could have served as confounders depending on their association with BCa survival. Compared to other antihypertensive drugs ATR-blockers are the newest drug group and use of ATR-blockers has come more general during the 90s in Finland. ATR-blockers have been more expensive at least in the 80s so that e.g. socioechonomical and lifestyle factors behind could at least partly explain the differing results among ATR-blockers especially compared to ACE-inhibitors.

In conclusion pre-diagnostic use of ATR-blockers associated with better BCa survival compared to non-users. In post-diagnostic use ATR-blockers, beta-blockers and calcium-channel blockers associated with better BCa survival. The association found was strongest among ATR-blockers which may indicate a molecular mechanism. However underlying better control of hypertension may partly explain the same direction results in many different drug groups and it may have prognostic role in BCa. More research particularly comparing ACE-inhibitors and ATR-blockers in mice or in tumour cells is needed to compare possible differences in responses to RAA-system pathway inhibition which could explain results in BCa survival.

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Table 1. Population characteristics.

	Non-users	ACE-inhibitors	ATR-blockers	Beta-blockers	Calcium-channel blockers	Furosemide	Other diuretics
n of women	36,743	20,742	16,552	33,611	20,367	18,347	33,753
BCa found in national screening program (%)	11,258 (30.6)	5180 (25.0)	4795 (29.0)	8162 (24.3)	4654 (22.9)	2799 (15.3)	7440 (22.0)
Median follow time years (IQR)	5.8 (0-20.01)	6.3 (0-21.01)	6.6 (0-19.85)	6.2 (0-21.01)	6.2 (0-21.01)	5.6 (0-19.93)	5.8 (0-19.53)
n of BCa deaths (% of users)	4542 (12.4)	2500 (12.1)	1314 (7.9)	4416 (13.1)	2474 (12.1)	4133 (22.5)	6077 (18.0)
n of all deaths (% of users)	7495 (20.4)	7080 (34.1)	3653 (22.1)	11,270 (33.5)	6997 (34.4)	10,288 (56.1)	14,269 (42.2)
Charlson comorbidity index points:							
0	28,594	14,220	11,587	23,600	14,146	11,582	23,332
1	1248	1511	1245	2145	1542	1348	2200
2 or over	6901	5011	3720	7866	4679	5417	8221
Age at diagnosis, median (IQR)	56(18-104)	67 (27-102)	64 (23-102)	66 (20-102)	68 (24-102)	71 (20-104)	67 (20-105)
Age at death (IQR)	65 (20-108)	76 (34-104)	73 (28-103)	74 (22-105)	77 (33-106)	79 (27-107)	76 (27-107)
Tumor extent at diagnosis, n(%)							
Localized	18,538 (50.5)	10,744 (51.8)	8825 (53.3)	17,227 (51.3)	10,589 (52.0)	8394 (45.8)	16,448 (48.7)
Locally advanced	12,441 (33.9)	6456 (31.1)	5227 (31.6)	10,681 (31.8)	6323 (31.0)	6081 (33.1)	10,988 (32.6)
Advanced	2877 (7.8)	1665 (8.0)	1080 (6.5)	2708 (8.1)	1572 (7.7)	1994 (10.9)	3127 (9.3)
Unknown	2877 (7.8)	1877 (9.0)	1420 (8.6)	2995 (8.9)	1903 (9.3)	1878 (10.2)	3190 (9.5)
Surgery a part of treatment, n	25,125	13,760	11,161	22,298	13,461	11,624	21,975
PostBCa hormone antagonist use, n	15,059	6745	5568	11,573	6603	6488	11,946
Statin use, n (%)	2809 (7.6)	6425 (31.0)	4990 (30.1)	9480 (28.2)	6549 (32.2)	4884 (26.6)	8904 (26.4)

Antidiabetic medication use; n (%)	2776 (7.6)	6260 (30.2)	4418 (26.7)	7766 (23.1)	5612 (27.6)	4976 (27.1)	8368 (24.8)

IQR= interquartile range, n= number, locally advanced: advanced only to regional lymphnodes, advanced: advanced widely than to regional lymphnodes. BCa=breast cancer

Table 2. Risk of breast cancer death by antihypertensive drug use before BCa diagnosis.

		Risk of BCa death	
Drug group	n of users/BCa deaths	HR (95% CI)$_{age\text{-}adjusted}$	HR (95% CI)$_{multiavariable\ adjusted*}$
ACE inhibitors	11,216/1545	1.01 (0.95-1.07)	1.00 (0.94-1.06)
ATR-blockers	7411/684	0.77 (0.71-0.84)	0.76 (0.69-0.82)
Average yearly dose of ATR-blocker (DDDs/yr)			
0-252	2489/277	0.87 (0.77-0.98)	0.82 (0.73-0.93)
252-394	2453/225	0.72 (0.63-0.83)	0.72 (0.63-0.82)
394→	2469/182	0.70 (0.60-0.81)	0.71 (0.61-0.82)
Beta-blockers	20,312/2831	0.92 (0.87-0.96)	0.95 (0.91-1.00)
Calcium-channel blockers	11,657/1644	0.94 (0.88-0.99)	0.98 (0.93-1.04)
Furosemide	6609/1186	1.35 (1.25-1.45)	1.26 (1.17-1.35)
Other diuretics	19,179/2990	1.07 (1.00-1.13)	1.07 (1.01-1.14)

ACE= angiotensin-converting enzyme, ATR= angiotensin-receptor, DDD= defined daily dose, HR= hazard ratio, CI= confidence interval. *= calculated cox regression model with adjustments of age at diagnosis, tumor extent, charlson-comorbidity index, primary treatment of BCa, obesity, participation in national screening program and use of hormone-receptor antagonists after BCa dg

Table 3. Risk of BCa death by antihypertensive drug use after BCa diagnosis.

