Estimation of Relative and Absolute Risk in a Competing-Risk Setting Using a Nested Case-Control Study Design: Example From the ProMort Study

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Abbreviations:

CI, Confidence interval

CIF, Cumulative incidence function

HR, Hazard ratio

NPCR, National Prostate Cancer Register of Sweden

ProMort, Prognostic factors for Mortality in prostate cancer

PSA, Prostate-specific antigen

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Abstract

We describe the Prognostic factors for Mortality in prostate cancer (ProMort) study, and use it to demonstrate how weighted likelihood method can be used in nested case-control studies to estimate both relative and absolute risks in the competing-risks setting. ProMort is a case-control study nested in the National Prostate Cancer Register of Sweden (NPCR), comprising 1,710 low- or intermediate-risk prostate cancer patients who died from prostate cancer (cases) and 1,710 matched controls. Cause-specific hazard ratios (HR) and cumulative incidence (CIF) of prostate cancer death were estimated in ProMort using weighted flexible parametric models and compared with the corresponding estimates from the NPCR cohort. We further draw 1,500 random nested case-control subsamples of NPCR and quantified the bias in the HR and CIF estimates. Finally, we compared the ProMort estimates with those obtained by augmenting competing risks cases, and by augmenting both competing risk cases and controls. The HRs of prostate cancer death estimated in ProMort were comparable to those in NPCR. The HRs of dying from other causes were biased, which introduced bias in the CIFs estimated in the competing risks setting. When augmenting both competing risk cases and controls, the bias was reduced.

Keywords: Absolute risk; Cumulative incidence function; Flexible parametric survival model; Inverse probability weighting; Nested case-control study; Weighted partial likelihood

Prostate cancer is one of the most common male cancers, with an estimated >1.1 million newly diagnosed men worldwide each year (1). In the current era of opportunistic prostate-specific antigen (PSA) screening, up to 80% of prostate cancer patients have localized disease (2, 3). The 10-year prostate cancer-specific mortality among men with localized disease varies from 5% to 29% depending on risk category (4). While radical treatment is generally recommended in high-risk disease, treatment choice for men with low- or intermediate-risk disease is a clinical dilemma (5). Treatment side effects must be balanced against the risk of dying from competing events and the risk of dying from prostate cancer, and traditional clinicopathological prognostic factors, such as Gleason score, tumor stage and PSA at diagnosis, are insufficient to identify those who may benefit from treatment. Hence, there is a strong clinical need to identify additional molecular prognostic factors. However, identifying molecular prognostic markers among men with low- or intermediate risk prostate cancer is challenging. Due to the low long-term disease-specific mortality in these patients, unfeasibly large tissue repositories with extensive follow-up are needed to identify and validate novel molecular prognostic markers.

The nested case-control study design and other cost-effective cohort subsampling techniques have been developed for the rare-event setting (6, 7). In these studies, relative rather than absolute risks are typically estimated. Estimates of absolute risk are however essential if a prediction model is to be clinically useful. Since the late 90s, different methods for unbiased and efficient estimation of absolute risks in nested case-control setting have been developed (8-14), and extened to the competing risks setting (10, 15-16). These methods are still underused in clinical epidemiological practice and there are very few examples of their practical application.

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We have used the National Prostate Cancer Register of Sweden (NPCR), a well-defined cohort of virtually all prostate cancer patients in Sweden since 1998, to design and conduct a nested case-control study (ProMort). The primary aim of ProMort is to identify a tissue-based, molecular signature of lethal prostate cancer for men with low- or intermediate-risk prostate cancer and to develop a clinically useful prognostic model predicting the individual risk of dying from prostate cancer.

In this paper, we describe the ProMort study and provide a practical demonstration of how relative risks of prostate cancer death can be estimated using the weighted likelihood method (11). We further estimate the absolute risks of prostate cancer death in the presence of competing risks by also modelling the relative risks of death from other causes using the same method. Since in the ProMort study, cases who died from other causes and their corresponding controls have not been selected using standard incidence density sampling (contrary to what was done for cases who died from prostate cancer), the estimates of the absolute risks of prostate cancer death may be biased to the extent to which the relative risks of death from other causes are biased. Hence we explore the magnitude of this bias and we compare our estimates with those obtained by augmenting competing risks cases (16), i.e., cases who died from causes other than prostate cancer, and both competing risk cases and corresponding controls (17). We also provide a practical description, including Stata programming code, of absolute risks estimation in the presence of competing risks in nested case-control studies.

