The Impact of Improved Population Life Expectancy in Survival Trend Analyses of Specific Diseases

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Background. Survival trend analyses examine mortality outcomes over time. The impact of conducting survival trend analyses without accounting for improved population survival has not been systematically studied.

Methods. The 1-year risk of death in the 100 most common hospital admissions for Ontario adults in 1994, 1999, 2004, and 2009 was determined. Generalized linear models were used to determine if adjusted death risk changed significantly over time with and without accounting for population survival.

Results. The statistical significance of temporal trends in survival changed after accounting for population life expectancy in 16 diagnoses (16 percent) (in 13 of 55 diagnoses, statistically significant *decreasing* mortality trends became insignificant; in 3 of 15 diagnoses, insignificant trends changed to a significant *increase* in mortality risk over time).

Conclusions. These results highlight the importance of accounting for population life-expectancy changes in survival trend analyses.

Key Words. Relative survival, survival trend analyses, generalized linear model

Survival trend analyses are studies that examine mortality outcomes over time in specific patient groups. They are often used to infer the effect of treatment modalities or practice patterns that change over time. Death is a common outcome in trend analyses because it is an important outcome and can be reliably measured using population-based death registries. Survival trend analyses are common with 15 such studies published in English between January and April 2014 (Appendix SA1). These studies will likely become more common in the literature as both administrative database repositories and disease registries age and develop increasingly farther look-back periods.

Attributing decreasing trends in death risk solely to improved care for a particular patient group can be erroneous because life expectancy in almost all developed countries has improved significantly over time. For example, between 1987 and 2012, life expectancy in Canada, the United States, and the

United Kingdom increased by 4.4 years (relative increase of 5.7 percent), 3.8 years (5.1 percent), and 5.1 years (6.8 percent), respectively. Similar improvements in population survival have been seen in most countries (Tuljapurkar, Li, and Boe 2000; Salomon et al. 2012). Failure to account for improved population survival could lead to invalid conclusions about the influence of patient treatment on survival. Of the 15 English-language survival trend analyses published in the first 4 months of 2014 (Appendix SA1), only three accounted for improved population survival in their analyses.

The influence of changes in population death risk on conclusions regarding survival trend analyses has not been systematically examined. This study examined the 100 most common hospitalization diagnoses in Ontario, Canada, between 1994 and 2009 to determine how often conclusions regarding disease-specific temporal survival trends change after accounting for population survival.

METHODS

Datasets Used in the Study

This study used population-based health administrative databases for Ontario, Canada, in which the costs of all hospital and physician services are covered by a universal health care system. Databases used in this study included Discharge Abstract Database (DAD), which captures all hospitalizations; Registered Persons Database (RPD), which captures each person's date of death, including those that occur out-of-province; and the Physicians' Services Database (PSD), which captures all physician clinical activities remunerated by the Ontario Health Insurance Plan. All databases were linked deterministically via encrypted health care numbers. The study was approved by the Ottawa Hospital Research Ethics Board.

Study Cohort

Population life-tables are required to measure survival trends relative to the population (see "Analysis" section below). When this study was done, 2009

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was the latest year for which life-tables were available for Ontario. To measure survival trends, 5-year decrements from 2009 were used; since Ontario administrative data became available in 1991, the earliest year possible for this study was 1994.

DAD was used to identify all adults (age greater than 18) admitted to any Ontario acute-care hospitals in 1994, 1999, 2004, or 2009. Exclusions included same-day surgeries, admissions to psychiatric facilities (because their data are captured in another dataset), admissions to in-patient rehabilitation or long-term care facilities (because they are distinct from acute hospitals), and admissions for obstetrical diagnoses (because the risk of 1-year mortality following admission for these conditions is extremely low). Finally, patients ineligible for health care coverage in Ontario were excluded since the capture of outcomes for these patients would be incomplete.

