

ASSOCIATION BETWEEN PROSTATE CANCER RISK, FASTING  
BLOOD GLUCOSE AND GLYCEMIC CONTROL: A LARGE  
FINNISH COHORT STUDY

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VILLE VIHERVUORI: ASSOCIATION BETWEEN PROSTATE CANCER RISK, FASTING  
BLOOD GLUCOSE AND GLYCEMIC CONTROL: A LARGE FINNISH COHORT STUDY

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Diabeteksen on havaittu olevan yhteydessä matalampaan riskiin sairastua eturauhassyöpään (PCa), mutta yhteys huonosti erilaistuneeseen, ns. high-grade -syöpään on epäselvä. Hyperglykemian merkitys eturauhassyövän riskitekijänä on niin ikään epäselvä.

Tutkimuksen tavoitteena oli arvioida yleistä eturauhassyöpäriskiä, sekä riskiä sairastua pahanlaatuisempaan (Gleason-luokitus 7-10) ja levinneeseen (TNM-luokituksen M1) syöpään miehillä, joiden paastoverensokeriarvot olivat diabeettisella tasolla.

Finnish Randomized Study of Screening for Prostate Cancer (FinRSPC) -tutkimukseen osallistuneiden miesten tiedot yhdistettiin paastoverensokeriarvojen mittaustulosten saamiseksi Fimlab-laboratorion tietokantaan. Verensokerimittausten tietoja oli saatavilla 17 860:lle miehelle, alkaen vuodesta 1978. Mittaustulosten perusteella jokaiselle miehelle laskettiin keskimääräinen vuosittainen verensokeritaso, ja heidät luokiteltiin verensokeritasoltaan joko normoglykeemisiksi, prediabeettisiksi tai diabeettisiksi. Seuranta alkoi FinRSPC-tutkimuksen alusta 1996–1999, ja jatkui eturauhassyöpädiagnosiin, kuolemaan tai vuoden 2014 loppuun asti.

Tutkimuksen tilastollisessa analyysissä käytettiin Coxin regressiomallia, joka oli vakioitu iän, FinRSPC-tutkimuksen satunnaistamisen, sekä eri lääkkeiden (statiinit, verenpainelääkkeet, tulehduskipulääkkeet, aspiriini, 5-alfa-reduktaasi-inhibiittorilääkiitys, alfasalpaajat sekä diabeteksen hoidossa käytetyt lääkkeet) suhteen. Analyysissä laskettiin riskiyhteyksien suhteet (HR) sekä 95 %:n luottamusvälit (CI) kokonaiseturauhassyöpäriskille, sekä erikseen Gleason 6-, Gleason 7-10-, paikallisille sekä levinneille syöville.

Tutkimuksen mediaani seuranta-aika oli 14,7 vuotta. Seurannan aikana diagnosoitiin yhteensä 1 663 uutta eturauhassyöpätapausta. Normoglykeemisiin miehiin verrattuna diabeettisen verensokeritason omaavien miesten riski sairastua eturauhassyöpään oli kohonnut (HR 1.52; 95 % CI 1.31-1.75). Riskin kohoaminen oli havaittavissa riippumatta kasvaimen Gleason-luokituksesta. Kohonnut riski oli yhteydessä kymmenen vuotta aikaisemmin koholla olleeseen verensokeritasoon (HR 1.34; 95 % CI 0.93-1.93). Diabeteksen hoitoon käytettävien lääkkeiden käyttö palautti riskin normoglykeemisten miesten tasolle.

Miehet, joiden paastoverensokeriarvot ovat diabeettisella tasolla, ovat suuremmissa riskissä sairastua eturauhassyöpään. Tämä riskin suureneminen on ilmeisesti pitkäaikainen, sillä kohonnut paastoverensokeritaso noin kymmenen vuotta ennen eturauhassyöpädiagnosia on yhteydessä riskin kohoamiseen. Diabeteksen hoitoon käytettävä lääkitys näyttää kuitenkin palauttavan riskin samalle tasolle kuin normoglykeemisillä miehillä.

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# 1. ABSTRACT

**Background:** Diabetes has been associated with lowered overall risk of prostate cancer (PCa), but the role of hyperglycemia as a PCa risk factor is unclear.

