Overestimation of prostate cancer mortality and other-cause mortality by the Kaplan-Meier method

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ZHU X, KRANSE R, BUL M, BANGMA CH, SCHRÖDER FH, ROOBOL MJ. Overestimation of prostate cancer mortality and other-cause mortality by the Kaplan-Meier method. *Can J Urol* 2013;20(3): 6756-6760.

Introduction: *To assess the extent of overestimation of the cumulative probability of death by the Kaplan-Meier method with the competing-risks regression analysis as reference approach.*

Materials and methods: *Data were derived from the screening arm of the Rotterdam branch of the European Randomized Study of Screening for Prostate Cancer (ERSPC). The screening arm consisted of 21210 men between the ages of 55 and 74 at study entry. Follow up concerning mortality was complete through 2008. Endpoints were 5 and 10 year cumulative probabilities of prostate cancer death and death from other causes. Relative bias was defined as the ratio of the cumulative probability of death as determined by the Kaplan-Meier method, relative to the cumulative probability obtained by the competing-risks analysis.*

Results: *According to the Kaplan-Meier method, the 5 year cumulative probability of death from prostate cancer was 0.0101, compared with 0.0099 according to the competing-risk analysis [1.8% overestimation]. At 10 year, these numbers were 0.0347 and 0.0321, respectively [8.0% overestimation]. For death from other causes, the cumulative probabilities at 5 year were 0.0399 and 0.0397 according to the Kaplan-Meier and the competing-risks method [0.6% overestimation], respectively. At 10 year, the probabilities were 0.141 and 0.139 [1.7% overestimation], respectively.*

Conclusions: *When competing events are present, the competing-risks regression analysis is to be preferred over the Kaplan-Meier method in the estimation of the cumulative probability of the event of interest.*

Key Words: competing-risks regression analysis, Kaplan-Meier estimate, other-cause mortality, prostate cancer mortality, prostate cancer screening, European Randomized Study of Screening for Prostate Cancer

Accepted for publication March 2013

Acknowledgment

The international coordination of the European Randomized Study of Screening for Prostate Cancer (ERSPC) has been supported since the study's initiation in 1991 by grants from Europe Against Cancer and the 5th and 6th framework program of the European Union, by many grants from agencies in the individual participating countries, and by unconditional grants from Beckman-Coulter-Hybritech Inc. Data referred to in this report are derived explicitly from the ERSPC Section Rotterdam, which is supported by grants from the Dutch Cancer Society, The Netherlands Organisation for Health Research and Development, the Abe Bonnema Foundation and by many private donations.

The authors also thank JBW Rietbergen, A Boeken-Kruger, GJ de Zwart, IW van der Cruijsen-Koeter, MO Boerma, A Prins, R Raaijmakers, and SH de Vries for performing the DRE/TRUS and prostate biopsies during the initial and repeat screening of ERSPC Rotterdam. CGAM Franken-Raab, DW Roobol, and M van Slooten-Midderigh are acknowledged for data collection and data entry.

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Introduction

The most widely used method to generate time-to-event and survival curves is the Kaplan-Meier method.[1] The complement of the disease-specific survival probability (i.e. 1 minus disease-specific survival probability) is often used to estimate the probability of death from an event of interest. However, if a patient experiences events other than the one of interest, i.e. dies from other causes (competing events), problems may arise: if the Kaplan-Meier method is used to estimate the disease-specific survival, competing events are censored in a noninformative way. These events are considered to provide the same information as regularly censored observations (i.e. those observations that are lost to follow up). This is clearly incorrect: men who die from another cause cannot die of the cause of interest. In the Kaplan-Meier approach, these censored observations are removed from the "at-risk" set and it is then assumed that the individuals removed would have had the same risk as those who were not censored. In general, this results in an overestimation of the probability of the event of interest.[2]

The competing-risks analysis is the appropriate approach to estimate the cumulative probability of an event of interest in the presence of competing events.[2-4] In prostate cancer research, competing-risks analysis is being used more and more and several papers with this approach have been published.

