OUTCOMES OF PSA-BASED PROSTATE CANCER SCREENING AMONG MEN USING NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

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Suomalaisessa eturauhassyövän seulontatutkimuksessa, joka on suurin komponentti Eurooppalaista eturauhassyövän seulonnan monikeskustutkimusta, todettiin pieni, ei-tilastollisesti merkitsevä alentuma eturauhassyöpäkuolleisuudessa tutkittaessa prostata spesifiseen antigeeniin (PSA) perustuvaa eturauhassyövän seulontaa verrattuna eurooppalaiseen vastaavaan tutkimukseen. PSA:han perustuva eturauhassyövän seulonta on kuitenkin ristiriitaista siihen liittyvän ylidiagnostiikan vuoksi. Ylidiagnostiikka aiheuttaa turhia kustannuksia ja kärsimystä niin yhteiskunnalle kuin potilaille. Aikaisemmissa tutkimuksissa todettiin tulehduskipulääkkeiden laskevan veren PSA-pitoisuuksia, todennäköisimmin vähentämällä intraprostaattisesta tulehduksesta johtuvia PSA:n nousuja. Omassa tutkimuksessani tutkimme, vaikuttaako eturauhassyövän seulonnan kohdistaminen tulehduskipulääkkeiden käyttäjiin eturauhassyöpäriskiin ja – kuolleisuuteen.

Tutkimuksen aineistona toimi Suomalaisen eturauhassyövän seulontatutkimuksen 78615 miestä, jotka oli satunnaistettu kahteen tutkimusryhmään. Tieto tutkittavien tulehduskipulääkkeiden käytöstä saatiin reseptitietokeskuksesta. Eturauhassyövän riskiä ja kuolleisuutta tutkittiin seulotuilla verrattuna seulomattomiin tulehduskipulääkkeiden käyttäjillä ja ei-käyttäjillä käyttämällä ikävakioitua Cox:in Regressio – mallia.

Tutkimustulokset olivat seuraavat: seulonta vähensi hyvin erilaistuneiden eturauhassyöpien (Gleason 6) ja paikallisten eturauhassyöpien diagnosointia tulehduskipulääkkeiden käyttäjillä verrattuna ei-käyttäjiin. Seulonta myös vähensi eturauhassyöpäkuolleisuutta tulehduskipulääkkeiden käyttäjillä, mutta ei ei-käyttäjillä. Tosin tulos ei ollut tilastollisesti merkitsevä.

Tämänhetkisen käsityksemme mukaan olemme ensimmäistä kertaa osoittaneet eturauhassyövän seulonnan olevan tehokkaampaa tulehduskipulääkkeiden käyttäjillä verrattuna ei-käyttäjiin. Tutkimuksessamme totesimme, että kohdistamalla seulonnan tulehduskipulääkkeiden käyttäjiin, diagnosoidaan vähemmän hyvin erilaistuneita eturauhassyöpiä ja paikallisia eturauhassyöpiä. Seulonnan kohdistaminen saattaa vähentää kyseisten syöpämuotojen ylidiagnostiikkaa.

SISÄLLYSLUETTELO

Outcomes of PSA-based prostate cancer screening among men using non-steroidal anti-inflammatory drugs

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ABSTRACT

Background: Finnish Randomized Study of Screening for Prostate Cancer (FinRSPC), the largest component of the European Randomized Study of Screening for Prostate Cancer (ERSPC), did show a smaller, non-significant reduction in prostate cancer-specific mortality by systematic PSA-based screening compared with the ERSPC results overall. Non-steroidal anti-inflammatory drugs (NSAIDs) reduce inflammation and also PSA elevation due to intraprostatic inflammation. We explored whether NSAID usage modifies the mortality effect of PSA-based screening.

Materials and methods: A cohort of 80,458 men from the FinRSPC were linked to a comprehensive national prescription database to obtain information on NSAID reimbursements prior to screening. Prostate cancer risk and mortality were compared between the FinRSPC screening arm and the control arm among NSAID users and non-users using age-adjusted Cox regression model.