		Risk of BCa death		Lag-time		
Drug group	n of users/BCa deaths	HR (95% CI)$_{\text{multiavariable adjusted*}}$	HR (95% CI) age-adjusted	1 year	3 years	5 years
ACE inhibitors	7467/1116	0.94 (0.88-1.00)	0.92 (0.86-0.98)	0.96 (0.90-1.03)	0.97 (0.90-1.05)	1.02 (0.93-1.11)
ATR blockers	6669/591	0.77 (0.71-0.84)	0.69 (0.63-0.75)	0.79 (0.72-0.86)	0.84 (0.76-0.93)	0.90 (0.78-1.02)
Beta-blockers	15,330/2280	0.93 (0.88-0.98)	0.92 (0.88-0.97)	0.96 (0.91-1.01)	0.98 (0.93-1.04)	0.97 (0.91-1.03)
Calcium-channel blockers	8553/1281	0.93 (0.87-0.99)	0.93 (0.88-0.99)	0.96 (0.90-1.02)	0.92 (0.86-0.99)	0.91 (0.84-0.99)
Furosemide	5902/1269	1.22 (1.13-1.32)	1.63 (1.51-1.76)	1.14 (1.06-1.23)	1.00 (0.92-1.10)	1.01 (0.90-1.13)
Other diuretics	16,226/2785	1.02 (0.96-1.08)	1.05 (0.99-1.11)	1.05 (0.99-1.12)	1.05 (0.99-1.12)	1.00 (0.93-1.08)

ACE= angiotensin-converting enzyme, ATR= angiotensin-receptor, DDD= defined daily dose, HR= hazard ratio, CI= confidence interval. *= calculated cox regression model with adjustments of age at diagnosis, tumor extent, statins, antidiabetic medication, antikoagulative drugs, charlson-comorbidity index, primary treatment of BCa, obesity, participation in national screening program and use of hormone-receptor antagonists after BCa dg

Table 4. Risk of BCa death by antihypertensive drug use after BCa diagnosis. Risk esimates by cumulative dose, duration and intensity of anti-HT drug use.

	Antihypertensive drug groups, HR (95% CI)*					
Amount of use DDDs	ACE-inhibitors	ATR-blockers	Beta-blockers	Calcium-channel blockers	Furosemide	Other diuretics
1st tertile	1.03 (0.96-1.12)	0.79 (0.73-0.86)	1.16 (1.10-1.23)	1.07 (1.00-1.15)	4.02 (3.79-4.26)	1.71 (1.62-1.80)
2nd tertile	0.85 (0.78-0.91)	0.70 (0.63-0.79)	0.88 (0.82-0.94)	0.85 (0.78-0.92)	2.44 (2.27-2.61)	1.09 (1.02-1.17)
3rd tertile	0.80 (0.71-0.90)	0.82 (0.69-0.96)	0.87 (0.80-0.95)	0.68 (0.60-0.77)	1.52 (1.38-1.67)	0.99 (0.90-1.07)
Duration of use (years)	ACE-inhibitors	ATR-blockers	Beta-blockers	Calcium-channel blockers	Furosemide	Other diuretics
1st tertile	0.95 (0.89-1.02)	0.74 (0.68-0.80)	1.05 (1.00-1.11)	0.99 (0.93-1.06)	3.57 (3.38-3.78)	2.34 (2.22-2.45)
2nd tertile	0.86 (0.78-0.94)	0.82 (0.73-0.93)	0.92 (0.84-1.00)	0.85 (0.78-0.93)	2.38 (2.20-2.57)	1.46 (1.36-1.56)
3rd tertile	0.82 (0.72-0.93)	0.82 (0.69-0.98)	0.90 (0.81-1.00)	0.75 (0.65-0.87)	1.64 (1.48-1.82)	1.30 (1.17-1.45)
Intensity of use, (DDDs/year)	ACE-inhibitors	ATR-blockers	Beta-blockers	Calcium-channel blockers	Furosemide	Other diuretics
1st tertile	1.06 (0.98-1.16)	0.94 (0.86-1.03)	1.26 (1.18-1.34)	1.16 (1.08-1.25)	3.84 (3.62-4.07)	1.92 (1.81-2.04)
2nd tertile	0.96 (0.88-1.04)	0.69 (0.62-0.77)	0.99 (0.92-1.05)	0.94 (0.86-1.02)	2.63 (2.44-2.84)	1.14 (1.06-1.23)
3rd tertile	0.73 (0.66-0.80)	0.62 (0.55-0.71)	0.82 (0.77-0.88)	0.62 (0.56-0.69)	1.76 (1.62-1.91)	1.06 (0.99-1.13)

1st tertile= lowest dose/duration/ intensity of use, 2nd tertile= between lowest and highest dose/duration/intensity of use, 3rd tertile= highest dose/duration/intensity of use. ACE= angiotensin-converting enzyme, ATR= angiotensin-receptor, DDD= defined daily dose, HR= hazard ratio, CI= confidence interval. *= calculated cox regression model with adjustments of age at diagnosis, tumor extent, charlson-

comorbidity index, primary treatment of BCa, obesity, participation in national screening program and use of hormone-receptor antagonists after BCa dg.

Table 5. Risk of BCa death among different antihypertensive drug use based on hormone-receptors.

Antihypertensive drug group	Risk of BCa death by hormone-receptor status (HR, 95% CI)*							
	ER-	ER+	PR-	PR+	HER2-	HER2+	All neg	All pos
ACE-inhibitors	0.60 (0.32-1.02)	0.81 (0.62-1.07)	0.73 (0.49-1.09)	0.81 (0.58-1.12)	0.63 (0.49-0.82)	1.49 (0.89-2.49)	0.45 (0.21-0.97)	1.52 (0.56-4.14)
ATR-blockers	0.60 (0.35-1.00)	0.85 (0.61-1.18)	0.76 (0.51-1.15)	0.89 (0.61-1.31)	0.80 (0.61-1.05)	0.95 (0.48-1.89)	0.53 (0.29-1.00)	0.22 (0.03-1.88)
Beta-blockers	1.18 (0.83-1.68)	0.97 (0.79-1.20)	1.01 (0.78-1.31)	1.06 (0.83-1.35)	1.04 (0.87-1.23)	1.00 (0.66-1.52)	1.07 (0.69-1.67)	0.64 (0.27-1.56)
Calcium-channel blockers	0.97 (0.63-1.49)	0.81 (0.62-1.06)	0.76 (0.55-1.06)	0.85 (0.62-1.16)	0.76 (0.61-0.95)	0.93 (0.56-1.54)	1.13 (0.66-1.95)	1.53 (0.52-4.50)
Furosemide	1.53 (0.91-2.60)	1.48 (1.08-2.04)	1.25 (0.85-1.84)	1.61 (1.10-2.36)	1.49 (1.15-1.93)	2.32 (1.12-4.77)	1.09 (0.58-2.05)	3.26 (0.80-13.30)
Other diuretics	1.11 (0.71-1.73)	0.92 (0.71-1.18)	1.18 (0.86-1.63)	0.88 (0.65-1.20)	0.97 (0.78-1.20)	0.51 (0.28-0.93)	1.37 (0.83-2.28)	0.45 (0.16-1.28)