Nevertheless, disease-specific mortality in the presence of competing events is still frequently estimated by the Kaplan-Meier method. Considering that elderly men with prostate cancer often die from other causes,[5-7] a study of the extent of the bias in the Kaplan-Meier estimate is informative and may help clinicians understand the need for competing-risks analysis in the estimation of disease-specific mortality.

Materials and methods

Study population

Data used in this study were derived from men with prostate cancer in the screening arm of the Rotterdam branch of the European Randomized Study of Screening for Prostate Cancer (ERSPC). The ERSPC was initiated in the early 1990s, to determine whether a reduction of prostate cancer mortality could be achieved by PSA-screening.[8,9] The study population and protocol in Rotterdam have previously been described in detail.[10] The trial is registered in the ISRCTN under number 49127736.

In summary, 42376 men, 55 to 74 years of age, identified from the population registry were randomized from 1993 to 1999 to a screening (n = 21210) or a control arm (n = 21166). Screening in the intervention arm was carried out with an interval of 4 years. A prostate biopsy was indicated for men with a PSA level >= 4.0 ng/mL and/or abnormal digital rectal examination and/or transrectal ultrasound examination. Since May 1997, a PSA threshold of >= 3.0 ng/mL was used as the sole screen-test. In screen-positive men, sextant biopsies were indicated which were lateralized from June 1996 as described by Eskew.[11] An additional biopsy was taken from any suspicious area on TRUS. After diagnosis of prostate cancer, the treatment decisions were left to the regional healthcare providers.

Data on mortality were collected by linkage to the national registry. Follow up for mortality analyses began at diagnosis and ended at death, or at a uniform censoring date (December 31, 2008). Causes of death were evaluated in a blinded fashion and according to a standard algorithm. Only deaths classified as definitely or probably caused by prostate cancer were classified as death from prostate cancer.[12]

Endpoints

Endpoints were 5 and 10 year probabilities of death from prostate cancer, and probabilities of death from other causes. Based on the probability estimated by the Kaplan-Meier method relative to that of the competing-risks analysis, we determined the extent of overestimation by the Kaplan-Meier method.

Statistical analysis

In the Kaplan-Meier method, men who were alive at the end of the study as well as patients experiencing competing events (death from causes other than the event of interest) were all considered censored in the same way. The Kaplan-Meier approach provides a nonparametric estimate of the overall survival probability in relation to the event of interest. Mortality, either death from prostate cancer or other causes, is calculated as the complement of the survival probability (i.e. 1 minus survival probability).

In the competing-risks analysis, death from causes other than prostate cancer is considered a competing event and vice versa. The estimation of the probability is a two-step process and has been described previously.[3,13] In summary, the probability of the event of interest for a given time interval is estimated as the product of the probability of experiencing the event of interest in that time interval given that the individual has survived both the event of interest and the competing events in prior time intervals. Next, cumulative probability is obtained by summing the

TABLE 1. **Cumulative probability of prostate cancer death**

	No. of men with cancer	No. of events	KM	CR	Overestimation
5 year	2419	24	0.0101	0.0099	1.8%
10 year	2419	96	0.0347	0.0321	8.0%

CR = competing-risks analysis; KM = Kaplan-Meier method

TABLE 2. **Cumulative probability of death from other causes than prostate cancer**

	No. of men with cancer	No. of events	KM	CR	Overestimation
5 year	2419	76	0.0399	0.0397	0.6%
10 year	2419	332	0.141	0.139	1.7%

CR = competing-risks analysis; KM = Kaplan-Meier method

above calculated probability and the probabilities from all previous time intervals.

All statistical analyses were performed with Stata, version 12 (Stata Corp, College Station, TX, USA). Competing-risks analysis was carried out with the stcompet package.[14]

Results

After excluding those men previously diagnosed with prostate cancer, 2419 out of 21210 men in the screening arm were diagnosed with prostate cancer through 2008. The median follow up was 11.1 years from randomization and 7.2 years from diagnosis. Of these men with cancer, 106 men (4.4%) died from the disease and 444 men (18.4%) died from other causes.

Table 1 provides the cumulative probabilities of prostate cancer death. At 5 year, the cumulative probability obtained from the Kaplan-Meier method was 0.0101, compared to 0.0099 according to the competing-risks analysis [ratio: 1.018]. This can be translated into an overestimation of 1.8%. At 10 year, the cumulative probabilities were 0.0347 and 0.0321, respectively [overestimation: 8.0%].

