Outcomes of screening for prostate cancer among men using statins

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Date of revision: 5.8.2021

Word count: 2,938

Formatted: Finnish

KEY POINTS

Question: Are benefits and harms of prostate cancer screening modified by use of cholesterol-lowering statin drugs?

Findings: We investigated effects of PSA screening by statin use in the Finnish Randomized Study of Screening for Prostate Cancer. Screening lowered incidence of advanced PCa similarly regardless of statin use, but increased detection of low-grade tumors less among statin users. Effect of screening on prostate cancer mortality was not significantly modified by statin use.

Meaning: PSA-based prostate cancer screening causes less overdiagnosis of low-risk malignancies statin users, with similar mortality benefits as in non-users. PSA-based screening may cause less harm among statin users.

ABSTRACT

Importance: Prostate specific antigen (PSA)-based screening for prostate cancer causes slight reduction in prostate cancer mortality, but considerable overdiagnosis of low-risk tumors. PSA levels are affected by use of cholesterol-lowering statin drugs, but impact on screening performance is unknown.

Objective: To investigate whether statin use affects outcomes of randomized PSA-based prostate cancer screening intervention.

Design: Finnish Randomized Study of Prostate Cancer Screening randomized men to PSA screening or routine care in 1996-1999. Follow-up continued until end of 2015.

Setting: Population-based study including all men 55-67 years old at baseline and residing in the Tampere or Helsinki areas, Finland. Information on statin purchases during 1996-2009 were obtained from national prescription registry.

Participants: Eligible men were identified from the population registry of Finland. Prevalent prostate cancer cases at baseline were excluded. A total of 80,458 men were randomized.

Intervention: Three invitations to PSA screening at 4-year intervals in 1996-2007 vs. routine care.

Main outcome: Risk for prostate cancer overall, high-risk disease and prostate cancer mortality in the screening arm versus the control arm as intention-to-treat analysis. Analysis stratified by statin use.

Results: The study comprised 78,615 men with statin purchase data available. While screening was associated with increased prostate cancer incidence among statin non-users (screening vs. control 11.2 vs 8.6 per 1000 person years (pys), rate ratio (RR) 1.31, 95% confidence interval (CI) 1.24-1.38), no similar increase in incidence was observed among statin users (6.9 vs 5.9 per 1000 pys, RR 1.02, 95% CI 0.95-1.10, P for interaction <0.001). Incidence of low-risk (Gleason 6) and localized tumors was lower among statin users, whereas detection of Gleason 8-10 tumors was similar. Screening lowered incidence of metastatic tumors similarly regardless of statin use. There was suggestion of PCa mortality reduction in the screening arm among non-users but not for statin users.

Conclusion and relevance: Statin use does not materially compromise benefits of PSA-based screening, but adverse effects may be lower among them.

Introduction

Systematic screening for prostate cancer (PCa) causes overdiagnosis of low-risk tumors and only modest reduction in PCa mortality.[1, 2] Screening for PCa is considered beneficial for early detection of clinically significant prostate cancer and decreasing PCa mortality.[2] The Finnish Randomized Study of Screening for Prostate Cancer (FinRSPC), the largest component of The European Randomized Study of Screening for Prostate Cancer reported no statistically significant benefit in PCa mortality by systematic prostate specific antigen (PSA)-based screening.[3] However, the benefit became clearer after a minimum of three screens.[4] Currently, the harms of systematic PSA-based PCa screening are considered to exceed the benefits by causing unnecessary diagnoses of clinically insignificant cancers.[1]

Serum PSA is influenced by benign conditions such as prostatic inflammation.[5] Some commonly used medications including statins influence PSA level.[6] Statins inhibit endogenous cholesterol production[7] and block protein prenylation, potentially influencing PCa cell proliferation and migration[8]. Statins may lower PSA by reducing intraprostatic inflammation or by inhibiting androgen signaling.[9] Reduction in PSA-levels among statin users has been observed in many studies.[10-14] Not all studies report a PSA reduction, though.[15] In a randomized placebo-controlled trial short-term high-dose atorvastatin lowered PSA compared to placebo in men with high-grade PCa, but not overall.[16] Another small single-arm trial reported a non-significant 12% decrease in PSA after Fluvastatin intervention.[17] The possible effect of statins on PSA levels could result from improved accuracy of PSA screening in detection of clinically relevant cancer owing to lower PSA levels among statin users, with fewer biopsies for borderline

PSA elevations and a reduction in detection of clinically irrelevant cancers. On the other hand, lower PSA could presumably also lead to delayed detection of PCa, causing cancers to be diagnosed more often at an advanced stage.

