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Mortality after radical prostatectomy in a matched contemporary cohort in Sweden compared to the Scandinavian Prostate Cancer Group 4 (SPCG-4) study

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Objective

To investigate if results in terms of absolute risk in mature randomised trials are relevant for contemporary decision-making. To do so, we compared the outcome for men in the radical prostatectomy (RP) arm of the Scandinavian Prostate Cancer Group Study number 4 (SPCG-4) randomised trial with matched men treated in a contemporary era before and after compensation for the grade migration and grade inflation that have occurred since the 1980s.

Patients and methods

A propensity score-matched analysis of prostate cancer mortality and all-cause mortality in the SPCG-4 and matched men in the National Prostate Cancer Register (NPCR) of Sweden treated in 1998–2006 was conducted. Cumulative incidence of prostate cancer mortality and all-cause mortality was calculated. Cox proportional hazards regression analyses were used to estimate hazard ratios (HR) and 95% confidence intervals (CIs) for a matching on original Gleason Grade Groups (GGG) and second, matching with GGG increased one unit for men in the NPCR.

Results

Matched men in the NPCR treated in 2005–2006 had half the risk of prostate cancer mortality compared to men in the SPCG-4 (HR 0.46, 95% CI 0.19–1.14). In analysis of men matched on an upgraded GGG in the NPCR, this difference was mitigated (HR 0.73, 95% CI 0.36–1.47).

Conclusions

Outcomes after RP for men in the SPCG-4 cannot be directly applied to men in the current era, mainly due to grade inflation and grade migration. However, by compensating for changes in grading, similar outcomes after RP were seen in the SPCG-4 and NPCR. In order to compare historical trials with current treatments, data on temporal changes in detection, diagnostics, and treatment have to be accounted for.

Keywords

Gleason Grade Groups, mortality, National Prostate Cancer Register of Sweden, Scandinavian Prostate Cancer Group Study Number 4, #PCSM, #ProstateCancer

Introduction

The Scandinavian Prostate Cancer Group Study number 4 (SPCG-4) is a randomised clinical trial that compared radical prostatectomy (RP) with watchful waiting in men with localised prostate cancer [1]. The trial recruited men from 1989 to 1999, with predominantly clinically detected cancer and demonstrated a survival benefit for men in the RP arm [2]. The SPCG-4 included men with localised prostate cancer and PSA levels of <50 ng/mL, who according to current risk categorisation were in the high range of intermediate-risk or in the high-risk category.

If the results for men in the RP group in the SPCG-4 are applicable to men who currently undergo RP is unknown. Even if current men appear to have similar cancer characteristics to men in the SPCG-4, these results may not be applicable as clinical practice in prostate cancer care has greatly evolved during the last two decades with earlier detection by use of PSA testing in asymptomatic men, more comprehensive diagnostic evaluation, changes in Gleason grading, and improvements in surgical techniques.

The aim of the present study was to assess if results after RP in the SPCG-4 are applicable to men currently treated with

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RP with similar cancer characteristics as men in the SPCG-4. We performed a propensity score-matched study comparing prostate cancer mortality and all-cause mortality for men in the RP group of the SPCG-4 with that of matched men in National Prostate Cancer Register (NPCR) of Sweden, diagnosed and treated in increasingly recent calendar periods. To compensate for the grade migration and grade inflation that have occurred [3], a comparison using an upgraded Gleason Grade Group (GGG) classification of men in the NPCR was also performed.

Patients and methods

Study groups

Data were retrieved for all 347 men in the RP group of the SPCG-4 trial [3]. All men were included between 1989 and 1999, and at inclusion were aged <75 years, had clinically localised disease (stage T1b/c or T2), PSA level <50 ng/mL, a negative bone scan, and a life-expectancy of ≥10 years.