Results: Screening increased the detection of Gleason 6 (HR 1.79, 95% CI 1.62-1.97 and HR 1.28, 95% CI 1.19-1.38) and localized prostate tumors (HR 1.50, 95% CI 1.39-1.63 and HR 1.04, 95% CI 1.98-1.10) more among NSAID non-users than users, respectively (p for interaction < 0.001 for both). This difference was observed in each three screening rounds. Detection of metastatic PCa was similar in both NSAID users and non-users.

Screening decreased prostate cancer mortality among men using NSAIDs (HR 0.79, 95% CI 0.67-0.94), but not among non-users (HR 1.00, 95% CI 0.65-1.56), though the difference was not significant. Acetaminophen usage was not associated with similar risk differences.

Conclusions: Screening detected fewer well-differentiated, localized tumors among NSAID-users than non-users. This suggests that PSA screening may cause less overdiagnosis within this sub-group.

INTRODUCTION

Benefits of screening for prostate cancer (PCa) with prostate-specific antigen (PSA) are controversial. Screening has been shown to be reduce PCa mortality, but it also causes overdiagnosis of indolent, early stage PCa and thus overtreatment1.

In laboratory studies, non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to reduce proliferation of PCa cells2, but in epidemiologic studies effects on prostate cancer risk or mortality have been conflicting3-5. On the other hand, several studies have demonstrated that NSAID usage lowers serum PSA6-8. Thus it could be presumed that NSAID usage may modify the effects of PSA-based screening. No studies to date have explored this topic.

We investigated the efficacy of PCa screening between NSAID users and non-users in the Finnish Randomized Study of Screening for Prostate Cancer (FinRSPC). We explored the effect of screening on overall prostate risk, risk of high-risk disease and risk of PCa death by NSAID usage. The goal of our study is to determine whether NSAID usage modifies the effect of screening on detection of high-risk PCa or PCa mortality.

MATERIALS & METHODS

Study cohort

The Finnish Randomized Study of Screening for Prostate Cancer is the largest component of the multicenter ERSPC trial, including 80,458 men aged 55, 59, 63, or 67 years at the start of the study1,9. Men with PCa diagnosis at baseline were excluded. The remaining men were randomized into two trial arms. The screening arm (SA) consisted 31,866 men and the control arm (CA) 48,278 men. Men in the screening arm were invited to their local outpatient clinic for PSA screening test.

The screening was carried out at four-year intervals. The first screening round was performed in 1996-1999, the second in 2000-2003 and the third in 2004-2007. After age 71, no re-invitations were made, thus men aged 67 at the beginning of the study were invited for screening only twice. Re-invitations stopped also if a person was diagnosed with PCa or had emigrated from the study area. Information on place of residence was obtained from the Population Register Center.

If serum PSA was greater or equal to 4.0 ng/ml, the man was referred to a urological clinic for diagnostic examinations, including digital rectal examination (DRE), transrectal ultrasound and prostate biopsy. PSA 3.0-3.9 ng/mL was an indication for an additional test, which in 1996-1998 was DRE and since 1999 a free/total PSA ratio with 16% as the cutoff. Men with any of the findings mentioned above were considered screen-positive and referred to a prostate biopsy.

Information on prostate cancer cases detected in the control arm, as well as cases in the screening arm detected between the screening rounds and among non-participants was obtained from the comprehensive nation-wide Finnish Cancer Registry. Clinical information was abstracted from medical records. Information on prostate cancer cases included date of diagnosis, Gleason grade, TNM stage and primary treatment.

All deaths in Finland are registered by the cause of death registry maintained by Statistics Finland. The accuracy of recorded PCa deaths was validated by cause of death committee adjudicating the cause of death based on medical records, blinded in terms of official cause of death and trial arm. This study included PCa cases and deaths until the beginning of 2013.

Information on NSAID usage

Information on use of NSAIDs during 1995-2009 for the whole study cohort was obtained from the prescription database of the Social Insurance Institution (SII) of Finland. The information included the date, drug dose, amount of doses and amount of packages for each drug purchase. SII is a governmental agency operating under the Ministry of Health. It provides reimbursements for outpatient purchases of physician-prescribed medications for Finnish residents. Over-the-counter purchases are not reimbursed, thus not recorded. Additionally, drugs used during hospital inpatient periods are not recorded.

Information on use of prescription-free NSAIDs (frequency, dose and duration) was collected in the third screening round by a questionnaire sent to men in the SA; 11,795 men participating at the third screening round, giving response rate of 92.6%.