The purpose of this study is to investigate the effect of PSA-based screening on PCa incidence and mortality separately among statin users and non-users.

Materials and Methods

FinRSPC comprised 80,458 men. The population characteristics have been described before[2-4]. In 1996-1999 all men aged 55, 59, 63, or 67 years at baseline and living in the Pirkanmaa or Helsinki districts were identified in the Finnish Population Registry and randomized. Men with prevalent PCa diagnosis were excluded at baseline. The remaining men were randomized into two groups, screening arm (31,872 men) and control arm (48,295 men). Screening arm was invited to consecutive PSA screenings at four-year intervals. Screening invitations stopped at PCa diagnosis, emigration from the study area, or at the age of 71 years. If PSA was greater or equal to 4 ng/ml men were invited to their local urological clinic for digital rectal examination (DRE), prostate ultrasound, and prostate biopsy. Information on opportunistic PSA-tests outside of the screening protocol was obtained from leading local laboratories. PSA tests outside the screening protocol were attended by 36,149 men.

Information on PCa diagnoses was obtained from the population-based nationwide Finnish Cancer Registry. Information about the date of diagnosis, Gleason grade, TNM-stage (both available for over 99% of participants) was collected from medical records. Additional information about weight and height was collected by sending a questionnaire to men in the screening arm along with the 3rd round screening invitations. Calculated BMI was available for 11,698 men (14.9% of the total study cohort). Information about socioeconomic status and employment was obtained from Statistics Finland, available for 77,072 men (98%).

Information about PCa deaths was obtained from the cause of death registry maintained by Statistics Finland (license number TK-53-1330-18), collected from mandatory death certificates. Information on deaths and PCa cases was available until the end of 2015. Records contain information about causes and dates of death. The FinRSPC cause of death committee evaluated the accuracy of PCa deaths recorded by the cause of death registry, regardless of the randomization arm. Accuracy of all PCa deaths that occurred in 1996-2003 were evaluated based on medical records. Records of PCa deaths were found to be 97% accurate.[3]

Statin use

Finnish citizens are entitled to reimbursements for purchases of physician-prescribed medication as part of the national health insurance provided by the Social Insurance Institution of Finland (SII).[18] All reimbursed purchases are recorded in the national prescription database. The study population was linked to the database to obtain information about medication purchases during 1996-2009. The data was available for 78,606 men, 97% of the FinRSPC study population. Only medication use before PCa diagnosis or end of 2009 (men free of PCa) was included in the analysis. Later medication use was not included as the screening intervention stopped by 2008. Information about medication purchases included the date of each purchase, dose, number of doses, and number of packages purchased. The registry does not record over-the-counter medication purchases or drugs administered during hospitalization. Statins are available in Finland by prescription only, thus they are comprehensively recorded by the registry.

Dose response by yearly amount of statin use was evaluated stratifying the analysis of the effect of screening on PCa incidence and mortality by tertiles of intensity of statin use, i.e. averagae yealy purchased amount of Defined Daily Doses of statins. Defined Daily Dose is the drug-specific average dose per day for a drug used for its main indication in adults.[19] Intensity of statin use was calculated by dividing cumulative Defined Daily Doses of all statin purchases with cumualtive number of years of usage. Doses were diveded by tertiles (low = average < 0.65 defined dose/day, medium = average 0.65 - 1.08 defined dose/day, high average >1.08 defined dose/day).

Statistical analysis

Median PSA values among men in the screening arm were calculated separately for statin users and non-users. Mann-Whitney U test was used to evaluate statistical significance of the difference between users and non-users.

PCa incidence and mortality were analyzed as randomized, comparing men in the screening arm to those in the control arm to assess rate ratios (RRs) and 95% confidence intervals (CIs) for PCa incidence and PCa-specific mortality. Intention-to-treat principle was used in the analyses, i.e. men randomized to the screening arm were analyzed in this arm regardless of whether they actually participated in screening. Analyses were performed separately among statin users and non-users. Only statin use prior to PCa diagnosis was included in the analysis.