**Objective:** To estimate PCa risk among men with diabetic fasting blood glucose level.

**Design, setting and participants:** The study population of the Finnish Randomized Study of Screening for Prostate Cancer (FinRSPC) was linked to the regional laboratory database for information on fasting glucose measurements since 1978. The data was available for 17,860 men. Based on the average yearly glucose level men were categorized as normoglycemic, prediabetic or diabetic. Follow-up started at the FinRSPC baseline in 1996-1999 and continued until prostate cancer diagnosis, death, or the end of 2014.

**Outcome measurements and statistical analysis:** Cox regression with adjustment for age, FinRSPC study arm and use of statins, antihypertensive drugs, NSAIDs, aspirin, 5 $\alpha$ -reductase inhibitors and alpha-blockers was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for prostate cancer overall and separately for Gleason 6, Gleason 7-10, non-metastatic and metastatic tumors.

**Results:** During the median follow-up of 14.7 years a total of 1,663 new PCa cases were diagnosed. Compared to normoglycemic men, men with diabetic blood glucose level had increased risk of PCa (HR 1.52; 95% CI 1.31-1.75). The risk increase was observed for all tumor grades. The risk increase persisted for a decade after the measurement. Use of antidiabetic drugs removed the risk association; p for difference < 0.001. Limitations include absence of information on lifestyle factors and limited information on BMI.

**Conclusions:** Men with diabetic fasting blood glucose level have an increased prostate cancer risk. The risk increase is long-term, initiating approximately a decade before the diagnosis. Use of antidiabetic drugs attenuates the risk increase.

**Keywords:** Prostate cancer; hyperglycaemia; glycaemic control

## **2. INTRODUCTION**

The relationship between established type 2 diabetes mellitus (DM) and different types of cancer has been investigated broadly. Studies have shown that people with DM have lower risk of developing prostate cancer (PCa) compared with non-diabetics (1,2). However, it is not clear whether this concerns also poorly differentiated PCa, as some studies have suggested that the risk could be elevated (3). Glucose metabolism may have an independent role in prostate cancer development and progression (4,5). However, the mechanism behind the risk association between diabetes and PCa is unclear. There is evidence that hyperglycemia and poor glycaemic control and the related hyperinsulinaemia could be the possible links (6-8). Yet there are very few studies concentrating on connections between PCa and blood glucose levels and glycaemic control, and the results from available studies are conflicting. Some have reported increased risk of advanced or aggressive PCa among men with higher glucose levels (9), while other studies have reported a protective association between hyperglycemia and PCa (4,10).

In this study we investigated the associations between fasting blood glucose and glycaemic control (glycated hemoglobin, HbA1c) and PCa risk overall and by Gleason grade and tumor stage in a cohort of men participating in The Finnish Randomized Study of Screening for Prostate Cancer (11).

## **3. MATERIALS AND METHODS**

### **3.1 Study cohort**

The Finnish Randomized Study of Screening for Prostate Cancer (FinRSPC) is the largest component of the multinational European Study of Prostate Cancer Screening (ERSPC) (12). In the FinRSPC, all men aged 55-67 from Tampere and Helsinki residential areas were identified between 1996 and 1999. After exclusion of prevalent prostate cancer cases identified from national Finnish Cancer Registry, a total of 80,144 men were randomly assigned either to be screened with PSA at four-year intervals (the screening arm, 31,866 men) or to control arm with no intervention and followed through

national registries (48,278 men). The screening finished in 2008, but the follow-up for cancer cases in this study extended until the end of 2014. The available information on prostate cancers were obtained through study database or through The Finnish Cancer Registry for men in the control arm. The information included date of diagnosis, tumor Gleason score and tumor stage at diagnosis, recorded in this study as non-metastatic (all M0 cases) and metastatic (all M1 cases).

The Finnish Cancer Registry is a nationwide registry collecting information of cancer diagnoses from all Finnish health care units and pathology laboratories through mandatory notifications. The registry covers more than 99% of all cancer cases diagnosed in Finland (13).

To obtain information on BMI the participants of the third screening round during 2004-2008 were mailed surveys asking height and weight along with the screening invitations (14). This information was available for 11,698 men in the FinRSPC cohort.