Statistical analysis

Cox proportional hazards regression was used to analyze age-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) for PCa risk and mortality by trial arm.

PCa risk both overall and by biopsy Gleason grade and M stage at diagnosis were compared between the screening arm and control arm stratified by NSAID usage and cumulative duration of use during the study period. Only NSAID usage occurring before PCa diagnosis was included. Separate analyses were stratified by use of coxibs, acetaminophen and aspirin. Effect of PSA screening on risk of PCa death was also analyzed separately among NSAID users and non-users. Effect modification by NSAID usage was evaluated by adding an interaction term between NSAID usage and the trial arm to Cox regression model.

For analyses on screening effects by screening round, NSAID usage for the whole study population was limited to usage that occurred in the time period before the screening round under analysis. Prostate cancer cases were limited to those detected at the time period before the initiation of next screening round. Prostate cancer deaths were limited to those occurring between screening and 1.1.2013.

Median PSA values were compared by NSAID usage at each screening round. Additionally, we evaluated the direction and magnitude of change in PSA among men who were not previous NSAID users, but started usage between the screening rounds.

The ability of PSA to predict screen-detected PCa among men in the screening arm was tested with receiver operating characteristics (ROC) analysis. Only cases diagnosed within four years of screening (i.e. between consecutive screening rounds) were included. Area Under the Curve (AUC) from a model including age and PSA was compared to a model including additionally ever-use of NSAIDs as well as amount and duration of NSAID usage. The comparison was performed separately for all three screening rounds.

All statistical tests are two-sided. Analyses were carried out using IBM SPSS statistics 22 software (Chicago, IL, USA)

RESULTS

Baseline characteristics

Population characteristics among NSAID users and non-users have been described in detail previously4. In short, prevalence of use for prescription NSAIDs was high in both study arms (77.7% screening arm, 74.7% control arm). NSAID users were also more likely to have used other drugs such as antidiabetic, antihypertensive and cholesterol-lowering drugs.

Effect of screening on prostate cancer incidence among NSAID users and non-users

Compared to the control arm, screening expectedly increased the overall PCa incidence, but less in NSAID users (HR 1.03, 95% CI 0.97-1.09) than in non-users (HR 1.45, 95% CI 1.34-1.57, p for interaction < 0.001) (Table 1). Analyses by type of NSAID (acetaminophen, acetylsalicylic acid and COX-inhibitors) showed a similar pattern as NSAIDs in general. Duration of NSAID usage further modified the effect of screening: among men who had more than two years of NSAID usage PSA screening did not increase the overall PCa incidence compared to the control arm (p for interaction < 0.001).

Also the effect of screening on incidence of Gleason 7-10 PCa depended on NSAID usage; screening lowered the incidence among NSAID users, but not among non-users (Table 1). Similarly, screening decreased incidence of metastatic PCa slightly more among NSAID users, although the difference to non-users was non-significant. The effect of screening tended to be similar for each NSAID (Table 1).

PSA screening and prostate cancer mortality by NSAID usage

Screening reduced PCa mortality in NSAID users (HR 0.79, 95% CI 0.67-0.94), but not in non-users (HR 1.00, 95% CI 0.65-1.56) (Table 2). However, the difference did not reach statistical significance. The duration of usage did not modify the effect of screening on PCa mortality. In separate analyses, effect of screening on prostate cancer mortality was also similar among aspirin, coxib and acetaminophen users and non-users (Table 2).

Effect of screening on prostate cancer incidence and mortality by NSAID usage at each screening round

Similar to the main analysis, screening increased PCa incidence less among NSAID users than among non-users at the first screening round (HR 1.99, 95% CI 1.64-2.41 and HR 2.56, 95% CI 2.19-2.99, p for interaction 0.048) (Table 3). The difference in PCa incidence between NSAID users and non-users diminished at subsequent screening rounds, though it remained significant.

Screening did not reduce PCa mortality significantly among NSAID users or non-users in the first or third screening rounds (Table 3). During the second round, screening lowered PCa mortality only among NSAID users (HR 0.73, 95% CI 0.59-0.91, p for interaction 0.06).