Poisson regression was used to analyze effects of screening on PCa incidence and PCa mortality. Men in the control arm were used as the reference. To ensure equal length of

follow-up for the entire study population the common closing date was Dec 31st, 2012 for men randomized in 1996 at Dec 31st, 2013 for men randomized in 1997, Dec 31st, 2014 for men randomized in 1998, and Dec 31st, 2015 for men randomized in 1999. The maximum follow-up time was 17 years. Follow-up time continued until PCa diagnosis, PCa death, emigration from the study area, or upon reaching the common closing date. The risk of PCa was analyzed overall, by Gleason score (categorized as Gleason 6, 7, 8-10) and by tumor TNM stage (categorized as localized disease; T1-T3aNx/0Mx/0 or advanced T3b-T4, all N1, all M1 cases). In total 962 men were lost to follow-up due to emigration from Finland.

Role of opportunistic PSA testing outside systematic screening protocol was evaluated in sensitivity analyses limited to men with at least one recorded PSA measurement , before the first FinRSPC screening. Thus, the subgroup aimed to eliminate the difference in opportunistic testing by statin use.

Graphs, figure on PSA distribution and Poisson regression analyses were performed using the Stata 16.0 software package (College Station, TX, USA).

The study protocol was reviewed and approved by the Ethics Committee of the Pirkanmaa Hospital District (tracking number R10167). Men in the screening arm gave informed consent for participation, while men in the control arm were followed via national registries using routinely collected data, thus informed consent was not required according to Finnish regulations.

Results

Population characteristics

The study population included 78,606 men. In the screening arm 12,059 (40%) men were statin ever-users and in the control arm 19,567 (41%). The median age at randomization was 59 years in both trial arms. Higher percentage of statin users were employed compared to non-users in both screening and control arm. Statin users engaged more likely to the first screening and had more opportunistic screening tests taken outside the study protocol compared to the non-users. However, proportion of screen positive men and compliance to undergo prostate biopsy after being screen positive were slightly lower among statin users than non-users. (Table 1.).

PSA distribution by statin use

Statin users had lower median PSA (1.18 ng/ml) than non-users (1.28 ng/ml), $p < 0.001$. Besides lower median, the distribution of PSA values followed similar pattern among statin users and non-users (Table 1, eFigure 1).

Cumulative incidence of PCa and PCa mortality by statin use and trial arm

Overall, PCa cases detected among men in the screening arm were more often Gleason 6 tumors and less often metastatic compared to PCa cases arising in the control arm (eTable 1). In both study arms, proportion of metastatic PCa cases was lower among statin users.

Cumulative PCa incidence increased along with time in both FinRSPC trial arms, although the influence of three screening grounds was visible among men in the screening arm (Figure 1). Incidence was lower among statin users in both trial arms, although it increased at same pace over time regardless of statin use.

Prostate cancer mortality remained lower among statin users than non-users in both FinRSPC trial arms (Figure 1). Also, accumulation of PCa deaths was slower among statin users regardless of the trial arm. In non-users, PCa mortality curves differed in favor of the screening arm after 10 years of follow-up. Among statin users no such difference between trial arms was observed.

Effect of screening on overall PCa risk and risk of clinically insignificant cancers by statin use

In total, 8,562 PCa cases were diagnosed. In the screening arm, PCa rate per 1000 person years was higher among statin non-users in both screening and control arm (11.2/1000 person years and 8.6/1000 person years, respectively) compared to users (6.0/1000 person years and 5.9/1000 person years, respectively). Opportunistic PSA tests were more common among statin users both in screening arm and control arm. (Table 1.)

Screening increased overall PCa incidence among non-users (11.2 vs. 8.6 per 1000 pys, RR 1.31, 95% CI 1.24-1.38), whereas among statin users screening did not increase the

risk for PCa overall (6.0 vs. 5.9 per 1000 pys, RR 1.02, 95% CI 1.95-1.10, P for interaction <0.001) (Table1, Figure 2 and eTable 2).

Screening increased the risk for Gleason 6 tumours compared to the control arm regardless of statin use, but less among statin users. For localized tumors, screening increased the risk among statin non-users compared to the control arm, but not among statin users. Screening did increase the risk for Gleason 7 cancers among non-users, but statin users screening lowered risk for Gleason 7 cancer compared to the control arm (1.9 vs. 2.2 per 1000 pys, RR 0.83, 95% CI 0.72-0.95, P for interaction 0.024) (Figure 2 and eTable 2).