The study cohort was linked to a nationwide prescription database of the Social Insurance Institution (SII) of Finland. The SII is a governmental agency providing reimbursements for the cost of physician-prescribed drugs to all Finnish citizens. From this database we obtained information on usage of prescribed antidiabetic drugs, antihypertensive drugs, statins, NSAIDs and aspirin during 1995-2009. Information on over-the-counter drug purchases or on drugs administered during hospital inpatient periods was not available.

### **3.2 Information on blood glucose level and glycated haemoglobin**

The information on results from each measurement of fasting plasma or blood glucose level and glycated hemoglobin (HbA1c) performed at the Pirkanmaa region were obtained from the Fimlab database and linked to the study cohort by using individual identifier number. The data was available from 1978 for fasting blood glucose level and from 1991 for HbA1c.

Fimlab Laboratories is one of the leading laboratory companies in Finland (15). Fimlab provides laboratory services, education and research in Pirkanmaa, Central Finland and Tavastia regions. A major part of laboratory measurements in the Pirkanmaa region are done in Fimlab laboratories.

The information on fasting glucose levels and HbA1c levels were available for 17,860 and 11,736 men, respectively. Each measured fasting glucose level was divided into three categories: normoglycemic if fasting glucose level was under or equal to 6.0 mmol/l measured from plasma or under or equal to 5.5 mmol/l measured from blood; pre-diabetic if glucose level was between 6.0 and 7.0 mmol/l (plasma) or between 5.6 and 6.1 mmol/l (blood) and diabetic if glucose level was over 7.0 mmol/l (plasma) or over 6.1 mol/l (blood). The HbA1c levels were also divided into three categories: normoglycemic if HbA1c was under 39 mmol/mol or under 5.7%, prediabetic if HbA1c was between 39 and 47mmol/mol or between 5.7 and 6.4%, and diabetic if HbA1c level was over 47mmol/mol or over 6.4%.

### **3.3 Statistical analysis**

We used Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (CIs) for overall risk of prostate cancer by fasting glucose and HbA1c levels. Analyses for Gleason 6 or less, Gleason 7-10, non-metastatic and metastatic tumors were performed separately. The follow-up commenced from the FinRSPC randomization (baseline) and ended at the date of death, diagnosis of prostate cancer, emigration or end of the follow-up time (31 December 2014), whichever came first. The time axis was years and month since the baseline. The model was adjusted for age only (age-adjusted analysis) and further for the FinRSPC study arm and the use of antihypertensive drugs, cholesterol-lowering drugs, NSAIDs and aspirin (multivariable-adjusted model).

For each calendar year we calculated the average yearly fasting glucose and HbA1c levels based on all measurements within that year. Fasting glucose level and HbA1c were analyzed as time-dependent variables, updated separately for each year after the baseline.

We further calculated the average blood glucose levels both before and after initiation of antidiabetic drug use, i.e. the first recorded purchase of any antidiabetic drug. Fasting glucose level before and after antidiabetic drug use was analyzed as time-independent variables.

The association between fasting glucose level and prostate cancer risk in subgroups was evaluated by repeating the analyses after stratifying the study population by background variables. We tested effect modification by adding an interaction term between blood glucose level and the effect modifier into

the Cox regression model. The interaction term was considered statistically significant if the p-value was  $\leq 0.05$ .

The temporal association between fasting glucose level and prostate cancer risk was evaluated by performing separate lag time analysis for measurements done ten and twenty years earlier.

We used IBM SPSS statistics software (version 23) to perform Cox regression analyses. All p-values are two-sided.

## **4. RESULTS**

### **4.1 Population characteristics**

Of the 17,860 men, 8,481 were normoglycemic, 5,812 were at the pre-diabetic range and 3,567 men were at the diabetic range of fasting glucose (Table 1). During the median follow-up of 14.7 years after the baseline, a total of 1,663 prostate cancers were diagnosed in the study cohort, 808 in the normoglycemic group, 454 in the pre-diabetic group and 401 in the diabetic group. Median BMI in the diabetic group was non-significantly higher compared to the normoglycemic group.

The use of cholesterol-lowering drugs, antihypertensive drugs and aspirin was more common in the diabetic group compared to the normoglycemic or pre-diabetic group. However, use of NSAIDs and 5 $\alpha$ -reductase inhibitors was less common in the diabetic group (Table 1).