METHODS

Study population

The National Prostate Cancer Register of Sweden (NPCR), The NPCR includes incident cases of prostate cancer in Sweden since 1998 and covers 98% of all prostate cancers registered in the Swedish National Cancer Register, to which reporting is mandatory by law (18, 19). Detailed descriptions of NPCR have been published previously (18, 20). In short, NPCR contains detailed information on mode of detection (PSA-screening, lower urinary tract symptoms, other), clinical TNM stage, biopsy tumor differentiation (Gleason score or WHO grade), serum PSA level at diagnosis and planned primary treatment within 6 months of diagnosis (conservative (active surveillance or watchful waiting), curative (radical prostatectomy or radiotherapy) and non-curative treatment (primary androgen deprivation therapy)). Since 2007, additional information regarding the biopsy procedure (number of cores taken at biopsy, number of positive cores, total length of all biopsy cores and combined length of cancer in all cores), prostate volume, curative treatment (type of prostatectomy, type of primary radiotherapy and neoadjuvant hormone therapy) and postoperative Gleason score has been reported to NPCR. Vital status is updated annually by linkage to the Swedish Population Register. Date and cause of death, coded according to ICD-10, are obtained through linkage to the Swedish Cause of Death Register. Prostate cancer specific death is defined as death where prostate cancer was coded as "underlying cause of death" and has been shown to be reliable, especially for localized disease (21, 22).

ProMort, ProMort is a case-control study nested among all men in NPCR diagnosed with low- or intermediate-risk prostate cancer between January 1, 1998 and December 31, 2011. We defined low- or intermediate-risk prostate cancer as a clinical tumor stage T1-T2, Gleason score ≤7 (or WHO grade 1 when information on Gleason grade was missing), serum PSA <20

ng/mL and no signs or non-assessed status of lymph node (N0 or Nx) or distant (M0 or Mx) metastases. At the time of linkage, follow-up was available until December 31, 2012. Among around 130,000 men in NPCR, 57,952 men fulfilled these criteria. Emigration occurred only among 0.23% men in NPCR and was not accounted for in the present analyses. We selected as cases all men who died from prostate cancer during follow-up (n=1,735), and randomly selected one control for each case, matched on year and hospital of diagnosis. The control had to be alive at the date of death of the respective case. This sampling scheme is often referred to as incidence-density sampling. Cases without an eligible control within the matching stratum (n=25) were excluded from the study. The final data set included 1,710 cases and 1,710 matched controls.

We abstracted information on age, clinical stage, Gleason score/WHO grade and PSA at diagnosis, as well as vital status and cause of death, from NPCR. Cause of death was coded as either “prostate cancer specific” or “other causes of death”. Tumor stage was coded as T1a, T1b, T1c and T2. We assigned Gleason score ≤6 to the 140 cases and 103 controls with WHO differentiation grade 1 but no information on Gleason score.

Diagnostic slides were retrieved from the pathology wards across Sweden and scanned at 40X using the Pannoramic 250 (3DHistech Ltd., Budapest, Hungary) digital slide scanner at Örebro University Hospital, Örebro, Sweden. After scanning, the images were uploaded to a specialized software based on the enhanced version of the Open Microscopy Environment Remote Objects (OMERO) platform (created and managed by the Centre for Advanced Studies, Research and Development in Sardinia (CRS4)) for visualizing, managing and annotating scientific image data (23). Once uploaded into the software, the slides are

reviewed by two independent genitourinary pathologists and scored according to the 2014 International Society of Urological Pathology (ISUP) modification of Gleason grading system (24). Non-low/intermediate risk prostate cancer patients (i.e., Gleason score >7) are excluded from future main analyses.

Due to the limited amount of tissue available for molecular analysis we have conducted two pilot studies to (i) determine the best performing DNA/RNA extraction kit in terms of the amount of tissue needed for the extraction, and the quality of the extracted DNA/RNA (manuscript in preparation) and (ii) estimate the number and thickness of slices that can be cut from the tissue blocks and the minimum amount of tissue (mm cancer) needed to extract sufficient amount of DNA/RNA for molecular analyses. Based on the outcome of these pilot studies and on a parallel systematic literature review, most promising molecular markers of lethal prostate cancer will be prioritized for the main tissue analyses.

