

Web Material

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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Web Appendix 1. Analysis plan

In our example the event of interest is death from prostate cancer, while the competing event is death from other causes.

Method 1

Sample two nested case-control studies, where:

1. Cases are all subjects who died from prostate cancer, $K = 1$, and incidence density sampling is used to select one control per case, matched on year and hospital of diagnosis (i.e. ProMort)
2. Cases are all subjects who died from other causes, $K = 2$, and incidence density sampling is used to select one control per case, matched on year and hospital of diagnosis.

Hence, there are two separate sets of controls for each endpoint.

Analysis steps:

1. Fit the flexible parametric proportional hazards model which is estimated on the log cumulative hazard scale where

$$\log[\Lambda_k(t|x_i, z_i)] = \log[\Lambda_{k,0}(t)] + \beta_k x_i + \gamma_k z_i$$

for each K , where x_i is a vector of covariates of interest and z_i is a vector of matching variables. The baseline log cumulative hazard function, $\ln[\Lambda_{k,0}(t)]$, is estimated using restricted cubic splines, so that

$$\log[\Lambda_k(t|x_i, z_i)] = s(\log(t)|\varepsilon_k, q_0) + \beta_k x_i + \gamma_k z_i$$

Where $s(\log(t)|\varepsilon_k, q_0)$ is a restricted cubic spline function basis of $\log(t)$ with a vector of knots q_0 and associated parameters ε_k .

$$\lambda_k(t|x_i, z_i) = \frac{d \log[\Lambda_k(t|x_i, z_i)]}{dt} = \frac{ds(\log(t)|\varepsilon_k, q_0)}{dt} \exp(\log[\Lambda_k(t|x_i, z_i)])$$

The parameters ε_k , β_k and γ_k can then be estimated by maximizing the weighted full likelihood:

$$\log[L(\varepsilon_k, \beta_k, \gamma_k)] = \sum_{i=1}^n (d_i \log[\lambda_k(t_i|x_i, z_i)] - \Lambda_k(t_i|x_i, z_i)) \omega_i$$

Where d_i is a binary event indicator, $d = 1$ if t_i is an observed time of the event k and $d = 0$ otherwise.

The weights are defined as

$$\omega_i = \frac{1}{p_i}$$

where p_i is a probability of being included in the nested case-control sample. For both the cases who died from prostate cancer and cases who died from other causes $p_i = 1$, while for controls we estimated p_i as

$$p_i = 1 - \prod_{T_i} \left(1 - \frac{m}{n_i - 1}\right)$$

T_i is the set of event times for both endpoints $K = 1, 2$ when subject i is a possible matched control and n_i is the risk set which satisfies the matching criteria at the time T_i .

2. Estimate the survival function:

$$S(t; x, z) = \prod_{t_j \leq t} [1 - (\lambda_1(\beta_1, \gamma_1) + \lambda_2(\beta_2, \gamma_2))]$$

3. Estimate the cumulative incidence function for endpoint of interest:

$$I_1(t; x, z) = \sum_{t_j \leq t} S(t_j; x, z) \lambda_1(\beta_1, \gamma_1)$$

Method 2

1. Sample a nested case-control study for the event of interest where cases are all subjects who died from prostate cancer, $K = 1$, and incidence density sampling is used to select one control per case, matched on year and hospital of diagnosis (i.e. ProMort)
2. Select all subjects who died from other causes, $K = 2$, and use controls selected for the endpoint 1 as controls for these cases.

Follow the same analysis steps as in Method 1.

1. Fit the flexible parametric proportional hazards models described for Method 1

The parameters $\varepsilon_k, \beta_k, \gamma_k$ can be estimated by maximizing the weighted full likelihood as in Method 1.

The weights ω_i and a probability of being included in the nested case-control sample p_i are still defined as in Method 1. However, T_i is now the set of event times only for

$K = 1$ when subject i is a possible matched control and n_i is the risk set which satisfies the matching criteria at the time T_i .

4. Estimate the survival function and the cumulative incidence functions described for Method 1.

Web Appendix 2. Stata codes

1. Estimating selection probability for controls

* Declare data as survival data (the time-scale is defined as time since the date of diagnosis, but the code can be applied to different time-scales).

* For ProMort and Method 2 failure event is death from prostate cancer, while for Method 2 failure event is death from prostate cancer and death from other causes

```
stset date_death, failure(status==1) origin(date_dg) exit(date_death) scale(365.25)
```

* Define matching strata (matching variables are year and hospital of diagnosis)

```
egen strata=group(diagyear hospital)
```

* Calculate the probability of being selected as a control within the matching stratum

```
gen p=.
```

```
sort strata _t
```

```
qui by strata: gen sum_status=sum(_d)
```

```
replace sum_status=. if _d!=1
```

```
gen num_control=1
```

* max_case – maximum number of cases in the matching stratum

```
foreach n of numlist 1/max_case {
```

```
    qui by strata: gen exit_t=_t if sum_status==`n'
```

```
    qui by strata: egen time=sum(exit_t)
```

```
    qui by strata: egen den=sum(float(_t)>=time & float(_t0)<=time)
```

```
    qui by strata: egen num=sum(float(_t)==exit_t & _d==1)
```

```
    replace p=1-min(1,num_control*num/(den-num)) if sum_status==`n'
```

```
    drop exit_t time den num
```

```
}
```

```
replace p=1 if p==.
```

```
gen k=1
```

