Mortality in the absence/presence of other causes

- Relative survival does not give us the probability an individual will die of their cancer.
- Relative Survival is a measure of survival in the absence of other causes, i.e. net probability.
- It gives us the probability of surviving in the hypothetical world where it is impossible to die of other cause.
- Unfortunately none of us live in this hypothetical world.
- $1 - R(t)$ is an estimate of the net probability of death due to cancer.
Net and Crude Mortality 1

Net Probability of Death = Probability of Death in a hypothetical world where the cancer under study is the only possible cause of death

Crude Probability of Death = Probability of Death in the real world where you may die of other causes before the cancer kills you

Net and Crude Mortality 2

- Net survival/mortality is useful for comparisons over time and between places.
- It may not be so relevant to individual patients.
- Patients live in the real world when they are at risk of dying from other cause.
- Crude mortality will be more relevant to them.
Cronin and Feuer[2] showed how crude mortality due to cancer and due to other causes can be calculated from life tables. Based on competing risks theory. Calculated separately in age groups. Time-scale split into large (yearly) time intervals. No individual level prediction using continuous covariate.

Figure 1 from Cronin & Feuer (SiM 2000;19:1729-1740)

Figure 1. Cumulative probability of death in men with localized prostate cancer over the age of 70.
Estimating crude mortality in relative survival models

- We show that crude mortality can be estimated after fitting a relative survival model.
- We use the flexible parametric models described this morning.
- However, the methodology could be applied to any relative survival model.
- Note that the fitting of the relative survival model is not any different, but we are using transformations the parameter estimates.
- The flexible parametric models allow individual level covariates to be modelled.
- See Lambert et al. 2009 (in press) for details [3].

Brief Mathematical Details

\( h(t) \) - all-cause mortality rate
\( h^*(t) \) - expected mortality rate
\( \lambda(t) \) - excess mortality rate

\[ h(t) = h^*(t) + \lambda(t) \]

\( S^*(t) \) - Expected Survival
\( R(t) \) - Relative Survival
\( S(t) = S^*(t)\lambda(t) \) - Overall Survival

Net Prob of Death = \( 1 - R(t) = 1 - \exp \left( - \int_0^t \lambda(u)du \right) \)

Crude Prob of Death (cancer) = \( \int_0^t S^*(u)R(u)\lambda(u)du \)

Crude Prob of Death (other causes) = \( \int_0^t S^*(u)R(u)h^*(u)du \)
Integrating

- The integrand is a non-linear function of the model parameters.
- The integration is performed numerically by splitting the time-scale into a large number, $n$, of small intervals (e.g. 1000).
- The predicted value of the integrand at each of the $n$ values of $t$ is obtained.
- The predicted cumulative incidence function is the sum of the these predicted values.
- The variance is a bit trickier, as the observation-specific derivatives need to be obtained. These are calculated numerically (Stata’s `predictnl` command).
- The approach is similar to that used by Carstensen when calculating survival functions from Poisson based survival models[1]

Example

- A model is fitted on the log cumulative hazard scale using restricted cubic splines are used to model the baseline excess hazard (6 knots).
- Restricted cubic splines are also used to model the effect of age (4 knots).
- The effects of age is also allowed to vary over time by incorporating interactions between the restricted cubic spline terms for age at diagnosis and a further set of restricted cubic splines for $\ln(t)$ (4 knots).
- Background mortality is incorporated and so this is a relative survival (excess mortality) model.
**Estimated Relative Survival**

- Ages: 45 years, 55 years, 65 years, 75 years, 85 years.

**Excess Hazard Ratios**

- Age 45 vs Age 65
- Age 55 vs Age 65
- Age 75 vs Age 65
- Age 85 vs Age 65
Net and Crude Probability of Death

Crude Probability of Death - Age 45

Paul C Lambert  Crude and Net Mortality  Regstat 2009, Sigtuna

Age 45 years

Probability of Death

Years from Diagnosis

Cancer  Other  All Cause
Crude Probability of Death - Age 55

Crude Probability of Death - Age 65
Sensitivity to the number of knots

- A potential criticism of these models is the subjectivity in the number and the location of the knots.
- A small sensitivity analysis was carried out where the following models were fitted.

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<th>Model</th>
<th>Baseline</th>
<th>Time-dependent</th>
<th>age</th>
<th>No. of Parameters</th>
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<th>BIC</th>
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<td>$d_{f_b}$</td>
<td>$d_{f_t}$</td>
<td>$d_{f_a}$</td>
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</tbody>
</table>
What does a hazard ratio of 0.8 mean?

- It is sometimes difficult for patients, clinicians etc to convert an estimated treatment effect to what it actually means in practice.
- Imagine that a new treatment reduced the mortality associated with cancer by 20%, i.e. an excess hazard ratio of 0.8.
- What impact will this have on the probability of death due to the cancer?
85 Year Old man

Man aged 85

Man aged 85

Paul C Lambert  Crude and Net Mortality  Regstat 2009, Sigtuna

23

85 Year Old man - Which line represents HR = 0.8?

Man aged 85

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24
85 Year Old man

![Graph showing Crude Probability of Death over Years from Diagnosis for a Man aged 85]

Man aged 85

Communication of Risk - Man aged 55

- Out of 100 people like you - by 5 years
  - Without Treatment
    - 55 will die of cancer
    - 2 will die of other causes
    - 43 will be alive
  - With Treatment
    - 48 will die of cancer
    - 2 will die of other causes
    - 50 will be alive
Communication of Risk - Man aged 85

- Out of 100 people like you - by 5 years
  - Without Treatment
    - 46 will die of cancer
    - 32 will die of other causes
    - 22 will be alive
  - With Treatment
    - 40 will die of cancer
    - 35 will die of other causes
    - 25 will be alive

Summary

- Measuring the crude mortality due to cancer and other causes are useful measures.
- They do not replace relative survival.
- Modelling has the advantage of estimating in continuous time, smaller standard errors, and making predictions for individual patients.
- The flexible parametric approach is a useful framework to estimate these quantities.
- Aim now is to move to more recent data to obtain individual level predictions using stage, risk factors, biomarkers etc.
[1] B. Carstensen. Demography and epidemiology: Practical use of the lexis diagram in
the computer age or: Who needs the cox-model anyway? Technical report,
Department of Biostatistics, University of Copenhagen, 2006.

patients in the presence of other causes: a crude analogue of relative survival.

probability of death due to cancer and other causes using relative survival models.
Statistics in Medicine, (submitted), 2009.