Effect of NSAID usage on PSA

In the first screening round, the median PSA levels did not differ by NSAID usage (Table 4), but at the second and third screening rounds, men who started NSAID usage between the screening rounds had non-significantly lower median PSA compared to the non-users, especially in users whose cumulative amount and duration of usage exceeded the median. The difference was largest in the third screening round. The median PSA increase from the previous measurement was lower among men who started NSAID usage between the screening rounds. The amount or duration of NSAID usage above median did not affect the median PSA change (Table 4).

The median percentage of free PSA was lower in NSAID users compared to non-users in the first screening round, but higher on two subsequent screening rounds (Table 4). Percentage of free PSA increased more between the screening rounds among men who started NSAID usage (Table 4).

PSA as predictor of PCa incidence and PCa death

AUC for PSA and age in predicting PCa and PCa death in each screening round was not significantly different between NSAID users and non-users (Table 5).

DISCUSSION

To our knowledge, our results suggest for the first time that PSA screening causes less overdiagnosis of localized, Gleason 6 PCa among NSAID users than non-users. The reduction in detection of Gleason 6 tumors was larger among those men who had used NSAIDs for more than two years, which supports a causal association not produced by unmeasured background factors or confounding by indication.

Our finding of slower progression of median PSA between the screening rounds among men who started NSAID usage supports previous studies reporting PSA lowering-effect of NSAIDs. 6,7 At the same time we observed increases in the median percentage of free PSA among NSAID users. This led to lower proportion of screen-positive men among NSAID users. The PSA effect diminished between the second and third screening rounds witch suggests that the impact of NSAIDs as a modifier of PSA values may decrease over time. Previous studies have demonstrated that NSAIDs lower PSA in men with chronic prostatitis when used in combination with antibiotics7,8. Thus NSAIDs may decrease the likelihood of PSA elevation due to inflammation and thus improve the accuracy of PSA-based prostate cancer screening. However, in ROC analyses NSAID usage did not improve prediction of screen-detected cancer by age and PSA. Thus further studies will be needed on what type of PCa NSAIDs mostly affect.

In the European Randomized Study of Screening for Prostate Cancer (ERSPC) a 21% reduction in PCa mortality was reported1. However, the result varied between the participating centers. In the Finnish Randomized Study of Screening for Prostate Cancer (FinRSPC), the largest component of the ERSPC, a modest 10% risk decrease by screening was observed9, whereas in the Swedish part of ERSPC clear reduction in PCa mortality was found10. Differences in NSAID usage between the ERSPC centers may have been one factor behind the differing responses.

Systemic and intraprostatic inflammation can elevate serum PSA levels but the association with PCa risk is controversial11,12. This makes serum PSA levels a controversial screening tool as elevated PSA leads to screen-positivity and results in prostate biopsies and often to overdiagnosis, i.e. detection of localized well-differentiated malignancies of without clinical significance. As NSAID use may reduce overdiagnosis associated with PSA screening, our results suggest that NSAID usage should be taken into account when considering targeted screening efforts.

A strength of our study was that we could assess the effect of screening in a randomized setting. Also information on physician-prescribed NSAID usage was comprehensive and free of recall bias as it was collected from a national database which routinely collects information from all Finnish residents regardless of health status. Information on prescription based purchases is exceptionally detailed, allowing us to accurately evaluate cumulative NSAID usage even in separate screening rounds.

A limitation in our study was that we did not have detailed information about prescription-free use of NSAIDs. Thus over-the-counter may have caused exposure misclassification and bias towards the null in our results. However, the exposure misclassification is unlikely to differ by screening trial arm, thus it may not have had a relevant effect.

CONCLUSION

We have demonstrated that use of NSAIDs reduces detection of Gleason 6 tumors associated with PSA-based prostate cancer screening. Furthermore, our findings suggested a larger mortality reduction by screening among men on NSAIDs, though the difference was not significant. Future studies on the efficacy of prostate cancer screening should consider prevalence of NSAID usage in the study population as screening may be more accurate in NSAID users.

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CONFLICTS OF INTEREST

The authors declare the following conflicts of interest:

TJ Murtola: lecture fees from Astellas, Janssen and MSD, paid consultant for Astellas and Jansen. A Vettenranta: 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.