* max_obs - maximum number of observations in the matching stratum with the largest sample size

```

foreach n of numlist 2/max_obs{
  foreach j of numlist 1(10)max_obs{
    qui by strata: replace k=k*p[_n-`j'] if _t0[_n]<=_t[_n-`j'] & _t[_n]>=_t[_n-`j'] & _n==`n' &
    _n>`j' & _d==0
    qui by strata: replace k=k*p[_n-(`j'+1)] if _t0[_n]<=_t[_n-(`j'+1)] & _t[_n]>=_t[_n-(`j'+1)]
    & _n==`n' & _n>(`j'+1) & _d==0
    qui by strata: replace k=k*p[_n-(`j'+2)] if _t0[_n]<=_t[_n-(`j'+2)] & _t[_n]>=_t[_n-(`j'+2)]
    & _n==`n' & _n>(`j'+2) & _d==0
    qui by strata: replace k=k*p[_n-(`j'+3)] if _t0[_n]<=_t[_n-(`j'+3)] & _t[_n]>=_t[_n-(`j'+3)]
    & _n==`n' & _n>(`j'+3) & _d==0
    qui by strata: replace k=k*p[_n-(`j'+4)] if _t0[_n]<=_t[_n-(`j'+4)] & _t[_n]>=_t[_n-(`j'+4)]
    & _n==`n' & _n>(`j'+4) & _d==0
    qui by strata: replace k=k*p[_n-(`j'+5)] if _t0[_n]<=_t[_n-(`j'+5)] & _t[_n]>=_t[_n-(`j'+5)]
    & _n==`n' & _n>(`j'+5) & _d==0
    qui by strata: replace k=k*p[_n-(`j'+6)] if _t0[_n]<=_t[_n-(`j'+6)] & _t[_n]>=_t[_n-(`j'+6)]
    & _n==`n' & _n>(`j'+6) & _d==0
    qui by strata: replace k=k*p[_n-(`j'+7)] if _t0[_n]<=_t[_n-(`j'+7)] & _t[_n]>=_t[_n-(`j'+7)]
    & _n==`n' & _n>(`j'+7) & _d==0
    qui by strata: replace k=k*p[_n-(`j'+8)] if _t0[_n]<=_t[_n-(`j'+8)] & _t[_n]>=_t[_n-(`j'+8)]
    & _n==`n' & _n>(`j'+8) & _d==0
    qui by strata: replace k=k*p[_n-(`j'+9)] if _t0[_n]<=_t[_n-(`j'+9)] & _t[_n]>=_t[_n-(`j'+9)]
    & _n==`n' & _n>(`j'+9) & _d==0
  }
}
gen p_final=1-k
replace p_final=1 if _d==1
gen ipw=1/p_final

```

2. Fitting a flexible parametric survival model

Variables included in the model:

1. Age at diagnosis (≤ 55 , $>55-65$, $>65-75$, >75) - age (coded as: 0, 1, 2, 3)
2. PSA value at diagnosis (<4 , $4-10$, ≥ 10) - psa (coded as: 0, 1, 2)
3. Gleason score (<7 , 7) - gleason (coded as: 0, 1)
4. Clinical tumor stage (T1a, T1b, T1c, T2) - tstage (coded as: 0, 1, 2, 3)
5. Year of diagnosis - diagyear (coded as: 1998-2011)
6. County of diagnosis - county (coded as: 1-22)

* Declare data as survival data

1. NPCR

```
stset date_death, fail(status==1) origin(date_dg) exit(date_death) scale(365.25)
```

2. ProMort

* casestr1 – variable denoting case/control status (1 - case, 0 – control)

```
stset date_death [pw=ipw], fail(casestr1==1) origin(date_dg) exit(date_death) scale(365.25)
```

* Fit a flexible parametric proportional hazards model

```
stpm2 i.age i.psa gleason i.tstage i.diagyear i.county, scale(hazard) df(2) eform vce(robust)
```


3. Estimating cumulative incidence function

* Expand the data, two rows of data per individual, one per each cause of death

```
expand 2
```

* Generate an indicator variable for each cause of death and an overall indicator

```
bysort id_var: gen cause=_n
```

```
gen cancer=(cause==1)
```

```
gen other=(cause==2)
```

```
gen event=(cause==status)
```

* Generate dummy variables for each category of factor variables included in the model

```
foreach var of varlist age psa gleason tstage diagyear county {
```

```
  levelsof `var', local(levels)
```

```
    foreach l of local levels {
```

```
      gen `var'`l'ca=`var'==`l' & cancer==1)
```

```
      gen `var'`l'oth=`var'==`l' & other==1)
```

```
    }
```

```
}
```

* Baseline categories:

1. Age at diagnosis - 55.1-65 (age1ca/age1oth),
2. PSA value at diagnosis - <4 (psa0ca/psa0oth),
3. Gleason score - ≤6 (gleason0ca/gleason0oth),
4. Clinical tumor stage - T1c (tstage2ca/tstage2oth),
5. Year of diagnosis - 2004 (diagyear2004ca/diagyear2004oth)
6. County of diagnosis - Västra Götaland (12) (county12ca/county12oth)

```
qui ds age0ca-county22oth
```

```
local all_vars `r(varlist)'
```

```
local omit_vars age1ca age1oth psa0ca psa0oth gleason0ca gleason0oth tstage2ca tstage2oth
```

```
diagyear2004ca diagyear2004oth county12ca county12oth
```

local vars: list all_vars-omit_vars

* Declare data as survival data

* 1. NPCR

```
stset date_death, failure(event) origin(date_dg) exit(date_death) scale(365.25)
```

* 2. ProMort, Method 1 and Method 2

```
stset date_death [pw=ipw], failure(event) origin(date_dg) exit(date_death) scale(365.25)
```

* Simultaneously fit cause specific hazards model for death from prostate cancer and death from other causes
stpm2 cancer other `vars', scale(hazard) dftvc(2) rcsbaseoff tvc(cancer other) nocons eform nolog vce(robust)