ER-=estrogen- receptor negative, ER+=estrogen- receptor positive, PR-=progesterone- receptor negative, PR+= progsterone -receptor positive, HER2-= HER2 -negative, HER2+= HER2 -positive, All neg= All three receptors (ER,PR, HER2) negative, All pos= All three receptors positive. ACE= angiotensin-converting enzyme, ATR= angiotensin-receptor, DDD= defined daily dose, HR= hazard ratio, CI= confidence interval. *= calculated cox regression model with adjustments of age at diagnosis, tumor extent charlson-comorbidity index, primary treatment of BCa, obesity, participation in national screening program and use of hormone-receptor antagonists after BCa dg.

PUBLICATION IV

Antihypertensive Drug Use and the Risk of Ovarian Cancer Death among Finnish Ovarian Cancer Patients—A Nationwide Cohort Study

Santala, E. E., Artama, M., Pukkala, E., Visvanathan, K., Staff, S., & Murtola, T. J.

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Article

Antihypertensive Drug Use and the Risk of Ovarian Cancer Death among Finnish Ovarian Cancer Patients—A Nationwide Cohort Study

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Simple Summary: According to the literature, antihypertensive drugs may affect the survival of ovarian cancer patients. We examined the association between different groups of antihypertensive drugs and ovarian cancer survival taking into account dose and duration of use as well as the simultaneous use of other drugs. With a 5-year follow-up, antihypertensive drugs were not associated with survival from ovarian cancer but with 10-year follow-up, ACE-inhibitors and with longer follow-up times also other antihypertensive drugs were associated with improved survival from ovarian cancer. The association between ACE-inhibitor use and ovarian cancer survival should be clarified in the future.

Abstract: Ovarian cancer (OC) has a poor prognosis. Hypertension may be a prognostic factor for OC, but it is unclear whether antihypertensive (anti-HT) drug use of modifies OC prognosis. We performed a population-based analysis assessing the effect of anti-HT drug use on OC mortality. A cohort of 12,122 women identified from the Finnish Cancer Registry with OC in 1995–2013 was combined with information on their anti-HT drug use during the same time period. Use of each anti-HT drug was analysed as a time-dependent variable. Analyses were run for five, ten and full follow-up (19-year) mortality with cardiovascular morbidity risk evaluated in competing risk analysis. No anti-HT drug group was associated with OC survival within five years after OC diagnosis. At ten years, a dose-dependent association was observed between pre-diagnostic ACE-inhibitor use and improved OC survival. With full follow-up, post-diagnostic high-intensity use associated with reduced OC death risk for multiple anti-HT drug groups. In competing risk analysis, only the post-diagnostic use of ACE-inhibitors associated with increased OC survival. Anti-HT drugs were not associated with survival benefits within five years after OC diagnosis. ACE-inhibitors may confer survival benefits in women with OC, but further confirmatory studies are needed.

Keywords: antihypertensive drugs; ovarian cancer survival; risk of cancer death; ACE-inhibitors

1. Introduction

Ovarian cancer (OC) is the eighth most common cancer and the second most common gynecological cancer after endometrial cancer suffered by Finnish women [1]. It has a poor prognosis with the majority of deaths occurring during the first five years after diagnosis.

Subsequently, there is a deceleration in the relative survival rate [2,3]. Unfortunately, the diagnosis of OC is often delayed, and disease prognosis is very poor in comparison to other gynecological cancers [1].

There are multiple histological subtypes of OC but the most common is high-grade serous carcinoma (HGSC) which is often diagnosed at an advanced stage. HGSC is responsible for the majority of all OC deaths and is one of the leading causes of death in women [4,5]. In addition to tumor histology, other prognostic factors are tumor extent, residual disease minimizing cytoreductive surgery, the patient's performance status as well as genetics such as BRCA-gene positivity which is associated with a slightly improved OC patient survival as compared to those who are BRCA negative [6].

Hypertension is not thought of as an independent risk factor for OC or cancer in general [7,8] but it has been associated with shorter overall survival among women with OC [9]. Antihypertensive (anti-HT) drugs may be beneficial in OC either via the systemic control of hypertension or other cardiovascular diseases or by some unknown beneficial mechanism of action directly against cancer cells. Beta-blockers and especially non-selective beta-blockers have been associated with better OC specific and overall survival [10–13], though not all investigators have been able to confirm this association [14–16]. According to one report, angiotensin-converting enzyme (ACE)-inhibitors, another anti-HT drug group with a different mechanism of action, might improve OC survival [16]. Angiotensin-receptor (ATR)-blockers, but not other anti-HT drugs, have also been associated with a longer recurrence-free time in patients with epithelial OC [17]. In vitro telmisartan, an angiotensin-receptor blocker, was demonstrated to inhibit cell proliferation and induce apoptosis in ovarian cancer cells [18]. The expression level of the AT_1-receptor (a target of ATR-blockers) in OC cells correlates with poor prognosis and reduced OC survival [19].

In order to estimate effect of any single anti-HT drug group on OC survival, it is essential to take into account the simultaneous use of anti-HT drugs and other drugs some of which may be potential confounders. By adopting this kind of approach, one can evaluate the underlying role of hypertension as it is the common indication of use for all anti-HT drugs; possible confounding by indication (i.e., hypertension) should affect all anti-HT drugs similarly regardless of their antihypertensive mechanism of action. On the other hand, if the risk association should be evident for one particular drug group with a distinct mechanism of action different from the other anti-HT drug groups, this would argue in favor of a molecular effect of this drug group to combat cancer progression. In addition, when evaluating the dose-dependence between drug use and OC survival, the amount of consumed drug should be taken into account although this has not been assessed in previous investigations. Due to the poor prognosis of OC, also the duration of follow-up time might affect risk estimates and should be considered. In previous studies, follow-up times have varied between 6 to 15 years.