Statistical analyses

In nested case-control studies, logistic regression (conditional or unconditional) is typically used to assess the association between the exposure and the outcome. When the interest also lies in absolute risk estimation, the baseline hazard function has to be estimated. Due to the disproportionate representation of controls in nested case-control studies, naïve estimates of the baseline hazard result in biased absolute risk estimates (8). However, the sampling probability of the controls can be estimated in the underlying population and used to adjust the contribution of controls. Different methods for calculating this probability have been proposed (10-13) and absolute risks estimation has been described in the context of the weighted partial likelihood approach, even in presence of a matched design (8, 9, 11,

12). In such analysis, matching is broken, cases and controls are weighted with an inverse of their marginal probability of being sampled, and unique individuals are pooled for analysis, keeping only one control record for controls who were selected more than once, and a case record for the control who later became a case (11).

When competing events preclude the occurrence of the primary event of interest the situation is more complex. Several approaches for dealing with competing risks in the cohort (25-34) and in the case-control setting (10, 15-16, 35) have been proposed. Due to the method of control selection for ProMort, in this paper, we focus on the cause-specific hazards approach. When a subject is at risk of having K different events, the cause-specific hazard, $\lambda_k(t)$, denotes the instantaneous rate of event k in subjects who are still alive at the time t and can be defined as:

$$\lambda_k(t) = \lim_{\Delta t \to 0} \frac{P(t \leq T < t + \Delta t, K = k | T \geq t)}{\Delta t}$$

The cumulative incidence function (CIF) for the event of interest k (i.e., prostate cancer death), $I_k(t)$, is a probability that a subject dies from the event k at the time t accounting for the fact that he can die from other cause(s) (i.e., death from other causes).

$$I_k(t) = P(T \leq t | K = k) = \int_0^t \lambda_k(u)\, exp\left\{-\int_0^u \sum_{k=1}^{K} \lambda_k(v) dv\right\} du = \int_0^t \lambda_k(u) \prod_{k=1}^{K} S_k(u) du$$

The CIF depends not only on the cause-specific hazard for the event of interest but also on the cause-specific hazard for the competing event(s) (26, 27).

35In this paper, we compare the relative risks (i.e. the hazard ratios (HRs)) and the absolute risks (i.e. the CIFs) estimated in ProMort using inverse probability weighting approach to those estimated in NPCR. Then we use two alternative approaches to estimate the HRs and

CIFs. In the first approach, denoted “Method 1”, we augment both the competing risk cases, i.e. cases who died from other causes, and the corresponding controls according to the incidence density sampling principle (17). In the second approach, denoted “Method 2”, we augment only the competing risk cases (16). The main idea behind the two methods is the reuse of the controls, and the cases, selected for one endpoint as controls in the analysis of another endpoint with or without a new control selection. These two methods are extensions of the inverse probability weighting approach to nested case-control studies with more than one endpoint, including competing risks (16, 17).

The inverse probability weighting methods have been described in the context of the partial likelihood (8, 9, 11, 12). Partial likelihood is used for the parameter estimation in the Cox proportional hazards model where the baseline hazard function does not depend on any parameters and is thus not estimated. Since we are interested in both the HRs and the CIFs, in this paper we use flexible parametric survival model (Royston-Parmar model) (28) instead of the Cox proportional hazards model. The flexible parametric model uses restricted cubic splines function of log time to model the baseline hazard function and its parameters are estimated by maximizing the full likelihood (29). In our analysis we use weighted full likelihood instead of the weighted partial likelihood. A detailed description of the step-by-step analysis plan for the Method 1 and the Method 2 and a formal definition of the weighted full likelihood are presented in the Appendix A1.

We calculated the weights as described by Kim (8), and fitted the flexible parametric model as described by Hinchliffe et al. (28). We selected the number of knots (1 internal knot, two degrees of freedom) and a suitable scale (proportional hazards) by minimizing the value of

Akaike and Bayes criterion (29). The number and location of the knots, however, are often not critical for a good fit of the model (28, 29). We simultaneously estimated cause-specific HRs and the corresponding 95% confidence intervals (CIs) of death from prostate cancer and death from other causes (29, 30), and obtained the CIFs by combing the cause-specific HR estimates (16, 17, 31).34 Time at risk was calculated from the date of diagnosis of prostate cancer until death or end of follow-up, whichever came first.