The 50 most common urgent and elective primary diagnoses in DAD (100 diagnoses in total) were selected for the study. Stratification by admission urgency was used for three reasons: this factor is an important prognosticator (elective patients have a much better survival); urgent admissions are twice as common as elective admissions; and crude survival trends varied significantly by admission status with death risks increasing significantly over time in urgent admissions but decreasing significantly in elective admissions. Select diagnoses required translating all primary diagnostic codes for the 2004 and 2009 cohorts from International Classification of Diseases (ICD) 10th revision to ICD-9-CM using cross-tables supplied by the Canadian Institute for Health Information. To identify potential problems with code conversion, the ranking of each diagnosis across the 4 years was compared; diagnoses exhibiting a significant change in rankings (defined as more than 50 percent relative difference) between the 1994–1999 cohorts and the 2004–2009 cohorts (in the absence of a temporal trend across all four cohorts) were excluded. The 50 most common urgent and elective primary diagnoses for all four annual cohorts combined were then identified and included in the study.

Outcome Status and Covariates

The study outcome was all-cause mortality within 1 year of admission to hospital. This was determined by linking to RPDB.

The Mortality Risk Score (Austin and van Walraven 2011) was used to control for patient death risk. This index uses patient age, gender, and Aggregated Diagnosis Group Score. The latter uses the Johns Hopkins ACG® (Adjusted Clinical Groups) System to risk adjust for diagnoses in patient

claims found in DAD and PSD for the 2 years prior to hospital admission. The Mortality Risk Score had excellent discrimination (c-statistic of 0.913) and calibration in an external validation cohort (Austin and van Walraven 2011).

Analysis

Within each diagnosis group, Poisson regression for rates (PROC GENMOD, SAS v 9.3; Dickman et al. 2004) was used to examine for trends in death risk. These generalized linear models accounted for each person's observation time, adjusted for each person's Mortality Risk Score, and expressed cohort year as a linear term. The parameter estimate for the latter was exponentiated to return the "adjusted incidence rate ratio for temporal trend." This describes the changes in adjusted 1-year death rate associated with each 5-year increase in time. For example, an incidence rate ratio (IRR) of 1.1 indicates that the 1-year death rate increased 10 percent for each 5-year increase in time.

Relative survival models were used to account for changes in 1-year mortality risk in the entire population (Dickman 2004; Dickman et al. 2004). Relative survival models are additive hazards models where the total hazard (or risk) of death in a patient group is the sum of the known hazard in the general population and the excess hazard in the patient group (Dickman et al. 2004). Risk of death in the general population was determined from Ontario life-tables for each cohort year stratified by gender and 5-year age strata. The parameter estimates for the relative survival model were also estimated using a generalized linear model with a Poisson error structure, with each patient's observation time as the offset variable, also using PROC GENMOD in SAS 9.3 (Dickman et al. 2004). Parameter estimates for cohort year were exponentiated to calculate the temporal trend relative excess risk (Suissa 1999), which was termed in this study as the "adjusted incidence rate ratio for temporal trend accounting for population survival." This is interpreted just like the IRR in that it quantifies the relative change in death risk (compared to a reference group) adjusted for the covariates in the model *and* accounting for mortality risk changes in the population.

Changes in the IRR after accounting for population survival were determined using three methods. The number and proportion of diagnoses for which the statistical significance of the IRR (defined as a 2-sided p -value $\leq .05$) changed was calculated. The absolute difference in the IRR (calculated as the absolute value for the difference of the IRR from both models) and relative

difference in the IRR (calculated as the absolute difference divided by IRR from the model accounting for population survival) from the models that did and did not account for population survival were also calculated. Each of these measures was stratified by admission urgency.

RESULTS

During the four study years, there was a total of 3,739,190 acute-care hospitalizations for Ontarian adults. Hospitalizations were excluded because of invalid health card numbers ($n = 86,279$, 2.3 percent); potentially inaccurate ICD10-ICD9 diagnostic code conversions ($n = 198,764$, 5.3 percent); obstetrical diagnoses (379,154, 10.1 percent); duplicate hospitalizations by the same person for the same diagnosis ($n = 281,288$, 7.5 percent); and admitting diagnoses that were not in the 50 most common urgent or elective diagnoses ($n = 1,313,107$, 35.1 percent). This left 1,480,598 hospitalizations in the study (39.6 percent of all hospitalizations during the study years); characteristics of the fifty most common urgent and elective primary diagnoses are described in Appendix SA2.