Here we have analysed the impact of anti-HT drug use on OC mortality taking into account simultaneous use of multiple drug groups, the cumulative amount of use and also the follow-up time. In order to test whether follow-up time modified the risk associations, we analysed separately five-year and ten-year mortality as well as the risk of OC death with the full follow-up time (maximum 19 years). Our working hypothesis was that the RAA-affecting drugs and beta-blockers might be able to improve the survival of OC patients.

2. Materials and Methods

2.1. Study Cohort

A cohort of 12,122 ovarian cancer cases was obtained from the Finnish Cancer Registry (FCR) database [20]. The database includes all ovarian cancer diagnoses made in Finland during 1995–2013 via mandatory reports from health care units. The data contain information on the date of OC diagnosis, tumor extent at diagnosis (categorized as localized, locally advanced, distally advanced, advanced to unknown extent, unknown), primary cancer treatment as well as date and cause of death obtained from the national registry of Statistics Finland.

We also obtained the number of 1st degree relatives (children, siblings and parents) from Statistics Finland. These were linked with Cancer Registry to obtain OC and breast cancer (BCa) cases among these individuals. This information was used to estimate the inherited cancer risk, for example due to BRCA 1 and 2 mutations [21]. The number of biological children was assessed because pregnancy and breastfeeding have been associated with a reduced OC risk [22,23]. From the birth date of the first child, we calculated the women's age at time of first labour, a factor claimed to influence the OC risk [24].

2.2. Information on Anti-HT Medication Use

The OC data were linked to the national prescription database maintained by the Finnish Social Insurance Institution (SII) to evaluate anti-HT drug use of the OC patients during the follow-up period 1995–2013. Information on statin and antidiabetic medication use was also obtained to evaluate simultaneous use. SII collects information on all prescribed drugs purchased in an outpatient setting as it provides reimbursements of prescribed drugs for every Finnish citizen. Over-the-counter drugs and drugs consumed in an in-patient setting, for example in hospitals, are not recorded in this database. Information of every purchase includes package size, number of packages bought, dose and the date of purchase.

Information on anti-HT drugs was obtained from the database using unique ATC-codes (Table S1). Anti-HT drugs were divided into six different groups based on their mechanism of action: angiotensin-converting enzyme (ACE) inhibitors (inhibiting ACE), angiotensin-receptor (ATR) blockers (blockade of the AT_1-receptor), beta-blockers (blocking B_2- and B_1-receptor or only B_1-receptor), calcium-channel blockers (block Ca^{2+}-influx in smooth muscle cells), furosemide and other diuretics (both increase diuresis although through different mechanisms). Furosemide was assessed separately because it is not primarily used for the treatment of hypertension.

2.3. Statistical Analyses

Anti-HT medication use was determined separately for usage before and after OC diagnosis. The aim was to evaluate the effect of different anti-HT drug use on OC mortality comparing users and non-users. No restrictions by diagnosis of hypertension were made: users of each anti-HT drug group were compared to non-users of anti-HT drugs.

First, a total yearly mg amount for each anti-HT drug for each participant was calculated based on yearly anti-HT drug purchases obtained from the SII-database. Then, the yearly anti-HT drug amount was divided by the drug-specific Defined Daily Dose (DDD) amount to allow a calculation of the total number of doses for each anti-HT drug group [25]. To estimate the use before the diagnosis, DDDs were calculated from 1995 to the year of the OC diagnosis and for the use after the diagnosis, between the year of the OC diagnosis and death/emigration/closing date 31 December 2013, whichever came first.

The intensity of anti-HT drug use was evaluated by dividing the cumulative number of DDDs with the duration of use separately for use before and after the diagnosis.

When estimating the risk of OC death according to the amount of dose, duration and intensity of anti-HT drug use, the participants were divided into three equal size groups based on the cumulative amount of DDDs, duration and intensity of use.

In post-diagnostic analyses, anti-HT medication use was evaluated as a time-dependent variable. User status (non-user/user) was formed for each follow-up year separately. Participants remained as non-users until the year of first drug purchase. All calendar years with any amount of use were recorded as usage years. After anti-HT drug use had been discontinued, participants remained in the user category to avoid bias caused by selective discontinuation of drugs, for example anti-HT drugs are not used in the palliative care of advanced cancer or heart failure [26].

Cox regression analyses was used in the calculation of hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between anti-HT use and the risk of OC death. Follow-up time continued until emigration, death or the closing date of 31 December 2013. All regression analyses were adjusted for the year of the OC diagnosis, age at diagnosis,

tumor extent at diagnosis, primary treatments of OC (surgery, cytostatic therapy, radiation or hormonal therapy), number of biological children, age at time of the first labour, number of 1st degree relatives (children, siblings, parents) with OC or breast cancer and use of statins and antidiabetic drugs. All anti-HT drugs were added to the model simultaneously as separate time-dependent variables when evaluating simultaneous use.

Long time associations and the possible role of a protopathic bias were evaluated by lagging the exposure of anti-HT drug use forward for one, three and five years. This means that we estimated the association between the risk of OC death and anti-HT drug use that had occurred for one, three or five years earlier [26]. The data were analysed using the SPSS statistics v. 25 program (IBM, New York, NY, USA).

3. Results

3.1. Population Characteristics

As expected, due to the dismal prognosis of OC, the median follow-up time in our cohort containing all women was short, 3.3 years and varied between 2.8–4.2 years in the different anti-HT drug groups (Table 1). Anti-HT drug use was common as 7856 ovarian cancer patients had been prescribed at least one anti-HT drug group during the follow-up. Participants using anti-HT medication were older at the time of OC diagnosis and used more often statins and antidiabetic medication in comparison to non-users.

Table 1. Population characteristics.