Subject-matter knowledge and data availability were used to identify important predictors of prostate cancer death. Age (categorized into 10 year categories, ≤55, >55-65, >65-75, >75), PSA (<4, 4-10, ≥10), Gleason score (<7, 7) and clinical tumor stage (T1a, T1b, T1c, T2) at diagnosis were included in the prognostic model. As the matching was broken, we additionally adjusted for the matching variables (8, 13). To avoid unnecessary loss of power due to the large number of matching hospital strata, we joined all the hospitals in the same county and adjusted for county and year of diagnosis. These analyses were performed in both the full cohort and the nested case-control study samples.

To further evaluate the method used for the relative and absolute risk estimation in ProMort, we drew 1,500 random nested case-control subsamples of NPCR using the same selection criteria as for ProMort (i.e. all cases and a random sample of matched controls). We calculated the absolute bias in HRs of death from prostate cancer and death from other causes on logarithmic scale as $\log(HR_{ncc})$-$\log(HR_{NPCR})$, where $\log(HR_{ncc})$ indicates the log(HRs) estimated in the 1,500 subsamples and $\log(HR_{NPCR})$ indicates the log(HRs) estimated in NPCR. We also computed the absolute bias in CIFs of dying from prostate cancer at 5, 10 and 15 years of follow-up. The absolute bias was defined as CIF_{ncc}-CIF_{NPCR} , where CIF_{ncc} indicates

CIFs estimated in 1,500 subsamples and CIF_{NPCR} indicates CIFs estimated in NPCR. In addition, we computed the coverage probability of the CIF 95% CIs estimated in the 1,500 subsamples at 5, 10 and 15 years of follow-up.

All analyses were conducted in Stata (version 12.1, StataCorp, College Station, Texas, USA) and R statistical package (version 3.3.3, Institute for Statistics and Mathematics, Vienna, Austria, http://www.Rproject.org).

RESULTS

Baseline characteristics of all men with low- or intermediate-risk prostate cancer in NPCR (n=57,952) and ProMort (1,710 cases, 1,710 controls) are presented in Table 1. Low- and intermediate-risk prostate cancer patients who had died from prostate cancer/cases were on average older at diagnosis and had more aggressive tumors, including higher proportion of Gleason score 7, T2 stage tumors and higher mean PSA at diagnosis, compared to men who had not died from prostate cancer/controls. Around 24% of the men who died from prostate cancer had been treated with curative intent, compared to over 50% among men who did not die from prostate cancer.

Results from the univariable analyses are presented in the Table 2. Age, PSA at diagnosis, Gleason score and clinical tumor stage were associated with the hazard of dying from prostate cancer with comparable point estimates in the NPCR and ProMort. Likewise, in the multivariable analyses, the risk of dying from prostate cancer increased with higher age, PSA, Gleason score and clinical tumor stage (Table 2). The point estimates in NPCR and ProMort were qualitatively similar, though in ProMort they were slightly overestimated for age and

clinical tumor stage, and underestimated for PSA (Figure 1). However, the mean absolute bias in the log(HRs) estimated in the 1,500 subsamples was generally close to zero for all covariates (Supplementary Table 1). The point estimates from the two alternative approaches were also comparable to the NPCR estimates (Supplementary Figure 1). The log(HRs) for death from other causes were generally biased for ProMort, with wide CIs (Figure 1). The mean absolute bias in the log(HRs) for other causes of death estimated in the 1,500 subsamples was close to zero for clinical tumor stage, Gleason score and PSA, but not for age (-3.813, -0.118 and 0.118 for age ≤55, 65-75 and >75, respectively) (Supplementary Table 2). Contrary to the other covariates, the distribution of log(HRs) for age ≤55 category was not normal. Few subjects in the age ≤55 category died from other causes and when no cases who died from other causes were sampled the estimated log(HR) were extreme and not reliable. The log(HRs) for death from other causes were generally comparable in NPCR and Method 1 and 2 (Supplementary Figure 1).

