AMBIGUITIES IN CALCULATING CANCER PATIENT SURVIVAL:
THE SEER EXPERIENCE FOR COLORECTAL AND PROSTATE CANCER

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ABSTRACT

When estimating survival from cancer registry data, there are several decisions to be made concerning record selection and method of calculation. For instance, should one use relative or disease-specific survival and how should one handle 'autopsy only' cases and cases with unknown cause of death. This study evaluates the effects of such decisions for survival from colorectal and prostate cancer in the SEER program.

The research population consists of cases of colorectal cancer and prostate cancer as reported to a SEER cancer registry from 1973 through 1994. Several alternative methods of estimating survival were evaluated. One method of disease-specific survival is chosen as index scenario, and variants in the selection of cancer cases and the method of estimating survival are compared to this index scenario. In general, the differences between the different survival estimates are small for colorectal cancer and somewhat larger for prostate cancer. The most substantial differences concern disease-specific versus relative survival for prostate cancer and inclusion versus exclusion of individuals with more than one cancer for both colorectal and prostate cancer.

There is no single best method for calculating cancer survival. Nevertheless, suggestions for calculating cancer survival when using SEER program data are derived from this study.

MESH HEADINGS

Bias; Cancer; Colorectal Neoplasms; Epidemiologic Methods; Prostatic Neoplasms; SEER Program; Survival Rate;
When estimating survival from cancer registry data, there are several decisions to be made concerning record selection and method of calculation. This paper only concerns estimating net survival that is intended to show the influence of having the disease in question. (Estève et al., 1994) The SEER program data contain enough detail to evaluate how a variety of decisions lead to different survival estimates: which primary cancers should be considered, use of relative or disease-specific survival, and in case of the latter, what is the right definition of disease-specific death, how to handle 'autopsy only' cases, 'death certificate only' cases and cases with unknown cause of death or with no known death certificate? The best choice may depend on the purpose of the survival estimate. Survival estimates can, for instance, be used for studying time trends, in order to monitor the eventual effect of dissemination of a new therapy or for studying the effect of stage at diagnosis or that of socio-economic status.

This study focuses on 5-year survival from colorectal cancer and 10-year survival from prostate cancer. Colorectal cancer was chosen as a common cancer with expectedly few difficulties concerning survival estimates. Prostate cancer is also common but expected to be accompanied by more ambiguities concerning survival calculation because the cause of death of a prostate cancer patient is often less clear and mortality from the cancer does not decrease as rapidly with time since diagnosis as in most other cancers.

MATERIAL AND METHODS

The research population consists of cases of colorectal cancer and prostate cancer as reported to a SEER cancer registry from 1973 through 1994. (National Cancer Institute, 1997) Colorectal cancer is defined by 'primary site' codes C18.0 through C20.9 and prostate cancer is defined by code C61.9 (Percy et al., 1990).

The index scenario was chosen so that the other methods of calculating survival used in this study could be derived by simple alterations. This index scenario is disease-specific survival with the following exclusions: carcinoma in situ, cases with unknown survival , cases with more than one primary cancer at
the time of last follow-up, cases without a death certificate or listing available to SEER, cases without a coded cause of death, cancers detected at autopsy only, cases known by death certificate only, and individuals coded to be of ‘other race’ according to Race recode B or of unknown race.

Table 1 shows the numbers exclusions from the index scenario. Some cancers are excluded for more than one reason.

Disease-specific survival is calculated by the actuarial method with one-month intervals. All causes of death due to cancer (underlying cause of death 140.0 through 209.9) are counted as death due to the disease under study.

Variants in the selection of cancer cases and the method of estimating survival are described by what is changed relative to this index scenario.

Relative survival

In contrast to disease specific survival, which treats deaths from causes other than the cancer as 'lost to follow up', relative survival is calculated by dividing observed survival by expected survival. (Ederer et al., 1961) Expected survival, which would have applied if the patient would not have the disease in question, is derived from the total population of people from which the diagnosed cases were drawn.

Relative survival was calculated by using SEER*Stat, a PC based survival system provided by NCI that defines relative survival as the ratio of the proportion of observed survivors in a cohort of cancer patients to the proportion of expected survivors in the U.S. population by race, sex, age, date of diagnosis. (National Cancer Institute, 1997).

Number of cancers in one individual

Two variants from excluding all individuals with a history of more than one cancer were studied: the first considered each primary colorectal cancer or prostate cancer, and the second considered only the first invasive colorectal or prostate cancer in an individual. If more than one primary cancer of the same site
was diagnosed at the same time, then only the one with the worst stage is considered, assuming the following order of increasing severity: localized, regional, unstaged, distant.