To obtain data on outcome after treatment in recent time periods, we retrieved data for men diagnosed and treated for localised prostate cancer between 1998 and 2006 in the NPCR of Sweden. In brief, the NPCR holds detailed information on prostate cancer characteristics, including tumour stage according to TNM, PSA level at diagnosis, Gleason grading of diagnostic biopsies, and primary treatment [1]. Since 1998, the NPCR captures 98% of all incident prostate cancer cases in Sweden compared with the Swedish Cancer Registry to which registration is mandated by law. Furthermore, in the Prostate Cancer data Base Sweden (PCBaSe), the NPCR has been cross-linked with other national healthcare registers and demographic databases by use of the unique Swedish personal identity number to obtain additional data including comorbidity and socioeconomic status [4,5].

Inclusion criteria for men in the NPCR were clinically localised disease (clinical stage T1b/c or T2) and PSA level <50 ng/mL. The exclusion criterion was presence of metastases. According to these criteria, 31 230 men in the NPCR were eligible for analysis.

Study design

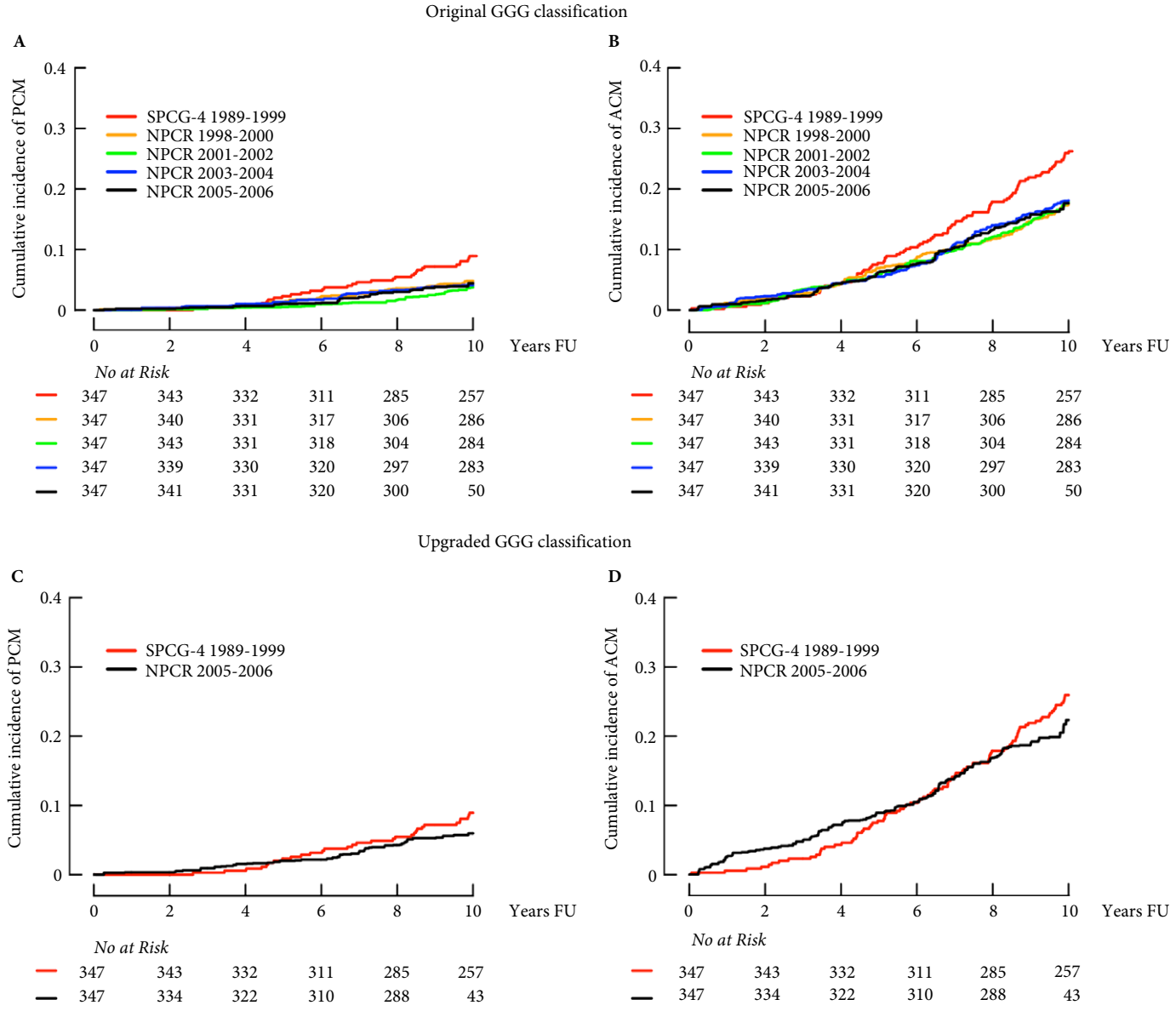
To compare men in the RP group of the SPCG-4 and men in the NPCR, a propensity score-matching of the likelihood to be a part of the SPCG-4 or NPCR was performed. First, eligible men in the NPCR were divided into four groups according to calendar period of prostate cancer diagnosis and primary treatment, 1998–2000; 2001–2002; 2003–2004; 2005–2006. Second, each man in the SPCG-4 was matched to one