* Predict cumulative incidence functions

```
foreach a in 0 1 2 3 {
```

```
  foreach p in 0 1 2 {
```

```
    if `a'==1 {
```

```
      if `p'==0 {
```

```
        stpm2cif cancer_`a'00`p' other_`a'00`p', cause1(cancer 1) cause2(other 1)
```

```
        stpm2cif cancer_`a'01`p' other_`a'01`p', cause1(cancer 1 gleason1ca 1) cause2(other 1 gleason1oth 1)
```

```
        stpm2cif cancer_`a'10`p' other_`a'10`p', cause1(cancer 1 tstage2ca 1) cause2(other 1 tstage2oth 1)
```

```
        stpm2cif cancer_`a'11`p' other_`a'11`p', cause1(cancer 1 gleason1ca 1 tstage2ca 1) cause2(other 1 gleason1oth 1 tstage2oth 1)
```

```
      }
```

```
      if `p'!=0 {
```

```
        stpm2cif cancer_`a'00`p' other_`a'00`p', cause1(cancer 1 psa`p'ca 1) cause2(other 1 psa`p'oth 1)
```

```
        stpm2cif cancer_`a'01`p' other_`a'01`p', cause1(cancer 1 psa`p'ca 1 g1ca 1) cause2(other 1 psa`p'oth 1 g1oth 1)
```

```
        stpm2cif cancer_`a'10`p' other_`a'10`p', cause1(cancer 1 psa`p'ca 1 tstage2ca 1) cause2(other 1 psa`p'oth 1 tstage2oth 1)
```

```

    stpm2cif cancer_`a'11`p' other_`a'11`p', cause1(cancer 1 psa`p'ca 1 gleason1ca 1
    tstage2ca 1) cause2(other 1 psa`p'oth 1 gleason1oth 1 tstage2oth 1)
  }
}
if `a'!=1 {
  if `p'==0 {
    stpm2cif cancer_`a'00`p' other_`a'00`p', cause1(cancer 1 age`a'ca 1) cause2(other 1
    age`a'oth 1)
    stpm2cif cancer_`a'01`p' other_`a'01`p', cause1(cancer 1 age`a'ca 1 gleason1ca 1)
    cause2(other 1 age`a'oth 1 gleason1oth 1)
    stpm2cif cancer_`a'10`p' other_`a'10`p', cause1(cancer 1 age`a'ca 1 tstage2ca 1)
    cause2(other 1 age`a'oth 1 tstage2oth 1)
    stpm2cif cancer_`a'11`p' other_`a'11`p', cause1(cancer 1 age`a'ca 1 gleason1ca 1
    tstage2ca 1) cause2(other 1 age`a'oth 1 gleason1oth 1 tstage2oth 1)
  }
  if `p'!=0 {
    stpm2cif cancer_`a'00`p' other_`a'00`p', cause1(cancer 1 age`a'ca 1 psa`p'ca 1)
    cause2(other 1 age`a'oth 1 psa`p'oth 1)
    stpm2cif cancer_`a'01`p' other_`a'01`p', cause1(cancer 1 age`a'ca 1 psa`p'ca 1
    gleason1ca 1) cause2(other 1 age`a'oth 1 psa`p'oth 1 gleason1oth 1)
    stpm2cif cancer_`a'10`p' other_`a'10`p', cause1(cancer 1 age`a'ca 1 psa`p'ca 1
    tstage2ca 1) cause2(other 1 age`a'oth 1 psa`p'oth 1 tstage2oth 1)
    stpm2cif cancer_`a'11`p' other_`a'11`p', cause1(cancer 1 age`a'ca 1 psa`p'ca 1
    gleason1ca 1 tstage2ca 1) cause2(other 1 age`a'oth 1 psa`p'oth 1 gleason1oth 1
    tstage2oth 1)
  }
}
}
}

```

Web Table 1. The Absolute Bias in log(HR) Estimates for Death From Prostate Cancer Defined as the Difference in log(HRs) Estimated in 1,500 Nested Case-Control Studies Sampled with Replacement from NPCR and log(HRs) Estimated in NPCR, $\log(\text{HR}_{\text{ncc}}) - \log(\text{HR}_{\text{NPCR}})$.

	$\log(\text{HR}_{\text{NPCR}})$	$\log(\text{HR}_{\text{ncc}})$		$\log(\text{HR}_{\text{ncc}}) - \log(\text{HR}_{\text{NPCR}})$		
		Mean	SD	Mean	25%	75%
Age						
≤55	-0.0055	0.0206	0.1665	0.0262	-0.0913	0.1390
65.1-75	0.9399	0.9581	0.0813	0.0182	-0.0328	0.0709
>75	1.9490	2.0266	0.1043	0.0777	0.0059	0.1492
PSA						
4-9.9	0.2489	0.2399	0.1435	-0.0090	-0.1076	0.0860
≥10	0.6024	0.6125	0.1481	0.0101	-0.0881	0.1124
Gleason score						
7	0.7726	0.8211	0.0925	0.0484	-0.0153	0.1080
Clinical T stage						
T1a	-0.0364	0.0230	0.1709	0.0594	-0.0583	0.1751
T1b	0.5141	0.6135	0.2091	0.0994	-0.0399	0.2448
T2	0.5545	0.5995	0.0885	0.0449	-0.0142	0.1024

Abbreviations: $\log(\text{HR}_{\text{NPCR}})$, Logarithm of the hazard ratios estimated in National prostate cancer register of Sweden (NPCR); $\log(\text{HR}_{\text{ncc}})$, Logarithm of the hazard ratios estimated from the 1,500 nested case-control studies sampled with replacement from NPCR; SD, Standard deviation; 25% and 75%, Lower and upper 25th percentile of the distribution of the absolute bias across 1,500 subsamples; PSA, Prostate Specific Antigen

Web Table 2. The Absolute Bias in $\log(\text{HR})$ Estimates for Other Causes of Death Defined as the Difference in $\log(\text{HRs})$ Estimated in 1,500 Nested Case-Control Studies Sampled with Replacement from NPCR and $\log(\text{HRs})$ Estimated in NPCR, $\log(\text{HR}_{\text{ncc}}) - \log(\text{HR}_{\text{NPCR}})$.

