

Estimating Prostate Cancer Net Survival and Cancer-Specific Death

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Abstract

Estimates of the risk of death from prostate cancer are valuable for making screening decisions. Knowing a man's risk of death from prostate cancer can help him select the best PSA threshold for biopsy. Estimates of All-Cause Death (ACD) risk are limited to the population studied. Estimates of Cancer-Specific Death (CSD) risk are more useful than ACD risk. There are two methods of estimating CSD risk: 1) Using records of the cause of death, and 2) Net survival methods that remove other causes from ACD risk. Net survival methods are superior to relying on cause of death because they do not depend on judgment; but they depend heavily on estimates of No-Cancer Death (NCD) risk. Here we present approaches to estimating CSD risk for datasets that may not have records of cause of death. We use data for prostate cancer from the U.S. Department of Veterans Affairs (VA) with data for over 14 million men and 33 million PSA tests. VA has superb death record data for veterans but does not have good records of cause of death. Therefore, net survival methods are the only way to estimate CSD risk for VA data, which puts a premium on accurate estimates of NCD risk.

Key Words: prostate cancer; net survival; Kaplan-Meier; all-cause death; cancer-specific death; no-cancer death

1. Introduction

We have developed Prostate Cancer Net-Survival Methods to estimate cancer-specific death (CSD) risk for large datasets that may not contain records of cause of death or may have only imperfect records. These novel methods are based on estimates of no-cancer death (NCD) curves. The estimation process uses a parameterized family of United States (US) survival and corresponding mortality curves to fit lower-bound NCD curves to the early years of all-cause death (ACD) curves for men in various age ranges with a low risk of prostate cancer death. Men with low Gleason scores and/or low levels of prostate-specific antigen (PSA) have a very low risk of prostate cancer death during those early

years, and their ACD curves provide excellent approximations of the corresponding NCD curves that are required.

1.1 Background on prostate cancer

Prostate cancer is the second leading cause of cancer death among US men. According to the American Cancer Society, nearly 30,000 US men die from prostate cancer each year, and one out of seven men are diagnosed with the disease [2]. Screening using the PSA blood test has contributed to an estimated 45% reduction in the incidence of prostate cancer death over the last two decades, but has also led to substantial over-treatment—often with surgery that may lead to impotence and incontinence [13]. Some doctors contend that PSA screening does more harm than good for US men. Citing the excessive harm of over-treatment, the US Preventative Services Task Force (USPSTF) recently recommended against screening for prostate cancer using the PSA blood test unless better screening methods could be developed [21].

New analysis underway by the authors of US Department of Veterans Affairs (VA) data for 14 million men and 32 million PSA tests suggests more effective ways of screening using dynamic analysis of PSA trends. The VA maintains superb death records for veterans but does not systematically capture cause of death.

1.2 Why We Need to Obtain CSD

Estimates of the risk of death from prostate cancer are valuable for making screening decisions. For example, knowing a man's risk of death from prostate cancer at his life expectancy can guide the selection of the most appropriate PSA threshold for biopsy. Estimates of all-cause death (ACD) risk are limited to the population studied. Estimates of cancer-specific death (CSD) risk are more useful than ACD risk for comparing different ages, treatments, and other variables.

Two main methods of estimating CSD risk are possible: 1) using doctor records of the cause of death, and 2) net survival methods that remove other causes of death from ACD risk. Because judgment is needed when terminal prostate cancer patients die from other apparent causes, cause-of-death records can be unreliable and are not generally available. Cause-of-death records can be excellent if carefully assessed as part of a major study, but can be problematic otherwise. Conceptually, the use of net survival methods is preferable, because these methods do not depend on judgment; however, they depend heavily on estimates of no-cancer death (NCD) risk, which may be difficult to determine accurately in some situations.

1.3 Statistics Literature Review

The aim of this paper is to estimate CSD by first obtaining an estimate of NCD from available data and then removing the NCD from the ACD. A number of papers have described approaches for relative survival as a way of estimating net survival. In much of this work, an estimate of NCD is obtained from a general population-based source. While the population will include deaths from the cause of interest, it is assumed that number of deaths from any particular cause will be small, so that the population will provide a reasonable estimate of the death rate omitting the particular cause. Hakulinen [9] accounts for different patterns of withdrawal within subgroups by using “expected life tables”, and Hakulinen and Tenkanen [10] show how a proportional hazards regression model may be adapted to obtain relative survival using generalized linear models. Estève et al. [6] use a maximum likelihood approach to estimate CSD that allows for the inclusion of covariates.

Cronin and Feuer [4] estimate the cumulative crude cause-specific probability of death using a relative survival approach, rather than using cause-of-death information, and apply their approach to localized prostate cancer in elderly men. Giorgi et al. [8] use B-splines to model non-proportional hazards in a relative survival model. Dickman et al. [5] use a regression model approach to estimate relative survival, while Stare et al. [19] also use a regression approach to obtain relative survival estimates, although for individuals. Pohar and Stare [17] provide a set of R [18] procedures to estimate relative survival for a number of models. Nelson et al. [14] use a flexible parametric model to estimate relative survival, and Hockey et al. [12] address generalizability of relative survival in longitudinal studies. Finally, Perme et al. [16] provide an approach to adjusting net survival for differences among countries.