*Disease-specific death*

In the index scenario, the widest definition for disease-specific death is used: all cancer deaths are considered to be disease-specific death. If only individuals are considered with one primary cancer, this seems reasonable. In order to check the extent to which this influences the estimates, two variants of disease-specific death are considered: a narrow definition in which disease-specific death from colorectal cancer is defined as cause of death from colon cancer or rectal cancer or from unspecified organs of the tractus digestivus; death from prostate cancer then is defined as simply from prostate cancer. The wider definition of disease-specific death for colorectal cancer or for prostate cancer includes death from metastases.

All nine combinations of number of primary cancers and definition of disease specific death are considered.

*Cases detected at autopsy*

Most cancers that are detected only at autopsy are not considered to have caused the death of the individual. Then they should best be regarded as prevalent cases of disease that apparently did not yet cause any harm to the individual. However, some of these cancers are attributed to have caused the death of the individual. In one variant the latter category of cancers is included in the survival estimate with zero survival.

*Cases known by death certificate only*

Death certificate only cases have a cause of death of cancer, but follow back with the hospital and physician did not yield evidence of a cancer diagnosis. We included 'death certificate only' only if cancer
is actually mentioned as the underlying cause of death. In order to check what is the maximum possible error by excluding these cases, these cases are included in two variants: assuming zero survival and assuming a survival for at least the survival period in consideration (5 or 10 years). The age of death is chosen as the age of diagnosis.

*Cases without death certificate or without coded cause of death*

Cases without death certificate or without coded cause of death are included in two variants: one assumed all deaths were disease-specific and one assumed all deaths were from other causes.

*Individuals of 'other race' or of unknown race*

As a variant to the index scenario, cancer cases from individuals of 'other race' or of unknown race are included in the cancer survival estimate.

**RESULTS**

An overview of the outcomes of the different methods of survival estimation is given in table 2 for colorectal cancer and in table 3 for prostate cancer.

In general, the differences between the outcomes for colorectal cancer are small. The differences are somewhat larger among the unstaged cases and among older individuals. The differences between the outcomes for prostate cancer are larger than for colorectal cancer. There they do not concentrate so much in the unstaged cases but also for prostate cancer the differences are larger among older men than among younger men.

*Disease-specific versus relative survival*

Under age 75 relative survival from colorectal cancer is about equal to disease specific survival except that staged cases have a slightly higher relative than disease-specific survival, compensated by a lower
relative survival of unstaged cases. Among older individuals relative survival tends to be higher than
disease-specific survival.

For prostate cancers the differences are much larger. In all stages and age categories for which survival
was estimated, relative survival shows higher outcomes than disease-specific survival, except for cases
with distant metastases under age 75.

Number of cancers in one individual

Among the 25,386 people who had a first colorectal cancer followed by diagnosis of one or more further
cancers survival is 69.1% in comparison to 51.6% for those who had only one primary cancer at the end
of follow-up. The 34,397 cases of colorectal cancer that are diagnosed among individuals with a previous
history of cancer show a slightly lower 5-year survival of 49.1%.

If only first colorectal cancers are taken into account these figures do not change much: 69.5% for people
who had a first colorectal cancer followed by diagnosis of one or more further cancers and 47.6% for
people who already have a history of another type of cancer.

The 17,184 cases of prostate cancer among people who had a first prostate cancer followed by diagnosis
of one or more further cancers have a 10-year survival of 39.5% (compared to 59.4% for the people only
one cancer), the 18,710 cases with previous history of cancer have a survival of 41.7%.

Table 2 and 3 show an expected tendency for survivals from cancers with more favorable stages to be
more influenced by other cancers.

