This is the accepted manuscript of the article, which has been published in Journal of Urology. 2017, 198(2), 305-309.
http://dx.doi.org/10.1016/j.juro.2017.02.069

Outcomes of prostate cancer screening by 5-alfa reductase inhibitor usage

Teemu J. Murtola*, Anniina Virkku, Kirsi Talala, Ulf-Håkan Stenman, Kimmo Taari, Teuvo LJ Tammela, Anssi Auvinen

From the University of Tampere, School of Medicine, Tampere, Finland (TJM, AV, TLJT), Tampere University Hospital, Department of Urology, Tampere, Finland (TJM, TLJT), Finnish Cancer Registry, Helsinki, Finland (KTalala), University of Helsinki and Helsinki University Hospital, Department of Clinical Chemistry, Helsinki, Finland (UHS), University of Helsinki and Helsinki University Hospital, Department of Urology, Helsinki, Finland (KTaari) and University of Tampere, School of Health Sciences, Tampere, Finland (AA)

Running head: Prostate cancer screening in 5-ARI users

Keywords: Mass screening; Prostatic neoplasms; 5-alpha reductase inhibitors

*Correspondence to: Dr. Teemu J. Murtola, Tampere University Hospital, Department of Urology, Teiskontie 35, M-building, 3rd floor, PL 2000, 33521 Tampere. E-mail: teemu.murtola@uta.fi. Phone: +358 3 311 65015

Abstract

PURPOSE

Prostate cancer (PCa) screening with prostate-specific antigen (PSA) reduces PCa mortality, but leads to overdiagnosis of indolent PCa. Use of 5-alpha reductase inhibitors (5-ARIs) lowers PSA and in theory could affect performance of PSA-based screening. We evaluated outcomes of PCa screening among 5-ARI users.

MATERIALS AND METHODS

The study was performed within the Finnish Randomized Study of Screening for Prostate Cancer. Of 80,454 men, 31,866 were randomized to be screened at four-year intervals during 1996-2004. Information on 5-ARI reimbursements before PCa during 1995-2009 was collected from the national prescription database for 78,615 men. We evaluated the effect of screening on PCa risk and mortality by 5-ARI usage using Cox regresison.

RESULTS

Men using 5-ARIs had higher median PSA and were more often screen-positive compared to non-users. Despite this, screening did not significantly affect PCa detection (HR 0.89, 95% CI 0.79-1.01) or mortality (HR 0.82, 95% CI 0.51-1.32) compared to the control arm among 5-ARI users. In ROC analysis, PSA and age did not predict Gleason 7-10 prostate cancer as accurately in 5-ARI users as among the non-users (AUC = 0.88 versus 0.79 in the first screening round).

CONCLUSIONS

PSA-based screening among men using 5-ARIs does not improve detection of high-grade or metastatic PCa or prevention of PCa deaths.

Introduction

Prostate cancer (PCa) screening with serum prostate-specific antigen (PSA) remains highly controversial, despite extensive research and evidence of benefit in a large multicentre randomized trial. Screening reduces PCa mortality[1] but it also leads to substantial overdiagnosis[1, 2]. Further, PSA is not a cancer-specific biomarker; it is influenced by a number of other factors such as chronic prostatitis and benign prostatic hyperplasia (BPH), which cause false positive screening results. Because it is unclear whether benefits of prostate cancer screening outweigh the harms, PCa screening is not recommended as a public health policy. However, it is possible that the efficacy of PCa screening could be improved by targeting screening to groups with increased risk of aggressive PCa.

