Prostate cancer screening with PSA, kallikrein panel and MRI

A preliminary report from the ProScreen randomized trial

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ABSTRACT

IMPORTANCE

Prostate-specific antigen (PSA) screening has potential to reduce prostate cancer mortality but frequently detects prostate cancer that is not clinically important.

OBJECTIVE

To describe rates of low-grade (Grade Group 1) prostate cancer and high-grade (Grade Group 2-5) prostate cancer using a screening protocol consisting of PSA, a four-kallikrein panel and magnetic resonance imaging.

DESIGN

Randomized clinical trial

SETTING

Helsinki and Tampere, Finland

PARTICIPANTS

The ProScreen trial randomized 61 193 men aged 50–63 years who were free of prostate cancer to screening or to a control group without a screening intervention in a 1:3 ratio between February 2018 and July 2020.

INTERVENTIONS

Men randomized to screening underwent PSA testing. Those with PSA ≥3.0 ng/mL underwent additional testing with a four-kallikrein panel risk score for high-grade prostate cancer. Men with a kallikrein panel score ≥7.5% underwent MRI of the prostate gland,

followed by targeted biopsies for those with abnormal prostate gland MRI findings. Data were collected until May 2023.

MAIN OUTCOMES AND MEASURES

In exploratory and descriptive analyses, the cumulative incidence of low-grade prostate cancer and high-grade prostate cancer after the first screening round were compared between study groups.

RESULTS

Of 60 745 eligible men with mean age 57.3 years, 15 201 were randomized to screening group and 45 544 to control group. Of 14 847 eligible men invited to screening, 7744 (51%) participated. Among the screened men, 32 low-grade prostate cancers (cumulative incidence 0.41%) and 128 high-grade cancers (1.65%) were detected. In the entire screening group, including participants randomized to screening who did not take part in screenings, there were 39 (0.26%) low-grade and 172 (1.13%) high-grade cancers. In the control group, 65 (0.14%) low-grade and 282 (0.62%) high-grade cancers occurred during a median follow-up of 3.2 years. The risk difference for the screening versus the control group (comparison of randomly assigned populations) was 0.11% (95% CI 0.03%–0.20%) for low-grade and 0.51% (95% CI 0.33%–0.70%) for high-grade cancer.

CONCLUSIONS AND RELEVANCE

In this preliminary descriptive report from a randomized clinical trial, compared to a control group that was not invited for screening, a single prostate cancer screening intervention that included PSA, a kallikrein panel for patients with PSA ≥3.0 mL, and MRI, detected one additional high-grade cancer per 200 men invited to screen and one low-grade cancer per

900 men invited to screen. These preliminary findings from a single round of screening should be interpreted cautiously, pending results of the primary mortality outcome.

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KEY POINTS

Question In this descriptive and preliminary report from a randomized clinical trial of a prostate cancer screening intervention that consisted of PSA testing, a four-kallikrein panel for men with PSA ≥3, and MRI, what were rates of prostate cancer detection, compared to a group not invited for screening?

Findings In this preliminary report from a clinical trial, in which 60 745 men aged 50-63 were randomized to either prostate cancer screening with PSA, a four-kallikrein panel for those with PSA ≥3.0 and MRI, or a control group not invited for screening, the first round of screening increased detection of high-grade prostate cancer by one case per 200 invited men and increased detection of low-grade prostate cancer by one case per 900 men.

Meaning In this preliminary descriptive report, a single prostate cancer screening intervention that included PSA, a kallikrein panel for patients with PSA ≥3.0, and MRI, the screening intervention detected one high-grade prostate cancer per 200 men invited to screen and one low-grade prostate cancer per 800 men invited to screen. These preliminary findings should be interpreted cautiously, pending results of the primary outcome of prostate cancer mortality.

Introduction

Screening for prostate cancer with PSA has the potential to reduce death from prostate cancer. However, PSA screening frequently detects prostate cancer that is not clinically significant but may result in unnecessary procedures and adverse effects.[1–3]

Several methods have been developed to increase specificity for high-grade prostate cancer. A kallikrein panel with four components (total PSA, free PSA, intact PSA and human kallikrein-2) has been shown to reduce the number of men referred to biopsy, while retaining sensitivity for high-grade cancer.[4-5] Magnetic resonance imaging (MRI) in men with elevated PSA may reduce the detection of low-grade prostate cancer (Grade Group 1 or Gleason score <7).[6–7]

The aim of the intervention in the population-based ProScreen trial was to reduce unnecessary diagnosis of prostate cancer while reducing prostate cancer mortality. This clinical trial used a three-phased screening algorithm with PSA, kallikrein panel score, and MRI, with biopsies reserved for men with suspicious results from all three tests (except MRI-negative men with PSAD ≥0.15 ng/mL).[8] Participants will undergo re-screening every 2-6 years, according to the baseline risk.