Table 1 Baseline characteristics of men in the RP arm of the randomised SPCG-4 trial and matched men in the NPCR of Sweden.

Variable	Study group, year of treatment				
	SPCG-4 1989–1999	NPCR 1998–2000	NPCR 2001–2002	NPCR 2003–2004	NPCR 2005–2006
Treatment, *n* (%)					
Watchful waiting	53 (15.3)	53 (15.3)	53 (15.3)	53 (15.3)	53 (15.3)
RP	289 (83.3)	289 (83.3)	289 (83.3)	289 (83.3)	289 (83.3)
External beam radiotherapy	4 (1.2)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Brachytherapy	1 (0.3)	4 (1.2)	4 (1.2)	4 (1.2)	4 (1.2)
Age, years					
Median (IQR)	65.0 (61.0–68.0)	64.0 (59.0–68.0)	64.0 (59.0–69.0)	64.0 (60.0–69.0)	65.0 (61.0–69.0)
PSA, ng/mL					
Median (IQR)	10.0 (6.2–18.0)	8.7 (6.0–14.0)	8.4 (5.8–14.1)	9.0 (5.8–15.0)	8.8 (5.3–14.0)
Clinical tumour stage, *n* (%)					
T1b	33 (9.5)	30 (8.6)	36 (10.4)	38 (11.0)	35 (10.1)
T1c	43 (12.4)	65 (18.7)	70 (20.2)	73 (21.0)	76 (21.9)
T2	271 (78.1)	252 (72.6)	241 (69.5)	236 (68.0)	236 (68.0)
GGG, *n* (%)‡					
GGG1	238 (68.6)	256 (73.8)	239 (68.9)	242 (69.7)	216 (62.2)
GGG2/3	91 (26.2)	77 (22.2)	93 (26.8)	86 (24.8)	113 (32.6)
GGG4	15 (4.3)	12 (3.5)	12 (3.5)	13 (3.7)	15 (4.3)
GGG5	3 (0.9)	2 (0.6)	3 (0.9)	6 (1.7)	3 (0.9)
Mode of detection, *n* (%)					
Screening	18 (5.2)	66 (30.0)	107 (32.3)	141 (42.5)	141 (42.6)
LUTS	329 (94.8)	154 (70.0)	224 (67.7)	191 (57.5)	190 (57.4)
PSA level (ng/mL), *n* (%)					
<4	43 (12.4)	30 (8.6)	31 (8.9)	40 (11.5)	55 (15.9)
4–10	131 (37.8)	186 (53.6)	184 (53.0)	173 (49.9)	149 (42.9)
10.1–20	101 (29.1)	88 (25.4)	93 (26.8)	90 (25.9)	106 (30.5)
>20	72 (20.7)	43 (12.4)	39 (11.2)	44 (12.7)	37 (10.7)