The 5-alpha reductase inhibitors (5-ARI) finasteride and dutasteride inhibit the conversion of testosterone into its active metabolite dihydrotestosterone, thereby decreasing prostate volume and serum PSA level.[3] Both 5-ARIs are used for treatment of BPH, finasteride also for male pattern baldness. 5-ARI usage has been reported to decrease PCa incidence compared to placebo, while increasing the proportion of high-grade tumors.[4, 5] This has been confirmed also in men who use these drugs to treat BPH.[6] It is unclear whether the increased proportion of high-grade tumors detected in 5-ARI-treated men is due to more efficient diagnostics during 5-ARI therapy (owing to reduced prostate volume) or to an absolute increase in the number of such tumors. Some studies suggest that 5-ARI usage improves the performance of PSA as a marker of high-grade PCa by reducing PSA elevations due to benign diseases and even intraprostatic inflammation.[6-8]

The purpose of this study is to investigate the effect of 5-alpha reductase inhibitor usage on the outcomes of prostate cancer screening. We hypothesise that screening would be more specific for detection of high-grade tumors in 5-ARI treated men. We evaluated its possible modifying effect on both PCa incidence and mortality in relation to screening.

Materials and methods

Study cohort

The Finnish Randomized Study of Screening for Prostate Cancer (FinRSPC) is the largest component of the European Randomized Study for Prostate Cancer Screening (ERSPC). It comprises 80,454 men born between 1929 and 1944 (aged 55, 59, 63 and 67 at entry) and living in the metropolitan areas of Helsinki and Tampere. The men were identified from the Finnish Population Register Centre. Those with a previous diagnosis of prostate cancer were identified from the Finnish Cancer Registry and excluded from the trial. During 1996-1999, men were randomly assigned either to the screening (31,866 men) or the control arm (48,278 men). The men randomized to the control arm were not contacted, but monitored through the Finnish Cancer Registry.

Men randomized to the screening arm were sent an invitation letter for the PSA screening test at 4-years intervals. A survey on prostate cancer family history and previous prostatic disease was included in the screening invitations. After a written informed consent, a blood sample was drawn for the determination of serum PSA at a local Cancer Society clinic in Helsinki or Tampere. Re-invitations for PSA screening were made every four years, but men older than 71 years were no longer invited.

Men with a serum PSA concentration greater than or equal to 4 ng/ml were referred to a local urological clinic for diagnostic evaluation comprising digital rectal examination (DRE), transrectal ultrasound and prostate biopsy. Men with PSA levels of 3.0-3.99 ng/ml were referred to an additional test, which was DRE during 1996 to 1998 and determination of the free/total PSA ratio (cut-off point 16%) since 1999. Men with a suspicious DRE or free/total PSA ratio <16% were referred for further examination in the same manner as men with PSA $\geq$ 4 ng/ml.

Prostate cancers were categorized by Gleason grade into low grade (Gleason 6 or less) or high/intermediate grade (Gleason 7-10) cases. Additionally, the cases were categorized according to the M stage at diagnosis as non-metastatic or metastatic.

Follow-up for cancer incidence and mortality started at randomization (1996-1999) and ended at death, emigration from Finland or the common closing date of follow-up December 31st, 2014, whichever came first. Information on vital status and place of residence was obtained from the Population Register Centre. Information on causes of deaths was obtained from Statistics Finland. Deaths among men with PCa during 1996-2003 were reviewed by a cause-of-death committee to validate the official causes of death, with excellent concordance.[2]

Information of 5ARI usage

Information on medication reimbursements during 1995-2009 was collected from the prescription database of the Social Insurance Institution of Finland (SII). SII provides reimbursements for the cost of physician-prescribed medicines as part of the National Health Insurance to all Finnish citizens. All reimbursements for a purchase of reimbursable prescription drugs are recorded in the database. Data from prescription database was obtained for 78,615 men (97.7% of the FinRSPC study cohort).

All 5-ARIs in clinical use for treatment of BPH in Finland are available only through a physician's prescription and thereby reimbursable and registered in the database. During the study period, the two 5-alpha reductase inhibitors licensed were finasteride and dutasteride (since 2005). 5-ARIs prescribed for treatment of male pattern baldness were not reimbursable and hence not recorded in the prescription database.