Median PSA was lower among diabetic men in all three FinRSPC screening rounds compared to normoglycemic men (Table 1).



**Table 1.** Population characteristics. Study cohort of 17,860 men from the Finnish Randomized Study of Screening for Prostate Cancer with at least one fasting blood/plasma glucose measurement available during 1978-2014.

	Average fasting blood glucose level during follow-up		
	Normoglycemic	Pre-diabetic	Diabetic
n of men	8,481	5,812	3,567
Median (IQR) follow-up	17.0 (15.1-18.0)	16.3 (13.8-18.0)	15.3 (7.1-17.0)
n of PCa cases	808	454	401
Gleason score; n (%)			
6 or less	409 (50.6)	215 (47.4)	203 (50.6)
7-10	384 (47.5)	230 (50.7)	189 (47.1)
Tumor stage; n (%)			
Localized	759 (93.9)	410 (90.3)	374 (93.3)
Metastatic	48 (5.9)	44 (9.7)	25 (6.2)
Median (IQR) PSA in			
1st screening round	1.02 (0.62-1.76)	0.97 (0.61-1.69)	1.01 (0.58-2.06)**
2nd screening round	1.30 (0.77-2.28)	1.23 (0.72-2.26)	1.16 (0.66-2.31)**
3rd screening round	1.43 (0.81-2.49)	1.39 (0.77-2.41)	1.19 (0.67-2.24)**
Median (IQR) BMI	26.0 (24.2-28.3)	27.7 (25.3-30.6)	28.6 (26.2-31.6)
Antidiabetic medication use; n(%) <sup>1</sup>	207 (2.4)	1,370 (23.6)*	2,376 (66.6)*
Cholesterol-lowering drug use; n(%)	3,291 (38.8)	2,708 (46.6)*	1,851 (51.1)*
Antihypertensive drug use; n (%)	5,481 (64.6)	4,387 (75.5)*	2,917 (81.8)*
NSAID use; n (%)	6,845 (80.7)	4,692 (80.7)	2,749 (77.0)*
Aspirin use; n (%)	1,536 (18.1)	1,159 (19.9)*	715 (20.0)*
5 $\alpha$ -reductase inhibitor use; n (%)	1,253 (14.8)	724 (12.5)*	384 (10.8)*

\* P < 0.05 compared to the normoglycemic group. Calculated with chi-square test.

\*\* P < 0.05 compared to the normoglycemic group. Calculated with Mann-Whitney U- test.

<sup>1</sup> Categorization based on average blood glucose level, thus also users of antidiabetic drugs may be included in the normoglycemic group if they have good blood glucose control

## **4.2 Fasting blood glucose, HbA1c and prostate cancer risk**

Compared to the normoglycemic men, overall PCa risk was elevated in diabetic, but not in pre-diabetic men; multivariable adjusted HR 1.52; 95% CI 1.31-1.75 (Table 2). The risk was similarly elevated regardless of tumor Gleason score. However, the risk elevation was limited to non-metastatic tumors; fasting blood glucose level was not associated with risk of metastatic prostate cancer (Table 2). Association between HbA1c levels and PCa risk was not statistically significant. However, the number of men in these analyses was low.

## **4.3 Effect modification by background variables**

The connection between fasting glucose level and PCa risk was affected by several background variables (Figure 1a). Diabetic blood glucose level was associated with increased risk in the FinRSPC screening arm but not in the control arm (p for interaction < 0.001). The risk association was also modified by the use of antihypertensive drugs; the association was weaker in users of these drugs (p for interaction 0.018). Further, use of antidiabetic drugs abolished the risk association (p for interaction < 0.001).

Similar risk modifications were observed also for Gleason score 8-10 tumors (Figure1b). However, the interactions were not statistically significant in this subgroup.

## **4.4 Role of change in fasting glucose levels after initiation of antidiabetic drug use**

Changes in fasting blood glucose levels after the initiation of antidiabetic drug use were not associated with changes in prostate cancer risk (Table 3). Similarly, no change in prostate cancer risk was observed by changes in fasting glucose levels after initiation of metformin use.