Men in the NPCR were grouped according to year of prostate cancer treatment and matched to their index case in the SPCG-4 on age, PSA level, GGG, clinical T stage, and primary treatment. ‡*GGG1, Gleason score 6; GGG2/3, Gleason score 7 without complete information on primary and secondary Gleason score, i.e., either (3 + 4) or (4 + 3); GGG4, Gleason score 8; GGG5, Gleason score 9–10.*

Fig. 1 Cumulative incidence of prostate cancer mortality (PCM) and all-cause mortality (ACM) in the SPCG-4 and the NPCR of Sweden. FU, follow-up after date of diagnosis or primary treatment. **A** and **B** based on original GGG. **C** and **D** based on upgraded GGG classification in the NPCR with an increase of one grade in GGG.



man in the NPCR in each of the four calendar periods by matching *per protocol*, i.e., the treatment actually received; RP, watchful waiting, external beam radiotherapy, or brachytherapy.

Prostate cancer grading and variable definition

GGG, i.e., the five-tiered Gleason classification recently proposed by International Society of Urological Pathology (ISUP) [6] was used in this study. The mode of detection of prostate cancer was treated as a categorical variable, as a diagnostic evaluation after a health check-up or in an evaluation due to LUTS. PSA level was treated as a categorical variable with four levels (<4, 4–10, 10.1–20, >20 ng/mL). Follow-up time was calculated from the date of prostate cancer diagnosis until death or last date of follow-up, which was 31 December 2014 for all men.

Statistical methods

Multiple imputation by chained equations was used to substitute for missing data in the SPCG-4. Specifically, Gleason classification was missing for 47 men, PSA level was missing for seven, and clinical T stage was missing for one

[7]. Five datasets with imputed values were constructed by use of data in the RP group and the watchful-waiting group. The imputation model included age, mode of detection, clinical T stage, Gleason grading or WHO grade, PSA level, follow-up time since prostate cancer diagnosis, and time to metastasis. The study groups in the NPCR were then created by use of propensity score-matching for patient age, PSA level, GGG, clinical T stage, and primary treatment. Based on these results, each man in the SPCG-4 was matched to one man in each of the four groups in the NPCR using nearest neighbour matching within a propensity score-based caliper of 0.3. Cumulative incidence of prostate cancer mortality and all-cause mortality was calculated for men in the SPCG-4 and in each of the four NPCR groups. Rubin's rule for multiple imputation was used to account for variability between the five-imputed dataset. [8]. Wald's test was used to assess difference between curves. Cox proportional-hazards regression analyses were used to estimate hazard ratios (HRs) with 95% CIs. Subsequently, to compensate for grade migration and grade inflation, a second matching in which GGG was increased one grade for men in the NPCR was performed, and the analyses were repeated. An analysis of relative survival based on the modified GGG in the NPCR was performed comparing the SPCG-4 and NPCR with the expected survival rates for Swedish population for each corresponding recruitment period retrieved from the Human Mortality dataset [9] with use of the Ederer II method in the 'relsurv' package [10]. All tests were two-sided and a $P < 0.05$ was considered statistically significant. Analyses were performed by use of the R statistical software, version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Propensity-matched men in the SPCG-4 and NPCR had similar baseline characteristics including median age and PSA levels, and similar distribution of clinical tumour stage and Gleason grading (Table 1). However, a higher proportion of men were PSA-detected as a part of a health check-up in the NPCR in the most recent calendar period compared to the SPCG-4 (43% vs 5%).

Men in the NPCR had a lower prostate cancer and all-cause mortality than men in the SPCG-4; however, this did not reach statistically significant levels in all separate time periods. Specifically, men in the NPCR diagnosed in 2005–2006 had a reduced risk of all-cause mortality (HR 0.66, 95% CI 0.46–0.95) and prostate cancer mortality (HR 0.46, 95% CI 0.19–1.14) compared to men in the SPCG-4 (Fig. 1A,B; Table 2). There were no statistically significant differences in prostate cancer and all-cause mortality between men diagnosed and treated in different calendar periods in the NPCR (Table S1).