Statistical analysis

Cox proportional hazards regression was used to calculate hazard ratios and 95% confidence intervals (CIs) for prostate cancer risk and disease-specific mortality for men in the screening arm compared to men in the control arm.

In the main analysis, we evaluated effects of 5-ARI usage before prostate cancer diagnosis on the efficacy of PSA screening by performing comparisons between the screening arm and the control arm separately for users and non-users of 5-ARIs. In analysis stratified by screening round, we estimated the effect of 5-ARI usage prior to screening or corresponding date in the control arm. Hence, we compared effects of screening among men on 5-ARIs in the screening arm and the control arm, and similarly among the non-users. Additionally, 5-ARI users were stratified by the amount and duration of medication usage.

The PSA concentration as a predictive marker for PCa by stage and grade was evaluated using ROC analysis. The Area Under the Curve (AUC) was calculated separately among 5-ARI users and non-users, comparing a model including age only to the model including both PSA and age in each screening round.

Statistical analyses were performed using IBM SPSS Statistics 21 software (Chicago, IL).

Results

Population characteristics

The study population included 9,316 (11.9%) 5-ARI users and 69,299 non-users (Table 1). The median age at baseline was 63 years for 5-ARI users and 59 years for non-users. The proportion of screen-positive men was higher (983 men, 10.6%) among 5-ARI users than non-users (3,239 men, 4.7%; p for difference < 0.001). Among the users 1,131 (12.1%) men were diagnosed with PCa, 7,122 (10.3%) men among the non-users. The numbers of PCa deaths were 98 (1.1%) and 736 (1.1%), respectively; p for difference = 0.93.

Compared to 5-ARI users, the overall median PSA values were significantly lower among non-users at each screening round (Table 1). However, among PCa cases the median PSA at diagnosis was lower among 5-ARI users for all tumor grades.

Effect of screening on prostate cancer risk by 5-ARI usage

Screening increased hazard ratio for prostate cancer diagnosis compared to the control arm among 5-ARI non-users (HR 1.19, 95% CI 1.14-1.25), but not among 5-ARI users (HR 0.89, 95% CI 0.79-1.01, p for interaction < 0.001). The risk decreased among 5-ARI users in inverse correlation with cumulative amount and duration of medication usage. (Table 2)

The risk-modifying effect of 5-ARI usage mainly concerned low-risk cancer: screening increased detection of Gleason 6 or less and localized tumors in 5-ARI non-users, whereas among the users no difference by FinRSPC study arm was observed (p for interaction <0.001 for both comparisons). However, the effect of screening on the risk of high-grade and metastatic PCa did not differ by 5-ARI usage (Table 2).

Effect of screening on prostate cancer mortality by 5-ARI usage

PSA screening significantly lowered the risk of PCa death among non-users of 5-ARIs (HR 0.60, 95% CI 0.51-0.71), but not among 5-ARI users (HR 0.82, 95% CI 0.51-1.32) (Table 3). However, the effect modification by 5-ARI use was statistically non-significant (p for interaction 0.12).

When stratified by the cumulative amount and duration of 5-ARI usage, hazard ratios for prostate cancer death tended to increase in long-term user (Table 3). However, statistical power was limited in the stratified analyses.

PSA as predictor of prostate cancer grade and stage among 5-ARI users

PSA and age were less accurate in prediction of tumor Gleason grade among 5-ARI users than among non-users at all three screening rounds. The AUCs for PSA and age as predictors of tumor stage were also lower in 5-ARI users compared to non-users in all screening rounds. (Table 4)

Sensitivity analyses

When each screening round was analyzed separately, PSA screening increased prostate cancer incidence in non-users, but not among 5-ARI users in the first two rounds (Table 5). No difference was observed in the third screening round. A risk difference was observed only for Gleason 6 tumors at the second screening round.