	$\log(\text{HR}_{\text{NPCR}})$	$\log(\text{HR}_{\text{ncc}})$		$\log(\text{HR}_{\text{ncc}}) - \log(\text{HR}_{\text{NPCR}})$		
		Mean	SD	Mean	25%	75%
Age						
≤55	-0.6123	-4.4252	7.0309	-3.8129	-1.6031	0.3715
65.1-75	0.9111	1.0296	0.3470	0.1185	-0.1182	0.3572
>75	2.0373	2.2255	0.3589	0.1882	-0.0537	0.4241
PSA						
4-9.9	-0.0353	0.0540	0.3454	0.0893	-0.1420	0.3187
≥10	0.1883	0.2681	0.3598	0.0798	-0.1692	0.3254
Gleason score						
7	0.0676	0.0658	0.2626	-0.0018	-0.1820	0.1730
Clinical T stage						
T1a	0.4883	0.4557	0.3555	-0.0326	-0.2642	0.2085
T1b	0.3496	0.2568	0.4387	-0.0929	-0.3724	0.2045
T2	0.1504	0.1164	0.2358	-0.0340	-0.1961	0.1277

Abbreviations: $\log(\text{HR}_{\text{NPCR}})$, Logarithm of the hazard ratios estimated in National prostate cancer register of Sweden (NPCR); $\log(\text{HR}_{\text{ncc}})$, Logarithm of the hazard ratios estimated from the 1,500 nested case-control studies sampled with replacement from NPCR; SD, Standard deviation; 25% and 75%, Lower and upper 25th percentile of the distribution of the absolute bias across 1,500 subsamples; PSA, Prostate Specific Antigen

Web Table 3. The Absolute Bias in CIF Estimates for Death from Prostate Cancer at 5, 10 and 15 years of follow-up. The Absolute Bias was Defined as the Difference in CIFs Estimated in 1,500 Nested Case-Control Studies Sampled with Replacement from NPCR and CIFs Estimated in NPCR, $CIF_{ncc}-CIF_{NPCR}$.

	CIF _{NPCR}	CIF _{ncc}		CIF _{ncc} -CIF _{NPCR}			Coverage probability
		Mean	SD	Mean	25%	75%	
At 5 years							
Age ≤55							
T1c, GS6, PSA <4	0.0027	0.0028	0.0007	0.0001	-0.0004	0.0005	99.01
T1c, GS6, PSA 4-9.9	0.0035	0.0035	0.0007	0.0000	-0.0005	0.0005	99.00
T1c, GS6, PSA ≥10	0.0050	0.0051	0.0011	0.0001	-0.0006	0.0008	99.16
T1c, GS7, PSA <4	0.0059	0.0064	0.0016	0.0006	-0.0006	0.0014	99.43
T1c, GS7, PSA 4-9.9	0.0075	0.0080	0.0017	0.0005	-0.0007	0.0015	99.50
T1c, GS7, PSA ≥10	0.0107	0.0116	0.0025	0.0009	-0.0009	0.0024	99.79
T2, GS6, PSA <4	0.0047	0.0052	0.0013	0.0005	-0.0005	0.0012	99.43
T2, GS6, PSA 4-9.9	0.0061	0.0064	0.0014	0.0004	-0.0006	0.0012	99.13
T2, GS6, PSA ≥10	0.0086	0.0093	0.0021	0.0007	-0.0008	0.0020	99.48
T2, GS7, PSA <4	0.0102	0.0117	0.0029	0.0016	-0.0006	0.0032	99.57
T2, GS7, PSA 4-9.9	0.0131	0.0146	0.0032	0.0015	-0.0008	0.0035	99.75
T2, GS7, PSA ≥10	0.0185	0.0210	0.0047	0.0025	-0.0008	0.0053	100.00
Average	0.0080	0.0088	0.0020	0.0008	-0.0007	0.0020	99.44
Age 55.1-65							
T1c, GS6, PSA <4	0.0027	0.0027	0.0005	0.0000	-0.0004	0.0003	98.78
T1c, GS6, PSA 4-9.9	0.0035	0.0034	0.0005	-0.0001	-0.0004	0.0002	98.19
T1c, GS6, PSA ≥10	0.0049	0.0049	0.0008	0.0000	-0.0006	0.0004	98.13
T1c, GS7, PSA <4	0.0059	0.0062	0.0012	0.0003	-0.0006	0.0011	98.99
T1c, GS7, PSA 4-9.9	0.0075	0.0077	0.0012	0.0002	-0.0007	0.0010	99.19
T1c, GS7, PSA ≥10	0.0106	0.0111	0.0019	0.0005	-0.0008	0.0017	98.89
T2, GS6, PSA <4	0.0047	0.0050	0.0010	0.0003	-0.0004	0.0009	99.49
T2, GS6, PSA 4-9.9	0.0060	0.0062	0.0009	0.0002	-0.0005	0.0007	99.19
T2, GS6, PSA ≥10	0.0085	0.0089	0.0015	0.0004	-0.0006	0.0013	99.40
T2, GS7, PSA <4	0.0101	0.0113	0.0023	0.0012	-0.0005	0.0025	99.59
T2, GS7, PSA 4-9.9	0.0130	0.0141	0.0023	0.0011	-0.0006	0.0024	99.55
T2, GS7, PSA ≥10	0.0184	0.0202	0.0034	0.0019	-0.0005	0.0039	99.40
Average	0.0080	0.0085	0.0014	0.0005	-0.0006	0.0014	99.07
Age 65.1-75							
T1c, GS6, PSA <4	0.0068	0.0069	0.0013	0.0001	-0.0008	0.0010	98.24
T1c, GS6, PSA 4-9.9	0.0087	0.0086	0.0013	0.0000	-0.0009	0.0008	98.15
T1c, GS6, PSA ≥10	0.0122	0.0124	0.0019	0.0002	-0.0011	0.0014	99.08
T1c, GS7, PSA <4	0.0145	0.0156	0.0032	0.0011	-0.0012	0.0030	98.82
T1c, GS7, PSA 4-9.9	0.0186	0.0196	0.0031	0.0010	-0.0012	0.0028	98.91
T1c, GS7, PSA ≥10	0.0261	0.0281	0.0046	0.0020	-0.0012	0.0047	98.91
T2, GS6, PSA <4	0.0117	0.0125	0.0025	0.0009	-0.0009	0.0024	98.99