There was a shift in the distribution of GGG between 1998 and 2012 in the NPCR. In men with T1c cancer and PSA levels of 4–10 ng/mL, the proportion of GGG1 decreased from 82% in 1998 to 40% in 2012, and there was a concomitant increase in the proportion of GGG2 and GGG3 (Fig. 2). Similar shifts in GGG were also seen for men with higher PSA levels and with T2 cancer.

The distribution of PSA levels in men with localised cancer and GGG1 and GGG2 in all eligible men in the NPCR was narrower, with a smaller proportion of outliers with high PSA levels than in the SPCG-4 (Fig. 3). For this reason, most men in the SPCG-4 were in the high range of intermediate-risk or in the high-risk category according to current risk categorisation. Only 31% of men in the SPCG-4 with clinically localised cancer and GGG1 had a PSA level of <10 ng/mL, i.e., within the limit for the current low-risk prostate cancer category [11].

In order to analyse outcome after compensating for changes in grading, we compared results in the SPCG-4 with men in the NPCR who received an upgrade of one grade in GGG. In order to have the most complete data, this analysis was restricted to men diagnosed in 2005–2006, as data on primary and secondary Gleason grade was more complete in this period than in previous periods, up from 29% in 1998–2000 to 75% in 2005–2006. Compared to the analysis based on the original GGG in both groups, the difference in mortality was mitigated (HR 0.71, 95% CI 0.35–1.43). A similar decrease in difference in all-cause mortality was also observed (HR 0.86, 95% CI 0.60–1.22) (Fig. 1C,D, Table 2). During the first years of follow-up, relative survival was above 100% in the SPCG-4 but after 5 years decreased somewhat and became very similar to that of men in the NPCR with modified GGG (Fig. S1). The 5-year relative survival was 100% for men in the SPCG-4 and 98% in the NPCR, and 10-year survival was 91% in the SPCG-4 and 94% in the NPCR.