Discussion

Compared to 5-ARI non-users, PSA levels and the resulting proportion of screen-positive men were higher among 5-ARI users. Despite this, prostate cancer detection did not differ between the screening and control arm in 5-ARI users. Further, screening did not affect prostate cancer mortality among 5-ARI users, though the difference between users and non-users was not significant. Elevated PSA levels are likely caused by underlying BPH which indicated 5-ARI use. Users have likely undergone some form of PSA testing as part of the diagnostic work-up for BPH, reducing the benefits achievable through systematic screening. Thus, our results suggest that 5-ARI users are probably not an ideal target group for PSA-based prostate cancer screening.

On the other hand, use of 5-ARIs decreased detection of non-metastatic and Gleason 6 tumors by screening, but did not affect detection of Gleason 7-10 or metastatic tumors or prostate cancer mortality. PCPT showed that 5-ARIs lower serum PSA among men with little or no LUTS.[4] Thus presumably the decreased detection of localized and well-differentiated tumors could have been due to lower likelihood of being screen-positive and resulting less prostate biopsies. However, the opposite was observed, men using 5-ARIs for BPH management had higher median PSA compared to the non-users and were more often screen-positive. This demonstrates that at the population-level, PSA elevation caused by the underlying BPH has more impact on the likelihood of being screen-positive than 5-ARI usage.

Another possible explanation is that as PSA testing is an integral part of BPH diagnostics, men who used 5-ARIs for BPH management had been tested for PSA at least once before the screening and therefore formed a pre-screened group. This may have diluted the effects of PSA-based screening in this subgroup.

Because the risk of Gleason 6 or non-metastatic prostate cancer among men in the FinRSPC screening arm decreased with longer duration of 5-ARI usage, our results suggest that 5-ARI usage may reduce overdiagnosis of low-risk tumors caused by benign causes of PSA elevation, such as BPH and prostatic inflammation. If the finding was entirely caused by 5-ARI users being pre-screened, there should be no association with duration of medication usage. The finding could reflect reduced risk of low-risk PCa in long-term 5-ARI use as demonstrated by the PCPT trial.[4]

Previous results from the PCPT trial have suggested that 5-ARI could be used to improve the performance of PSA as a marker for high-grade prostate cancer .[7, 8] Our results do not support these findings, as the risk of Gleason 7-10 disease was similar between the trial arms among 5-ARI users and non-users. However, the difference can be due to dissimilarities of the study populations; in our study, the majority of the 5-ARI users are BPH patients, whereas in the PCPT, the participants had little or no lower urinary tract symptoms at baseline [4]. Unlike PCPT, our study did not have protocol-mandated end-of-study biopsies. Thus detection of indolent tumors was likely lower in our study.

Another difference compared to the PCPT is that correction coefficients for PSA values among 5-ARI users were not routinely used in our study. The criteria for screen-positivity were similar regardless of 5-ARI use. Use of correlation coefficients when deciding on taking a prostate biopsy was up to the discretion of the treating physician. This could potentially cause differences in PCa detection between 5-ARI users and non-users. However, it does not affect our comparisons of screening arm and control arm within the groups of 5-ARI users and non-users.

Our results support previous studies reporting no difference in prostate cancer mortality by 5-ARI usage.[9-12] Our study suggests that screening may be more efficacious in reducing prostate cancer mortality among men not using 5-ARIs, although the effect modification by 5-ARI use was not statistically significant. Usage of these drugs could be considered in future studies on targeted prostate cancer screening.

Overall, the effect of screening on prostate cancer mortality was not as clear in FinRSPC as it was in the Rotterdam and Gothenburg sections of the ERSPC. One likely explanation is differing prevalence of opportunistic screening in the control group, but differing prevalence of BPH and associated 5-ARI usage may also play a role. As PSA measurement is part of diagnostic work-up of LUTS, men with BPH represent a group with high likelihood of undergoing screening outside the screening trial protocols.