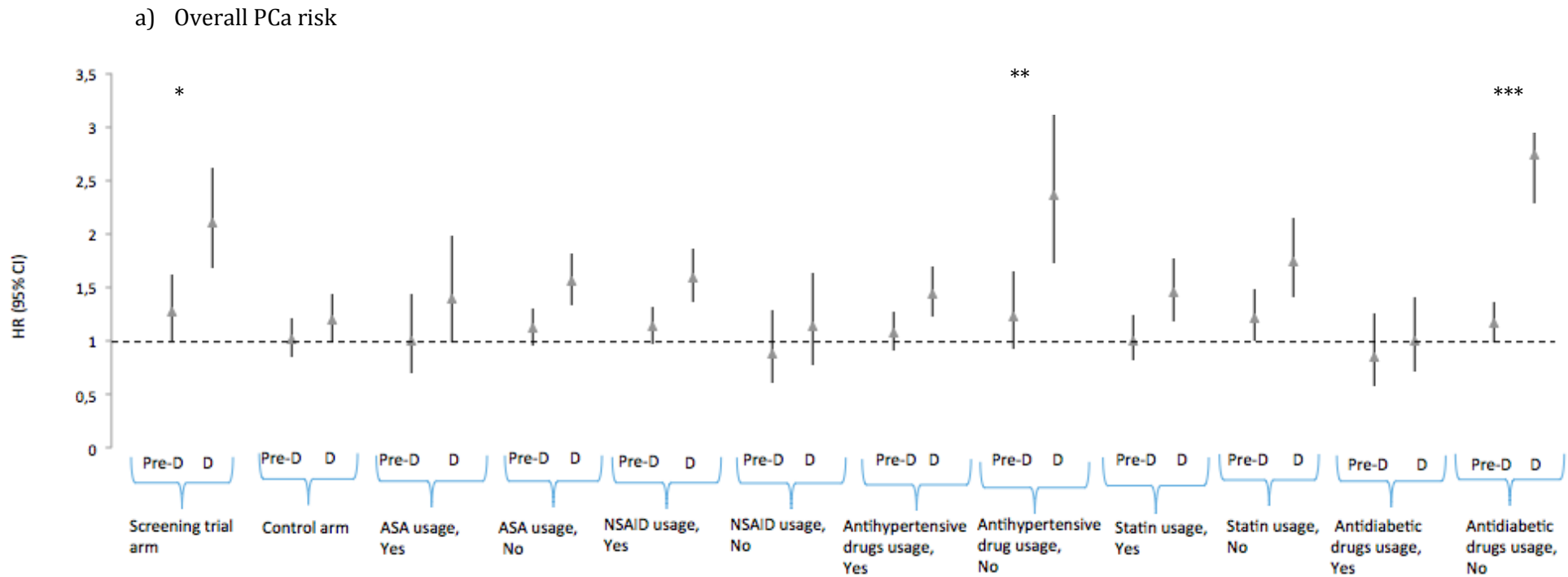
#### **4.5 Long-term effects of fasting glucose levels**

Blood glucose level measured 10 years earlier was borderline significantly associated with elevated PCa risk as in our main analysis; diabetic fasting glucose level was associated with increased risk of non-metastatic tumors and Gleason 6 or less tumor (Table 4). However, no risk associations were observed for the blood glucose levels measured two decades earlier.

**Table 2.** Prostate cancer risk by average fasting blood glucose and HbA1c level. Study cohort of 17,860 men from the Finnish Randomized Study of Screening for Prostate Cancer.