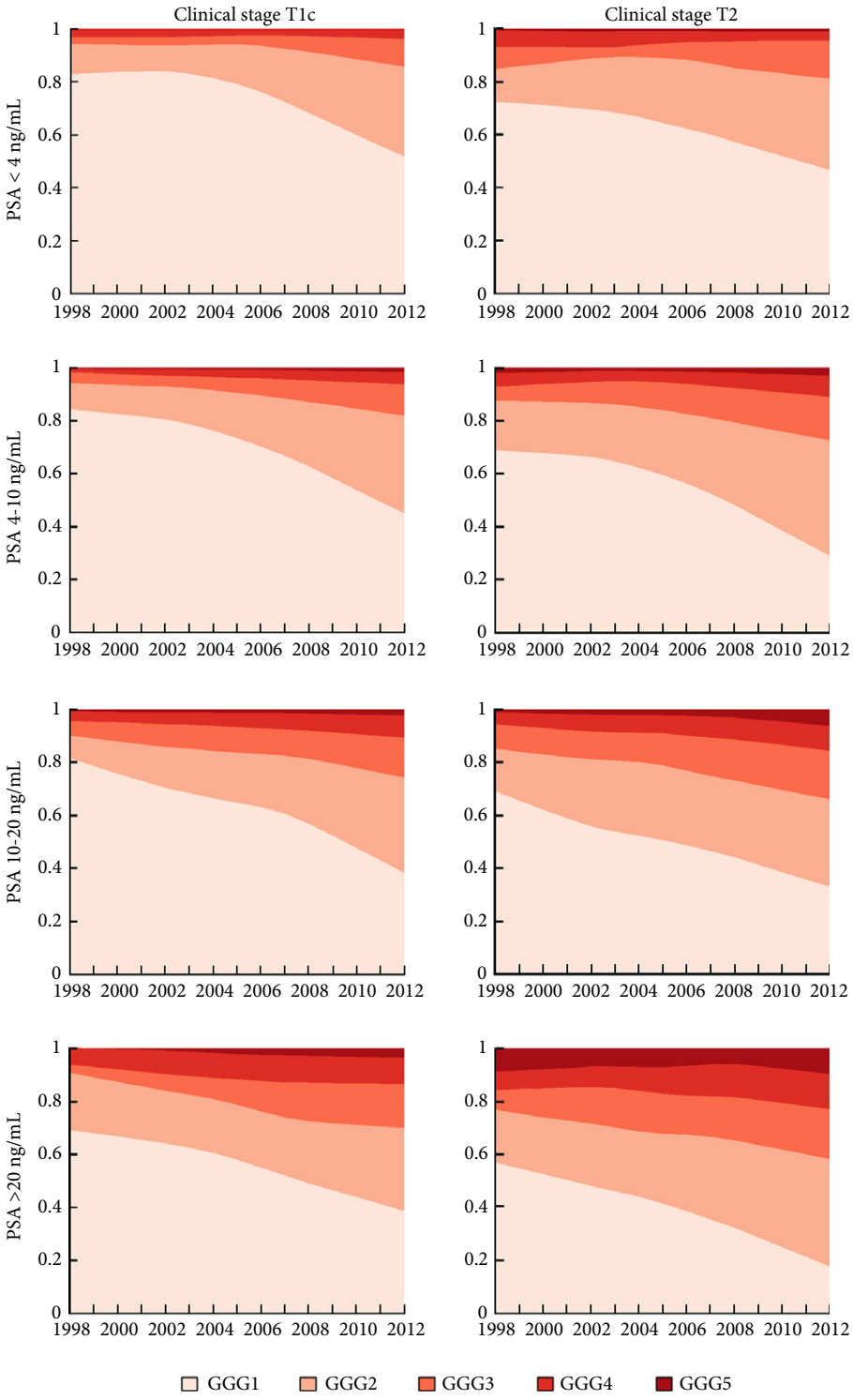
Discussion

In this comparison of outcomes between the RP arm in the randomised SPCG-4 trial and men matched for cancer

Table 2 Adjusted HRs and 95% CIs for risk of prostate cancer mortality and risk of all-cause mortality for matched men in the NPCR vs men in the RP group of the SPCG-4.

Original GGG classification		
	Prostate cancer mortality HR (95% CI)	**All-cause mortality HR (95% CI)**
SPCG-4	1.00 (Ref.)	1.00 (Ref.)
NPCR 1998–2000	0.50 (0.22–1.10)	0.63 (0.44–0.91)
NPCR 2001–2002	0.40 (0.18–0.90)	0.66 (0.45–0.97)
NPCR 2003–2004	0.44 (0.22–0.87)	0.67 (0.48–0.94)
NPCR 2005–2006	0.46 (0.19–1.14)	0.66 (0.46–0.95)
Modified GGG classification		
	HR (95% CI)	**HR (95% CI)**
SPCG-4	1.00 (Ref.)	1.00 (Ref.)
NPCR 2005–2006	0.71 (0.35–1.43)	0.86 (0.60–1.22)