A strength of our study is that it is based on a large, population-based randomized trial of PSA-based prostate cancer screening. We had the possibility to compare the outcomes at three screening rounds, and thus evaluate the influence of repeated screening. The national prescription database provided extensive and accurate information on medication usage. Since the information is collected routinely for all Finnish citizens, our results are not affected by recall bias.

The study also has some limitations. There was no randomization for 5-ARI usage and therefore, the effect of BPH as the indication is difficult to disentangle from the effects of medication. Furthermore, the information of medication usage is based on medication purchases and the actual medication use may be lower.

Conclusions

In a randomized trial of PSA-based prostate cancer screening, the proportion of screen-positive men was higher among men using 5-ARIs, but no difference in terms of medication use was found in prostate cancer detection or mortality between the trial arms.

Conflicts of interest

TJ Murtola: lecture fees from Astellas, Janssen and MSD, paid consultant for Astellas and Jansen. A Virkku: none. UH Stenman: 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. U-H Stenman: none, TLJ Tammela: paid consultant for Astellas, GSK, Pfizer, Orion Pharma and Amgen, A Auvinen: lecture fee from MSD, paid consultant for Epid Research.

References

1. Schröder FH, Hugosson J, Roobol MJ, "Prostate-cancer mortality at 11 years of follow-up", *N Engl J Med,* vol. 366, no. 11, pp. 981, 2012.
2. Kilpeläinen TP, Tammela TL, Malila N, "Prostate cancer mortality in the Finnish randomized screening trial.", *J Natl Cancer Inst,* vol. 105, no. 10, pp. 719, 2013.
3. Marberger, M., "Drug Insight: 5alpha-reductase inhibitors for the treatment of benign prostatic hyperplasia", *Nat Clin Pract Urol,* vol. 3, no. 9, pp. 495, 2006.
4. Thompson IM, Goodman PJ, Tangen CM, "The influence of finasteride on the development of prostate cancer.", *N Engl J Med,* vol. 349, no. 3, pp. 215, 2003.
5. Andriole GL, Crawford ED, Grubb RL 3rd, "Mortality results from a randomized prostate-cancer screening trial", *N Engl J Med,* vol. 360, no. 13, pp. 1310, 2009.
6. Murtola TJ, Tammela TL, Määttänen L, "Prostate cancer incidence among finasteride and alpha-blocker users in the Finnish Prostate Cancer Screening Trial.", *Br J Cancer,* vol. 101, no. 5, pp. 843, 2009.
7. Thompson IM, Chi C, Ankerst DP, "Effect of finasteride on the sensitivity of PSA for detecting prostate cancer.", *J Natl Cancer Inst,* vol. 98, no. 16, pp. 1128, 2006.
8. Murtola TJ, Gurel B, Umbehr M, "Inflammation in Benign Prostate Tissue and Prostate Cancer in the Finasteride Arm of the Prostate Cancer Prevention Trial", *Cancer Epidemiol Biomarkers Prev.*, vol 25, pp. 463, 2016.
9. Azoulay L, Eberg M, Benayoun S, "5alpha-Reductase Inhibitors and the Risk of Cancer-Related Mortality in Men With Prostate Cancer.", *JAMA Oncol,* vol. 1, no. 3, pp. 314, 2015.
10. Preston MA, Wilson KM, Markt SC, "5alpha-Reductase inhibitors and risk of high-grade or lethal prostate cancer.", *JAMA Intern Med,* vol. 174, no. 8, pp. 1301, 2014.
11. Kjellman A, Friis S, Granath F, "Treatment with finasteride and prostate cancer survival.", *Scand J Urol,* vol. 47, no. 4, pp. 265, 2013.
12. Murtola TJ, Karppa EK, Taari K, "5-Alpha reductase inhibitor use and prostate cancer survival in the Finnish Prostate Cancer Screening Trial." *Int J Cancer,* vol. 138, no. 12, pp. 2820, 2016.