For net-survival methods, the accuracy and robustness of CSD estimates depend on the appropriateness and reasonableness of the method used to obtain NCD for the population under consideration. Country of residence and age are starting points for defining the population from which to estimate NCD and may be appropriate in some circumstances. They are not sufficient for estimating NCD for populations of men diagnosed with prostate cancer and especially not for men treated with surgery for prostate cancer. Healthier men tend to live longer. Men cared for by various health-care systems, including the VA, tend to be healthier than average men, some of whom may not be cared for by any healthcare system. Men diagnosed with prostate cancer tend to be healthier than average men because unhealthy men tend not to be screened and biopsied for prostate cancer. Men treated with surgery for prostate cancer tend to be healthier than men diagnosed with prostate cancer because the least healthy men tend not to be treated with surgery. Therefore, we would like a reference population from which to estimate NCD that closely matches the health levels and corresponding death risks of the population being analyzed. This article describes how we can estimate NCD using a subset of the actual population being analyzed that has very low risk of prostate cancer death in the early years after diagnosis.

1.4 Outline of Manuscript

In Section 2, we describe the approach taken to estimate the cancer-specific death curve. Section 3 presents a validation of our approach using published data and demonstrations of the robustness of the approach using published and VA data. Finally, in Section 4, we draw conclusions.

2. Methods

We are interested in analyzing populations of men where death is recorded but the cause of death is unavailable. Our goal is to estimate cancer-specific death curves (CSD[t]) for men in various age ranges who have been diagnosed with a range of cancer severities and may or may not have been treated. To achieve this goal, we use net-survival methods based on an age-appropriate family of estimated no-cancer death curves (NCD[t]). In this article, we introduce new methods to estimate an age-appropriate family of NCD(t) curves from age range-specific groups of men with low risk of cancer death in the early years after diagnosis. The approach uses a three-stage procedure. In the first stage, a set of shapes of death curves are defined based on US Life Tables.[3] In the second stage, these shapes are applied to the early years of low prostate cancer death risk all-cause death curves (ACD[t]) for various age ranges by selecting, for each age range, the appropriate death curve from the set of curves defined in the first stage. The result is a set of preliminary NCD(t) curves for each age range. In the third stage, a consistent family of age-appropriate NCD(t) curves

is estimated by fitting a response surface as a function of age to the preliminary NCD(t) curves for each age range.

2.1 Net-Survival Methods to Calculate Cancer-Specific Death Curves

Under the assumption that different causes act independently on mortality, $S_{AC}(t) = S_{NC}(t) \times S_C(t)$ where $S_{AC}(t)$ is the survival curve for all-cause (AC) mortality, $S_{NC}(t)$ is the survival for no-cancer (NC), and $S_C(t)$ is the cancer-specific (C) survival. This implies that:

$$S_C(t) = \frac{S_{AC}(t)}{S_{NC}(t)} \quad (1)$$

A Kaplan-Meier [15] estimate is obtained for $S_{AC}(t)$ for the group for which the cancer-specific net survival is desired. Once we have an estimate of $S_{NC}(t)$, the estimate of $S_C(t)$ is readily obtainable from (1). As usual, the cumulative all-cause death distribution function, $ACD(t) = F_{AC}(t) = 1 - S_{AC}(t)$, the no-cancer death, $NCD(t) = 1 - S_{NC}(t)$, and the cancer-specific death, $CSD(t) = 1 - S_C(t)$.

2.2 Choosing a Low-Risk Group and Data Estimation Range to Estimate NCD(t)

To obtain an estimate of $S_{NC}(t)$ and corresponding NCD(t) for a given age range, we first choose a data set that is likely to have a very low risk of cancer death, for example, men diagnosed and perhaps treated for prostate cancer with low Gleason scores or low prostate-specific antigen (PSA) blood test levels. These men are very unlikely to die of prostate cancer within the early years after diagnosis, and, therefore, the early years of their $S_{AC}(t)$ and corresponding ACD(t) curves are likely to allow good estimates of no-cancer $S_{NC}(t)$ and corresponding NCD(t) curves.

The data estimation range (DER) used to estimate $S_{NC}(t)$ and NCD(t) curves should balance the benefits of a longer DER, which would provide a more stable fit to the survival curve, against the benefits of a shorter DER, which would be less sensitive to the influence of cancer death on the estimated NCD(t) curves.

We define t_e as the end time of the DER. Ideally, t_e should be increased (to include more data) until the risk of cancer death begins to increase the estimate of the later years of NCD(t) by a small amount (before it becomes material). A value for t_e may be chosen using independent results and/or by iterative procedures that determine at what level increasing t_e begins to increase the later years of NCD(t) enough to suggest the greater influence of cancer death. For example, we will show in the results section the indication by independent analysis that prostate cancer-specific death is negligible for the first 6 years following a diagnosis of low-risk cancer, and then gradually increases. We will also show for other data that values of t_e between 6 and 10 years results in nearly identical estimates of the age-appropriate family of NCD(t) curves.

It is likely that men diagnosed and possibly treated for prostate cancer will be healthier than the general population. If these men were unhealthy and possibly near death, it is unlikely that they would be diagnosed or treated. Consequently, the data set will have initial survival that is better-than-expected from population data. To minimize the effect of this selection bias against unhealthy men possibly near death, we exclude from consideration the initial part of the survival and corresponding mortality curve in our estimation of the NCD(t) curve.