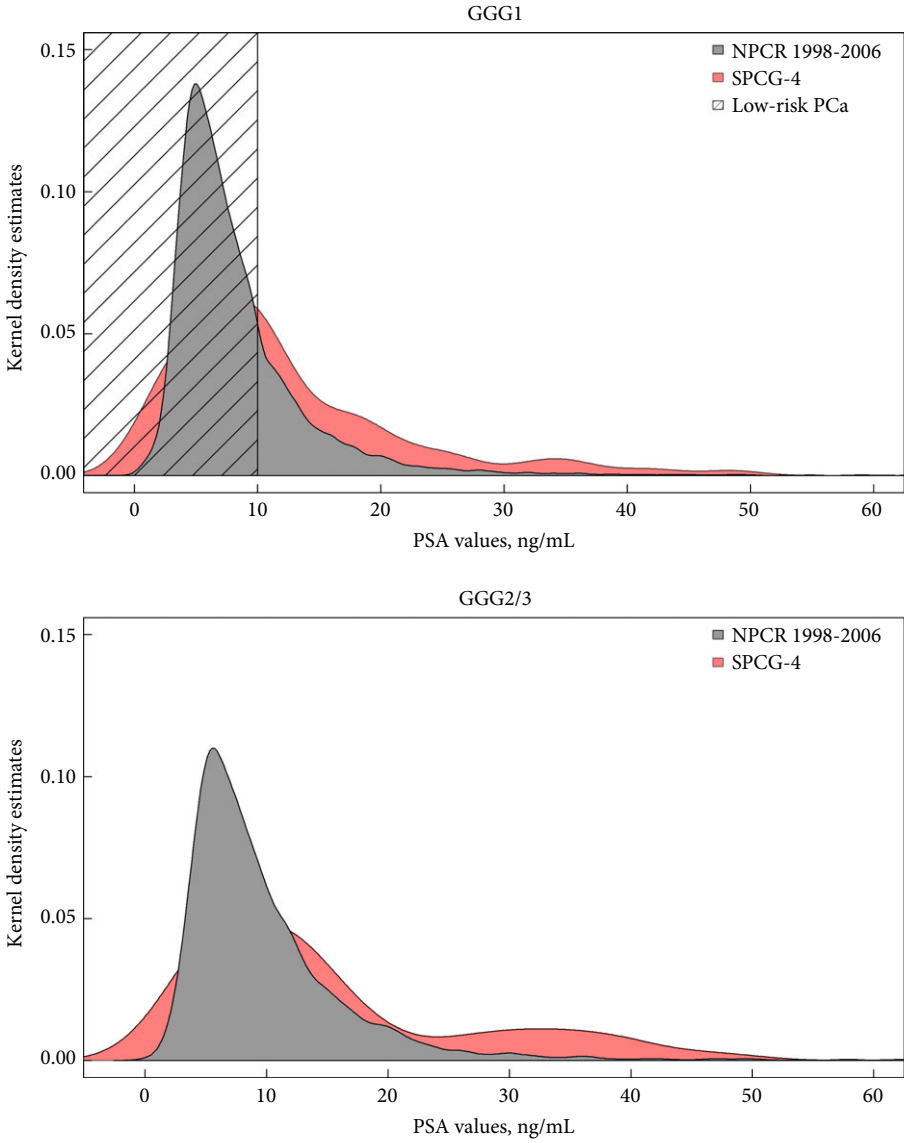
Fig. 2 Distribution of GGG in the diagnostic biopsy set in the NPCR per levels of PSA and clinical T stage between 1998 and 2012.



characteristics and treatment in the NPCR of Sweden, men in the NPCR had half the prostate cancer mortality of that for men in the SPCG-4. However, after compensating for the grade migration and grade inflation that have occurred by increasing GGG one grade in the NPCR, the difference in mortality was mitigated.

Changes in several factors over time could potentially have affected the difference in outcome after RP in men in the

Fig. 3 Distribution of PSA levels in the SPCG-4 and the NPCR. PSA levels of all men in the NPCR eligible for the study (inclusion criteria: clinical stage T1b/c or T2, PSA level <50 ng/mL, and absence of metastases; *n* = 31 230). Striped area indicates threshold level of PSA for low-risk prostate cancer according to the National Comprehensive Cancer Network (NCCN) definition, i.e., local clinical stage T1–2, GGG1 and PSA level <10 ng/mL. GGG2/3 = Gleason score 7 without complete information on primary and secondary Gleason score, i.e., either Gleason score 3+4 or Gleason 8 score 4+3.



SPCG-4 and the more recently treated men in the NPCR. For instance, case finding by PSA testing in asymptomatic men has increased. In 2007, more than half of Swedish men aged 55–69 years had undergone a PSA test and the uptake has continued to increase [12,13]. PSA testing of asymptomatic men leads to detection of many small low-risk cancers with low Gleason grade [12–16]. In parallel, there has been an increase in number of cores obtained in TRUS-guided prostate biopsy procedures that have caused a grade migration, with a higher yield of high-grade cancer [17–19]. In the NPCR, the median number of cores obtained in the diagnostic biopsy session increased from 6 cores in 1998 to 10 cores in 2012 and this trend has continued [17–19]. In the SPCG-4, the majority of men had ≤6 biopsy cores taken, and 14% of men underwent fine-needle aspiration for cytology that were WHO graded.