	CIF _{NPCR}	CIF _{ncc}		CIF _{ncc} -CIF _{NPCR}			Coverage probability
		Mean	SD	Mean	25%	75%	
T2, GS6, PSA 4-9.9	0.0150	0.0157	0.0024	0.0008	-0.0009	0.0023	99.08
T2, GS6, PSA ≥10	0.0210	0.0226	0.0036	0.0017	-0.0010	0.0041	99.58
T2, GS7, PSA <4	0.0250	0.0283	0.0057	0.0034	-0.0007	0.0069	99.24
T2, GS7, PSA 4-9.9	0.0320	0.0355	0.0057	0.0036	-0.0006	0.0071	99.16
T2, GS7, PSA ≥10	0.0446	0.0508	0.0082	0.0061	0.0001	0.0112	99.16
Average	0.0197	0.0214	0.0036	0.0017	-0.0009	0.0040	98.94
Age >75							
T1c, GS6, PSA <4	0.0169	0.0193	0.0038	0.0024	-0.0004	0.0047	99.58
T1c, GS6, PSA 4-9.9	0.0217	0.0242	0.0038	0.0025	-0.0001	0.0049	99.50
T1c, GS6, PSA ≥10	0.0298	0.0345	0.0055	0.0046	0.0009	0.0079	98.99
T1c, GS7, PSA <4	0.0359	0.0434	0.0092	0.0075	0.0009	0.0130	98.99
T1c, GS7, PSA 4-9.9	0.0460	0.0543	0.0095	0.0083	0.0014	0.0141	98.74
T1c, GS7, PSA ≥10	0.0627	0.0766	0.0133	0.0139	0.0044	0.0214	96.81
T2, GS6, PSA <4	0.0286	0.0348	0.0070	0.0062	0.0012	0.0104	98.99
T2, GS6, PSA 4-9.9	0.0367	0.0436	0.0071	0.0069	0.0017	0.0113	98.66
T2, GS6, PSA ≥10	0.0501	0.0617	0.0101	0.0116	0.0045	0.0181	96.64
T2, GS7, PSA <4	0.0602	0.0774	0.0162	0.0172	0.0055	0.0271	97.82
T2, GS7, PSA 4-9.9	0.0769	0.0964	0.0168	0.0195	0.0079	0.0298	95.38
T2, GS7, PSA ≥10	0.1036	0.1345	0.0228	0.0309	0.0153	0.0447	89.76
Average	0.0474	0.0584	0.0104	0.0110	0.0036	0.0173	97.49
At 10 years							
Age ≤55							
T1c, GS6, PSA <4	0.0099	0.0098	0.0023	-0.0001	-0.0017	0.0013	97.93
T1c, GS6, PSA 4-9.9	0.0127	0.0123	0.0025	-0.0004	-0.0021	0.0011	97.93
T1c, GS6, PSA ≥10	0.0179	0.0176	0.0037	-0.0003	-0.0030	0.0021	98.27
T1c, GS7, PSA <4	0.0213	0.0223	0.0054	0.0010	-0.0028	0.0039	98.86
T1c, GS7, PSA 4-9.9	0.0272	0.0278	0.0059	0.0006	-0.0035	0.0041	98.54
T1c, GS7, PSA ≥10	0.0383	0.0396	0.0087	0.0014	-0.0049	0.0064	99.29
T2, GS6, PSA <4	0.0171	0.0179	0.0044	0.0008	-0.0024	0.0032	99.14
T2, GS6, PSA 4-9.9	0.0219	0.0224	0.0048	0.0005	-0.0030	0.0034	98.81
T2, GS6, PSA ≥10	0.0308	0.0320	0.0071	0.0011	-0.0040	0.0055	98.94
T2, GS7, PSA <4	0.0366	0.0402	0.0099	0.0036	-0.0035	0.0091	99.41
T2, GS7, PSA 4-9.9	0.0467	0.0501	0.0109	0.0034	-0.0045	0.0099	99.25
T2, GS7, PSA ≥10	0.0653	0.0709	0.0156	0.0056	-0.0058	0.0147	99.82
Average	0.0288	0.0302	0.0068	0.0014	-0.0034	0.0054	98.85
Age 55.1-65							
T1c, GS6, PSA <4	0.0097	0.0094	0.0018	-0.0004	-0.0016	0.0008	96.97
T1c, GS6, PSA 4-9.9	0.0125	0.0118	0.0017	-0.0007	-0.0019	0.0004	96.89
T1c, GS6, PSA ≥10	0.0176	0.0169	0.0027	-0.0006	-0.0025	0.0010	97.31
T1c, GS7, PSA <4	0.0209	0.0213	0.0042	0.0004	-0.0028	0.0031	98.15
T1c, GS7, PSA 4-9.9	0.0268	0.0267	0.0042	-0.0001	-0.0031	0.0025	98.57
T1c, GS7, PSA ≥10	0.0375	0.0382	0.0064	0.0007	-0.0036	0.0047	98.40
T2, GS6, PSA <4	0.0168	0.0171	0.0033	0.0003	-0.0021	0.0024	98.40
T2, GS6, PSA 4-9.9	0.0215	0.0214	0.0032	-0.0001	-0.0024	0.0020	98.74
T2, GS6, PSA ≥10	0.0301	0.0307	0.0049	0.0006	-0.0029	0.0036	98.74