Disease-specific death

Of the individuals with colorectal cancer selected according to the index scenario who die within 5 years
from cancer, 94.5% have a cause of death according to the narrow definition of disease-specific death,
3.0% died from metastases and 2.5% from other cancer death. Of colorectal cancer cases where the cancer
is the first among more than one cancer and who die within 5 years from cancer, only 64.1% have a cause
of death in the narrow definition of disease-specific death. For cases with a previous cancer, this is 75.4%. The fraction attributed to dying from metastases does not depend strongly on sequence number: 3.5% for first among more cases as well as for cases with a previous cancer. The fraction dying from other cancers is much higher among those with more than one cancer: 32.4% for first cases and 21.1% for later cases. Of the individuals with prostate cancer selected according to the index scenario who die within 10 years from cancer, the figures are very similar to those of colorectal cancer: 94.4% died from prostate cancer, 2.1% from metastases and 3.5% from other cancer death. Of prostate cancer cases where prostate cancer is the first among more than one cancer and who died of cancer within 10 years, only 23.6% died from prostate cancer and for prostate cancer cases with a history of other cancer: 41.2%. The fraction dying from metastases among individuals with prostate cancer is clearly higher if one has more than one cancer: 5.8% for first cases and 4.7% for later cases. Also here, the fraction dying from other cancers is high: 70.6% for first cases and 54.1% for later cases. Because few individuals who die with only one cancer are attributed to dying from metastasis or dying from another cancer, survival estimates do not increase much when applying the narrow definition of disease-specific death instead of the index scenario: 53.5% versus 51.6% for colorectal cancer and 61.2% versus 59.4% for prostate cancer. Among individuals with more than one cancer, narrowing the definition of disease-specific death has a much greater influence. Survival from colorectal cancer is 79.3% versus 69.1% for first cases and 58.8% versus 49.1% for later cases. For prostate cancer the effect is even larger: 80.1% versus 39.5% for first cases and 66.6% versus 41.7% for later cases. Tables 2 and 3 also show that selection of only first colorectal or prostate cancers makes little difference. 

*Cases detected at autopsy and cases known by death certificate only*

Including cancer cases detected at autopsy, whose deaths are attributed to the given cancer, lowers survival estimates. However, the number of cases involved is relatively small, so the effect on survival estimates is not substantial. Also the number of 'death certificate only' cases is relatively low, thus having
little influence on survival estimates.

*Cases without death certificate or without coded cause of death*

Including individuals without death certificate or without cause of death leads to higher survival estimates and including them as disease-specific death leads to lower estimates than the index scenario.

*Individuals of 'other race' or of unknown race*

Individuals who are coded to be of race 'other' have a markedly higher survival from respectively colorectal cancer (61.6%, n=786) and prostate cancer (65.7%, n=594) than individuals with a specified racial code. Individuals of unknown race have a very high survival: 89.9% for colorectal cancer (n=1033) and 94.5% for prostate cancer (n=3387). Therefore including those two groups in the survival estimate leads to a slight increase as shown in tables 2 and 3. At the end of known follow up in SEER, 87.0% of colorectal cancer cases of individuals of unknown race are considered as being still alive versus 36.3% of individuals with specified race, for prostate cancer this is 95.8% versus 53.9%. Among individuals of unknown race, 52.5% of colorectal cancer is diagnosed in stage 'localized' (versus 33.3% among individuals with specified race), and 25.2% is unstaged. For prostate cancer, 41.5% is staged localized among individuals of unknown race (versus 58.1% among individuals with specified race) and 48.3% of cases from unknown race is unstaged.

Figure 1 gives an overview of the differences between survival percentage of variants with the index scenario of 5-year colorectal cancer survival and 10-year prostate cancer survival.

**DISCUSSION**

In 5-year survival from colorectal cancer each of the different methods of estimating survival which were
used in this study gave similar results. Differences in 10-year survival from prostate cancer are more substantial and perhaps best explained by the fact that the underlying cause of death is often unclear and the period of follow up since diagnosis was longer.

Net survival is an adjustment of observed survival that accounts for mortality from other causes. Therefore differences from methods of net survival are expected to be larger with increasing mortality from other causes. This is the case for prostate cancer compared to colorectal cancer where follow up time is longer and cases are older.

**Disease-specific versus relative survival**

Relative survival does not require accurate registration of causes of death but it is crucial that mortality in the background population is representative for the risk of cases to die from other causes than those to be attributed to the disease.

An obvious advantage of disease-specific survival is that it only needs information on diagnosed cases but it is crucial that the registered cause of death from the specific disease is accurately counting deaths that are to be attributed to the disease.

The SEER program usually uses relative survival in order to avoid problems in death misclassification and because of ambiguities in definitions (Brown et al., 1993; Percy et al., 1990).