This preliminary and exploratory report describes rates of high-grade and low-grade prostate cancer diagnoses after the first screening round in this clinical trial. Rates of high-grade prostate cancer and low-grade prostate cancer were compared to a control arm that was not offered screening.

METHODS

Trial Design

The trial protocol can be found in Supplemental file 1 and statistical analysis plan in Supplemental file 2. The protocol was reviewed by the Ethics Committee of the Helsinki University Hospital (HUS 2910/2017). The need for an informed consent from the control group was waived. Permission to collect data on cancer cases from the hospital records and cancer registry was obtained from the National Institute for Health and Welfare (THL 676/2018). Enrolment took place between May 2018 and May 2022, and outcome data until June 2023 was included in the analyses.

This clinical trial is a randomized, population-based pragmatic screening trial of men aged 50–63 years. The age range was chosen to allow at least two screening rounds before age 71 for all men. The screening intervention comprises plasma PSA, a four-kallikrein panel, and a multiparametric MRI of the prostate. Re-screening interval is risk-stratified based on the first-round PSA: men with PSA ≥3.0 ng/mL are invited after two years, those with PSA 1.5–2.99 ng/mL after four, and with PSA <1.5 ng/mL at six years. Individuals who decline to screen after initial invitations are also invited to the subsequent screening rounds. The primary endpoint is prostate cancer mortality. Process measures and ancillary endpoints include incidence of high-grade and low-grade prostate cancer, sensitivity for high-grade cancer, incidence of advanced disease, quality of life, and cost-effectiveness.

Here we report results comparing cancer detection among men invited for screening in the intervention group with men in the control group receiving usual standard of care with no intervention (main analysis comparing randomly assigned populations) and among men attending the screening with the control group (ancillary per protocol or ‘screening

received' analysis). Study design, statistical analysis plan, and a pilot study evaluating the feasibility and acceptability of the study procedures have been published previously.[8–10]

Participants and Randomization

We identified all men aged 50–63 and residing in the cities of Helsinki and Tampere, Finland at baseline in 2018 through the Population Data Services Agency and randomized them prior to consent (Zelen design)[11-12] to the screening or control group using a 1:3 allocation ratio. Randomization was performed (using computer-generated pseudo-random numbers) by a trial statistician (J Raitanen) in four batches (approximately 15 000 men each time) between February 2018 and July 2020 (Figure 1). No blinding was used.

Men free of prostate cancer at entry were eligible for inclusion.

Men allocated to the screening group were sent an information package describing the aims and procedures of the trial, and a consent form by the trial coordinator (K Natunen). Besides consent, the participants also provided information on previous PSA measurements (for any reason), prior prostate biopsies, and family history of prostate cancer. Men in the control group were not contacted (apart from questionnaire surveys mailed to a random sample on health care costs and quality of life of 6026 men [13%] for later analyses).

Blood sampling

Participating men had a 30 mL peripheral venous blood sample drawn and separated into whole blood, plasma, and serum. The blood samples were drawn, and PSA analyzed by HUSLAB (Helsinki) or Fimlab (Tampere) laboratory network. If the PSA was ≥3.0 ng/mL, plasma was shipped to Lund University, Wallenberg Research laboratories at Skåne University Hospital in Malmö, Sweden, for determination of the four kallikrein risk score

(comprising total PSA, free PSA, intact PSA, and human kallikrein-2). For free and total PSA dual-label DELFIA Prostatus total/free PSA-Assay[13] calibrated against World Health Organization (WHO) 96/670 (PSA-WHO) and WHO 68/668 (free PSA-WHO) standards was used, and assays for intact PSA and human kallikrein-related peptidase 2 used F(ab')2 fragments of monoclonal capture antibodies to reduce nonspecific assay interference.[14] A pre-specified statistical model based on the man's age and the four kallikrein markers[15] was applied to estimate the probability of high-grade prostate cancer expressed as the kallikrein panel risk score ranging theoretically 0–100% (commercially available as the 4Kscore test in the US). Risk scores ≥7.5% were considered positive as recommended in the literature.[16] However, prior prostate biopsy or digital rectal examination findings were not utilized in the calculation of the score.