	Overall		Gleason 6 or less		Gleason 7-10		Localized PCa		Metastatic	
	HR (95% CI) <sub>age-adjusted</sub>	HR (95% CI) <sub>multivar.-adjusted</sub>	HR (95% CI) <sub>age-adjusted</sub>	HR (95% CI) <sub>multivar.-adjusted</sub>	HR (95% CI) <sub>age-adjusted</sub>	HR (95% CI) <sub>multivar.-adjusted</sub>	HR (95% CI) <sub>age-adjusted</sub>	HR (95% CI) <sub>multivar.-adjusted</sub>	HR (95% CI) <sub>age-adjusted</sub>	HR (95% CI) <sub>multivar.-adjusted</sub>
<b>Fasting blood glucose level</b>										
Normal	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Pre-diabetic	1.07 (0.99-1.23)	1.09 (0.95-1.26)	1.03 (0.84-1.27)	1.08 (0.95-1.26)	1.09 (0.89-1.34)	1.10 (0.90-1.36)	1.10 (0.94-1.27)	1.13 (0.97-1.31)	0.75 (0.43-1.31)	0.74 (0.42-1.30)
Diabetic	1.36 (1.19-1.56)	1.52 (1.31-1.75)	1.26 (1.04-1.53)	1.48 (1.21-1.81)	1.38 (1.13-1.70)	1.46 (1.18-1.81)	1.39 (1.21-1.61)	1.57 (1.35-1.82)	0.99 (0.58-1.69)	0.94 (0.54-1.64)
<b>HbA1c level</b>										
Normal	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Pre-diabetic	1.13 (0.88-1.44)	1.15 (0.90-1.47)	1.07 (0.75-1.54)	1.11 (0.77-1.59)	1.17 (0.83-1.64)	1.18 (0.84-1.66)	1.13 (0.87-1.46)	1.16 (0.89-1.50)	1.05 (0.42-2.62)	1.08 (0.43-2.70)
Diabetic	0.95 (0.73-1.23)	1.04 (0.80-1.35)	0.77 (0.53-1.13)	0.89 (0.60-1.31)	1.08 (0.75-1.53)	1.11 (0.77-1.59)	0.87 (0.67-1.15)	0.96 (0.73-1.26)	1.77 (0.73-4.30)	1.83 (0.74-4.52)

**Figure 1.** Association between prostate cancer risk and blood glucose level in subgroup analysis. Study cohort of 17,860 men from the Finnish Randomized Study of Screening for Prostate Cancer.



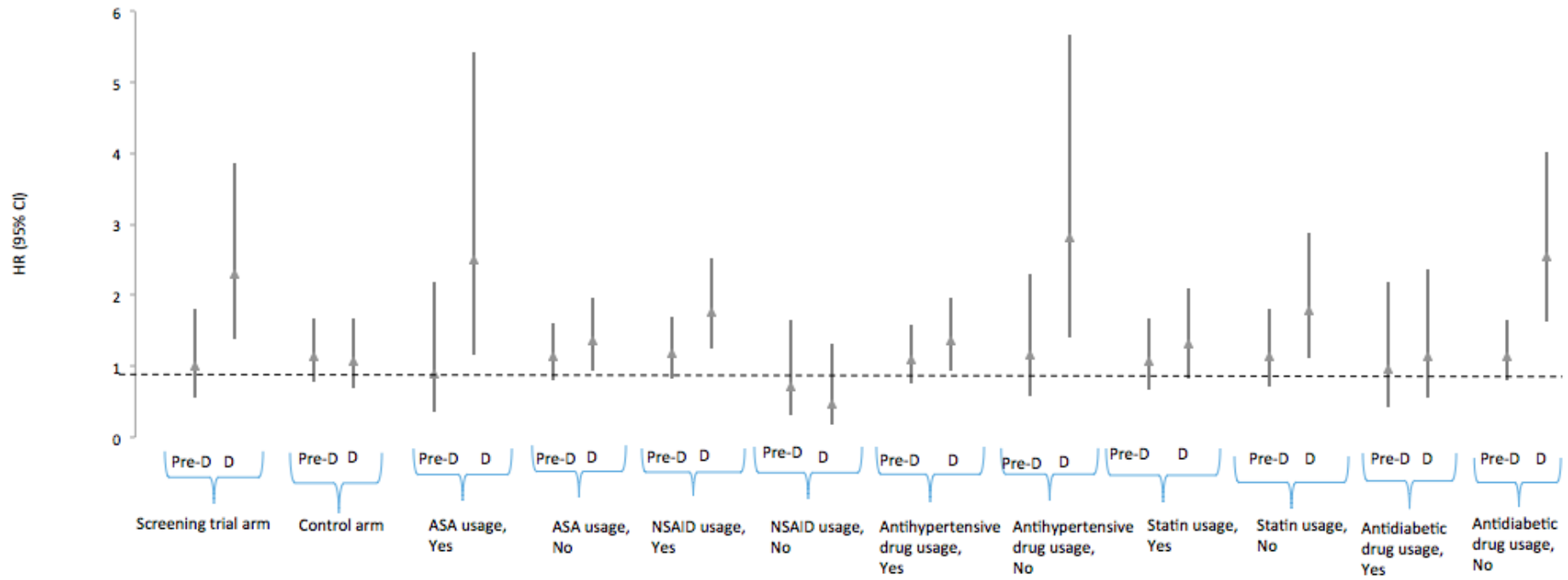
Pre-D = pre-diabetic, D = diabetic blood glucose level

