Operationalizing and extending the guidelines for cancer mortality and survival analyses
Motivation

• Obesity and invasive breast cancer (p1895)
  - Expected; confirmed hypothesis
  - Unexpected (at first)
    • Culprit was terminology; time-scale, cohort

Deliverable #1
Guidelines for cancer mortality and survival analyses

Death (mortality)
- Full cohort
- Time begins at enrollment
- Graph cumulative hazard; begins at zero on y-axis

Survival
- Survivor cohort
- Time-origin begins at diagnosis
- Graph survivorship function; begins at unity(100%) on y-axis

Choice of adjustment variables (i.e., strata and covariates) may differ between survival and ‘incident’ death

Figure poached from P2892 proposal (Elizabeth Cespedes)
Deliverable #2

• Obesity and Breast and Colorectal Cancer Mortality in the Women’s Health Initiative: Considerations in Design and Interpretation of Studies (p2892; Elizabeth Cespedes, Marian Neuhouser, Ross Prentice, Bette Caan)
  – Contrast cancer Death vs. cancer Survival
    • Compare HR(95%CI) by BMI group
  – Parse Death into Incidence + Survival
    • Time to breast cancer Death (from enrollment) =
      Time to breast cancer Incidence (from enrollment) +
      Survival time (from cancer diagnosis)
Deliverable #2 (toy example)

– Toy example to demonstrate influence of time-scale

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<tbody>
<tr>
<td><strong>A. Full cohort</strong></td>
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<td>Events from enrollment</td>
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<tr>
<td>I: Invasive Breast Cancer</td>
<td>2744 (0.43)</td>
<td>2894 (0.45) 1.12 (1.06, 1.19)</td>
<td>1656 (0.50) 1.31 (1.23, 1.40)</td>
<td>998 (0.52) 1.45 (1.34, 1.57)†</td>
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<td>D1: Breast cancer death</td>
<td>325 (0.04)</td>
<td>348 (0.05) 1.06 (0.90, 1.23)</td>
<td>203 (0.05) 1.09 (0.90, 1.32)</td>
<td>158 (0.07) 1.48 (1.20, 1.83)†</td>
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<td>D2: Death (all-causes) after breast Cancer</td>
<td>552 (0.08)</td>
<td>582 (0.08) 1.06 (0.94, 1.20)</td>
<td>365 (0.09) 1.26 (1.09, 1.45)</td>
<td>250 (0.11) 1.59 (1.35, 1.88)†</td>
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<td>D2*: I + S2 (i.e., HRI x HRS2)</td>
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<td><strong>B. Survivor cohort</strong></td>
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<tr>
<td>Events from diagnosis of breast cancer</td>
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<tr>
<td>S1: Survival (breast cancer death)</td>
<td>296 (1.59)</td>
<td>314 (1.64) 0.97 (0.82, 1.15)</td>
<td>182 (1.66) 0.82 (0.67, 1.01)</td>
<td>136 (2.14) 0.97 (0.77, 1.23)</td>
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<tr>
<td>S2: Survival (all-causes)</td>
<td>552 (2.96)</td>
<td>582 (3.05) 0.95 (0.84, 1.08)</td>
<td>365 (3.33) 0.90 (0.78, 1.05)</td>
<td>250 (3.93) 1.08 (0.90, 1.29)</td>
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† P-val ≤ 0.002.

Models adjusted for age, race/ethnicity, education, bilateral oophorectomy, Gail 5-year risk of breast cancer, estrogen-alone use and duration, estrogen and progesterone use and duration, smoking status, diabetes mellitus, alcohol consumption, self-reported health at baseline, and stratified by baseline age group, WHI study (OS vs. CT), HT trial randomization group, dietary trial randomization group, hysterectomy status, Calcium/Vitamin D Randomized Trial randomization group (time-dependent) and extended follow-up (time-dependent).
Deliverable #2 (toy example)

• Significant positive association between BMI group and Death from and after breast cancer
  – Association with Death can be attributed to the significant positive association between BMI group and Incidence
  – No evidence that association is even partially due to survival

• Preliminary results (not shown) suggest above holds with additional survival related covariates
Deliverable #2 (toy example)

- Why $HR_{\text{Death}} \sim HR_{\text{Incidence}} \times HR_{\text{Survival}}$?

- $\text{Probability}(A \cap B) = \text{Probability}(A) \cdot \text{Probability}(B|A)$

Tree diagram poached from Wikipedia
https://en.wikipedia.org/wiki/Tree_diagram_%28probability_theory%29
Utility(past)

- Published that E+P increased the risk of Death from and after breast cancer.
- Presented Incidence, Survival and Death
- P2892 will help emphasize, connect the dots

Figure 1. Invasive breast cancer incidence by estrogen plus progestin use at baseline. Analyses were adjusted for age, race or ethnic group, body mass index, education, smoking status, alcohol use, self-reported health, level of physical activity, presence or absence of a family history of breast cancer, estimated breast-cancer risk based on the Gail model, and bilateral oophorectomy and stratified by baseline age group. All statistical tests were two-sided. CI = confidence interval; HR = hazard ratio.

Figure 2. Survival after breast cancer diagnosis by estrogen plus progestin use at baseline. Analyses were adjusted for age, race or ethnic group, body mass index, education, smoking status, alcohol use, self-reported health, level of physical activity, presence or absence of a family history of breast cancer, estimated breast-cancer risk based on the Gail model, bilateral oophorectomy, and age at diagnosis and stratified by baseline age group. All statistical tests were two-sided. CI = confidence interval; HR = hazard ratio.
Utility(past)

• “In summary, estrogen plus progestin use is associated with increased breast cancer incidence...Because prognosis after a breast cancer diagnosis is similar for combined hormone therapy users and non-users, increased breast cancer mortality on a population basis can be expected”

• Ability to parse enhance audience understanding and recall

\[
\begin{align*}
\text{HR}_{\text{bc Incidence}} & \quad 1.55 \times \text{HR}_{\text{bc Survival}} & \quad 1.02 \sim \text{HR}_{\text{Death after bc}} & \quad 1.65
\end{align*}
\]

Conclusion

• Death (full cohort; time from enrollment) and Survival (survival cohort; time from diagnosis) are vastly different

• May be possible to parse Death into Incidence and Survival

• Important to consider all three events
  – Useful for interpretation
  – Can imagine situations where HRs corresponding to Incidence and Survival are not statistically significant
  – But when jointly considered jointly or combined (i.e., Death = Incidence + Survival), a significant association may be observed