Tables

Table 1. Population characteristics. Cohort of 78,615 men from the Finnish Randomized Study of Screening for Prostate Cancer.

	5-ARI usage		
	None	Any	P for difference
n of men	69,299	9,316	
Age at baseline (median, IQR)	59 (55-63)	63 (59-67)	0.001
n of PCa cases	7,122 (10.3%)	1,131 (12.1%)	<0.001
Gleason score; n (% of cases)			
6 or less	3,661 (51.4%)	534 (47.2%)	0.07
7-10	3,291 (46.2%)	574 (50.8%)	<0.001
Tumor stage			
Regional	6,589 (92.5%)	1,064 (94.1%)	<0.001
Metastatic	524 (7.4%)	65 (5.7%)	0.54
n of deaths	24,379 (35.2%)	2,411 (25.9%)	<0.001
PCa deaths; n(% of all deaths)	736 (1.1%)	98 (1.1%)	0.93
PSA (ng/ml) overall; median (IQR)			
1st screening round	1.07 (0.63-1.94)	1.61 (0.76-3.33)*	<0.001
2nd screening round	1.30 (0.76-2.39)	1.80 (0.93-3.23)*	<0.001
3rd screening round	1.40 (0.80-2.52)	1.83 (0.91-3.18)*	<0.001
screen positive; n (%)	3,239 (4.7%)	983 (10.6%)*	<0.001
PSA at diagnosis by PCa grade; median (IQR)			
Gleason 6 or less	4.49 (3.06-6.51)	3.95 (2.60-6.11)**	0.03
Gleason 7	4.29 (2.74-6.92)	3.76 (2.68-6.11)	0.08
Gleason 8-10	3.66 (1.93-7.76)	2.10 (1.17-3.51)**	0.01

Table 2: Effect of PSA-based screening on prostate cancer incidence by 5-ARI usage. Cohort of 78,615 men from the Finnish Randomized Study of Screening for Prostate Cancer.

			Overall	Gleason ≤ 6	Gleason 7-10	Localized	Metastatic
	n of PCa cases (screening arm vs. control arm)	n of men (Screening arm vs. control arm)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
5-ARI users	386/745	3,384/5,932	0.89 (0.79-1.01)	1.00 (0.84-1.20)	0.79 (0.66-0.94)	0.91 (0.80-1.03)	0.65 (0.38-1.12)
5-ARI non-users	3,039/4,083	26,810/42,489	1.19 (1.14-1.25)	1.60 (1.50-1.71)	0.88 (0.82-0.95)	1.24 (1.19-1.31)	0.66 (0.55-0.80)
P for difference by 5-ARI use			< 0.001	< 0.001	0.13	< 0.001	0.52
Cumulative quantity of 5-ARI use (doses)							
1st tertile (28-240)	157/290	1,134/1,986	0.95 (0.78-1.15)	1.07 (0.83-1.38)	0.77 (0.57-1.06)	0.98 (0.80-1.19)	0.47 (0.16-1.41)
2nd tertile (241-1,086)	133/238	1,150/1,941	0.91 (0.74-1.13)	0.96 (0.71-1.29)	0.88 (0.64-1.20)	0.93 (0.74-1.15)	0.82 (0.38-1.77)
3rd tertile (1,087 or more)	96/217	1,100/2,005	0.78 (0.61-0.99)	0.89 (0.58-1.37)	0.74 (0.55-0.99)	0.80 (0.63-1.02)	0.57 (0.17-1.59)
Duration of 5-ARI usage							
1st tertile (1-2 years)	231/405	1,757/3,029	0.98 (0.83-1.15)	1.13 (0.92-1.40)	0.78 (0.60-1.01)	1.02 (0.86-1.20)	0.45 (0.19-1.02)
2nd tertile (3-4 years)	67/141	628/1,092	0.79 (0.59-1.06)	0.66 (0.42-1.03)	0.93 (0.63-1.37)	0.74 (0.54-1.01)	1.80 (0.69-4.66)
3rd tertile (longer than 4 years)	88/199	999/1,811	0.77 (0.60-0.99)	0.88 (0.56-1.40)	0.74 (0.55-1.00)	0.81 (0.63-1.04)	0.28 (0.06-1.23)

Table 3: Effect of PSA-based screening on PCa mortality by 5-ARI usage. Cohort of 78,615 men from the Finnish Randomized Study of Screening for Prostate Cancer.