The differences between disease-specific and relative survival, particularly in prostate cancer, may be due to bias in either of the two methods. On the one hand, too many deaths of patients with prostate cancer may be attributed to prostate cancer as the underlying cause of death, leading to an underestimate of net survival. On the other hand, expected survival (used for relative survival) may be underestimated due to the use of life tables based on the entire U.S.A. instead of the areas of the SEER program and/or because individuals diagnosed with prostate cancer may have a lower risk of dying from causes unrelated to prostate cancer. An underestimate of expected survival implies a too large correction for mortality from other causes, thus an overestimate of net survival. These biases seem unlikely to cause all of the 10%
difference in survival estimates since that would imply around 20% lower mortality from other causes than average for individuals under age 75 (expected 10-year survival is 61%). There are signs that the misclassification of the cause of death is occurring on a substantial scale. The introduction of PSA screening has led to a huge, temporary, increase in incidence of prostate cancer due to the early detection of prevalent cases, which was accompanied by an increase in registered prostate cancer mortality. (Feuer et al., 1999) A tendency to mistakenly attribute death to prostate cancer for someone with a history of that disease would explain at least part of the differences between relative and observed survival as well as the coincidence of increasing incidence and mortality of prostate cancer around the time of introduction of PSA screening.

Definition of disease-specific death

It appeared from this study that the problem of inaccurate specification of cancer death is rather limited. The question remains which definition is closest to the truth. There are 1839 individuals with colorectal cancer selected for the index scenario who are attributed to have died from cancer but not from a cause in the narrow definition nor from metastases, and 1287 of such prostate cancer cases. Among those 3126 cases, the largest number of deaths (942) is attributed to lung cancer. One may wonder if this is due to an incorrect specification of cause of death, or to primary lung cancer that has not reached the SEER program as reportable incidence. The next two largest categories among colorectal cancer cases concern liver and pancreas cancer, and among prostate cancer, bladder and pancreas cancer (likely candidates for misspecification). But the next larger categories concern stomach cancer, ovarian and prostate cancer among colorectal cancer cases and colorectal cancer among prostate cancer cases, which do not seem likely to be misspecified.

One might consider a thorough review of all of the mortality codes and consider whether they are likely candidates for misspecification. In that case, one might also consider some causes of death that are not due to cancer but may be due to therapy, such as sepsis.
**Number of cancers in one individual**

When estimating net survival for individuals with more than one cancer, not all cancer deaths should be regarded as disease-specific, but only a more narrow definition of disease-specific death is useful. The observed differences by number of cancers can be explained by a bias due to case selection: individuals who die quickly after the diagnosis of their first cancer have little opportunity of having a next cancer and cancer cases which are the first of a sequence are selected for having longer survival. It is not correct to discard all cancer cases among individuals with more than one cancer if one is interested in an accurate estimate of net survival. For instance, if one is interested in estimating prognosis at diagnosis, there is no way to know in advance if the individual will be diagnosed with another cancer later on, then one should at least also consider individuals who have the cancer of interest as first in a series of more than one diagnosed cancer.

**Cases detected at autopsy**

From the perspective of determining prognosis for someone diagnosed with cancer, clearly cases detected at autopsy should not be included in the survival estimate. But from a perspective of evaluation of early detection, they should be included because earlier diagnosis and treatment possibly improves their prognosis.

**Cases known by death certificate only**

The probability of observing a case identified by death certificate only increases if one or more of the regular reporting sources to the registry are not involved. This may very well be associated with a different survival, probably worse than other types of cases. The theoretical maximum overestimate from disregarding 'death certificate only' cases shows from attributing them zero survival. This study shows that the overestimate is at most quite small. At older ages and when selecting unstaged cases, the possible
bias is larger.

Trying to estimate the theoretical maximum underestimate by assuming that 'death certificate only' cases have a long survival is problematic. It is not known to which age category the individual should be attributed. Also, one should then consider the possibility of an unknown quantity of unregistered cases of cancer that are still alive.

*Cases without death certificate or without coded cause of death*

Leaving out cases without death certificate or with unknown cause of death, leads to an overestimate of net survival because those who are still alive but who will have the same problem at death, are not left out.

Of colorectal cancer cases selected according to the index scenario dying within 5 years with a known cause of death, 76.7% die from cancer. If one assumes that this is the same for people of whom no death certificate is available, then the survival estimate that assumes that cases with no death certificate are dying from disease-specific cause is closer to the truth than when assuming they are dying from other causes. In prostate cancer survival it is not so clear because only 48.8% of prostate cancers cases dying within 10 years die from prostate cancer. A probable reason for the absence of a death certificate is having moved out of the region of the SEER program, which may be associated with the probability of dying from the cancer.

For those who have an unknown cause of death the percentage who have in fact died from the cancer in question may be quite different, but that group is considerably smaller than the group without death certificate.

*Individuals of 'other race' or of unknown race*

The high survival rates of individuals of unknown race is probably due to death certificate often yielding an individual's race, consequently many individuals who have died are selected out of this category. This
mechanism also causes a slight underestimate of survival in other racial categories.