CIFs and 95% CIs of dying from prostate cancer for different combinations of risk factors at 5, 10 and 15 years from diagnosis are presented in Figure 2. Overall, the cumulative incidence of prostate cancer death at 5, 10, and 15 years from diagnosis in ProMort and NPCR were similar. However, the bias in the ProMort estimates increased with age, and was especially notable at age >75 years (Figure 2). The mean absolute bias in the CIF estimates across the 1,500 subsamples and across all combinations of covariates was less than 0.008 at all follow-up times (Supplementary Table 3). However, it is worth noting that the mean absolute bias for age >75 years was 0.011, 0.025 and 0.025 at 5, 10 and 15 years of follow-up, respectively, while it was less than 0.004 across all other combinations of covariates at all follow-up times. The actual coverage probability averaged over all combinations of covariates was generally

conservative at over 97% at all follow-up times (Supplementary Table 3). However, for some combinations of covariates with the age>75 years, the coverage probability is less than the nominal value. CIFs estimated using the two alternative approaches, especially from the Method 1, were consistently similar to the estimates from the NPCR (Supplementary Figure 2).

DISCUSSION

Novel prognostic markers of lethal prostate cancer are needed to aid risk assessment and decision making for low- and intermediate-risk prostate cancer patients. ProMort, a large case-control study nested in the well-annotated population-based cohort NPCR, aims to assess new molecular markers of lethal prostate cancer and develop a clinically useful model predicting prostate cancer mortality. ProMort cases and controls were selected using standard incidence-density sampling with the aim of estimating the relative risk of dying from prostate cancer. In this study, we have demonstrated that the relative risks of prostate cancer death estimated in ProMort are comparable to those in the full NPCR cohort. The estimates of relative risk of dying from other causes, on the other hand, are biased, and this introduces some bias in the absolute risks estimated in the competing risks setting. We have also shown that augmenting competing risks cases, or both the cases and the controls, reduces the bias in the relative risks of dying from other causes and thus also the bias in the absolute risks of dying from prostate cancer estimated in a competing risks setting.

With 57,952 study participants and up to 15 years of follow-up, NPCR is, to the best of our knowledge, the largest cohort of men with low- or intermediate-risk prostate cancer, with detailed clinicopathological data, in the world. Even though death from prostate cancer

among low- and intermediate-risk prostate cancer patients is a rare event, our sample size is sufficient to study prostate cancer specific mortality as the main outcome. One of the limitations of NPCR is that all data are collected through routine clinical work and no central histopathological review is conducted (20). Furthermore, information on additional histopathological characteristics, potentially useful for predicting lethal prostate cancer, such as primary and secondary Gleason grade pattern, length of cancer or percentage of biopsy core positivity, is available in NPCR only for the subset of men diagnosed with prostate cancer from 2007 onwards (20). However, through digitalized diagnostic slide review we aim to obtain not only centrally re-assigned Gleason score and minimize bias due the changes in the Gleason scoring system over time and inter-pathologist variability, but also information on these additional histopathological characteristics for all cases and controls included in ProMort.

Development of prognostic models and prediction of the absolute risk of a disease are traditionally carried out in cohort studies. However, in many chronic diseases the outcome of interest is rare to the extent that cohort studies become unfeasible, and the nested case-control design may be a viable and cost-effective alternative. Methods for unbiased and efficient estimation of absolute risks in nested case-control studies were developed in the late 90s (10, 12). However, even though recent studies have confirmed their feasibility (8, 9, 11, 13), these methods are still underused in clinical epidemiological practice. In this study, we analyzed a real-life nested case-control data using inverse probability weighting method proposed by Samuelson (12), which is easily implemented in the standard statistical software (Stata code is available in Appendix A2). The absolute risks estimated using the inverse probability weighting method are shown to be precise in the matched design, even

when fine matching is used (11). Furthermore, it has been shown that controls can be re-used to make valid inferences on secondary, non-exclusive, outcomes (32, 33), and the extensions to the competing risk setting have been developed (15-16). It is important to note that we did not explore other approaches for estimating absolute risks in the competing risk setting, such as dealing with a nested case-control study as a missing data problem (17) and the approach based on subdistribution hazards (34, 3535). We preferred to model the cause-specific hazards as their interpretation is easier when compared to the subdistribution hazards, and proportionality assumed on the hazard scale is mathematically not satisfied on subdistribution hazard scale (36).