Effect of screening on risk of aggressive and advanced prostate cancer

In general, statin use overall did not modify the effect of screening on Gleason 8-10 and advanced PCa (Figure 2 and eTable 2).

Effect of screening on prostate cancer-specific mortality

Screening caused no statistically significant impact on PCa mortality, although risk estimates suggested a slight risk decrease among non-users of statins (Figure 2 and eTable 3). Statin use did not significantly modify this risk association, and the point estimate was close to unity among statin users.

Effect of contamination by opportunistic PSA testing

Effect of opportunistic PSA testing outside the systematic FinRSPC screening protocol was evaluated by stratifying the analysis to men with at least one recorded PSA test apart from the FinRSPC testing or no opportunistic screening tests at all before the first screening. Among men with one or more screening opportunistic screening tests screening increased detection of PCa more among non-users than statins users (28.4 vs. 16.2 per 1000 pys, RR 1.72, 95% CI 1.39-2.12 and 11.8 vs. 7.2 per 1000 pys, RR 1.66 95% CI 1.20-2.30, respectively).

The findings were similar among men with no opportunistic screening tests, suggesting that effect modification by statin use is not related to differences in opportunistic testing (Table 2).

Dose response

Crude PCa incidence decreased in inverse correlation with intensity of statin use similarly in both trial arms (Figure 3). However, the effect of screening on PCa incidence and mortality among statin users remained similar regardless of intensity of usage

(eTable 4)

(eTable 4)

(eTable 4)

Discussion

Our subgroup analysis of the Finnish Randomized Study of Screening for Prostate Cancer demonstrates that while PSA-based screening has a similar effect on incidence of advanced PCa among statin users and non-users, incidence of low-grade PCa is not materially increased by screening among statin users. Therefore, PSA-based screening may cause less harms among statin users while benefits remain similar. A non-significant reduction in PCa mortality was found among statin non-users, while no difference was observed in men using statins. To our knowledge, this is the first study to explore outcomes of a randomized PSA-based screening intervention in men using statins.

Statins inhibit 3-hydroxy-3-methylglutal-coenzyme A (HMG-CoA) reductase, thus inhibiting cholesterol biosynthesis.[20] Previously suggested direct antitumor effects of statins include inhibition of cell proliferation, inflammation, angiogenesis, invasion, and metastasis, as well as induction of apoptosis and autophagy of PCa cells.[9] Cholesterol is essential in the synthesis of androgens that promote PCa growth and PSA secretion.[21-22] The fact that also other cholesterol-lowering medications have been associated with a lower Pca risk supports an effect mediated by reduced serum cholesterol.[23]

Statin users had a lower median PSA in our study, concordant with some previous studies.[24] One possible mechanism is hemodilution of PSA in overweight or obese men.[25-26] People with dyslipidemia are 60-70% more likely to be obese.[27] Statins may also reduce local inflammation in the prostate, which also would lower PSA.[28] In vitro models have suggested statins to impair androgen receptor signaling by reducing

androgen receptor activity and expression, resulting in decreased PSA secretion, cell growth inhibition and induction of apoptosis.[29-30] In a randomized placebo-controlled trial short-term high-dose atorvastatin intervention lower PSA compared to placebo in men with high-grade PCa, but not overall.[16] Another clinical study reported a non-significant 12% reduction in PSA after Fluvastatin intervention.[17]

The possible effect of statins on PSA levels could result from improved accuracy of PSA screening in detection of clinically relevant owing to lower PSA levels among statin users with fewer biopsies for borderline PSA elevations and a reduction in detection of clinically irrelevant cancers. Reduction in detection of low-grade tumors among statin users is probably due to lower PSA. This is supported by the lower proportion of screen-positive men among statin users. The proportion of men who underwent opportunistic PSA testing outside the trial was larger among statin users in both trial arms. Also, compliance with referrals to prostate biopsy among screen-positive men was slightly lower in statin users. Statin use is likely associated with health-conscious behavior and increased health care service use.[31] This could create a bias towards the null when estimating the effect of systematic PSA-based screening in this group.

Participation in opportunistic PSA testing before 1st screening did not modify lowering of the incidence of PCa by screening. Proportion of screen-positive men was only 2% lower among statin users than non-users in the screening arm. Thus, statin use does not necessitate corrections in thresholds for screening positivity or prostate biopsy.