To implement exclusion of initial data, we define t_s as the start time of the DER. Ideally, t_s should be decreased (to include more data) until the selection bias begins to increase the estimate of the initial years of $NCD(t)$ by a small amount (before it becomes material). A value for t_s can be chosen using iterative procedures that determine at what level decreasing t_s begins to increase the $NCD(t)$ enough to suggest the greater influence of selection bias for healthy men. For example, we will show in the results section that t_s of approximately 0.0 years is appropriate for one set of published results, and that t_s from 0.0 to 1.0 years produces nearly identical results for the VA population. For these cases, we conclude that reasonably low levels of t_s fail to have a material effect on estimates of $NCD(t)$.

2.3 Estimating $S_{NC}(t)$ and $NCD(t)$

The process of estimating $S_{NC}(t)$ and $NCD(t)$ begins by dividing the study population into a set of age ranges, that sometimes may overlap (such as 50–60 and 55–65) to provide more ranges for estimation of a stable family of age-appropriate $NCD(t)$ curves. Each age range is divided into a series of cancer severity ranges based, in the examples, on prostate tumor Gleason score and on the prostate-specific antigen (PSA) blood test. Finally, for each age range, the lowest cancer severity range with the lowest risk of cancer death and sufficient data is selected: Gleason scores of 2–4 and PSA levels of 4–6 for our two populations.

For each age range, we focus on men in a low cancer death-risk study group and estimate a Kaplan-Meier survival curve and a corresponding all-cause mortality curve, $ACD(t)$. For this $ACD(t)$ curve, we consider only data points in the DER from t_s to t_e . $NCD(t)$ is obtained from this segment of the mortality curve, which corresponds to the Kaplan-Meier survival curve, by fitting a polynomial function to the years from t_s to t_e of the mortality curve. To account for the initial downward mortality bias from healthy diagnosed men, the $NCD(t)$ function is initially linear and becomes quadratic after the initial period. The initial linear portion is required because a quadratic through the origin does not always fit the early part of the curve sufficiently, due to the expected early lower risk of death, i.e., the y-intercept or offset of the best-fit polynomial will be negative. This fitted polynomial curve is extrapolated to obtain our estimate of $NCD(t)$. The final piecewise polynomial is given by:

$$\widehat{NCD}(t) = \begin{cases} D \times t & 0 \leq t \leq t_l \\ A \times t^2 + B \times t + C & t_l < t \end{cases} \quad (2)$$

where t_l is the upper bound of the time over which $NCD(t)$ is linear. t_l is not a critical value, in part because it has a very minor effect on the calculation of $CSD(t)$. Ideally, t_l should create a plausible-looking $NCD(t)$ pattern with a positive linear slope. We choose a reasonable and convenient rule that leads to modest linear slope, where t_l is the time at which $NCD(t)$ has reached one-half the positive value of the offset: $A \times t_l^2 + B \times t_l + C = -C/2$. That is, we choose t_l as the value where the linear part of the curve rises above the x-axis a distance equal to half the negative offset captured by the C coefficient. In our first example, there is no offset ($C = 0$), and t_l is zero. In our second example, the offset is $C = -1.2\%$, and t_l is a very reasonable 1.7 years. The results are insensitive to moderate changes in t_l . The initial linear region has no effect on the projected $NCD(t)$ curve and has no effect on the calculated $CSD(t)$ curve beyond t_l . The downward offset, C , is a useful estimate of the initial healthy selection bias. To ensure continuity, the slope of the linear region is $D = \frac{A \times t_l^2 + B \times t_l + C}{t_l}$.

2.4 Obtaining a family of No-Cancer Death Curves

Selecting a larger value for t_e , such as 6 years, limits—but does not eliminate—the influence of cancer death on our estimate of the $NCD(t)$ curve. Low levels of prostate cancer-specific death near the end of the t_e limit may cause the quadratic equation to

inappropriately curve upwards from a true NCD(t) curve. In order to minimize this inappropriate curvature effect, we use an independent family of NCD(t) curves that constrains the curvature of the quadratic equation to appropriate amounts.

Because prostate cancer deaths are a very small fraction of overall US Mortality, US mortality curves based on the US Life Tables [3] provide good estimates of NCD(t) curves for the first 10 or 15 years after diagnosis.

The shape of the NCD curve will change depending on the age of the group of people being considered. To ensure that the shape of the family of curves changes in a smooth fashion with age, the relationship of the A and B parameters of the quadratic in (2) are constrained to change together. We use US Life Tables [3] to obtain expressions for the coefficients of t^2 and t (A and B) as functions of the US age group. Figure 1 shows the fit of quadratic curves to the cumulative all-cause US deaths for a number of beginning US ages. These quadratic curves fit the US mortality extremely well ($R^2 > 99.9\%$ for each US age considered).

Next, the estimates of A and B are modeled as polynomial functions of USAge, yielding:

$$A = 2.857E - 07 \times USAge^2 - 4.589E - 06 \times USAge - 0.0002497$$

$$B = 1.0388E - 06 \times USAge^3 - 0.0001467 \times USAge^2 + 0.007214 \times USAge - 0.1200 \tag{3}$$

The coefficients of determination for these models for A and B are 99.86% and 99.97%, respectively. The coefficients A and B define the shape (curvature and slope) of the family of mortality curves. To summarize, four steps are taken to estimate the NCD(t) curve for each age range:

1. The group with low risk of cancer is selected.
2. An initial DER is selected to determine the Kaplan-Meier segment considered in the estimation process.
3. Least squares methods are used to determine the best-fit parameters of equation (2) constrained by equation (3). In practice, this means solving for the parameter USAge to determine A and B and for the parameter C to determine the offset.
4. The second and third steps may be repeated to help choose the most appropriate DER.