ProMort was designed to provide unbiased estimates of the cause-specific HRs of dying from prostate cancer. We show that the HRs estimated in ProMort were comparable with the estimates derived from the full cohort (NPCR) and the absolute bias over 1,500 subsamples of NPCR was close to zero (Supplementary Table 1). On the other hand, the HRs of dying from other causes estimated in ProMort were biased. However, the absolute bias over 1,500 subsamples was close to zero for PSA, clinical tumor stage and PSA, but it was larger for age, especially age ≤55 years (Supplementary Table 2). As estimates of CIF for death from prostate cancer depend on both cause-specific hazards, the CIFs estimated in ProMort, although generally similar to CIFs estimated in NPCR, show some bias, especially for age >75 years. Similarly, the absolute bias in CIFs over 1,500 subsamples of NPCR and across all covariate combinations is close to zero at 5, 10 and 15 years after diagnosis and average coverage probability is conservative at all follow-up times. However, for age >75 years, the bias in CIF estimates increases and the coverage probability decreases. Alternative approaches with augmented competing risk cases (16), and especially with augmented

competing risk cases and controls (17), resulted in less biased CIF estimates. For ProMort, where cases and controls were sampled to gain efficiency, we therefore decided to use a two-step approach. First, we will use the current data to identify promising molecular markers, and then, if necessary, we will replicate the CIF estimates under the Method 1 or Method 2 sampling scheme.

5. Conclusion

To the best of our knowledge, ProMort is the world's largest series of lethal low- and intermediate-risk prostate cancer patients and constitutes a valid setting for identification of clinically relevant prognostic biomarkers for men with low- and intermediate-risk prostate cancer. By comparing the predictive models developed in the case-control data with those developed in the underlying cohort, we have demonstrated that accurate estimates of the relative risks of dying from prostate cancer can be estimated in ProMort. However, in the competing risks setting, nested case-control studies with augmented competing risks cases and controls provide more valid absolute risks estimates.

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Conflict of interest

Authors have no conflicts of interest to declare.

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Figure 1. Logarithm of the cause-specific hazard ratios and 95% confidence intervals of the risk of dying from prostate cancer and other causes estimated in NPCR and in ProMort, Sweden, 1998-2011. Reference categories (age >55-65, PSA <4, Gleason score <7, clinical tumor stage T1c) and estimates for the matching variables (year and county of diagnosis) are not shown in the figure.

PSA, prostate-specific antigen; log(HR), Logarithm of the hazard ratio; NPCR, National Prostate Cancer Register of Sweden

Figure 2. Cumulative incidence function and 95% confidence intervals of dying from prostate cancer for men with low- and intermediate-risk prostate cancer in NPCR and in ProMort, Sweden, 1998-2011. CIFs were estimated for different combinations of risk factors at 5 (A), 10 (B) and 15 (C) years of follow-up. Year (2004) and county (Västra Götaland) of diagnosis were kept constant.

NPCR, National prostate cancer register of Sweden; T, Clinical tumor stage; GS, Gleason score; PSA, prostate-specific antigen

Table 1. Baseline Characteristics of Low- and Intermediate-Risk Prostate Cancer Patients in NPCR and of Cases and Controls in ProMort, Sweden, 1998-2011