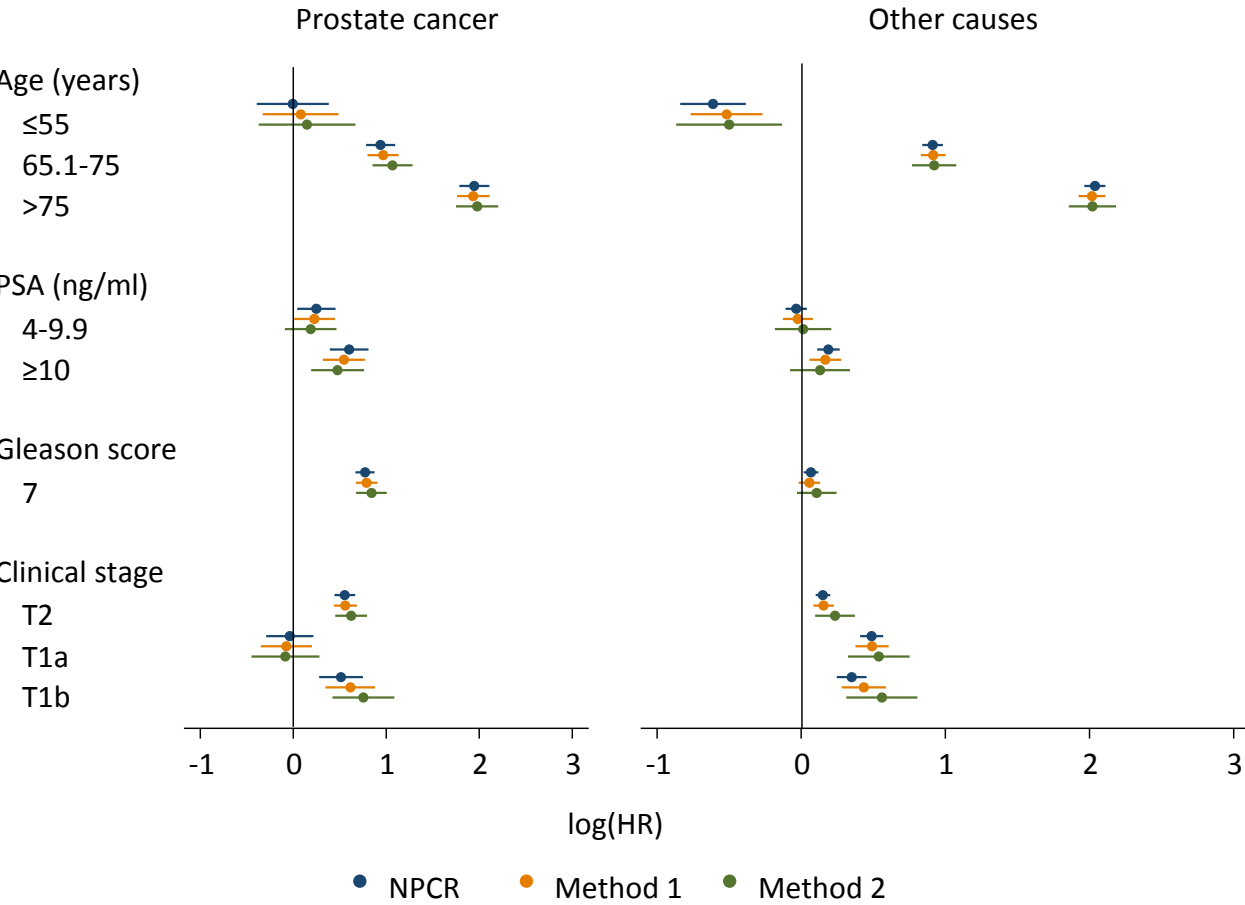
	CIF _{NPCR}	CIF _{ncc}		CIF _{ncc} -CIF _{NPCR}			Coverage probability
		Mean	SD	Mean	25%	75%	
T2, GS7, PSA <4	0.0358	0.0385	0.0077	0.0026	-0.0030	0.0074	99.41
T2, GS7, PSA 4-9.9	0.0458	0.0481	0.0077	0.0023	-0.0032	0.0072	99.33
T2, GS7, PSA ≥10	0.0637	0.0684	0.0113	0.0047	-0.0032	0.0115	99.33
Average	0.0282	0.0290	0.0049	0.0008	-0.0027	0.0039	98.35
Age 65.1-75							
T1c, GS6, PSA <4	0.0231	0.0230	0.0043	-0.0002	-0.0034	0.0027	98.15
T1c, GS6, PSA 4-9.9	0.0297	0.0288	0.0041	-0.0009	-0.0038	0.0017	97.65
T1c, GS6, PSA ≥10	0.0409	0.0407	0.0063	-0.0002	-0.0047	0.0036	98.24
T1c, GS7, PSA <4	0.0490	0.0513	0.0102	0.0023	-0.0053	0.0088	98.66
T1c, GS7, PSA 4-9.9	0.0626	0.0642	0.0101	0.0015	-0.0056	0.0078	98.66
T1c, GS7, PSA ≥10	0.0854	0.0896	0.0146	0.0042	-0.0059	0.0132	98.74
T2, GS6, PSA <4	0.0392	0.0412	0.0080	0.0020	-0.0035	0.0067	98.91
T2, GS6, PSA 4-9.9	0.0502	0.0515	0.0077	0.0013	-0.0041	0.0064	98.66
T2, GS6, PSA ≥10	0.0685	0.0721	0.0114	0.0036	-0.0047	0.0109	99.41
T2, GS7, PSA <4	0.0820	0.0908	0.0180	0.0087	-0.0041	0.0197	99.16
T2, GS7, PSA 4-9.9	0.1043	0.1128	0.0177	0.0085	-0.0043	0.0200	98.99
T2, GS7, PSA ≥10	0.1403	0.1553	0.0247	0.0150	-0.0030	0.0306	99.08
Average	0.0646	0.0684	0.0114	0.0038	-0.0044	0.0110	98.69
Age >75							
T1c, GS6, PSA <4	0.0496	0.0557	0.0119	0.0061	-0.0023	0.0133	99.50
T1c, GS6, PSA 4-9.9	0.0638	0.0695	0.0122	0.0057	-0.0027	0.0131	98.99
T1c, GS6, PSA ≥10	0.0827	0.0937	0.0173	0.0110	-0.0011	0.0218	98.74
T1c, GS7, PSA <4	0.1013	0.1204	0.0276	0.0191	-0.0005	0.0362	99.33
T1c, GS7, PSA 4-9.9	0.1290	0.1485	0.0286	0.0195	-0.0003	0.0378	98.32
T1c, GS7, PSA ≥10	0.1636	0.1957	0.0387	0.0320	0.0045	0.0567	96.39
T2, GS6, PSA <4	0.0802	0.0963	0.0215	0.0161	0.0009	0.0290	98.99
T2, GS6, PSA 4-9.9	0.1026	0.1192	0.0223	0.0166	0.0012	0.0307	97.98
T2, GS6, PSA ≥10	0.1302	0.1577	0.0304	0.0275	0.0053	0.0474	96.39
T2, GS7, PSA <4	0.1591	0.2010	0.0455	0.0418	0.0103	0.0707	95.89
T2, GS7, PSA 4-9.9	0.2003	0.2445	0.0468	0.0441	0.0117	0.0738	93.79
T2, GS7, PSA ≥10	0.2462	0.3117	0.0589	0.0655	0.0241	0.1046	88.08
Average	0.1257	0.1512	0.0301	0.0254	0.0043	0.0446	96.87
At 15 years							
Age ≤55							
T1c, GS6, PSA <4	0.0215	0.0209	0.0050	-0.0006	-0.0042	0.0022	96.91
T1c, GS6, PSA 4-9.9	0.0275	0.0263	0.0055	-0.0013	-0.0053	0.0021	97.32
T1c, GS6, PSA ≥10	0.0385	0.0375	0.0082	-0.0011	-0.0069	0.0039	97.85
T1c, GS7, PSA <4	0.0458	0.0468	0.0114	0.0010	-0.0073	0.0074	98.22
T1c, GS7, PSA 4-9.9	0.0584	0.0583	0.0125	-0.0001	-0.0087	0.0075	98.11
T1c, GS7, PSA ≥10	0.0812	0.0819	0.0183	0.0007	-0.0123	0.0119	98.63
T2, GS6, PSA <4	0.0368	0.0377	0.0093	0.0008	-0.0059	0.0064	98.69
T2, GS6, PSA 4-9.9	0.0471	0.0471	0.0102	0.0000	-0.0074	0.0061	98.39
T2, GS6, PSA ≥10	0.0655	0.0661	0.0148	0.0006	-0.0098	0.0100	98.51
T2, GS7, PSA <4	0.0777	0.0825	0.0204	0.0048	-0.0095	0.0159	99.12
T2, GS7, PSA 4-9.9	0.0987	0.1030	0.0226	0.0043	-0.0118	0.0181	98.92