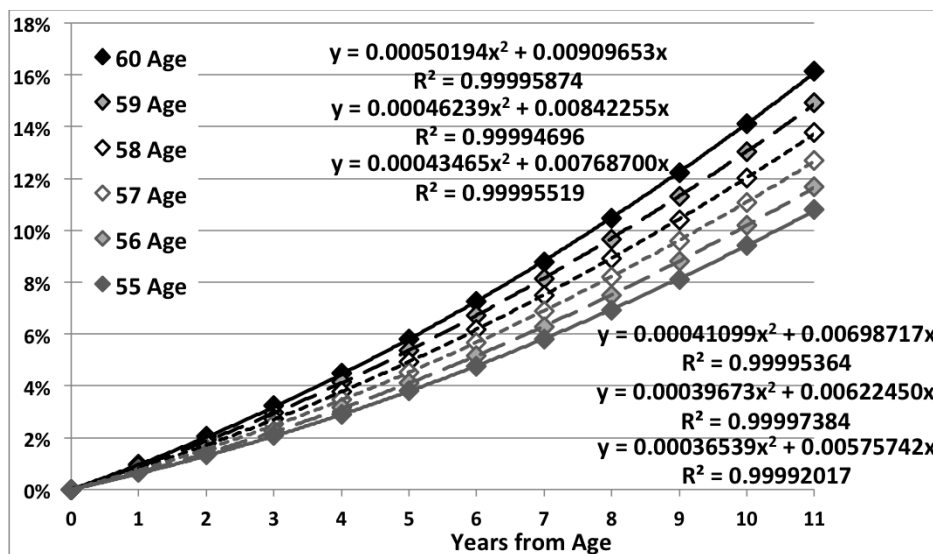


Figure 1. All-cause death curves by age, from 55 to 60 years, from United States Life Tables with fitted quadratic curves.

2.5 Estimating a Consistent Family of NCD Curves as a Function of Age

For any age range, such as 55–65 years, the average age (AAge) in the range may vary among cancer risk groups. For example, AAge may tend to increase as PSA increases. To deal with this variation in AAge for an age range, we have developed a process for estimating a consistent family of NCD curves as a function of age. It can be thought of as an NCD vs. time surface as a function of age. This process has the added benefit of using the results of all ranges to generate a “smooth” best estimate of a consistent family of NCD curves.

The process is very similar to the one used to constrain parameters A and B using USAge. For each age range, the quadratic parameters (A, B, and C) of NCD(t) are estimated and AAge is calculated. Each quadratic parameter of NCD(t) is plotted vs. AAge for all age ranges. Least squares methods are used to estimate a quadratic (or cubic) equation for A, B, and C as functions of AAge.

For each study group with an age range and cancer severity, AAge is calculated and NCD(t) is determined from the consistent family of NCD curves defined as a function of AAge by the following equation:

$$\text{NCD}(t | \text{AAge}) = A(\text{AAge}) \times t^2 + B(\text{AAge}) \times t + C(\text{AAge}) \quad (4)$$

2.6 Estimating NCD Using ACD for a Group with Low Risk of Cancer Death

We demonstrate, and later validate, our Prostate Cancer Net-Survival Method using results from a highly regarded article by Peter Albertsen [1], MD, and colleagues published in 2005. The article estimates 20-year survival based on a competing risk analysis of men who were diagnosed with clinically localized prostate cancer and treated with observation or androgen withdrawal therapy alone, stratified by age at diagnosis and histological findings (Gleason score).

Gleason score is a measure of cancer aggressiveness that is estimated by a pathologist from cancer tissue samples obtained by biopsy. The article reports results for five Gleason score ranges: 2–4, 5, 6, 7, and 8–10, with 2–4 being the least aggressive and the least deadly. As an example, we consider the 55–59 years age range. The first step is to estimate the NCD curve as a lower bound to the Gleason score 2–4 ACD curve, as shown on Figure 2.

Our goal is to obtain an estimate of NCD from the early span of the lowest Gleason ACD curve that embodies very little risk of prostate cancer death. A variety of studies suggest the risk of prostate cancer death is very low for the first 6 years after diagnosis of low-risk prostate cancer. [11], [7] For example, in Figure 2, the doctor-determined CSD curve for low-risk, Gleason 2–4 cancer is assumed to have negligible prostate cancer deaths in the first six years.

To assess the sensitivity of the procedure on the estimated CSD to changes in the NCD curve, we choose a low- and a high-sensitivity case for the NCD curve (see Figure 2). These curves bracket the best estimate NCD curve, which is the estimated lower bound to the Gleason 2–4 ACD curve. The sensitivity cases will be used in the validation process. A range of values for t_s from 0 to 3 years was tested with minimal effect on the parameters of the quadratic curve. Therefore, t_s was set equal to zero. The simplified version of the quadratic function (without offset) is $\text{NCD}(t) = A \times t^2 + B \times t$ for $t > 0$, where $t_s = 0$, $C = 0$, and D in (2) is not used.