\* P for interaction = 0.229 for pre-diabetic,  $p < 0.001$  for diabetic men

\*\* P for interaction = 0.435 for pre-diabetic,  $p = 0.018$  for diabetic men

\*\*\* P for interaction = 0.153 for pre-diabetic,  $p < 0.001$  for diabetic men

b) Risk of Gleason 8-10 PCa



Pre-D = pre-diabetic, D = diabetic blood glucose level

**Table 3.** Impact of change in fasting blood glucose level after initiation of antidiabetic drug use. Study cohort of 17,860 men from the Finnish Randomized Study of Screening for Prostate Cancer.

Prostate cancer risk					
	Overall	Gleason 6 or less	Gleason 7-10	Localized PCa	Metastatic
	HR (95% CI) <sub>multivar.-adjusted</sub>	HR (95% CI) <sub>multivar.-adjusted</sub>	HR (95% CI) <sub>multivar.-adjusted</sub>	HR (95% CI) <sub>multivar.-adjusted</sub>	HR (95% CI) <sub>multivar.-adjusted</sub>
Change in fasting blood glucose level					
No change	Ref	Ref	Ref	Ref	Ref
Decrease	0.82 (0.49-1.36)	0.85 (0.39-1.84)	0.74 (0.37-1.47)	0.67 (0.38-1.20)	2.87 (0.87-9.50)
Increased	0.83 (0.55-1.26)	1.07 (0.59-1.93)	0.62 (0.34-1.13)	0.85 (0.54-1.29)	0.92 (0.23-3.68)

**Table 4.** Association between the fasting blood glucose level 10 and 20 years earlier and prostate cancer risk. Study cohort of 17,860 men from the Finnish Randomized Study of Screening for Prostate Cancer.

Prostate cancer risk					
	Overall	Gleason 6 or less	Gleason 7-10	Localized PCa	Metastatic
	HR (95% CI) <sub>multivar.-adjusted</sub>	HR (95% CI) <sub>multivar.-adjusted</sub>	HR (95% CI) <sub>multivar.-adjusted</sub>	HR (95% CI) <sub>multivar.-adjusted</sub>	HR (95% CI) <sub>multivar.-adjusted</sub>
Average fasting blood glucose level 10 years earlier					
Normal	Ref	Ref	Ref	Ref	Ref
Pre-diabetic	1.27 (0.78-1.90)	0.63 (0.26-1.52)	1.70 (0.98-2.92)	1.16 (0.73-1.86)	1.97 (0.44-8.82)
Diabetic	1.34 (0.93-1.93)	1.62 (0.97-2.69)	1.31 (0.67-1.91)	1.41 (0.97-2.04)	0.38 (0.04-3.42)
Average fasting blood glucose level 20 years earlier					
Normal	Ref	Ref	Ref	Ref	Ref
Pre-diabetic	0.30 (0.04-2.20)	0.65 (0.08-5.07)	-	0.32 (0.04-2.35)	-
Diabetic	0.97 (0.41-2.32)	-	1.78 (0.68-4.67)	0.90 (0.36-2.26)	1.51 (0.15-37.8)

## 5. DISCUSSION

In this study we observed an association between fasting blood glucose level and elevated prostate cancer risk. This association was more noticeable in the screening arm, and concerned both poorly and well-differentiated cancers. Previous studies suggest that diabetes mellitus and use of antidiabetic drugs are associated with lowered overall prostate cancer risk, while the risk of high-grade tumors may be elevated (16-19). Our findings do not support the risk lowering association for diabetes as a condition, as diabetic fasting blood glucose levels were associated with increased, not lowered prostate cancer risk. This supports role of hyperglycemia as prostate cancer risk factor. Nevertheless, use of antidiabetic drugs abolished the risk increase observed with diabetic fasting blood glucose level. Therefore our study indirectly supports anticancer effects of antidiabetic drugs, but the mechanism of action is probably unrelated to blood glucose levels.