	CIF _{NPCR}	CIF _{ncc}		CIF _{ncc} -CIF _{NPCR}			Coverage probability
		Mean	SD	Mean	25%	75%	
T2, GS7, PSA ≥10	0.1356	0.1434	0.0319	0.0078	-0.0151	0.0281	99.59
Average	0.0612	0.0626	0.0142	0.0014	-0.0087	0.0100	98.35
Age 55.1-65							
T1c, GS6, PSA <4	0.0208	0.0198	0.0037	-0.0010	-0.0037	0.0014	96.72
T1c, GS6, PSA 4-9.9	0.0267	0.0248	0.0036	-0.0018	-0.0045	0.0005	96.39
T1c, GS6, PSA ≥10	0.0370	0.0352	0.0056	-0.0019	-0.0058	0.0016	96.64
T1c, GS7, PSA <4	0.0442	0.0443	0.0088	0.0001	-0.0065	0.0056	98.15
T1c, GS7, PSA 4-9.9	0.0565	0.0555	0.0089	-0.0010	-0.0071	0.0046	98.15
T1c, GS7, PSA ≥10	0.0778	0.0778	0.0132	0.0000	-0.0090	0.0079	98.07
T2, GS6, PSA <4	0.0355	0.0356	0.0069	0.0001	-0.0049	0.0045	98.32
T2, GS6, PSA 4-9.9	0.0454	0.0445	0.0068	-0.0009	-0.0056	0.0035	98.57
T2, GS6, PSA ≥10	0.0625	0.0625	0.0103	0.0000	-0.0075	0.0063	98.49
T2, GS7, PSA <4	0.0746	0.0787	0.0157	0.0041	-0.0074	0.0134	99.08
T2, GS7, PSA 4-9.9	0.0949	0.0980	0.0158	0.0031	-0.0085	0.0127	99.41
T2, GS7, PSA ≥10	0.1290	0.1356	0.0226	0.0066	-0.0095	0.0204	98.99
Average	0.0587	0.0594	0.0102	0.0006	-0.0067	0.0069	98.08
Age 65.1-75							
T1c, GS6, PSA <4	0.0465	0.0447	0.0088	-0.0018	-0.0082	0.0036	96.89
T1c, GS6, PSA 4-9.9	0.0596	0.0558	0.0085	-0.0038	-0.0097	0.0016	96.47
T1c, GS6, PSA ≥10	0.0797	0.0761	0.0129	-0.0036	-0.0124	0.0045	96.64
T1c, GS7, PSA <4	0.0962	0.0974	0.0205	0.0012	-0.0137	0.0141	98.07
T1c, GS7, PSA 4-9.9	0.1222	0.1206	0.0203	-0.0016	-0.0158	0.0112	97.73
T1c, GS7, PSA ≥10	0.1606	0.1615	0.0291	0.0009	-0.0185	0.0195	98.07
T2, GS6, PSA <4	0.0768	0.0779	0.0161	0.0011	-0.0101	0.0106	98.15
T2, GS6, PSA 4-9.9	0.0980	0.0968	0.0160	-0.0012	-0.0123	0.0090	97.73
T2, GS6, PSA ≥10	0.1290	0.1300	0.0232	0.0010	-0.0156	0.0156	98.40
T2, GS7, PSA <4	0.1552	0.1654	0.0348	0.0102	-0.0139	0.0319	98.15
T2, GS7, PSA 4-9.9	0.1952	0.2026	0.0345	0.0074	-0.0164	0.0303	98.24
T2, GS7, PSA ≥10	0.2497	0.2638	0.0466	0.0141	-0.0184	0.0450	97.73
Average	0.1224	0.1244	0.0226	0.0020	-0.0138	0.0164	97.69
Age >75							
T1c, GS6, PSA <4	0.0830	0.0882	0.0243	0.0053	-0.0123	0.0212	97.48
T1c, GS6, PSA 4-9.9	0.1065	0.1083	0.0255	0.0019	-0.0159	0.0175	97.06
T1c, GS6, PSA ≥10	0.1294	0.1369	0.0347	0.0075	-0.0180	0.0289	97.73
T1c, GS7, PSA <4	0.1611	0.1817	0.0523	0.0207	-0.0173	0.0554	97.39
T1c, GS7, PSA 4-9.9	0.2029	0.2190	0.0541	0.0161	-0.0206	0.0501	96.55
T1c, GS7, PSA ≥10	0.2381	0.2678	0.0681	0.0297	-0.0180	0.0761	95.88
T2, GS6, PSA <4	0.1268	0.1448	0.0422	0.0180	-0.0121	0.0449	96.05
T2, GS6, PSA 4-9.9	0.1611	0.1756	0.0442	0.0144	-0.0172	0.0434	96.22
T2, GS6, PSA ≥10	0.1896	0.2160	0.0564	0.0264	-0.0146	0.0629	96.13
T2, GS7, PSA <4	0.2345	0.2820	0.0796	0.0475	-0.0090	0.1015	94.03
T2, GS7, PSA 4-9.9	0.2345	0.3322	0.0801	0.0427	-0.0157	0.0954	93.45
T2, GS7, PSA ≥10	0.3258	0.3905	0.0917	0.0647	-0.0024	0.1278	92.02
Average	0.1828	0.2119	0.0544	0.0246	-0.0144	0.0604	95.83