MRI, Biopsies, and Pathology

Men with kallikrein panel risk scores ≥7.5% were referred to the urology department at Helsinki or Tampere University Hospital. First, a 1.5 T or 3 T multiparametric (T2-weighted, diffusion-weighted, and dynamic contrast-enhanced) MRI of the prostate was performed. The MRI images were evaluated by radiology teams with both abdominal and general radiologists. The images were graded according to the Prostate Imaging Reporting and Data System (PI-RADS) version 2.1.[17] The PI-RADS score for a region of interest (RoI) indicates the level of suspicion for high-grade prostate cancer on a scale of 1–5, where a higher score indicates higher suspicion; scores 3–5 were considered positive. Each RoI was marked on the MRI images using the DynaCad software. Men with a PI-RADS score of 3–5 were referred to software-targeted transrectal fusion biopsies of the suspected lesions, with 2–4 cores per RoI using the UroNav system. No routine systematic biopsies were taken except

for men with a negative MRI (PI-RADS<3) but elevated PSA density (>0.15 ng/mL^2) – for them 10–12 cores were obtained to avoid missing high-grade cancers.

Each biopsy core was separately evaluated according to the ISUP guidelines[18] by uropathologists at Helsinki and Tampere University Hospitals. Grade Group (GG) 1 cancers were regarded as low grade and those in GG 2-5 as high grade.[19]

Clinical features including GG, clinical stage and treatment were abstracted from the hospital records including pathology databases for all cases (including those identified from the cancer registry) by study nurses and the trial coordinator.

Study Outcomes

The primary outcome of the trial is prostate cancer mortality with analyses planned at 10 and 15 with no data currently available. The current report gives preliminary results from the first screening round on detection of high-grade and low-grade cancer, on results of the screening tests, and frequency of biopsy referral. Incident prostate cancer cases since randomization were identified from the population-based Finnish Cancer Registry with a high completeness of coverage[20] and from the hospital pathology databases.

Sample Size Calculation

Pre-trial sample size calculations indicated that with 111 000 men in the trial with 1:3 allocation would provide a statistical power of 0.89 to detect a 25% relative risk reduction in prostate cancer mortality at 15 years (see Statistical analysis plan).[10]

Statistical Analyses

The analyses of this preliminary and descriptive report were not covered by the statistical analysis plan focusing on the main outcome of prostate cancer mortality. The risk of high-

grade and low-grade prostate cancer was evaluated as cumulative incidence, with the number of cases relative to number of men, with follow-up started at randomization. The number of cases relative to the duration of total follow-up time in person-years (incidence density) was not used because screening always induces lead-time due to earlier detection and therefore results in poor comparability of rates between the trial arms.

The main analysis was based on the study population as allocated by randomization (both screening participants and participants randomized to screening who did not take part in screenings included in the screening group), with the effect of screening quantified as risk difference between the entire screening and control groups as an indicator of the population level impact of the screening program. An ancillary analysis comparing cumulative incidence in the screened men in the intervention group and all men in the control group (per protocol analysis) is presented as an indicator of the performance of the screening process. Information on Grade Group was missing for 16 cancer cases (2.8%) and the main analysis is based on a complete case analysis with an ancillary analysis including imputation of the missing GGs is reported in the Appendix Table 4. Missing values were imputed based on the observed GG distribution (see Appendix 1).

Exact 95% confidence intervals (CI) for the cumulative incidences and for their differences and ratios in group comparisons were calculated using Poisson regression with Stata statistical software (version 18).

Results

Participants

Men with a previous diagnosis of prostate cancer were identified through a linkage with the Finnish Cancer Registry and hospital pathology databases (n=295) and excluded prior to randomization. Some previously diagnosed cases were identified only after randomization due to delayed cancer registration (98 in the screening and 350 in the control group). After exclusions, 60 745 men were eligible.

Of the eligible men, 45 544 were assigned to the control group and 15 201 to the screening group. The mean age at entry was 57.3 years in both groups.

Men allocated to screening (N=353, 2.3%), who had emigrated or deceased after randomization and were therefore not invited, were included in the analysis. Of the 15 201 men invited to screening, 7744 (51%) participated by December 31, 2022. Participation proportion increased with age from 47.3% at ages 50-54 to 54.5% at 60-64 years. Participation proportion was 49.3% in Helsinki and 55.5% in Tampere. Of the participants with questionnaire data, 2884 (44%) reported previous PSA measurements and 195 (3%) prior prostate biopsies (Table 1). Similar or slightly higher proportions were also reported by men in the control group (Appendix Table 1).