	NPCR				ProMort			
	Dead from PCa (n=1,735)		Not dead from PCa (n=56,217)		Cases (n=1,710)		Controls (n=1,710)	
	n	%	n	%	n	%	n	%
Year of diagnosis								
1998-2000	591	34.06	5,377	9.56	578	33.80	578	33.80
2001-2004	751	43.29	14,339	25.51	741	43.33	741	43.33
2005-2008	336	19.37	19,239	34.22	334	19.53	334	19.53
2009-2011	57	3.29	17,262	30.71	57	3.33	57	3.33
Age at diagnosis (mean, SD)								
	73.75 (7.75)		67.21 (7.99)		73.73 (7.75)		67.62 (7.76)	
Age at diagnosis (10-year categories)								
≤55	29	1.67	3,168	5.64	29	1.70	80	4.68
>55-65	205	11.82	19,731	35.10	200	11.70	568	33.22
>65-75	699	40.29	23,725	42.20	690	40.35	756	44.21
>75	802	46.22	9,596	17.06	791	46.26	306	17.89
Gleason score								
≤6	948	54.64	39,114	69.58	927	54.21	1328	77.66
7	787	45.36	17,103	30.42	783	45.79	382	22.34
Tumor stage								
T1	2	0.12	58	0.10	2	0.12	2	0.12
T1a	76	4.38	2,829	5.03	75	4.39	119	6.96
T1b	94	5.42	1,366	2.43	92	5.38	51	2.98
T1c	534	30.78	33,104	58.89	521	30.47	854	49.94
T2	1,029	59.31	18,860	33.55	1,020	59.65	684	40.00
PSA (mean, SD)								
	10.36 (4.56)		7.99 (4.08)		10.36 (4.58)		8.77 (4.29)	
PSA								
<4	116	6.69	7,239	12.88	116	6.78	176	10.29
4-9.9	754	43.46	33,659	59.87	740	43.27	933	54.56
≥10	865	49.86	15,319	27.25	854	49.94	601	35.15
Follow-up time in years (median, 25th and 75th percentile)								
	5.87 (3.58-8.57)		5.55 (3.08-8.35)		5.86 (3.59-8.51)		9.86 (7.56-12.09)	
Cause of censoring[a, b]								
Death								
Prostate cancer	1,735	100.00			1,710	100.00	80	4.68
Other causes			7,968	14.17			262	15.32
Administrative[c]			48,249	85.83			1,368	80.00
Initial treatment								
Conservative	798	46.80	20,804	37.87	785	46.70	648	38.53
Curative	412	24.16	29,653	53.98	407	24.21	849	50.48
Non-curative	495	29.03	4,476	8.15	489	29.09	185	11.00
Missing	30		1,284		29		28	

Abbreviations: NPCR, National prostate cancer register; PCa, prostate cancer; SD, standard deviation;

PSA, prostate-specific antigen

[a] No right censoring in the study was assumed due to the very low percentage (0.23%) of loss to follow-up

[b] For ProMort controls, censoring refers to the follow-up after the sampling into the ProMort study

[c] Administrative censoring was on December 31, 2012

Table 2. Univariable and Multivariable Flexible Parametric Proportional Hazards Model of the Risk of Dying From Prostate Cancer Among Low- and Intermediate-Risk Prostate Cancer Patients in the NPCR and in the ProMort, Sweden, 1998-2011

	NPCR				ProMort[a]			
	Univariable		Multivariable		Univariable		Multivariable	
	HR[b]	95% CI	HR[b]	95% CI	HR[b]	95% CI	HR[b]	95% CI
Age (10-year categories)								
≤55	0.92	0.62, 1.36	0.99	0.67, 1.47	1.03	0.64, 1.66	1.07	0.63, 1.82
>55-65	1.00		1.00		1.00		1.00	
>65-75	2.87	2.46, 3.36	2.56	2.19, 2.99	3.12	2.53, 3.86	2.90	2.32, 3.63
>75	9.15	7.84, 10.68	7.02	5.97, 8.25	10.34	8.23, 13.00	8.06	6.26, 10.38
PSA (ng/mL)								
<4	1.00		1.00		1.00		1.00	
4-9.9	1.40	1.15, 1.70	1.28	1.05, 1.57	1.22	0.92, 1.63	0.99	0.72, 1.35
≥10	2.91	2.39, 3.54	1.83	1.48, 2.25	2.60	1.94, 3.48	1.43	1.03, 1.98
Gleason score								
≤6	1.00		1.00		1.00		1.00	
7	2.99	2.71, 3.29	2.17	1.95, 2.40	3.04	2.56, 3.59	2.23	1.84, 2.72
Tumor stage[c]								
T1a	1.21	0.95, 1.55	0.96	0.75, 1.24	1.40	1.00, 1.95	0.79	0.52, 1.20
T1b	2.87	2.29, 3.60	1.67	1.32, 2.12	3.84	2.59, 5.70	2.25	1.49, 3.41
T1c	1.00		1.00		1.00		1.00	
T2	2.61	2.35, 2.91	1.74	1.56, 1.95	3.00	2.54, 3.54	1.83	1.51, 2.23

Abbreviations: NPCR, National prostate cancer register; HR, hazard ratio; 95% CI, 95% confidence intervals; PSA, prostate-specific antigen

[a] Duplicate observations (n=150) are excluded from the analysis

[b] Additionally adjusted for year and county of diagnosis

[c] Subjects with non-sub-classified T1 stage (NPCR: n=60, 2 cases and 58 controls; ProMort: n=3, 2 cases and 1 control) are excluded from the analysis