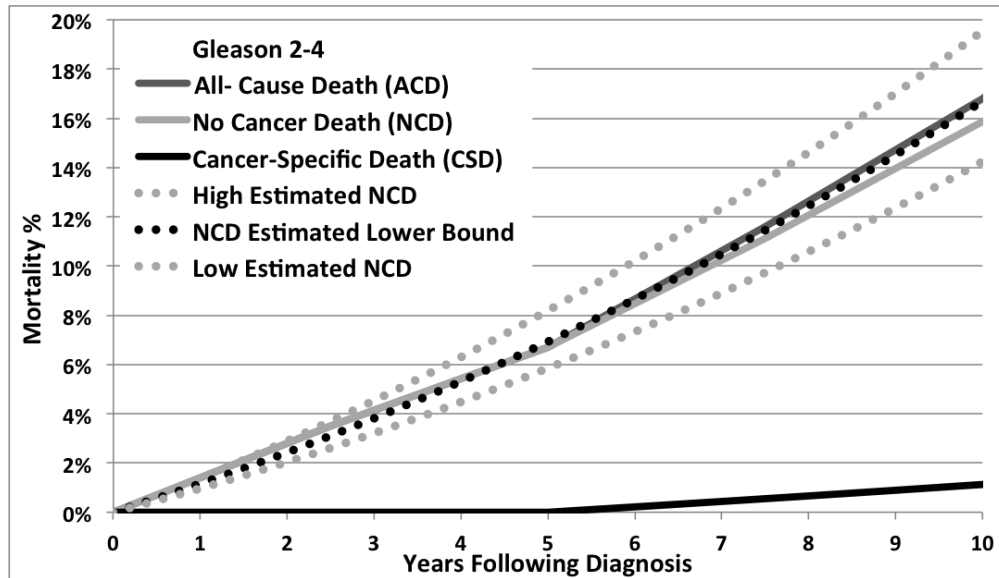


Figure 2. All-cause death, estimated no-cancer death, and cancer-specific death for men of 55–59 years of age and Gleason scores of 2–4 obtained from Albertsen et al. [1]. High- and low-sensitivity cases for NCD are also illustrated and will be used later for analysis of CSD sensitivity to variation in NCD.

2.7 Validating the Prostate Cancer Net-Survival Method vs Cause of Death

The NCD curve estimated from low-risk (Gleason score of 2–4) cancer is compared to NCDs from Albertsen [1] for both Gleason scores 2–4 and 7 and is subsequently used to estimate CSDs for both Gleason 2-4 and 7, which are then compared to the corresponding CSDs from Albertsen [1].

To evaluate robustness, the high- and low-sensitivity cases for the NCD curve shown in Figure 2 are used to estimate corresponding CSDs for both Gleason scores 2–4 and 7, which are then compared to the corresponding CSDs from the Albertsen [1]. Variation in CSD curves is calculated to measure robustness vs. high and low variation in NCD curves.

2.8 Estimating NCD Using ACD for a Group with Low Risk of Cancer Death

We demonstrate and later show the robustness of our Prostate Cancer Net-Survival Method using results from our analysis of VA data. The first step is to estimate the NCD curve as a lower bound to the ACD curve, as shown in Figure 3 on an expanded scale graph. A low NCD curve, shown in Figure 3, will be used to evaluate robustness. A range of values for t_s from 0 to 3 years was tested with negligible effect. t_s was set equal to 1.0. The full version of the quadratic function is needed (with linear period):

$$\begin{aligned} \text{NCD}(t) &= A \times t^2 + B \times t + C \text{ for } t > t_1 \\ &= D \times t \text{ for } 0 \leq t \leq t_1 \text{ (early linear period),} \end{aligned}$$

$$\text{where } D = \frac{A \times t_1^2 + B \times t_1 + C}{t_1} \text{ and } t_1 = 1.7 \text{ years}$$

2.9 Applying the Prostate Cancer Net-Survival Method to VA Data

To assess robustness, the low-sensitivity case NCD curve shown on Figure 3 is used to estimate corresponding CSDs for both PSA levels 4–6 and 12–20. For each PSA level range, CSD curves are calculated for both the best estimate and low-sensitivity case for NCD to measure robustness of the CSD curve to changes in the NCD curve. For each PSA

range, R^2 is calculated for both CSD curves and compared. The difference between the PSA levels 4–6 and 12–20 CSD curves is also calculated for both the best estimate and low-sensitivity case for NCD to measure robustness of the implications of the CSD curves. For prostate cancer screening decisions, the increase in cancer death risk from one PSA level to another is often more important than the level of death risk. In these cases, the sensitivity of the difference in CSD for two different PSA levels is an important measure of robustness. We calculate the change in the difference between CSD curves for PSA levels 4–6 and 12–20 for the best estimate and low estimate of CSD.