Among participants randomized to screening, the median PSA was 0.94 ng/mL (IQR 0.58–1.67 ng/mL) with PSA ≥3.0 ng/mL in 752 men (9.7%). The four-kallikrein panel was analyzed for the men with PSA ≥3.0 ng/mL and the median kallikrein panel risk score was 11.7% (IQR 6.6–21.3%). Of those measurements, 526 (70%) were positive findings (kallikrein panel risk score ≥7.5%).

Of 526 men with PSA ≥3 and kallikrein panel score ≥7.5%, 509 (97%) underwent MRI. Of them, 211 (41%) had a PI-RADS score of 3–5, indicating lesions suspected of high-grade cancer, and were referred to prostate biopsy. Targeted transrectal prostate biopsies (only) were performed in 209 men (99%) with positive MRI, 2.7% of the participants. In addition, all 53 men with a negative MRI (PI-RADS <3) but PSA density ≥0.15 ng/L^2 (median 0.20 ng/mL^2, IQR 0.17–0.27 ng/mL^2) had a systematic biopsy (10–12 cores). Hence, altogether 3.4% of the participants (262/7744) were biopsied.

Cancer detection

Of the targeted biopsies, 136 (65%) showed prostate cancer (1.5 biopsies to detect a cancer). Of the cases, 22 were low grade (GG 1) and 113 high grade (52 GG 2 and 61 GG 3–5 with one missing GG) (Figure 1). In addition, 25 cancers (45%, 10 GG 1, 11 GG 2, 4 GG 3–5) were detected in systematic biopsies of the 53 men with PSA density ≥0.15 ng/mL (Appendix Table 2). The overall cancer detection was 2.07% (161/7,744, 95% CI 1.76–2.40%). Detection of high-grade cancer increased with age, PSA, the four-kallikrein panel risk score, and the PI-RADS score (Appendix Table 2).

Of the screen-detected cancers, 32 (20%) were low-grade and 128 (80%) high-grade (63 GG 2 and 65 GG 3–5, one case with a missing GG). The yield of high-grade cancers was 1.65% (128/7744, 95% CI 1.37%–1.94%) and that for low-grade cancer was 0.41% (32/7744, 95% CI 0.27%–0.56%) (Figure 2). A detailed description of the cases is provided in Appendix Tables 2–4.

Among the 7457 men allocated to the screening group, who did not participate, 58 prostate cancers (7 GG 1 [cumulative incidence 0.1%] and 44 GG 2–5 [0.6%], 7 with missing GG) were diagnosed between randomization and end of 2022.

In the entire screening group, 39 (18%) low-grade and 172 (82%) high-grade cancers were diagnosed (cumulative incidence 0.26% and 1.13%, respectively) with eight cases (3.7%) lacking GG.

Among the 45 544 control group men, 355 new prostate cancers were detected during a median follow-up of 3.2 years from randomization until end of 2022 and of those, 65 were low grade (18%) and 282 high grade (79%) (eight or 2.3% with missing GG). This corresponds to a cumulative incidence of 0.14% and 0.62%, respectively (Table 2).

Analysis comparing randomly assigned groups

The main analysis contrasting the entire screening group (including participants randomized to screening who did not take part in screenings) with the control group, i.e., randomly assigned populations yielded a risk difference of 0.11% (95% CI 0.03%–0.20%) for low-grade cancer and 0.51% (95% CI 0.33%–0.70%) for high-grade cancer (Figure 3). For any prostate cancer, the risk difference was 0.66% (95% CI 0.45%–0.87%), corresponding to a risk ratio of 1.85 (95% CI 1.56–2.19).

Ancillary analyses with imputation of missing values and per protocol analysis

A modified analysis of the randomly assigned populations with imputation of the missing GG (n=16, 2.6%) is shown in Appendix Table 5.

A supplementary analysis comparing the 7744 screening participants with the control group (per protocol analysis) gave a risk difference of 0.27% (95% CI 0.12%–0.41%) for low-grade cancers and 1.03% (95% CI 0.74%–1.33%) for high-grade cancers (Table 2). For any prostate cancer, the risk difference was 1.30% (95% CI 0.97%–1.63%). Clinical stage distribution was more favorable in the screen-detected cases than in the control group, but cases among the

participants randomized to screening who did not take part in screenings had more frequently extraprostatic involvement (Appendix Table 6). Accordingly, primary treatment involved more frequently active surveillance and less androgen deprivation therapy in the screening group than control group, and especially in screen-detected cases (Appendix Table 7).