Differences in screening outcomes by statin use did not depend on intensity of statin use. This suggests that the difference may not be caused by statin use directly, but rather by systematic differences between statin users and non-users, or alternatively by effects not related to statin dose. Serum cholesterol is heavily influenced also by other factors, such as dietary fat intake. Therefore, extent of cholesterol lowering at a given dose varies between individuals, and effect of statins on cholesterol level is not necessarily dose-dependent.

Several previous studies have estimated statin use and prostate cancer risk. Some studies found a decreased overall risk of PCa among statin users,[32-35] while others report opposite results[36-39]. Most studies have reported lowered risk of advanced prostate cancer in statin users than non-users.[40] In our study, screening decreases incidence of advanced PCa both in statin users and non-users. Therefore, statin users may benefit from screening similarly as non-users, even if the risk of advanced PCa is lower among them.

Strengths of our study come from a large study population undergoing randomized screening intervention, with intention-to-treat analysis showing results by assigned intervention arm. The data on medication usage is exceptionally detailed and available for the entire population-based study cohort. Information about cancer cases, Gleason grade, and metastatic status are comprehensive and reliable. The Finnish population is of homogenous Caucasian heritage, which minimizes bias by ethnicity. A long duration of follow up is essential considering the slow progression of PCa. An important strength is also registry-based information on opportunistic PSA tests outside of systematic screening protocol allowing evaluation of effect of contamination

A limitation is the homogenous Caucasian population of Finland; therefore, the results of this study may not be generalizable to other ethnicities.

CONCLUSION

PSA-based screening decreased incidence of advanced PCa similarly among statin users and non-users, but with less increase in detection of low-grade localized tumors in statin users than non-users. Screening resulted in a non-significant PCa mortality reduction among non-users of statins but showed no reduction among statin users.

Prostate cancer screening causes less overdiagnosis of low-risk tumors among statin users. Further studies should clarify how statin use and ensuing reduction in cholesterol affect PSA in men with and without prostate cancer.

ACKNOWLEDGEMENT

TJ Murtola reports consultant fees from Astellas, Ferring and Janssen Cilag; Speaker's fees from Astellas, Novartis and Janssen Cilag.

K Taari reports research funding from Medivation/Astellas/Pfizer, Orion, Myovant.

TLJ Tammela reports Research funding and consulting fees from Bayer, Lidds AB and Astellas; Consulting fees from Janssen.

A Auvinen reports consulting fees from Epid Research Inc.

The authors report no other conflicts of interest in this work.

Role of funders: The study was funded by nonrestrictive research grants from the Competitive State Research Financing of the Expert Responsibility area of the Tampere University Hospital (grant number 9T036), Finnish Cancer Society (grant number 3122800563) and Academy of Finland (grant number 3121330724). Funders had no role in the Design and conduct of the study; Management, analysis, and interpretation of the data; Preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Access to data and data analysis:.Arla Vettenranta and Jani Raitanen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

FIGURE TITLES AND LEGENDS

Figure 1. Effect of Screening on Cumulative Prostate Cancer Incidence and Mortality,

Stratified by Statin Use (Panel A cumulative incidence, Panel B cumulative mortality). Study population of 78,606 men from the Finnish Randomized Study of Prostate Cancer.

Figure 2. Effect of Screening on Various Outcomes, Stratified by Statin Use. Incidence of prostate cancer overall and clinically non-significant disease as defined by Gleason score, TNM stage and mortality. Study population of 78,606 men from the Finnish Randomized Study of Screening for Prostate Cancer.

Figure 3. Prostate Cancer Incidence (number of cases/1,000 person years) among Statin Users by Statin Dose. Study population of 78,606 men from the Finnish Randomized Study of Screening for Prostate Cancer. Doses diveded by tertiles (low = average < 0.65 defined doses/day, medium = average 0.65 - 1.08 defined doses/day, high average >1.08 defined doses/day).