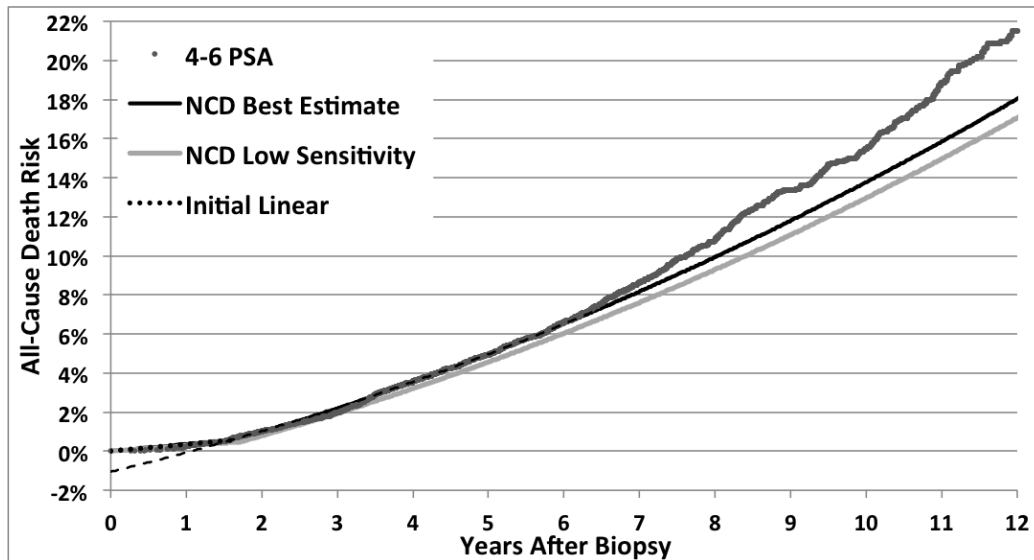


Figure 3. All-cause death and estimated no-cancer death for men of 55–65 years of age and PSA levels 4–6 obtained from VA data. A low-sensitivity case for the NCD curve is also illustrated and will be used later for sensitivity analysis of CSD to variation in NCD.

3. Results

Two data sets are used to show how our Prostate Cancer Net-Survival Methods are applied, to validate their accuracy, and to demonstrate their robustness.

3.1 Validating the Prostate Cancer Net-Survival Method vs Cause of Death

First, we validate our procedure by applying it to the published data in Albertsen [1]. For ages 55–59 years and a Gleason score of 7, Figure 4 shows how well the estimated NCD curve (black dots) matches the actual NCD curve (calculated from Albertsen [1]; solid light gray) with the poor fits of the unreasonably extreme high- and low-sensitivity cases for the NCD curve (gray dots). Figure 4 also shows the very close match between the estimated CSD curve (gray dots) and the actual CSD curve (calculated from Albertsen [1]; solid black) and the surprisingly good fits of the other CSD curves (light gray dots) based on the high- and low-sensitivity cases for the NCD curve. Our Prostate Cancer Net-Survival Method is very robust, because unreasonably extreme variation in the estimates of NCD leads to very little variation in estimated CSD. For the best estimate of NCD, the CSD R^2 is 0.9997. CSD R^2 is 0.9977 for the high-sensitivity case for NCD and 0.9981 for the low-sensitivity case for NCD.

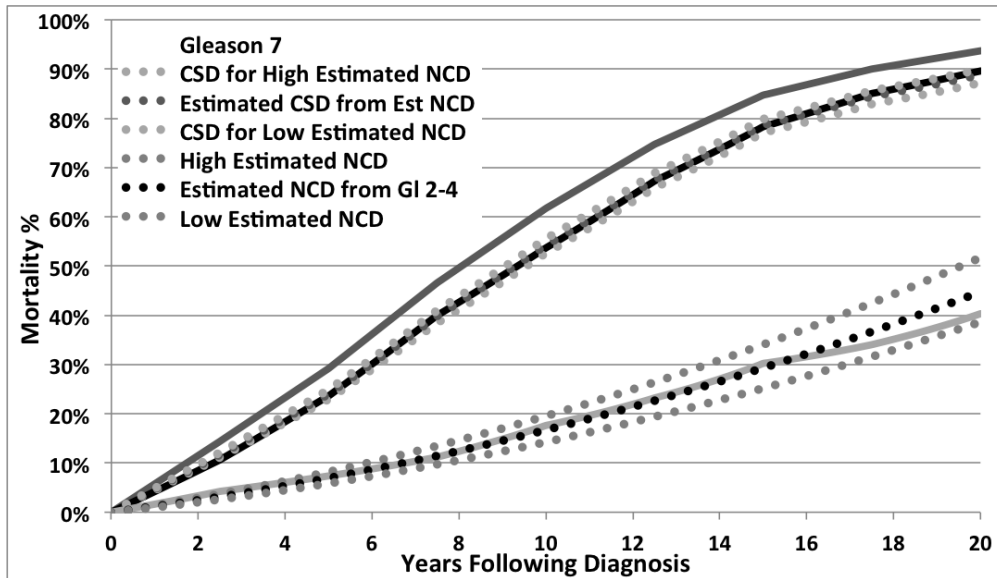


Figure 4. All-cause death, actual and estimated no-cancer death, and actual and estimated cancer-specific death for men of 55-59 years of age and Gleason scores of 7 obtained from Albertsen et al. [1]. High- and low-sensitivity cases for NCD are also illustrated with corresponding variation in CSD shown.

3.2 Apply the Prostate Cancer Net-Survival Method to VA Data

Based on VA data, Figure 5 shows ages 55–65 years ACD(t) for PSA level 4–6 and the substantially higher ACD(t) for PSA level 12–20. The solid black curve shows the best estimate for NCD(t) for ages 55–65 years based on PSA level of 4–6. The solid gray curve shows the low-sensitivity case NCD(t) curve used to evaluate robustness.

Based on VA data, Figure 6 shows the estimated CSD(t) curves with NCD(t) removed using our net-survival methods based on the best estimate of NCD(t).