Table 2 summarizes the cumulative probabilities of death from other causes. The cumulative probabilities at 5 year were 0.0399 and 0.0397 according to the Kaplan-Meier and the competing-risks method [overestimation: 0.6%], respectively. At 10 year, the probabilities were 0.141 and 0.139 [overestimation: 1.7%], respectively.

Figure 1 shows the cumulative probability of death from prostate cancer, whereas the risk of death from other causes is depicted in Figure 2. The probabilities calculated by both methods are nearly identical at the beginning, the Kaplan-Meier approach will lead to incremental overestimation of both risks, over time.

Discussion

In the Kaplan-Meier method, the estimate of the probability of an event at a certain time is the product of 1) the probability that an individual has survived just prior to that time, and 2) the conditional probability of experiencing the event beyond that time. The cumulative probability is then the sum of these conditional probabilities over time. In the competing-risks approach, the cumulative probability can be

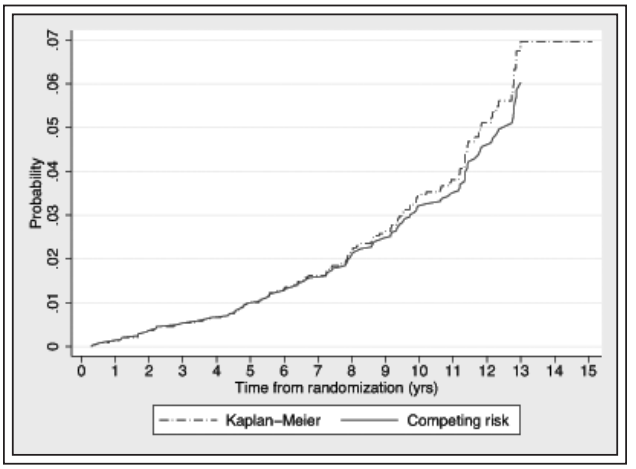

Figure 1. Cumulative probability of prostate cancer death.

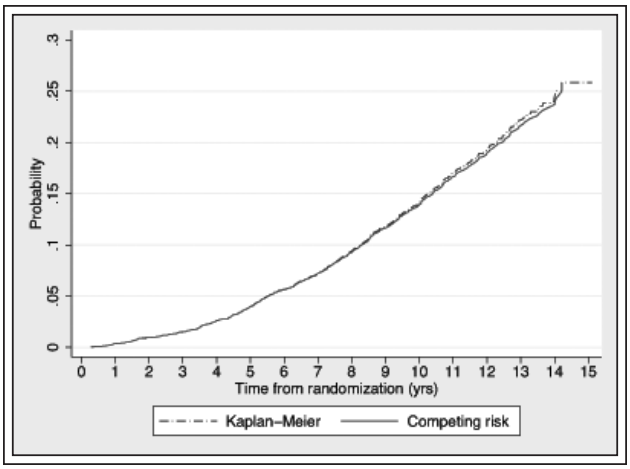

Figure 2. Cumulative probability of death due to other causes than prostate cancer.

calculated similarly. The difference lies in the calculation of the probability of an event-free survival just prior to a certain time (step 1). In the Kaplan-Meier method, when an individual experiences an event other than the one of interest (e.g. dies from another cause), he is considered censored in a noninformative way and is eliminated from the risk set, and therefore not included in the calculation of the survival probability. Hence, the Kaplan-Meier method results in overestimation of the disease-specific mortality in the presence of competing events. In the competing-risks analysis, we account for other events and calculate the probability of survival from any event, i.e. both the event of interest as well as the other competing events.

As a result of the difference in the methods, the competing-risks analysis provides a projection of the actual rate in the study cohort by taking into account the presence of competing events, whereas the Kaplan-Meier method is aimed to provide estimates relative to a population not subject to censoring.[3,4,13,15] However, it should be noted that individuals who are lost to follow up are censored in both approaches. Therefore, if a substantial part of the study cohort has an incomplete follow up, caution is needed in interpreting both the Kaplan-Meier and competing-risks estimate.