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Table 1. Descriptive characteristics. Study population of 78,606 men from the Finnish Randomized Study of Prostate Cancer Screening

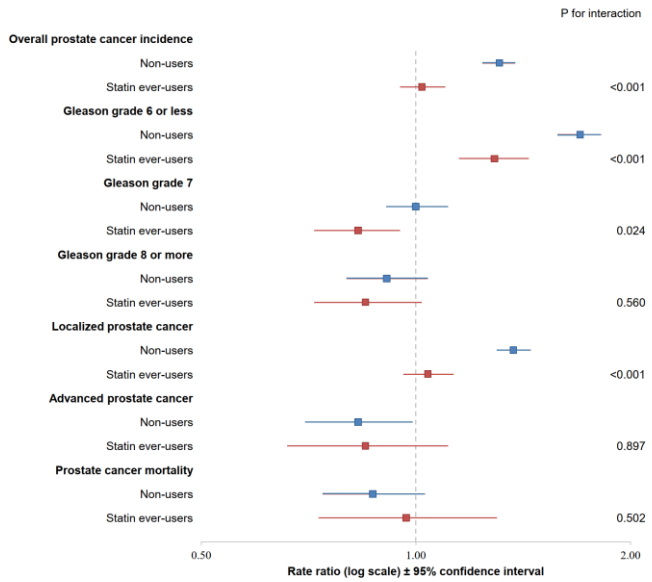
	Screening arm		Control arm	
	Statin users	**Statin non-users**	**Statin users**	**Statin non-users**
Number of participants	12,059	18,277	19,567	28,703
Person years	179,441	231,251	293,675	369,184
Baseline characteristics				
Age at randomization; median (IQR)	59 (55-63)	59 (55-63)	59 (55-63)	59 (55-63)
Years of follow-up until PCa diagnosis; median (IQR)	17 (13-19)	17 (9-19)	17 (14-19)	17 (9-18)
Years of follow-up until death; median (IQR)	18 (16-19)	17 (12-19)	18 (17-19)	17 (11-19)
Median Body Mass Index[a] (IQR)	27.4 (24.3-29.7)	26.4 (23.9-28.4)		
Employed[b] (%)	5,885 (48.8%)	8,421 (46.1%)	9,433 (48.2%)	13,249 (46.2%)
Screening characteristics				
Median PSA level ng/ml	1.18	1.28		
N of Compliance to screening 1st round (%)	8,970 (74.4%)	11,814 (65.0%)	-	-
N (%) screen positive	619 (5.1%)	1,358 (7.4%)	-	-
N of screen positive men who subsequently had prostate biopsy	578	1,299		
Compliance % for biopsy among screen positive men	93.4%	95.7%		
Number of proportion of men with any opportunistic PSA screening before 1st screening	476 (3.9%)	689 (3.8%)	671 (3.4%)	880 (3.1%)
Outcomes				
N of PCa diagnoses during follow up	1,072	2,600	1,718	3,172
PCa rate / 1000 person years	6.0	11.2	5.9	8.6
PCa mortality	75	212	125	372
PCa mortality rate / 1000 person years	0.4	0.9	0.4	1.0
All deaths	2,933	5,846	4,652	9,764
death rate / 1000 pys	16.3	25.3	15.8	26.4

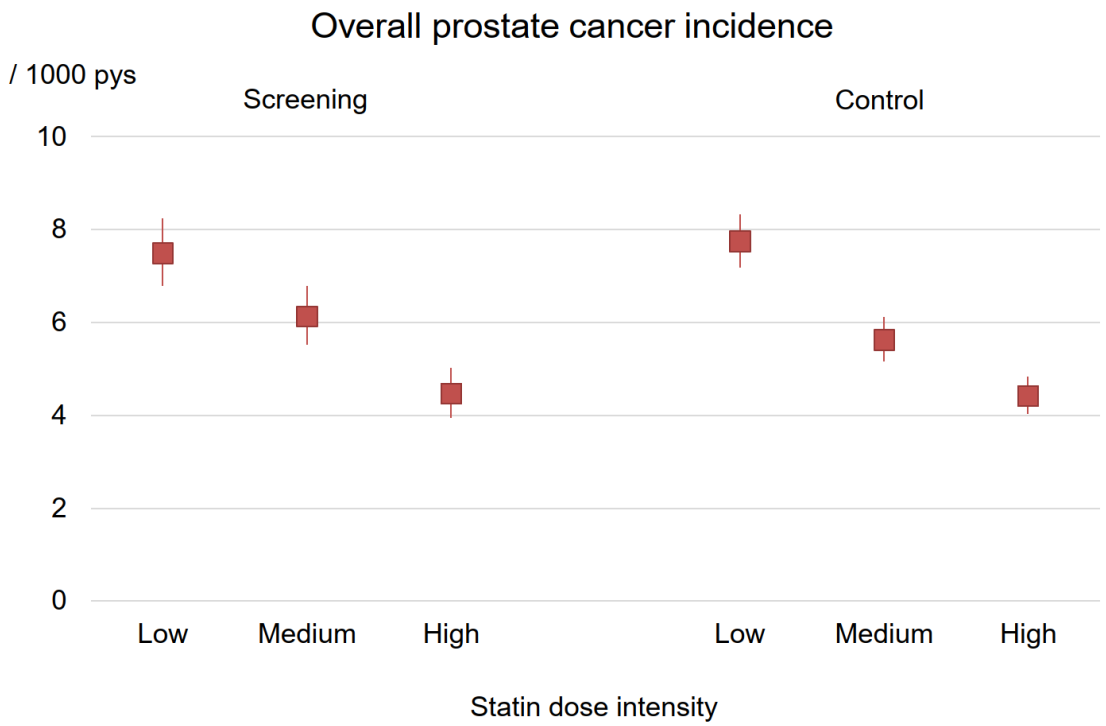
Abbreviation: FinRSPC = Finnish Randomized Study of Screening for Prostate Cancer, IQR = interquartile range [a]Body Mass Index available for 11,698 men in the screening arm [b]men who were employed, students or entrepreneurs