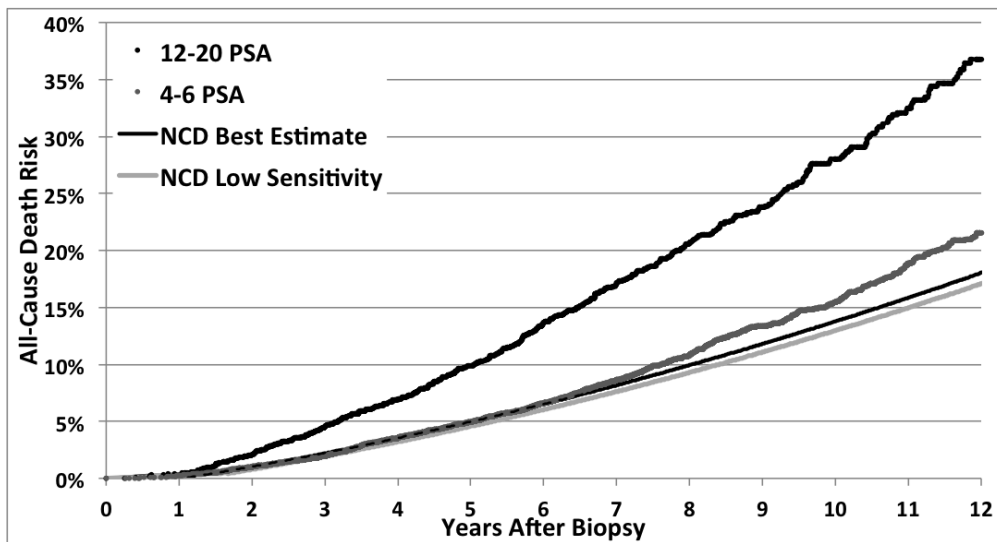


Figure 5. All-cause death for men of 55–65 years of age and PSA levels 4–6 and 12–20 and estimated no-cancer death from men of PSA levels 4–6 obtained from VA data. The low-sensitivity case for NCD is also illustrated and will be used later for analysis of CSD sensitivity to variation in NCD.

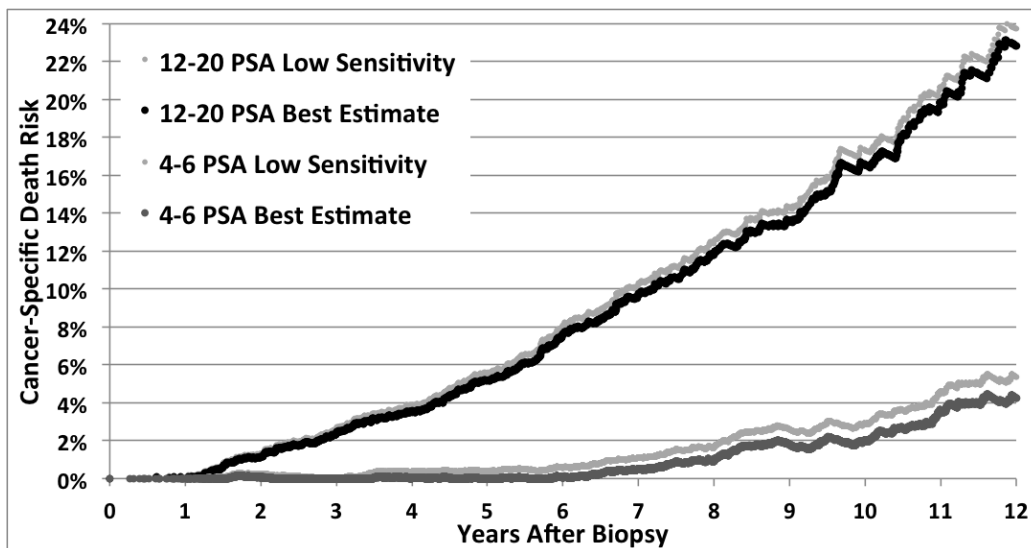


Figure 6. Estimated cancer-specific death for men of 55–65 years of age and PSA levels 4–6 and 12–20 from VA data.

3.3 Evaluating the Robustness of the Method for VA Data

To evaluate robustness, the low-sensitivity case NCD curve is used to estimate corresponding CSDs for both PSA levels 4–6 and 12–20. In Figure 6, the gray curves demonstrate robustness of the method by showing the negligible increase in the CSD(t) curves that result from use of the unreasonably low-sensitivity case NCD(t) curve.

Differences in best estimated and low sensitivity CSD curves at their maximum values are calculated to measure robustness of the procedure. CSD for the low-NCD sensitivity case, compared to the best estimate, increases by only 0.96% of a point for PSA level 12–20 CSD curves and by only 1.13% of a point for PSA level 4–6 CSD curves.

The difference between the PSA levels 4–6 and 12–20 CSD curves is also assessed for the best estimates and low sensitivity cases. At the maximum values of the CSD curves, the difference between high and low PSA levels is 20.45% using the best estimate of NCD and 20.28% using the low-sensitivity case for NCD. The decrease in the difference is only 0.17% of a point using the low sensitivity cases rather than the best estimates.