	HR (95% CI) for PCa death in the FinRSPC screening arm compared to the control arm
5-ARI non-users	0.60 (0.51-0.71)
5-ARI users	0.82 (0.51-1.32)
P for interaction	0.12
Cumulative quantity of 5-ARI use (doses)	
1st tertile (28-240)	0.51 (0.22-1.17)
2nd tertile (241-1,090)	0.79 (0.36-1.75)
3rd tertile (1,090 or more)	1.64 (0.64-4.18)
Duration of 5-ARI usage	
1st tertile	0.62 (0.32-1.20)
2nd tertile	1.02 (0.40-2.60)
3rd tertile	1.36 (0.44-4.18)

Table 4: PSA as predictor of prostate cancer grade and stage by 5-ARI use in three consecutive screening rounds.. Cohort of f 78,615 men from the Finnish Randomized Study of Screening for Prostate Cancer.

	Gleason 7-10 PCa		
	1st screening round	2nd screening round	3rd screening round
5-ARI usage before the screening round	AUC (95% CI)*	AUC (95% CI)*	AUC (95% CI)*
None	0.88 (0.87-0.89)	0.88 (0.88-0.89)	0.92 (0.91-0.93)
Any	0.79 (0.70-0.88)	0.78 (0.72-0.85)	0.84 (0.79-0.91)
	Metastatic PCa		
	1st screening round	2nd screening round	3rd screening round
5-ARI usage before the screening round	AUC (95% CI)*	AUC (95% CI)*	AUC (95% CI)*
None	0.87 (0.86-0.88)	0.88 (0.88-0.89)	0.93 (0.92-0.94)
Any	0.73 (0.64-0.82)	0.78 (0.73-0.84)	0.82 (0.77-0.88)

* From ROC analysis including age and PSA value measured at the analysed screening round

Table 5: Effect of PSA-based screening on prostate cancer incidence compared to non-screening in three screening rounds, analysis stratified by 5-ARI usage before the screening round. Cohort of 78,615 men from the Finnish Randomized Study of Screening for Prostate Cancer.

	1st screening round			2nd screening round			3rd screening round		
	Overall PCa	Gleason 6	Gleason 7-10	Overall PCa	Gleason 6	Gleason 7-10	Overall PCa	Gleason 6	Gleason 7-10
5ARI usage before the screening round	(HR 95% CI)	(HR 95% CI)	(HR 95% CI)	(HR 95% CI)	(HR 95% CI)	(HR 95% CI)	(HR 95% CI)	(HR 95% CI)	(HR 95% CI)
None	1.60 (1.45-1.77)	1.97 (1.74-2.22)	1.30 (1.07-1.59)	1.31 (1.20-1.42)	1.72 (1.55-1.92)	0.84 (0.72-0.97)	1.13 (1.04-1.23)	1.49 (1.31-1.69)	0.92 (0.82-1.03)
Any	0.78 (0.43-1.42)	0.93 (0.46-1.88)	0.45 (0.13-1.62)	0.72 (0.51-1.00)	0.81 (0.52-1.24)	0.61 (0.36-1.04)	1.02 (0.80-1.31)	1.22 (0.83-1.77)	0.88 (0.63-1.23)
P for interaction	0.019	0.40	0.11	0.001	0.001	0.27	0.43	0.31	0.79