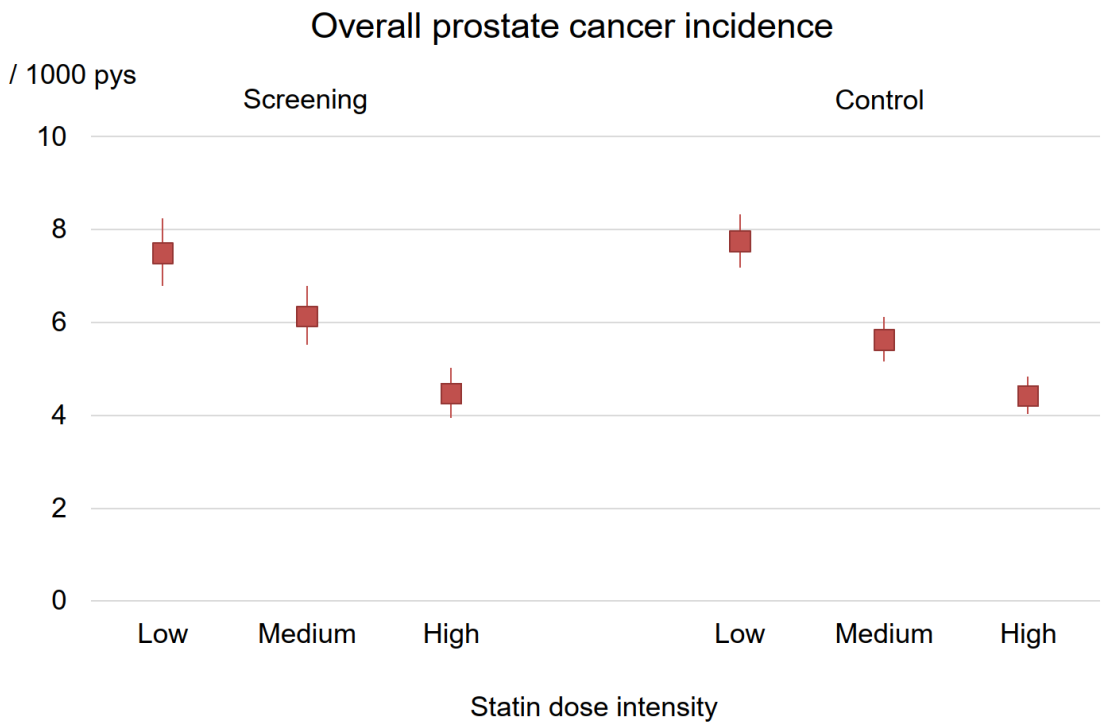
Table 2. Effect of screening on PCa incidence overall and PCa –specific mortality among statin users and non-users by one or more or no opportunistic PSA-tests taken. Study population of 78,606 men from the Finnish Randomized Study of Screening for Prostate Cancer