(A)							
Characteristics of the Study Population according to Their Pre-Diagnostic Antihypertensive Drug Use.							
	Non-Users *	**ACE-Inhibitors**	**ATR-Blockers**	**Beta-Blockers**	**Calcium-Channel Blockers**	**Furosemide**	**Other Diuretics**
n of women	6841	2217	1144	3072	1889	1139	2800
n of biological children, median (IQR)	2 (0–13)	2 (0–12)	2 (0–8)	2 (0–12)	2 (0–10)	2 (0–10)	2 (0–10)
				n of 1st degree relatives with OC or BCa			
0	6490	2125	1091	2947	1813	1097	2684
1	325	87	50	119	70	40	107
2 or over	26	5	3	6	6	2	9
Median follow up time, years (IQR)	4.4 (0–19)	2.4 (0–18)	2.0 (0–17)	2.1 (0–18)	1.8 (0–18)	0.8 (0–18)	1.9 (0–18)
n of OC deaths (% of users)	2485 (36)	879 (40)	431 (38)	1427 (46)	908 (48)	633 (56)	1340 (48)
n of all deaths (% of users)	3140 (46)	1134 (49)	559 (36)	1825 (59)	1179 (62)	820 (72)	1737 (62)
Age at diagnosis, median (IQR)	58 (0–113)	70 (18–101)	70 (27–101)	71 (25–101)	73 (30–98)	78 (22–101)	72 (29–101)
				Tumor extent at diagnosis, *n* (%)			
Local	2357 (34)	630 (28)	280 (24)	757 (25)	416 (22)	229 (20)	660 (24)
Locally advanced	3050 (45)	944 (43)	526 (46)	1454 (47)	912 (48)	507 (45)	1339 (48)
Advanced	492 (7.2)	274 (12)	156 (14)	372 (12)	250 (13)	181 (16)	332 (12)
Unknown	631 (9.2)	289 (13)	133 (12)	378 (12)	246 (13)	186 (16)	368 (13)

Table 1. *Cont.*

Radical surgery, *n* (% of users)	2548 (37)	637 (29)	305 (27)	781 (25)	462 (24)	237 (21)	728 (26)
Cytostatic therapy, *n* (% of users)	2951 (43)	817 (37)	416 (36)	1147(37)	684 (36)	312 (27)	1019 (36)
Antihormonal therapy, *n* (% of users)	103 (1.5)	29 (1.3)	9 (0.8)	31 (1.0)	23 (1.2)	17 (1.5)	41 (1.5)
Statin use, *n* (% of users)	1144 (17)	1140 (51)	612 (53)	1470 (48)	899 (48)	448 (39)	1242 (44)
Antidiabetic medications; *n* (% of users)	453 (6.6)	656 (30)	303 (26)	714 (23)	464 (25)	322 (28)	715 (26)

(B)

Characteristics of the Study Population Subdivided by Post-Diagnostic Antihypertensive Drug Use

	Non-Users *	**ACE-Inhibitors**	**ATR-Blockers**	**Beta-Blockers**	**Calcium-Channel Blockers**	**Furosemide**	**Other Diuretics**
n of women	6810	1525	1005	2757	1395	1380	2292
n of biological children, median (IQR)	2 (0–13)	2 (0–12)	2 (0–8)	2 (0–10)	2 (0–10)	2 (0–10)	2 (0–11)
				n of 1st degree relatives with OC or BCa			
0	6450	1468	962	2648	1337	1321	2203
1	332	54	41	102	53	54	83
2 or over	28	3	2	7	5	5	6
Median follow up time, years (IQR)	4.3 (0–19)	2.9 (0–19)	2.3 (0–17)	2.3 (0–19)	2.2 (0–19)	1.2 (0–19)	2.3 (0–19)
n of OC deaths (% of users)	2450 (36)	575 (38)	355 (35)	1254 (45)	617 (44)	829 (560)	1126 (49)
n of all deaths (% of users)	3045 (45)	770 (50)	462 (46)	1658 (60)	834 (60)	1068 (77)	1447 (63)
Age at diagnosis, median (IQR)	58 (0–113)	69 (18–101)	69 (29–101)	71 (22–101)	72 (30–98)	77 (22–101)	71 (21–101)
				Tumor extent at diagnosis, *n* (%)			
Local	2357 (35)	487 (32)	265 (26)	693 (25)	345 (25)	225 (16)	541 (24)
Locally advanced	2937 (43)	635 (42)	453 (45)	1339 (49)	660 (47)	751 (54)	1170 (51)
Advanced	506 (7.4)	159 (10)	140 (14)	321 (12)	171 (12)	184 (13)	251 (11)
Unknown	691 (10)	193 (13)	108 (11)	309 (11)	167 (12)	170 (12)	250 (11)
Radical surgery, *n* (% of users)	2539 (37)	487 (32)	285 (28)	744 (27)	383 (27)	250 (18)	623 (27)
Cytostatic therapy, *n* (% of users)	2757 (40)	614 (40)	396 (39)	1109 (40)	548 (39)	511 (37)	984 (43)
Antihormonal therapy, *n* (% of users)	90 (1.3)	30 (2.0)	7 (0.7)	37 (1.3)	25 (1.8)	23 (1.7)	33 (1.4)

Table 1. *Cont.*

Statin use, *n* (% of users)	1205 (18)	756 (50)	547 (54)	1321 (48)	642 (46)	453 (33)	920 (40)
Antidiabetic medication; *n* (% of users)	467 (6.8)	464 (30)	275 (27)	662 (24)	343 (25)	321 (23)	562 (25)

IQR = interquartile range, *n* = number, locally advanced: advanced only to regional lymph nodes, advanced: advanced widely to other locations as well as regional lymph nodes. OC = ovarian cancer. BCa = breast cancer. * = women who have not used any anti-HT drugs during the follow-up time.

3.2. Anti-HT Drug Usage before OC Diagnosis

Regardless of follow-up time, furosemide associated with an increased risk of OC death (Table 2). This elevated risk association was observed with every dose, duration and intensity of furosemide use.

Table 2. Risk of ovarian cancer death by antihypertensive drug use before OC diagnosis.