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Table 1 Effect of screening on prostate cancer incidence overall and by stage and grade among users and non-users of non-steroidal anti-inflammatory drugs. Study population of 78,615 men from the Finnish Randomized Study of Screening for Prostate Cancer

	HR (95% CI) for prostate cancer in the FinRSPC screening arm compared to the control arm				
Subgroups:	Overall PCa	Gleason 6	Gleason 7-10	Localized PCa	Metastatic PCa
NSAID users					
None	1.45 (1.34-1.57)	1.79 (1.62-1.97)	1.04 (0.92-1.20)	1.50 (1.39-1.63)	0.84 (0.60-1.18)
Any	1.03 (0.97-1.09)	1.28 (1.19-1.38)	0.79 (0.73-0.86)	1.04 (0.98-1.10)	0.63 (0.50-0.80)
P for interaction	< 0.001	< 0.001	< 0.001	< 0.001	0.163
Years of usage					
less than 2 years	1.12 (1.04-1.20)	1.44 (1.31-1.59)	0.79 (0.71-0.88)	1.14 (1.06-1.23)	0.62 (0.46-0.83)
more than 2 years	0.92 (0.85-1.00)	1.06 (0.94-1.20)	0.79 (0.71-0.90)	0.92 (0.84-1.01)	0.64 (0.44-0.94)
Acetaminophen users					
None	1.20 (1.14-1.26)	1.49 (1.40-1.58)	0.88 (0.82-0.95)	1.23 (1.17-1.29)	0.67 (0.55-0.82)
Any	0.86 (0.75-0.98)	1.07 (0.88-1.30)	0.73 (0.61-0.86)	0.86 (0.74-0.98)	0.81 (0.50-1.32)
Years of usage					
less than 2 years	0.93 (0.81-1.08)	1.18 (0.95-1.47)	0.78 (0.65-0.94)	0.95 (0.81-1.11)	0.88 (0.50-1.53)
more than 2 years	0.63 (0.47-0.84)	0.75 (0.49-1.14)	0.54 (0.37-0.79)	0.58 (0.42-0.79)	0.62 (0.22-1.74)
Aspirin users					
None	1.17 (1.12-1.22)	1.45 (1.37-1.55)	0.87 (0.81-0.93)	1.19 (1.13-1.25)	0.67 (0.55-0.82)
Any	1.01 (0.83-1.21)	1.40 (1.07-1.82)	0.69 (0.53-0.91)	1.05 (0.86-1.29)	1.03 (0.55-1.93)
Years of usage					
less than 2 years	1.05 (0.84-1.31)	1.46 (1.06-2.01)	0.74 (0.53-1.02)	1.12 (0.87-1.43)	1.08 (0.51-2.26)
more than 2 years	0.93 (0.66-1.30)	1.29 (0.81-2.04)	0.60 (0.36-0.99)	0.95 (0.66-1.36)	0.88 (0.26-3.02)
Coxib users					
None	1.07 (1.01-1.12)	1.31 (1.21-1.40)	0.84 (0.78-0.91)	1.07 (1.01-1.14)	0.63 (0.50-0.79)
Any	0.91 (0.81-1.01)	1.12 (0.95-1.31)	0.75 (0.65-0.88)	0.90 (0.79-1.01)	0.57 (0.35-0.92)
Years of usage					

less than 2 years	0.96 (0.84-1.10)	1.16 (0.95-1.41)	0.82 (0.69-0.99)	0.96 (0.83-1.12)	0.66 (0.38-1.16)
more than 2 years	0.80 (0.65-0.98)	1.03 (0.77-1.36)	0.61 (0.47-0.81)	0.76 (0.61-0.95)	0.38 (0.14-0.99)

Table 2 Effect of screening on prostate cancer –specific mortality among users and non-users of non-steroidal anti-inflammatory drugs. Study population of 78,615 men from the Finnish Randomized Study of Screening for Prostate Cancer.