*Observed survival*

This study has not considered possibilities of error in the observed (or crude) survival. The number of cases in the register with unknown survival is limited and therefore their maximum influence on estimated survival is small. Besides that, cases that are lost to follow up are not likely to have a radically different survival from other cases after the moment of loss. Also, the number of cancer cases that are diagnosed but do not reach the registry appears to be limited considering how few cases are known to the registry by death certificate only.

**CONCLUSION**

There is no single best method for calculating survival from cancer in the SEER program. Different methods can give different outcomes, but for most variants considered the differences are small. The most substantial differences in this study concern disease-specific versus relative survival for prostate cancer and the inclusion or exclusion of individuals with more than one cancer for both cancers investigated.

*Suggestions for calculating cancer survival in the SEER program*

1. Since disease-specific and relative survival are subject to different forms of bias of variable magnitude, it is advisable to apply both methods, to compare the outcomes and to try to explain the differences. The preferred method may be different depending on cancer site and the study objectives.

2. Various definitions of disease-specific death are possible. When considering individuals with only one cancer, the definition is not crucial. It is advisable to consider which codes of cancer death should be included as disease-specific death and which should not, depending on their probability to be inaccurately coded deaths with respect to the cancer for which survival is estimated. Also some codes for non-cancer death may be considered such as sepsis.
3. One should consider including individuals with more than one cancer. If one applies the narrow
definition of disease-specific death, this is not problematic. If one wants to include all cancer deaths
as disease-specific, one can estimate the difference between the narrow and wider definition from the
individuals with only one cancer and extrapolate that difference to those with more than one cancer.
In relative survival this is only a problem if incidence at different cancer sites is correlated.

4. Cases detected at autopsy dying from other causes than the cancer are generally not relevant for
survival estimates. For evaluating early detection, the other 'autopsy only' cases should be included as
having zero survival, but for prognosis at time of diagnosis, they should be included.

5. Cases with unknown survival time, known by death certificate only, without death certificate, and
without coded cause of death should be excluded from a baseline survival estimate. The percentage of
these cases should be noted.

6. The maximum bias due to exclusion of cases known by death certificate only can be shown by
assuming that these cases have zero survival. The maximum bias due to exclusion of cases without
death certificate or without coded cause of death can be determined by assuming that these cases die
from disease-specific death.

7. If one is not categorizing survival by race, then survival from cases among individuals of 'other race'
or of unknown race should be included in the estimate.

REFERENCES

Brown, B.W., Brauner, C. and Minnotte, M.C., Noncancer deaths in white adult cancer patients. J Natl


Table 1
Number of primary cancers in the SEER program from 1973 through 1994, reason for exclusion for the index scenario of survival calculation and remaining number of cases

<table>
<thead>
<tr>
<th>Reason for Exclusion</th>
<th>Colorectal Cancer</th>
<th>Prostate Cancer</th>
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<tbody>
<tr>
<td>Total number of cases</td>
<td>265,463</td>
<td>225,358</td>
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</tbody>
</table>

Exclusion because of:

- Carcinoma in situ: 14,188, 374
- Unknown survival: 3,419, 4,605
- Sequence number > 0: 67,240, 38,167
- No death certificate: 6,463, 5,111
- Unknown cause of death: 499, 561
- Autopsy only and cancer death: 523, 817
- Autopsy only and death from other causes: 833, 2,441
- Death certificate only: 2,062, 1,347
- Other race: 1,006, 689
- Unknown race: 1,577, 3,601

Remaining cases in index scenario: 179,545, 174,861
Table 2: 5-year survival from colorectal cancer in the SEER program from 1973 through 1994 according to different methods of estimation, differences of the odds and the odds of the index scenario of more than 20% are in italics

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<td>include other race/unknown race</td>
<td>51.8%</td>
<td>54.6%</td>
<td>86.8%</td>
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DCO = death certificate only; COD = cause of death; narrow definition = COD 153.0-154.1, 159.0-159.9; wider definition = narrow + COD 195.0-199.9
Table 3: 10-year survival from prostate cancer in the SEER program from 1973 through 1994 according to different methods of estimation, differences of the odds and the odds of the index scenario of more than 20% are in italics.

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DCO = death certificate only; COD = cause of death; narrow definition = COD 185.0-185.9; wider definition = narrow + COD 195.0-199.9
figure 1
Differences between survival percentage for different methods of estimating survival and the survival percentage of the index scenario for colorectal cancer (5-year survival) and prostate cancer (5-year survival)