Abbreviations: CIF_{NPCR} , Cumulative incidence functions estimated in the National Prostate Cancer Register of Sweden (NPCR); CIF_{ncc} , Cumulative incidence functions estimated from the 1,500 nested case-control studies sampled with replacement from NPCR; SD, Standard deviation; 25% and 75%, lower and upper 25th percentile of the distribution of the absolute bias across 1,500 subsamples; T, Clinical tumor stage; GS, Gleason score; PSA, Prostate Specific Antigen

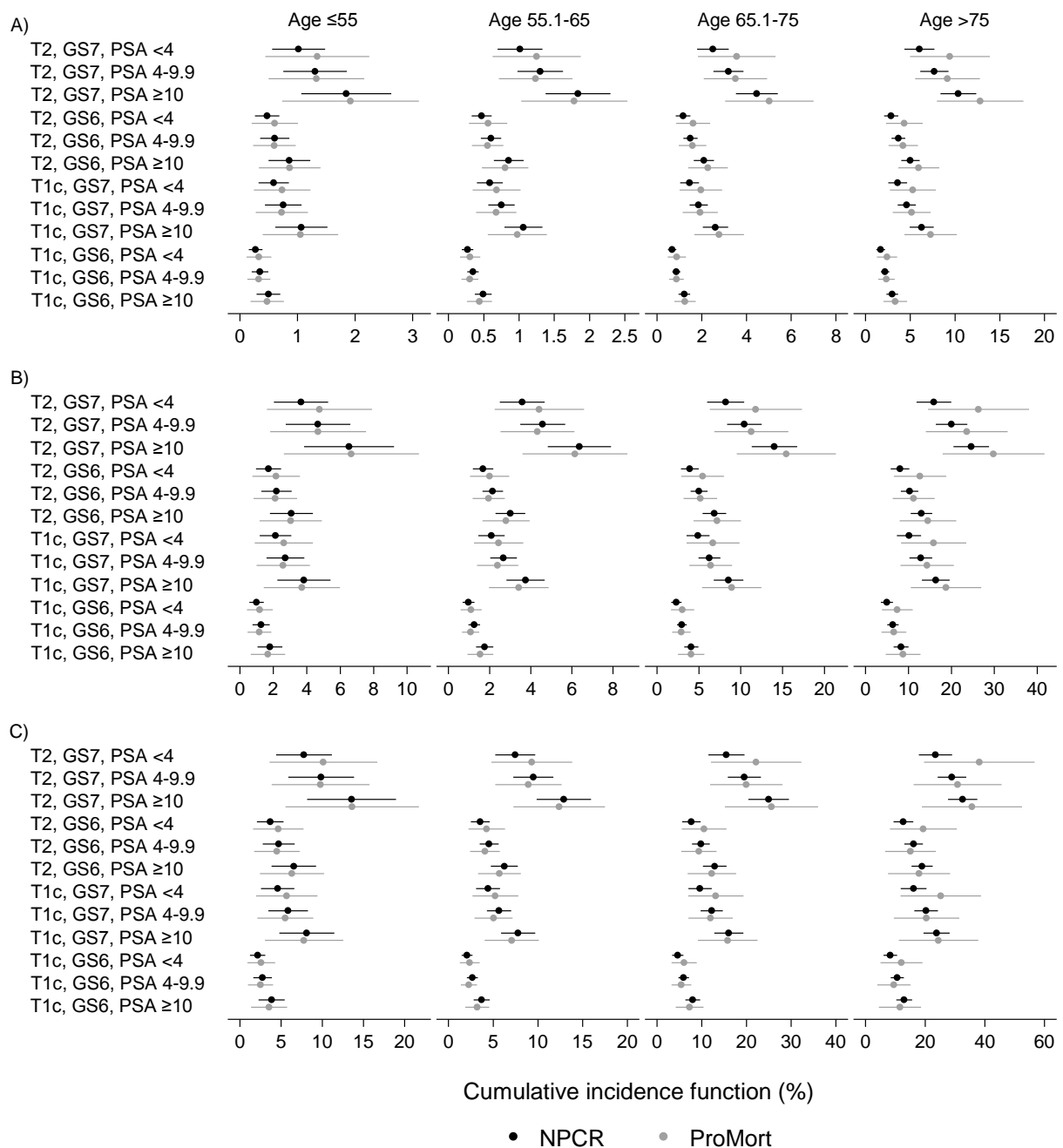
Web Figure 1. Logarithm of the cause-specific hazard ratios and 95% confidence intervals of the risk of dying from prostate cancer and other causes estimated in NPCR, Sweden, 1998-2011, and using Method 1 and Method 2. Reference categories (age 55.1-65, PSA <4, Gleason score ≤6, clinical tumor stage T1c) and estimates for the matching variables (year and county of diagnosis) are not shown in the figure.

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



Web 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



Web Figure 3. Cumulative incidence function and 95% confidence intervals of dying from prostate cancer for men with low- and intermediate-risk prostate cancer in NPCR, Sweden, 1998-2011, and using Method 1 and Method 2. 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.

Abbreviations: T, Clinical tumor stage; GS, Gleason score; PSA, prostate-specific antigen, NPCR, National Prostate Cancer Register of Sweden