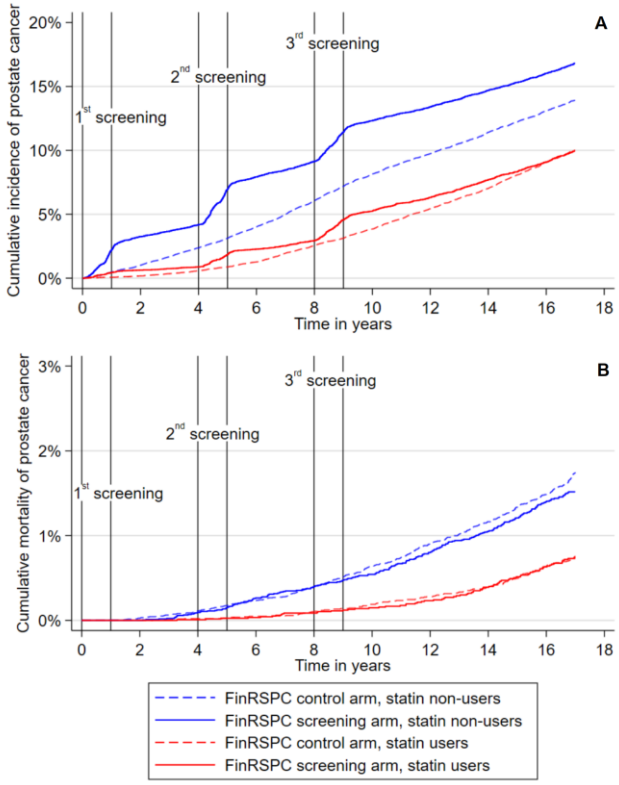
Status of statin use none/any	**PCa incidence overall by study arm (ref. = control arm)**				**PCa mortality by study arm (ref. = control arm)**			
	One or more opportunistic PSA tests		**No opportunistic PSA tests**		**One or more opportunistic PSA tests**		**No opportunistic PSA tests**	
	RR (95% CI)	**P for interaction**	**RR (95% CI)**	**P for interaction**	**RR (95% CI)**	**P for interaction**	**RR (95% CI)**	**P for interaction**
Never-use of statins	1.72 (1.39-2.12)		1.28 (1.21-1.35)		1.39 (0.71-2.73)		0.83 (0.70-0.99)	
Any use of statins	1.66 (1.20-2.30)	0.818	0.99 (0.92-1.07)	<0.001	3.87 (1.23-12.1)	0.132	0.86 (0.64-1.17)	0.860
< 0.65 defined dose/day	1.95 (0.20-3.16)	0.650	0.92 (0.81-1.04)	<0.001	5.94 (1.26-28.0)	0.094	0.65 (0.39-1.06)	0.327
0.65-1.08 defined dose/day	1.88 (1.01-3.50)	0.816	1.07 (0.93-1.22)	0.012	a		0.88 (0.53-1.45)	0.870
>1.08 defined dose/day	1.22 (0.65-2.29)	0.269	1.00 (0.86-1.16)	0.003	0.62 (0.06-6.88)	0.548	1.29 (0.71-2.34)	0.163

a = convergence not achieved, Abbreviations: FinRSPC= Finnish Randomized Study of Screening for Prostate Cancer, RR = rate ratio, CI = confidence interval, PSA = Prostate-specific antigen


P for interaction
Overall prostate cancer incidence
Non-users
Statin ever-users
<0.001
Gleason grade 6 or less
Non-users
Statin ever-users
<0.001
Gleason grade 7
Non-users
Statin ever-users
0.024
Gleason grade 8 or more
Non-users
Statin ever-users
0.560
Localized prostate cancer
Non-users
Statin ever-users
<0.001
Advanced prostate cancer
Non-users
Statin ever-users
0.897
Prostate cancer mortality
Non-users
Statin ever-users
0.502
0.50
1.00
2.00
Rate ratio (log scale) ± 95% confidence interval


Overall prostate cancer incidence
/ 1000 pys
Screening
Control
10
8
6
4
2
0
Low
Medium
High
Low
Medium
High
Statin dose intensity


Overall prostate cancer incidence
/ 1000 pys
Screening
Control
10
8
6
4
2
0
Low
Medium
High
Low
Medium
High
Statin dose intensity


A
Cumulative incidence of prostate cancer
20%
15%
10%
5%
0%
1st screening
2nd screening
3rd screening
0
2
4
6
8
10
12
14
16
18
Time in years
B
Cumulative mortality of prostate cancer
3%
2%
1%
0%
1st screening
2nd screening
3rd screening
0
2
4
6
8
10
12
14
16
18
Time in years
FinRSPC control arm, statin non-users
FinRSPC screening arm, statin non-users
FinRSPC control arm, statin users
FinRSPC screening arm, statin users