3.4 Assessing the Reasonableness of the Low-Sensitivity VA Case for NCD

The previous section demonstrated the robustness of the cancer-specific death curves to substantial downward error in the estimate of the no-cancer death curve. In this section, we present evidence that suggests the low-sensitivity case for NCD is unreasonably low, which suggests that the practical robustness of the method is even greater than suggested in the previous section. The low-sensitivity case for NCD implies a 0.6% cancer death rate 6 years after diagnosis, as shown by the black arrows on Figure 7, in addition to a 6.1% no-cancer death rate. At 6 years, ACD = 6.7%, NCD = 6.0%, and CSD = 0.6%. These results imply that 9.0% of total deaths are caused by prostate cancer (0.6%/6.7%) for men aged 55–65 years who are diagnosed with low-risk prostate cancer with PSA levels of 4–6. This percentage (9.0%) is implausibly high for men with low-risk prostate cancer who are typically treated with surgery or radiation. The corresponding Albertsen [1] results for low-risk cancer (measured by a Gleason score of 2–4) imply that, for men not treated with surgery or radiation, less than 1% of total deaths are caused by prostate cancer 6 years after

diagnosis. Alternatively, analysis of studies of Johns Hopkins prostate cancer patients treated with surgery by Han [11] and Freedland [7], suggest that much less than 1% of total deaths are caused by prostate cancer 6 years after diagnosis with a PSA level of 4–6. The logic is simple: the chance of prostate cancer recurrence in the first few years after diagnosis and treatment is low for men with PSA levels of 4–6, and subsequent death in the following few years is rare; prostate cancer seldom leads to very rapid progression to death. Consequently, the probability of prostate cancer death in the first 6 years after diagnosis and treatment is extremely low, with simulations showing a probability of much less than 0.5% of all deaths.

Therefore, the low-sensitivity case for NCD is extremely and unreasonably low, and our method is even more robust than suggested in the previous section.

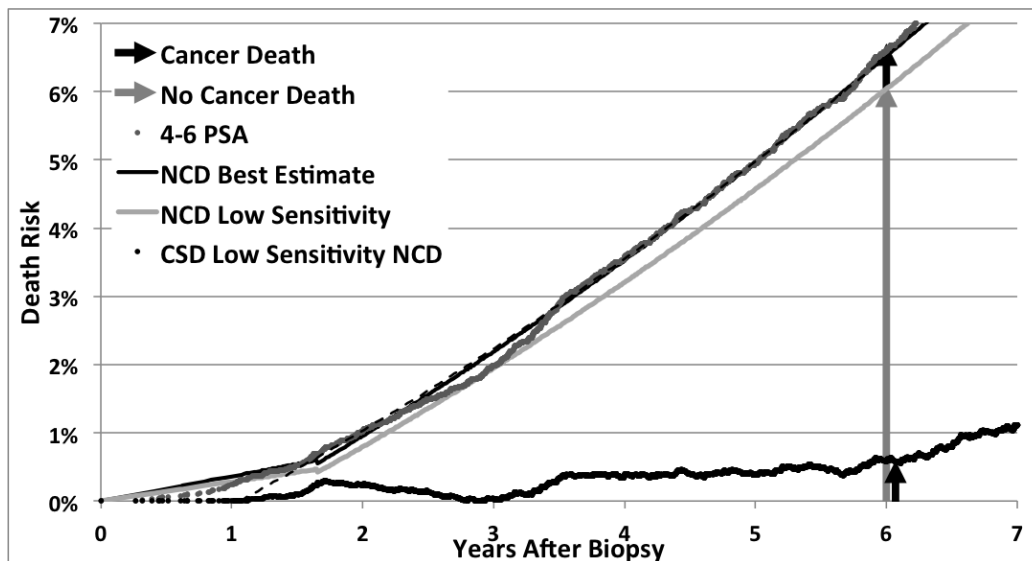


Figure 7. For men of 55–65 years of age and PSA levels 4–6, all-cause death, best estimate, and low-sensitivity case for no-cancer death and cancer-specific death, with arrows at 6 years showing no-cancer death (gray) and cancer death (black).

4. Conclusions/Discussion

Estimates of cancer-specific death are useful for clinical decisions and for comparisons of groups where the underlying no-cancer risk of death may vary (by age, treatment, etc.). However, cancer as a cause of death is often unavailable or unreliable in very large populations, such as from the VA, that otherwise offer the opportunity for invaluable analysis. For example, using the methods described in this article, the authors have demonstrated the important result that fast exponential growth in PSA levels above a no-cancer baseline is highly indicative of deadly prostate cancer. This important result fulfills the request of the USPSTF [21] for new methods to help identify deadly cancers as part of a screening process.

New net-survival methods to estimate cancer-specific death using appropriate age-adjusted estimates of no-cancer death are described. No-cancer death curves are estimated using data from the early years of groups of men of a specific age range who have very low risk of death from prostate cancer. These low-risk groups are identified by either low Gleason scores from the pathological analysis of tumors, or low levels of the PSA biomarker prior

to diagnosis. The parameters of the quadratic no-cancer death curves are constrained to reasonable relationships using an analysis of US survival and corresponding mortality curves. Finally, a consistent family of no-cancer death curves is estimated as a function of age using an analysis of a series of sometimes overlapping age ranges. The consistent family of curves provides estimates of no-cancer death as a continuous function of age and time, and considers all age ranges together to smooth out minor sampling variation for various age ranges. The consistent family of curves as a continuous function of age is useful because the average age may vary among groups with the same age range.

These methods have been shown to be very accurate when validated using previously published results from a highly regarded study of prostate cancer death with careful determination of cause of death Albertsen[1]. These methods have been shown to be very robust when evaluating that study population, as well as the VA population of interest. By “robust”, we mean that a range of plausible sensitivity cases of no-cancer death curves causes negligible changes in the corresponding cancer-specific death curves and even less change in the differences among the corresponding cancer-specific death curves. These accurate, robust, and practical new methods open up valuable new opportunities for analysis of large populations where cause of death is not available or not reliable.

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