Discussion

In this preliminary and exploratory report from a population-based randomized clinical trial, a single round of a screening protocol combining PSA, a kallikrein panel risk score, and MRI before targeted biopsy resulted in a biopsy rate of 3% and detected one additional high-grade prostate cancer per 200 men invited to screening, compared to a control group that did not undergo screening. The screening intervention detected one additional low-grade prostate cancer per 900 men invited to screening, compared to control. However, these results were descriptive and should be interpreted provisionally, pending results from the trial on the primary outcome of prostate cancer mortality.

Our detection rate of high-grade cancer (1.7%) among screening participants was comparable to that in the initial screening round of ERSPC (1.8%), while detection of low-grade cancer was dramatically lower (0.4% vs. 3.2%),[21] despite the younger population in our trial. In the UK CaP trial, detection of high-grade cancer was also comparable (2.1% for men aged 50–69 years)[22], while the U.S. PLCO showed low detection of high-grade cancer at the first screen despite older age range (0.5%).[23]

In our trial, 9.7% of the men had PSA ≥3 ng/mL, adding the kallikrein panel reduced the proportion of screen-positive men to 6.8% and MRI by further to 2.7%. In addition, 0.7% were referred to systematic biopsies due to elevated PSA density despite negative MRI, with 40% of the detected cases low-grade cancer compared with 16% in targeted biopsies. This feature was a precaution to minimize potential for missing high-grade cancers and prevent harm for participants.

Recently, two randomized trials were published evaluating an MRI-based pathway in a screening setting. The Göteborg2 randomized population-based screening trial reported a

detection rate of 0.9% for high-grade cancer with PSA and MRI in the experimental group, which is slightly lower than in our study (1.7%).[24] The detection of low-grade cancer, on the other hand, was somewhat higher in Göteborg2 (0.6% compared with 0.4% in our trial). The proportions of men biopsied were comparable (2.8% in Göteborg2, 2.7% in our trial).

In the Sthlm3-MRI study, 1532 men with PSA ≥3 ng/mL were randomized to either systematic biopsy without MRI or to MRI with targeted and systematic biopsy in men with PI-RADS score ≥3.[25] Biopsies were performed on approximately 4.4% of the men eligible for the experimental group (including those with PSA >1.5 who were not randomized), while this was only 2.7% of the participants in our trial. The proportion of low-grade cancer (18%) in the MRI arm was comparable to the screened men in our trial (20%), though a direct comparison is challenging due to different study designs.

The control group in this trial was not offered screening and hence the comparator represents the current screening practice in the population. Consequently, the results inform about the absolute population-level effect of introducing systematic screening to a population with an existing, though non-systematic screening activity. The results are directly applicable to populations with a similar level of PSA testing. The reports from the two Swedish trials (Göteborg2 and Sthlm3-MRI) compared different diagnostic approaches within a screened cohort and did not include a non-screened control group.[24-25] Their results inform about the effects of adding MRI to a PSA-based screening regimen among screening participants.

The strengths of this trial include comprehensive inclusion of the target population (covering all men in the source population), larger number of randomized men than in the two Swedish trials, a high participation (51% compared with 26% in the Sthlm3-MRI study[25]

and 47% in the Göteborg2 trial[24]) and excellent compliance with diagnostic examinations. A Zelen design with randomization before consent, which is possible since the Finnish regulation does not require consent from the control population, allowed comprehensive inclusion of the entire target population.[11-12] Inter-reader variability of the MRI and pathology in the two trial centers has been evaluated.[26–27] Fair to moderate agreement was observed (kappa 0.4–0.6 for PI-RADS scores and 0.7 for histopathology grade groups). These results are similar to other published comparisons and reflect the pragmatic trial setting. The pragmatic approach serves to maintain comparability across the trial arms. In addition, it ensures robustness of the results over time, because any changes in diagnostic or therapeutic practices will similarly affect both trial arms. Further, such an approach with normal procedures in evaluating histopathology and radiology should enable generalization of the results to other similar settings.

Limitations

This study has limitations, and the current results are not appropriate for changing practice. First, the absolute differences between the two trial groups were very small and their clinical importance remains unclear. Second, prior screening reported by a substantial proportion of the participants may reduce cancer detection compared with a screening-naïve population, though the findings did not show material differences between participants with and without previous PSA tests. Third, the results are based on a single screen and some high-grade prostate cancers were likely missed, though they may be captured at subsequent rounds. No data on cancers missed at screening is currently available and interval cancer incidence is needed to assess sensitivity.