Drug Group	*n* of Users/OC Deaths	Risk of OC Death, Follow-Up Time		
		0–5 Years	0–10 Years	0–18.9 Years
		HR (95% CI) Multiavariable Adjusted *	HR (95% CI) Multiavariable Adjusted *	HR (95% CI) Multiavariable Adjusted *
ACE inhibitors	2217/879	1.06 (0.98–1.14)	0.92 (0.87–0.98)	0.91 (0.82–1.01)
Intensity of ACE-inhibitor use (DDDs/year)				
Low intensity	740/296	1.08 (0.97–1.21)	1.01 (0.92–1.10)	0.94 (0.80–1.10)
Moderate intensity	738/338	1.05 (0.94–1.17)	0.94 (0.86–1.03)	0.96 (0.83–1.12)
High intensity	739/245	1.03 (0.91–1.16)	0.84 (0.77–0.92)	0.84 (0.71–0.99)
ATR-blockers	1144/431	0.95 (0.87–1.04)	1.00 (0.93–1.08)	0.96 (0.84–1.10)
Beta-blockers	3072/1427	1.02 (0.95–1.09)	1.03 (0.98–1.09)	1.15 (1.05–1.25)
Calcium-channel blockers	1889/908	0.99 (0.91–1.07)	1.07 (1.01–1.14)	1.07 (0.97–1.19)
Furosemide	1139/633	1.25 (1.14–1.38)	1.26 (1.16–1.36)	1.35 (1.20–1.53)
Other diuretics	2800/1340	0.99 (0.92–1.06)	1.07 (1.01–1.14)	1.11 (1.01–1.21)

OC = ovarian cancer, ACE = angiotensin-converting enzyme, ATR = angiotensin-receptor, DDD = defined daily dose, HR = hazard ratio, CI = confidence interval. * = calculated Cox regression model with adjustments of age at diagnosis, year of OC diagnosis, tumor extent, surgery, cytostatic therapy, antihormonal therapy, radiation therapy, number of biological children, age at first labour, number of 1st degree relatives with OC or breast cancer and compared to non-users.

ACE-inhibitors were associated with decreased 10-year OC mortality (HR: 0.92 95% CI: 0.87–0.98) as compared to non-users. Both 5- and 10-year OC mortality declined dose-dependently when the intensity of ACE-inhibitor use increased and thus were lowest for those in group with the highest intensity of ACE-inhibitor use (HR: 0.84 95% CI: 0.77–0.92 at 10 years). No such similar risk decrease or dose-dependence in the risk associations was observed for any other anti-HT drug group. In the full follow-up time (maximum 19 years), high-dose, long duration and high-intensity treatments with beta-blockers and calcium-channel blockers were associated with an increased risk of OC death.

3.3. Anti-HT Drug Use after OC Diagnosis

Post-diagnostic ACE-inhibitor use was associated with a reduced OC mortality with full follow-up (HR: 0.81 95% CI: 0.71–0.93) (Table 3). The use of ATR-blockers also associated with decreased OC death risk but only for 10-year mortality. In contrast, consumption of other anti-HT drugs was not associated with a decreased OC death risk.

Table 3. Risk of OC death according to antihypertensive drug use after the OC diagnosis.

Antihypertensive Drug Group	*n* of Users/OC Deaths	*n* of Person Years	Risk of OC Death, Follow-Up Time		
			0–5 Years	0–10 Years	0–18.9 Years
Drug Group, Intensity of Use (DDDs/year)	***n* of Users/*n* of OC Deaths**	***n* of Person Years**	**HR (95% CI) Multiavariable Adjusted ***	**HR (95% CI) Multiavariable Adjusted ***	**HR (95% CI) Multiavariable Adjusted ***
ACE inhibitors			1.00 (0.92–1.09)	0.87 (0.81–0.92)	0.81 (0.71–0.93)
Low intensity	743/210	0–15	1.13 (1.02–1.24)	1.03 (0.96–1.11)	0.94 (0.83–1.06)
Moderate intensity	740/197	0–14	0.82 (0.72–0.92)	0.81 (0.74–0.87)	0.67 (0.57–0.79)
High intensity	742/285	0–14	0.81 (0.62–1.06)	0.71 (0.59–0.84)	0.18 (0.08–0.37)
ATR blockers			0.95 (0.87–1.04)	0.90 (0.84–0.98)	0.99 (0.91–1.08)
Low intensity	634/114	0–14	0.96 (0.86–1.08)	0.94 (0.87–1.02)	0.90 (0.78–1.05)
Moderate intensity	634/85	0–13	0.91 (0.80–1.03)	0.86 (0.79–0.94)	0.62 (0.51–0.76)
High intensity	631/227	0–4	0.86 (0.69–1.07)	0.85 (0.72–1.01)	0.42 (0.26–0.68)
Beta-blockers			0.99 (0.92–1.06)	0.98 (0.93–1.03)	0.97 (0.87–1.08)
Low intensity	1385/416	0–14	1.10 (1.02–1.19)	1.09 (1.03–1.15)	1.22 (1.11–1.34)
Moderate intensity	1382/396	0–14	0.84 (0.77–0.92)	0.94 (0.89–1.00)	0.85 (0.76–0.95)
High intensity	1382/710	0–14	0.81 (0.65–1.02)	0.81 (0.68–0.97)	0.64 (0.47–0.88)
Calcium-channel blockers			0.91 (0.84–0.99)	1.04 (0.97–1.11)	1.39 (1.25–1.54)
Low intensity	796/270	0–13	1.11 (0.99–1.24)	1.15 (1.06–1.25)	1.19 (1.04–1.37)
Moderate intensity	794/182	0–8	0.86 (0.77–0.95)	0.96 (0.89–1.04)	0.83 (0.73–0.96)
High intensity	792/283	0–12	0.85 (0.71–1.01)	0.98 (0.86–1.13)	0.67 (0.50–0.90)
Furosemide			1.13 (1.04–1.22)	1.34 (1.25–1.44)	1.06 (0.97–1.16)
Low intensity	928/475	0–18	1.43 (1.31–1.56)	1.66 (1.55–1.78)	2.52 (2.27–2.78)
Moderate intensity	692/299	0–14	1.27 (1.14–1.42)	1.46 (1.34–1.59)	1.78 (1.57–2.03)
High intensity	929/430	0–13	0.98 (0.86–1.13)	1.27 (1.14–1.41)	1.32 (1.10–1.57)
Other diuretics			0.98 (0.91–1.05)	1.07 (1.01–1.13)	1.39 (1.22–1.59)
Low intensity	1221/612	0–18	1.18 (1.08–1.28)	1.25 (1.18–1.33)	1.58 (1.44–1.74)
Moderate intensity	1163/383	0–15	0.89 (0.80–0.98)	1.01 (0.94–1.09)	1.00 (0.88–1.14)
High intensity	1186/515	0–13	1.03 (0.88–1.19)	1.00 (0.89–1.11)	0.95 (0.77–1.17)

OC = ovarian cancer, ACE = angiotensin-converting enzyme, ATR = angiotensin-receptor, DDD = defined daily dose, HR = hazard ratio, CI = confidence interval. * = calculated Cox regression model with adjustments for age at diagnosis, year of OC diagnosis, tumor extent, surgery, cytostatic therapy, antihormonal therapy, radiation therapy, number of biological children, age at first labour, number of 1st degree relatives with OC or breast cancer and compared to non-users.

