

Measuring the Effect of Including Multiple Cancers in Survival Analyses

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Background

- In survival analyses using cancer registry data, second and subsequent primary cancers diagnosed in individuals are typically excluded.
- The wisdom of including only first primary cancers in comparative studies of survival between cancer registries, or over time within a single registry, has recently come into question (Brenner & Hakulinen 2007; Rosso et al. 2009).

The case for multiple cancers

- The ability to find and exclude cases with previously diagnosed cancer in a cancer registry depends largely on how long the registry has been in operation prior to the time period of interest.
- The prognosis for persons diagnosed with a subsequent primary cancer has been shown empirically to be poorer—with very few exceptions—than that for those diagnosed with only one cancer.
- Thus the practice of restricting survival analyses to first primary cancers may lead to biased comparisons—both between cancer registries with different running times and over time within a cancer registry.



Purpose

- To examine the impact of including multiple primary cancers in the derivation of survival estimates using data from the Canadian Cancer Registry.

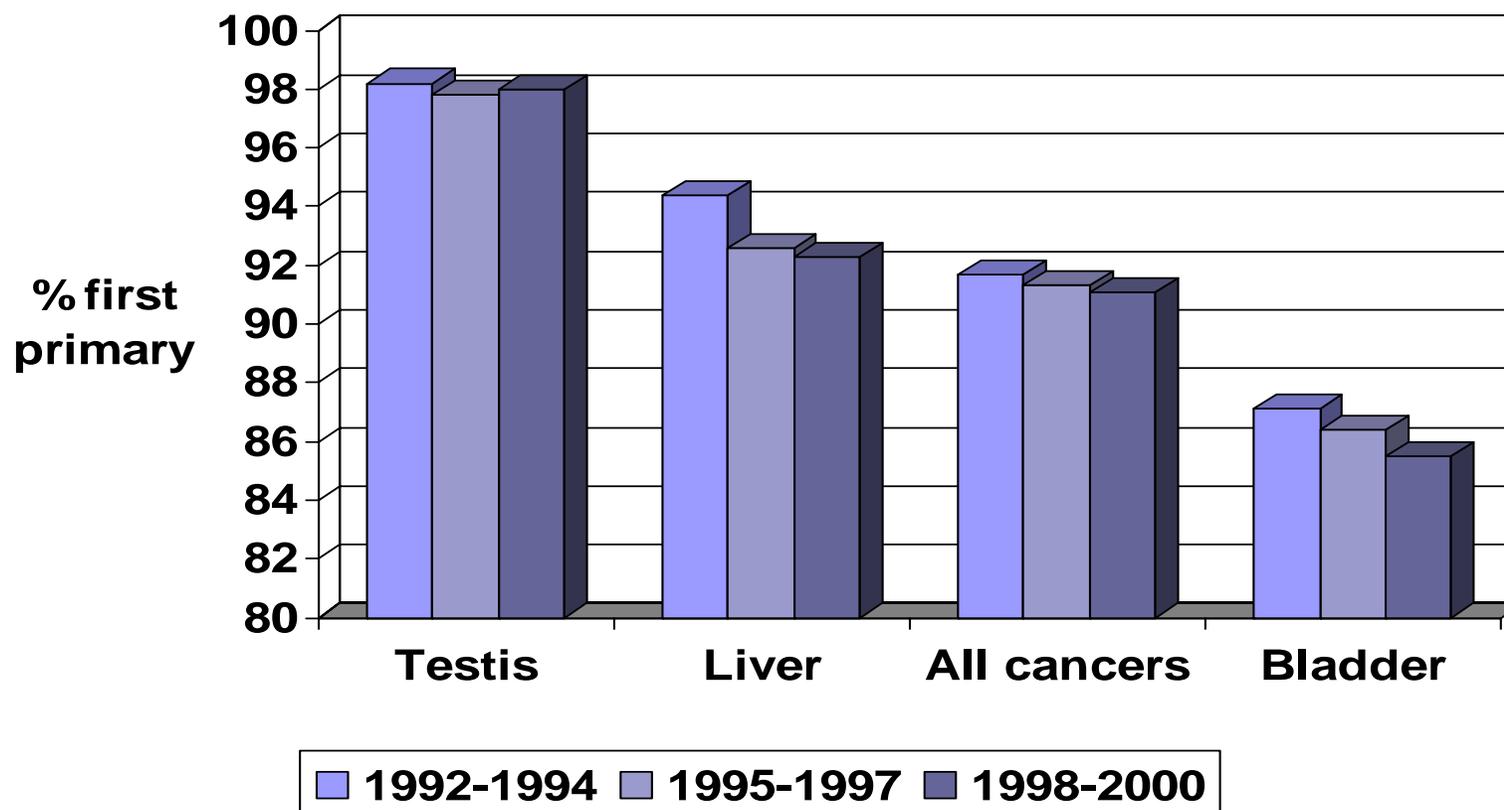
Data sources

- Cases were identified using the Canadian Cancer Registry (CCR).
- Any pre-1992 cancer history of persons on the CCR was obtained through record linkage with the National Cancer Incidence Reporting System.
- Mortality follow-up—through Dec 31, 2005—was determined primarily through record linkage to the Canadian Vital Statistics Death Database.

Methods

- The analysis file was created using the multiple primary coding rules of the International Agency for Research on Cancer.
- Five-year relative survival estimates for persons aged 15-99 years at diagnosis were derived using all eligible primary cases from the CCR and then again using first primary cases.
- The cohort method of survival analysis was used—three time frames were considered: 1992-1994, 1995-1997 and 1998-2000; the focus will be on 1998-2000.
- Data from the province of Quebec were excluded primarily because of issues in correctly ascertaining the vital status of cases from this province.

Proportion of cases that were first cancers for selected cancers, by time period, Canada*



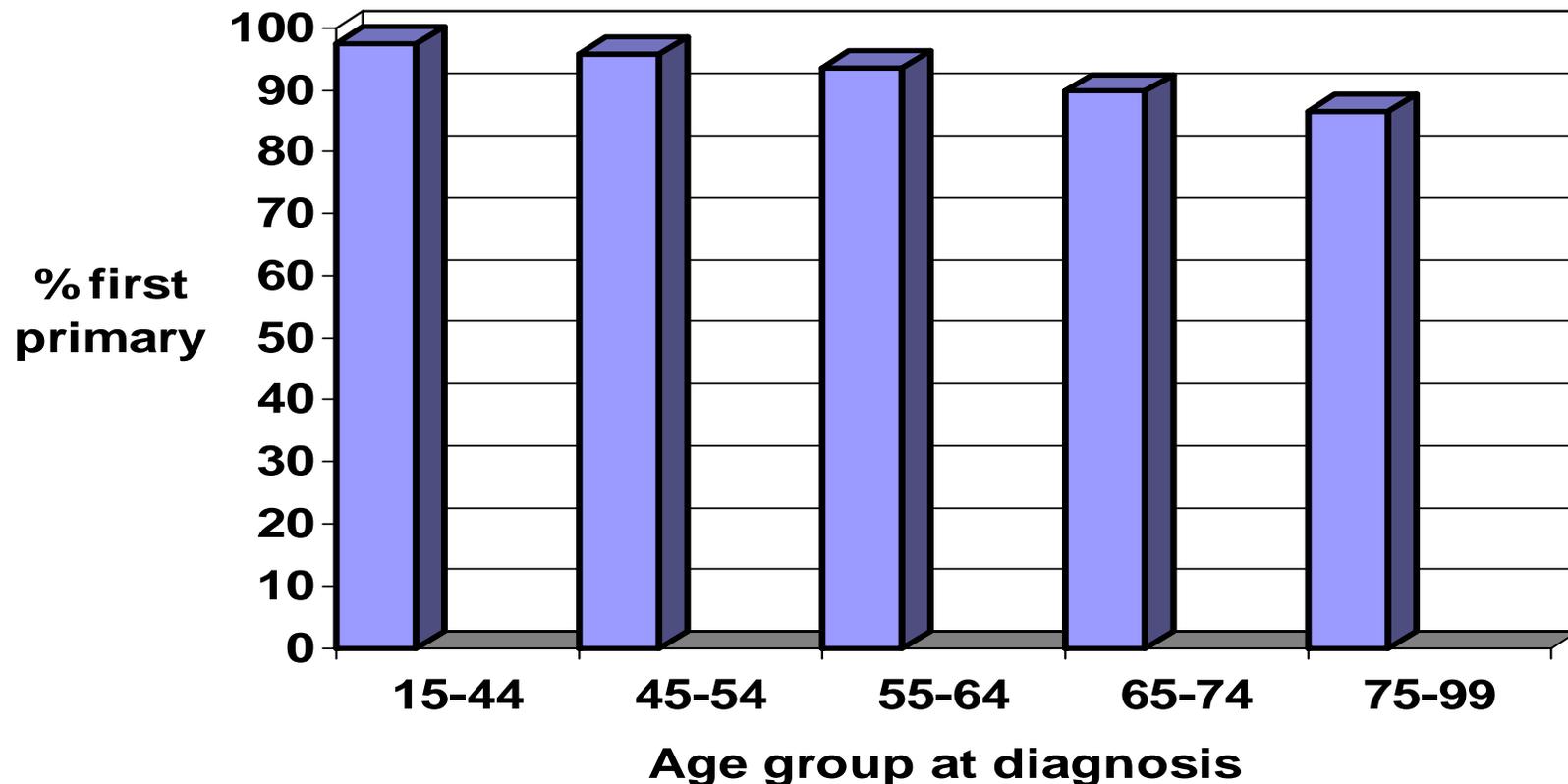
Data Source: Canadian Cancer Registry, Statistics Canada and Provincial/Territorial Cancer Registries