Furthermore, the modification of the Gleason classification by ISUP in 2005 [20] resulted in a grade inflation and as a consequence of this, cancers that were previously graded as GGG1 are now frequently graded as GGG2. This change in classification has resulted in an apparent decrease in the risk of biochemical recurrence after RP [3]. Thus, more extensive biopsy procedures led to a grade migration and the change in

Gleason classification led to a grade inflation. Together, these two changes strongly affected the assessment of outcome in more recent calendar periods. Despite the propensity matching that was performed, changes in grading are a likely cause for the lower prostate cancer mortality and all-cause mortality in matched men in the NPCR diagnosed and treated in 1998–2006 compared to men in the SPCG-4 recruited in 1988–1998.

To compensate for the grade migration and grade inflation, we matched men in the SPCG-4 with men in the NPCR with one higher grade of GGG. After this compensation, the difference in prostate cancer mortality was mitigated, suggesting that a large part of the difference in outcome is related to changes in Gleason grading.

In parallel to changes in grading and other diagnostic procedures, surgical techniques have improved and this has led to better oncological and functional outcomes after RP [21]. However, the difference in positive surgical margins between the SPCG-4 and NPCR is modest, 35% in the SPCG-4 and 20–32% in the NPCR [22,3]. Speculatively, improvements in the treatment of men with a cancer recurrence after RP, including postoperative radiotherapy and systemic therapy, could also possibly have affected the comparison.

Overall survival of the general population in Sweden has improved since 1988. In order to account for this improvement, relative survival was also analysed. We compared men in the SPCG-4 and matched men in the NPCR with one higher GGG grade with the expected survival rates for men in the Swedish population during the respective recruitment period. During the first 5 years, men in the SPCG-4 had better survival than the background population, illustrating the selection bias of healthy subjects to a clinical trial. In contrast, for men in the NPCR, a population-based clinical cancer register, i.e., with 'real-world data', there was a slightly lower relative survival. Beyond 5 years after RP there was a modest and almost similar decrease in survival in the SPCG-4 and NPCR corresponding to survival for men with intermediate-risk prostate cancer in the present era [23].

Thus, in order to apply absolute risks from old and mature trials to men treated recently, comprehensive data on temporal changes in detection, diagnostic evaluation and treatment have to be incorporated into the analysis in order to interpret the results correctly. Our present data indicate that survival after RP in the SPCG-4 is similar to that of men with intermediate-risk prostate cancer who underwent RP in 2000s.

Lack of a uniform reassessment of Gleason grading, absence of information on the extent of cancer on biopsies, prostate volume, and comorbidity for men in the SPCG-4, are limitations of our present study. Strengths of our present study include a landmark randomised trial and a large population-based clinical cancer register with comprehensive data for an extended time period, with documented high data quality allowing for propensity matching to men in the SPCG-4 [5,24].

In conclusion, survival after RP in the randomised SPCG-4 trial recruited in 1988–1999, in which a majority of men had low-risk cancer according to the criteria of that time period, was similar to survival in men with intermediate-risk cancer according to contemporary categorisation due to the grade migration and grade inflation that has occurred since the 1990s. To compare and interpret old and mature trials correctly, data on temporal changes in detection, diagnostics, and treatment have to be incorporated into analysis.

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Conflicts of Interest

Walter Cazzaniga certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g., employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

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Abbreviations: GGG, Gleason Grade Group; HR, hazard ratio; ISUP, International Society of Urological Pathology; NPCR, National Prostate Cancer Register (of Sweden); RP, radical prostatectomy; SPCG-4, Scandinavian Prostate Cancer Group Study number 4.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. HRs and 95% CIs for risk of prostate cancer mortality and risk of all-cause mortality between matched men in the NPCR treated in different calendar periods.
Fig. S1. Relative survival of men in the RP arm of the SPCG-4 and matched men in the NPCR treated in 2005–2006 matched with one grade higher GGG. FU, follow-up.