A dose-dependence between ACE-inhibitor use and OC death was observed: the risk of OC death was lowest in those individuals with the highest intensity use of ACE-inhibitors. However, a dose-dependence was observed also among all other anti-HT drugs regardless of follow-up time as the risk of OC death decreased along with increasing intensity of anti-HT use. Nonetheless, risk estimates remained elevated as compared to non-users with the exception of high-intensity use of ACE-inhibitors, ATR-blockers, beta-blockers and calcium-channel blockers with full follow-up (Table 3). Furosemide and diuretics were associated with an increased risk of OC death with all follow-up times but especially with low intensity use.

In the lag time analyses, a decreased risk of OC death was seen in the ACE-inhibitor group even 5 years after use with full follow-up (Table 4). No such similar direction lag in risk associations was observed for any other anti-HT drug group; the risk associations vanished with even a 1-year time lag. The risk increase among furosemide was especially evident with the 1-year time-lag but then was attenuated to a non-significant level (Table 4).

Table 4. Risk of OC death according to antihypertensive use after OC diagnosis. Use of antihypertensive drugs lagged for one, three and five years.

Antihypertensive Drug Group	Risk of OC Death, Follow-Up Time		
	0–5 Years	0–10 Years	0–18.9 Years
Drug Group, Lag-Time (Years)	HR (95% CI) Multiavariable Adjusted *	HR (95% CI) Multiavariable Adjusted *	HR (95% CI) Multiavariable Adjusted *
ACE inhibitors			
1	1.04 (0.96–1.14)	0.89 (0.83–0.94)	0.82 (0.73–0.91)
3	1.02 (0.93–1.12)	0.86 (0.81–0.92)	0.74 (0.65–0.84)
5	1.03 (0.92–1.14)	0.85 (0.79–0.91)	0.74 (0.64–0.86)
ATR blockers			
1	0.98 (0.89–1.07)	0.93 (0.86–1.00)	0.87 (0.76–1.00)
3	1.03 (0.93–1.15)	0.99 (0.91–1.08)	0.98 (0.84–1.15)
5	1.14 (0.98–1.33)	1.09 (0.98–1.21)	0.95 (0.75–1.20)
Beta-blockers			
1	1.04 (0.97–1.11)	1.01 (0.96–1.07)	1.05 (0.96–1.14)
3	1.04 (0.97–1.12)	1.00 (0.94–1.06)	1.06 (0.96–1.17)
5	1.01 (0.93–1.11)	0.97 (0.91–1.03)	1.06 (0.94–1.19)
Calcium-channel blockers			
1	0.96 (0.89–1.04)	1.08 (1.01–1.15)	1.06 (0.95–1.18)
3	0.95 (0.87–1.04)	1.06 (0.98–1.14)	1.09 (0.97–1.23)
5	0.99 (0.89–1.11)	1.04 (0.96–1.13)	1.11 (0.96–1.28)
Furosemide			
1	1.16 (1.06–1.26)	1.35 (1.25–1.46)	1.42 (1.27–1.59)
3	1.04 (0.93–1.18)	1.16 (0.98–1.14)	1.19 (1.03–1.39)
5	1.00 (0.82–1.22)	0.93 (0.82–1.05)	1.04 (0.84–1.29)
Other diuretics			
1	0.99 (0.92–1.06)	1.06 (1.00–1.13)	1.07 (0.98–1.17)
3	0.93 (0.86–1.01)	1.01 (0.95–1.07)	0.98 (0.88–1.09)
5	0.95 (0.86–1.05)	1.01 (0.94–1.09)	1.08 (0.95–1.23)

OC = ovarian cancer, ACE = angiotensin-converting enzyme, ATR = angiotensin-receptor, DDD = defined daily dose, HR = hazard ratio, CI = confidence interval, * = calculated Cox regression model with adjustments for age at diagnosis, year of OC diagnosis, tumor extent, surgery, cytostatic therapy, antihormonal therapy, radiation therapy, number of biological children, age at first labour, number of 1st degree relatives with OC or breast cancer and compared to non-users.

3.4. Sensitivity Analyses

We also ran competing risk analysis where deaths due to cardiovascular diseases were analysed as the competing cause of death (Table S2). In this analysis, post-diagnostic use of ACE-inhibitors continued to be associated with a lowered risk of OC death (HR: 0.73 95% CI: 0.58–0.91) similar to the main analysis with the full follow-up. However, for all other anti-HT drug groups, the risk associations were no longer statistically significant and none of the anti-HT drug groups, with the exceptions of diuretics and furosemide, were associated with an increased risk of OC death.

4. Discussion

In our cohort study, follow-up time clearly modified the risk association between anti-HT drug use and ovarian cancer death. None of the drug groups were associated with 5-year mortality, with the possible exception of diuretics. A decreasing risk trend among users of ACE-inhibitors and also among users of other anti-HT drugs in post-diagnostic use was only observed when the follow-up time was ten years or longer. This indicates that the control of hypertension may have prognostic benefits in OC, as the use anti-HT drugs was associated with survival regardless of the drug's mechanism of action. However, in sensitivity analysis, where cardiovascular morbidity was analysed as a competing cause of death, only ACE-inhibitors were associated with a significantly improved OC survival.

Therefore, our study provides some support for the proposal that ACE-inhibitors confer oncological benefits in women with OC.