*Excluding Quebec

Effect on crude survival

- The inclusion of second and subsequent cancers in the analysis of cases diagnosed in 1998-2000 resulted in a 1.3% lower value in crude 5-year relative survival for all cancers combined (i.e., 60.2% to 58.8%).
- Lower crude relative survival ratios (RSRs) were observed for all cancers.
- The largest difference in crude RSRs was associated with bladder cancer (-2.7%); the smallest with lung cancer (-0.1%).

Proportion of cases that were first cancers by age group at diagnosis, all cancers combined, 1998-2000, Canada*



Data Source: Canadian Cancer Registry, Statistics Canada and Provincial/Territorial Cancer Registries

*Excluding Quebec

Effect on survival by age group

- For all cancers combined, the inclusion of second and subsequent cancers in the analysis of cases diagnosed in 1998-2000 resulted in lower five-year RSRs in each age group.
- The magnitude of the difference increased with age from -0.4% (15-44 years) to -1.3% (75-99).
- In each of the eldest three age groups the largest differences were observed for thyroid cancer. Otherwise, the largest differences were observed for bladder (-3.6%, 75-99 years), oral (-2.4%, 65-74), and leukemias and oral (-1.7%, 55-64).

Effect on age-standardization survival estimates

- The effect of including multiple cancers on five-year relative survival estimates was somewhat attenuated by age-standardization (e.g., from 1.3% to 1.0% for all cancers combined).
- Survival estimates were lower for all cancers studied except lung cancer.
- For the majority of cancers the difference was less than 1.0%.
- The effect was greatest for bladder cancer (-2.4%) followed by oral cancer (-1.9%)—cancers that had the first and third lowest proportions of first cancers, respectively.
- Cancers for which there was virtually no difference (e.g., lung, pancreatic, ovarian and liver) tended to be those with a poor prognosis.

Other theoretical considerations in literature

- Even when the bias is small or virtually non-existent, it has been argued that the exclusion of subsequent primaries in survival analyses is unnecessary and leads to a reduction in the precision of estimates.
- The exclusion practice may, in theory, actually bias estimates of relative survival, as people with previous primary cancers are generally included in estimates of the denominator of the relative survival ratio.

Conclusion

- Inclusion of second and subsequent primary cancers in the analysis tended to lower estimates of relative survival, the extent of which varied by cancer and age and depended in part on the proportion of first primary cancers.

In Practice

- A non-exhaustive list of groups currently second and subsequent cancers in survival analyses includes the Finnish Cancer Registry, a collaboration of German cancer registries, and the EUNICE survival collaboration.
- Other Nordic countries, the EUROCCARE-5 working group and possibly others have plans to follow suit.
- These results should be of value not only to those considering the merits of implementing this approach, but also to those interpreting the subsequent changes in survival.

References

- Brenner H, Hakulinen T. Patients with previous cancer should not be excluded in international comparative cancer survival studies. *Int J Cancer* 2007; 121:2274-8.
- Rosso A, De Angelis R, Ciccolallo L, et al. Multiple tumours in survival estimates. *Eur J Cancer* 2009; 45:1080-94.



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Further information on this study

Ellison LF. Measuring the effect of including multiple cancers in survival analyses using data from the Canadian Cancer Registry. *Cancer Epidemiol.* DOI: 10.1016/j.canep.2010.06.015.