Some previous studies have reported association between diabetes and lowered PSA compared to non-diabetic men (20-22). Concordantly, median PSA was lower also in our study. This would presumably lead to lower incidence of PCa, as fewer prostate biopsies would be performed due to PSA elevation. In a setting of prostate cancer screening this would mean lower PCa incidence among diabetic men especially in the FinRSPC screening arm. In contrast, we observed a stronger association with increased PCa risk in the FinRSPC screening arm, which suggests that prostate cancer incidence among diabetic men is higher compared to non-diabetic men even if the median PSA is lower. The risk elevation seems to apply to all tumor grades as the risk elevation was observed also for high-grade tumors.

A previous meta-analysis of 14 epidemiological studies found increased risk of several cancer types for elevated HbA1c, excluding prostate cancer (4). Concordantly, we did not observe risk associations with HbA1c, only with fasting blood glucose levels.

Another previous study has examined the association between blood glucose and prostate cancer risk. (23). In this case-cohort study of 500 participants insulin concentrations and glucose concentrations were determined from a single overnight fasting serum sample 5 to 12 years before prostate cancer diagnosis. The study suggests an association between PCa risk and elevated fasting serum insulin, but not with elevated glucose levels. In contrast to our study, the observed blood glucose levels were mainly in the normal range, and no diabetic blood glucose levels were



observed. Thus our results are in concordance with this previous study, as we did not observe any risk increase even in men with pre-diabetic blood glucose level, only among men at diabetic glucose level.

The significance of blood glucose as PCa risk factor is supported by our earlier findings in which we found connection between changes in genes associated to glucose metabolism and PCa risk (5). Previously reported lower PCa risk among men with diabetes could be explained by use of antidiabetic medication; for example lower PCa risk has been reported among metformin users (24-27). In this study the use of antidiabetic drugs abolished the observed association between high blood glucose levels and elevated risk of prostate cancer. This supports that the treatment of diabetes could remove the risk increase associated with hyperglycemia. However, the changes in blood glucose level after initiation of antidiabetic drug use during the follow-up was not connected to PCa risk, which suggests that the possible antitumor effects of antidiabetic drugs are mediated through mechanisms other than blood glucose control. However, confirmation will be needed from other studies as confidence intervals were relatively wide in our risk estimates.

The association between blood glucose level and PCa risk is likely to be long-term, because the elevated risk was observable also for the fasting blood glucose level measured a decade earlier. This suggests that diabetic glucose level could increase the risk of initiation of prostate cancer development. To our knowledge this is the first study to examine long-term associations between fasting blood glucose and prostate cancer risk. However, we did not observe risk associations by HbA1c level, which reflects long-term glucose balance. HbA1c results were available for fewer participants than were fasting glucose measurements, thus these analyses were limited by lowered statistical power. Nevertheless, this difference between the risk associations between HbA1c and fasting glucose suggests that the interaction between blood glucose, insulin and prostate cancer may be complex.

Strengths of our study include large population-based cohort and information on blood glucose measurements starting from the 1980's. We were also able to evaluate the effect of antidiabetic drug on the risk association through comprehensive national prescription database free of recall bias.

The study also has some limitations. We had no information on lifestyle factors, such as smoking, diet or physical activity, which could possibly affect prostate cancer risk and cause confounding

(28-30). The available information on BMI was also limited. Because of these factors, residual confounding is possible.

In conclusion, diabetic fasting blood glucose level is associated with elevated PCa risk in a population-based cohort of Finnish men, especially in the setting of systematic PSA-based screening. The risk association is long-term, observed a decade in advance of the diagnosis. Use of antidiabetic drugs removes the risk association, supporting the risk lowering effect of these drugs.

## **6. FUNDING**

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## **7. CONFLICTS OF INTERESTS**

TJ Murtola: lecture fees from Astellas, Janssen and MSD, paid consultant for Astellas and Jansen. Ville JY Vihervuori: none. J Lahtela: none. K Talala: none, K Taari: lecture fee from GSK, consultant fee from Abbvie, research funding from Medivation and congress travel support from Astellas and Orion. TLJ Tammela: paid consultant for Astellas, GSK, Pfizer, Orion Pharma and Amgen, A Auvinen: lecture fee from MSD, paid consultant for Epid Research.

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