OC has an overall poor prognosis; in Finland, the five-year relative survival was 44% in the time period 2016–2018 [1]. Among women over 75 years old, the five-year relative survival was less than 25% [1]. This may explain why follow-up time exerts such an impact on the results. Most deaths in OC occur within a few years after the diagnosis. Those women still alive five years after diagnosis likely had either a localized or a less aggressive subtype of disease at diagnosis, when curative-intent treatment is still possible. This may reflect their more active contact with health care professionals, which in turn may include also better management of hypertension and other chronic conditions compared to those women diagnosed with an advanced stage cancer and dying early of the disease. This may introduce a selection bias in the analysis if it is not taken into account in follow-up time, a problem we avoided here.

Women using anti-HT drugs are at a higher risk for cardiovascular morbidity and mortality as compared to non-users. The higher cardiovascular mortality among medication users may appear to modify their observed cancer mortality, creating a bias that favours medication users; in simple terms, if the cardiovascular mortality is high among anti-HT users then their cancer mortality may appear to be low as these women succumb to cardiovascular causes before dying of cancer. We controlled for this possible bias in the competing risk regression model. This analysis confirmed the bias: the risk decrease for all other drug groups except for the ACE-inhibitors became diminished to non-significance. However even in this analysis, the risk decrease among ACE-inhibitor users remained evident, providing further support for the benefits of this drug group.

One previous study has reported a decreased risk of OC death among post-diagnostic ACE-inhibitor users [12]. Previous investigators have also reported better OC survival among beta-blocker users [10–13]. The follow-up times in these studies have varied between 6 and 15 years with no restrictions for follow-up time or separate analyses for 5-year mortality being applied. Our study does not support a decreased risk of OC death among beta-blocker or ACE-inhibitor users with a five-years follow-up after the OC diagnosis. With a longer follow-up of over ten years, a risk decrease with high-intensity use was observed for several drug groups. When one observes the same trends of risk estimates for multiple anti-HT drug groups with different mechanisms of action, this suggests that the common underlying indication of all of these drugs, i.e., hypertension, may be behind the risk association rather than a direct mechanism of any particular drug group. In our study, furosemide and other diuretics associated with decreased OC survival whereas previous investigators have not evaluated the risk association for these drug groups.

Both ACE-inhibitors and ATR-blockers affect the renin-angiotensin aldosterone system (RAA-system) which controls blood pressure and electrolyte balance in the kidneys. ACE-inhibitors block the whole pathway (activity mediated by both AT_1- and AT_2-receptors) by inhibiting the formation of these receptors' natural agonist, angiotensin II. In contrast, ATR-blockers block only the AT_1-receptor, just one of the targets of angiotensin II with other receptors such as AT_2-receptors left unaffected. The stronger risk association observed for ACE-inhibitors might indicate that blockade of the AT_2-receptor (which ATR-blockers do not antagonize) might have some prognostic value. One can speculate that the RAA-system may have a role in OC progression.

Furosemide use associated with an increased risk of OC death; this drug was analysed separately as it is not primarily used for hypertension control but rather in the management of oedema, for example in cases of heart failure or advanced cancer. It was included, nevertheless, to estimate the possible role of diuretic use in general. We noted that especially a short duration furosemide use associated with an increased risk of OC death. This might be explained by underlying oedema in terminal cancer which is managed with short time furosemide administration. In chronic conditions like heart failure, furosemide is used for longer treatment periods and at higher doses; therefore risk estimates for long-term/high-

dose use are less likely to be affected by this kind of confounding by indication, as was observed in our study.

The strengths of our study are the utilization of detailed and reliable national cancer and prescription databases which cover all OC cases during the follow-up period and include all anti-HT drugs purchased by these OC patients during the same time period [20,27]. We were able to take into account simultaneous use of multiple anti-HT drugs which is very common in clinical practice and also the administration of statins and antidiabetic drugs which might also have a prognostic role and thus serve as confounders. We also adjusted for primary OC treatment, age and tumor extent at diagnosis and family history for OC or BCa to control for a selection bias. Instead of evaluating only anti-HT user status, we also assessed cumulative dose, duration and intensity of anti-HT drug use; this represents a major difference and a clear advantage when compared to previous studies. By being able to analyze simultaneously multiple anti-HT drug groups, we could estimate the prognostic role of hypertension management in general versus the use of a particular drug group with a distinctive mechanism of action.

Our follow-up time was also long enough to allow us to estimate separately short-term and long-term mortality, which is essential in OC which often has a poor short-term prognosis.

We did not have information if the anti-HT drugs were actually consumed as we only had information on purchases. Further, we did not have information on blood pressure levels of the participants or indications for medication use, which might have affected the results if hypertension is an independent prognostic factor. We did not have information on the specific indication of anti-HT drug use; for example, ACE-inhibitors, ATR-blockers, beta-blockers and diuretics are first line treatments also in coronary artery disease and heart failure even without hypertension. However, we were able to control for this potential bias by evaluating for cardiovascular mortality among anti-HT drug users. We did not have direct information on possible comorbidities but we could control for comorbidities by taking into account simultaneous use of multiple drugs as a surrogate. In addition, the adjustment for OC treatment also partly adjusts for comorbidities as they may limit the possibilities for curative surgery. The HR for the highest intensity of post-diagnostic ACE-inhibitor use with full follow-up was 0.18 (95% CI: 0.08–0.37) which is a very low value and may be indicative of a selection bias. However, it is unclear what kind of bias would affect only high-intensity users but not low intensity ACE-inhibitor users. We also did not have information on OC progression and possible treatments after OC diagnosis which may cause systematic difference between users and non-users.

5. Conclusions

In conclusion, the use of anti-HT drugs does not associate with 5-year OC mortality, with the exception of diuretics. Follow-up time modifies the risk associations; with a longer follow-up, high-intensity use of several drug groups associates with improved survival. When the effect of cardiovascular mortality is taken into account, only ACE-inhibitors are associated with improved OC survival in the long term. If confirmed in further studies, ACE-inhibitors may provide a novel way to exert a positive impact on OC mortality.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/cancers13092087/s1, Table S1: ATC-codes for antihypertensive drugs, Table S2: Risk of OC death by antihypertensive drug use. A competing risk analysis.

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