In the present study, we assessed the extent of the overestimation by the Kaplan-Meier method in calculating prostate cancer mortality and other-cause mortality in a screening setting. Our results show that the Kaplan-Meier method performs very well for mortality from other causes, but leads to increasing overestimation with respect to disease-specific mortality. This is to be expected since prostate cancer mortality is relatively uncommon when compared to other causes of death. After 5 years of follow up, the cumulative probability of the Kaplan-Meier method was almost identical to that of the competing-risks approach; the overestimation was small: 1.8% for prostate cancer death and 0.6% for death from other causes. This finding can be explained by the fact that merely 5% of the study cohort (120 out of 2419 men with cancer) experienced an event at 5 year (either prostate cancer death or death from other causes).

However, with longer follow up and therefore more events (i.e. 16.9% at 10 year; 408 out of 2419 men), the Kaplan-Meier method leads to incremental bias of the cumulative probabilities. At 10 year, the overestimation of disease-specific mortality is 8.0%. It is to be expected that this percentage will increase in the future.

Although not unexpected, we observed that men with prostate cancer have a much larger risk of dying from causes other than the disease. At 5 and 10 years after diagnosis, the risks were 4.0 and 4.3 fold according to our data. Cronin et al has previously demonstrated the impact of competing events in men with localized prostate cancer over the age of 70: 90% die within 15 years of diagnosis of which 18% from the disease and 72% from other causes.[16] The impact of age and Gleason grade on the probability to die from prostate cancer in relation to other causes has also been shown by the well-known Albertsen tables.[7] For example, a man diagnosed at age 60 with Gleason score 8-10 tumor and managed conservatively has a chance of 81% of dying from prostate cancer versus 16% from other causes after 15 years. In contrast, a patient diagnosed at age 70 with a Gleason 6 tumor has a 30% chance of death from prostate cancer and a 59% chance of death from other causes.

As comorbidity is likely to affect the prognosis of men with prostate cancer, it should be accounted for when choosing the optimal management strategy.[6,17,18] Daskivich et al found in a retrospective series of 1482 men with nonmetastatic prostate cancer that each point increase in Charlson score was associated with a 2 fold increase in mortality from other causes. Conversely, prostate cancer mortality was rare, especially in men with low and intermediate risk prostate cancer (0.4% and 3% respectively versus 8% in high risk patients).[17]

When comparing the extent of overestimation between death from prostate cancer versus death from other causes, we observed a larger bias for the first (e.g. 8.0% at 10 year versus 1.7% for death due to other causes). This is a logical finding as more deaths from other causes emerged during follow up than deaths from prostate cancer. Indeed, the extent of the resulting bias of the Kaplan-Meier estimate is positively correlated with the frequency of the competing event.

Our data indicate that the Kaplan-Meier method may provide reasonable estimates when the number of competing events and follow up is limited. In certain situations, the cumulative probability of an event of interest estimated using the Kaplan-Meier method and the competing-risks analysis can even be similar. For instance, when there are no competing events, that is, when there is only one type of failure, the estimate of the cumulative probability of the event derived from the Kaplan-Meier method and the competing-risks analysis will be identical.[2] However, in case of multiple nonindependent events, competing-risks analysis is needed. This approach does not rely on independence assumptions and hence is more widely applicable to survival scenarios than Kaplan-Meier estimates.

Data used in the present study were derived from the screening arm of the Rotterdam branch of the ERSPC study. Data were prospectively collected and the endpoint (i.e. cause of death) was determined by an independent committee. However, it must be kept in mind that the risks calculated here are only for the purpose to demonstrate the extent of bias of the Kaplan-Meier method. The probabilities cannot be used as reference for urologists or consultation of patients as prostate cancer diagnosis in the screening arm is strongly associated with lead time and overdiagnosis.[19]

Conclusion

In conclusion, when competing events are present, the competing-risks analysis is to be preferred over the Kaplan-Meier method in the estimation of the cumulative probability of the event of interest. Failure to account for such competing events results in an overestimation of the risk. Although the overestimation may seem small on the short term, competing-risks analysis should be applied because it is the correct method. □

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