Conclusions

In this preliminary descriptive report from a randomized clinical trial, compared to a control group, a single prostate cancer screening intervention that included PSA, a kallikrein panel for patients with PSA ≥3.0, and MRI, the screening intervention detected one additional high-grade cancer per 200 men invited to screen and one low-grade cancer per 900 men invited to screen. These preliminary findings should be interpreted provisionally, pending results of the primary mortality outcome.

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Trial registration: The trial protocol was registered prior to commencement in clinicaltrials.gov (NCT03423303).

Conflict of Interest Disclosures:
HL is named on a patent on assays to measure intact PSA and a patent for a statistical method to detect prostate cancer commercialized by OPKO Health (4KScore). HL receives royalties from sales of this test, has stock in OPKO Health, and is on SAB for Fujirebio Diagnostics Inc. TLJT was an investigator in clinical trials sponsored by Pfizer, Astellas, Bayer, Lidds Ab and MSD. MM has received lecture fees from Amgen., Astellas and Orion Corporation. AR has consulted for Bayer, Janssen Pharmaceuticals, and Orion Corporation. The other authors declare no conflicts of interest.

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LEGENDS FOR FIGURES

Figure 1. CONSORT diagram of the ProScreen trial.

Figure 2. Screening results expressed per 1 000 invited men (upper panel) and per 1 000 participating men (lower panel).

TABLE 1. Characteristics of the trial population

	Screening arm*		Control arm, N (%)
	Screening participants, N (%)	All men invited to screening, N (%)	
Age (years)			
50–54	2413 (31)	5104 (34)	15,752 (35)
55–59	2896 (37)	5668 (37)	16,539 (36)
60–64	2435 (31)	4429 (29)	13,251 (29)
Center			
Helsinki	5506 (71)	11,171 (73)	33,117 (73)
Tampere	2238 (29)	4030 (27)	12,425 (27)
Previous PSA (N=6745)			
Past 12 months	907 (13)		
Past 12–24 months	845 (13)		
Past 3–5 years	806 (12)		
More than 5 years ago	416 (6)		
Never	3771 (56)		
Previous prostate biopsy (N=6513)			
Yes	195 (3)		
Prostate cancer in a first-degree relative (N=6513)			
Yes	927 (14)		

TABLE 2. Prostate cancers diagnosed by trial arm, screening participation, and Grade Group (GG).

Grade Group	Screening arm		Control arm N=45,542	Risk difference in screened men (screening participants) vs. control arm	Risk difference in screening vs. control group (randomly assigned populations)
	Participants N=7744	All invited men N=15,201			
All cancers	161 (2.08%)	219 (1.44%)	355 (0.78%)	1.30% (95 % CI 0.97–1.63)	0.66% (95 % CI 0.45–0.87)
With known GG	160 (2.07%)	211 (1.39%)	347 (0.76%)	1.30% (95 % CI 0.97-1.63)	0.62% (95 % CI 0.42–0.83)
Low Grade (GG 1)	32 (0.41%)	39 (0.26%)	65 (0.14%)	0.27% (95 % CI 0.12–0.42)	0.11% (95 % CI 0.03–0.20)
High Grade (GG 2–5)	128 (1.65%)	172 (1.13%)	282 (0.62%)	1.03% (95 % CI 0.74–1.33)	0.51% (95 % CI 0.33–0.70)
Detailed classification by Grade Group					
Grade Group 1	32 (0.41%)	39 (0.26%)	65 (0.14%)	0.27% (95% CI 0.12–0.42)	0.11% (95% CI 0.03–0.20)
Grade Group 2	63 (0.81%)	76 (0.50%)	121 (0.27%)	0.55% (95% CI 0.34–0.75)	0.23% (95% CI 0.11–0.35)
Grade Group 3	45 (0.58%)	57 (0.37%)	62 (0.14%)	0.44% (95% CI 0.27–0.62)	0.24% (95% CI 0.14–0.34)
Grade Group 4–5	20 (0.26%)	39 (0.26%)	99 (0.22%)	0.04% (95% CI -0.08, 0.16)	0.04% (95% CI -0.05, 0.13)
Missing Grade Group	1 (0.01%)	8 (0.05%)	8 (0.02%)		