	HR (95% CI) for prostate cancer death in the FinRSPC screening arm compared to the control arm			
Pattern of users	All NSAID users	Acetaminophen users	Aspirin users	Coxib users
None	1.00 (0.65-1.56)	0.78 (0.64-0.94)	0.81 (0.69-0.97)	0.82 (0.68-0.99)
Any	0.79 (0.67-0.94)	0.92 (0.69-1.23)	0.85 (0.49-1.47)	0.80 (0.58-1.11)
less than 2 years	0.67 (0.52-0.86)	0.75 (0.39-1.44)	0.83 (0.39-1.81)	0.94 (0.58-1.53)
more than 2 years	0.75 (0.52-1.09)	0.53 (0.19-1.45)	1.03 (0.29-3.66)	0.26 (0.06-1.15)

Table 3 Prostate cancer incidence and mortality in the FinRSPC screening arm compared to control arm by screening round among men who had used NSAIDs before the screening

	PCa incidence				PCa mortality		
	Number of screening round				Number of screening round		
	1st	2nd	3rd		1st	2nd	3rd
	HR (95% CI)	HR (95% CI)	HR (95% CI)		HR (95% CI)	HR (95% CI)	HR (95% CI)
n of PCa cases (users/non-users)	262/320	432/222	685/226	n of PCa deaths (users/non-users)	72/70	49/32	18/9
NSAID usage before screening							
None	2.56 (2.19-2.99)	1.87 (1.68-2.09)	1.25 (1.15-1.35)		0.85 (0.69-1.06)	1.03 (0.78-1.36)	0.99 (0.67-1.48)
Any	1.99 (1.64-2.41)	1.55 (1.41-1.70)	1.12 (1.07-1.18)		0.77 (0.60-0.99)	0.73 (0.59-0.91)	0.82 (0.65-1.04)
P for interaction	0.048	0.010	0.038		0.55	0.06	0.40

Table 4 Median PSA and change in PSA value between screening round among NSAID users and non-users

	1st screening round		2nd screening round			3rd screening round		
Initiation of NSAID use between screening rounds	Median PSA	n (%) of screen-positive men	Median PSA	Median PSA change from previous screening	n (%) of screen-positive men	Median PSA	Median PSA change from previous screening	n (%) of screen-positive men
No	1.07	2,042 (18.6%)	1.33	0.26 (ref)	1,109 (16.7%)	1.46	0.13 (ref)	474 (14.7%)
Yes	1.07	1,702 (17.6%)	1.30	0.23	1,940 (16.2%)	1.40	0.10	1,273 (13.4%)
Total amount of usage above median	1.07	810 (17.5%)	1.29	0.22*	946 (15.9%)	1.37	0.08	619 (13.3%)
Total duration of usage above median	1.07	852 (17.9%)	1.28	0.21*	810 (15.7%)	1.35	0.07	478 (13.3%)
	Free/total PSA ratio		Free/total PSA ratio	Change in free/total PSA ratio		Free/total PSA ratio	Change in free/total PSA ratio	
None	26.40		26.15	-0.25 (ref)		28.50	2.35 (ref)	
Any	26.02		26.30	0.28		28.90	2.60	
Total amount above median	26.10		26.40	0.30*		29.00	2.60	
Total duration above median	26.20		26.50	0.30*		29.20	2.70	

* P-value ≤ 0.01 for change in PSA among men who initiated NSAID usage between two screening rounds compared to men who did not. Calculated using linear regression with natural logarithm of the change in PSA or free/total PSA as the dependent variable and amount or duration of NSAID usage, age and use of 5-alpha-reductase inhibitors and antidiabetic medication use as the explanatory variables

Table 5 Median PSA and change in PSA value between screening round among NSAID users and non-users

	1st screening round (1996-1999)		2nd screening round (2000-2003)		3rd screening round (2004-2008)	
NSAID usage*	None	Any	None	Any	None	Any
n of PCa cases before next screening round	564	527	976	2,123	1,841	6,135
AUC (95% CI) for PCa risk	0.87 (0.85-0.89)	0.87 (0.84-0.90)	0.80 (0.77-0.82)	0.78 (0.76-0.80)	0.77 (0.74-0.81)	0.76 (0.74-0.78)
n of PCa deaths after screening	367	285	207	367	145	508
AUC (95% CI) for PCa death	0.74 (0.68-0.79)	0.76 (0.71-0.82)	0.74 (0.65-0.82)	0.77 (0.69-0.84)	0.81 (0.62-1.00)	0.86 (0.74-0.98)

* NSAID usage status before the screening