Patient cohorts changed notably over time (Table 1). The number of admissions in both urgent and elective groups decreased between 1994 and 2009. Overall, patients became notably older over time with this trend being statistically significant in 77 percent of the diagnostic groups. The Mortality Risk Score increased significantly over time in the majority of diagnoses. Crude 1-year death risk was significantly higher in urgent versus elective admissions with trends in death risk for these groups having opposite directions (increasing in urgent, decreasing in elective).

After adjusting for death risk using the Mortality Risk Score, the majority of both urgent and elective admissions exhibited a significant *decrease* in adjusted 1-year death risk over time. The adjusted incidence rate ratio for temporal trend ranged from 0.54 (indicating a 46 percent relative decrease in adjusted 1-year death risk for each 5-year increase in time) to 1.31 with a median value of 0.91 (Figure 1, horizontal axis). In 55 diagnoses (55 percent), mortality risk *decreased* significantly over time; it *increased* significantly over time in five diagnoses (5 percent). Results were comparable for urgent and elective admissions (Appendix SA2).

Death risk in the entire population also decreased notably during the study period (Appendix SA3). After accounting for improved population survival, conclusions about mortality trends changed in 16 of 100 diagnoses

Table 1: Description of Adults Admitted to Ontario Hospitals with 50 Most Common Urgent and Elective Diagnoses

	1994	1999	2004	2009	Overall
Urgent admissions					
<i>N</i>	267,448	264,949	256,696	224,654	1,013,747
Median age (IQR)	66 (48–77)	67 (50–78)	69 (52–80)	71 (57–82)	68 (51–79)
Male	131,695 (49.2%)	129,238 (48.8%)	126,641 (49.3%)	110,993 (49.4%)	498,567 (49.2%)
Mortality risk score (Austin and van Walraven 2011)	57 (37–72)	60 (39–75)	62 (42–77)	66 (48–80)	61 (41–76)
Dead within 1-year of admission	50,964 (19.1%)	53,396 (20.2%)	52,995 (20.6%)	51,552 (23.0%)	208,907 (20.6%)
Elective admissions					
<i>N</i>	143,452	113,947	105,042	104,410	466,851
Median age (IQR)	57 (42–69)	61 (46–72)	61 (47–72)	62 (50–73)	60 (46–71)
Male	69,234 (48.3%)	53,923 (47.3%)	53,247 (50.7%)	53,613 (51.3%)	230,017 (49.3%)
Mortality risk score (Austin and van Walraven 2011)	44 (25–60)	50 (31–64)	50 (33–65)	52 (36–66)	49 (31–64)
Dead within 1-year of admission	7,827 (5.5%)	6,408 (5.6%)	5,147 (4.9%)	4,361 (4.2%)	23,748 (5.1%)

Notes. Trends in crude death risks increased significantly for urgent admissions (Cochran–Armitage Trend Z-score -32.9 , $p < .0001$) but decreased significantly for elective admissions (Cochran–Armitage Trend Z-score 15.4 , $p < .0001$). IQR, interquartile range.

Figure 1: Trend Analysis of Adjusted 1-Year Death Risk in Most Common Hospitalizations, 1994–1999

Notes. The influence of each 5-year increase in time on adjusted 1-year death rate in the 50 most common diagnoses in both urgent and elective admissions is presented as the adjusted incidence rate ratio for temporal trend (horizontal axis) and that accounting for population survival (vertical axis). With both statistics, values less than 1 indicate a decreased risk of death over time. Both models accounted for expected death risk using the Mortality Risk Score (Austin and van Walraven 2011) but the adjusted incidence rate ratio accounting for population survival also adjusted for life expectancy in the general population. *Gray dots* indicate that the trend in adjusted incidence rate ratio between 1994 and 2009 was statistically significant in both models; *circles* indicate that the trend was not significant in either model; *triangles pointing down* indicate that only the adjusted incidence rate ratio trend was significant; *triangles pointing up* indicate that only the adjusted incidence rate ratio accounting for population survival was significant.

(16 percent). Of 55 diagnoses whose mortality risk decreased significantly over time, trends in 13 (23.6 percent) became statistically nonsignificant after accounting for population survival (Figure 1, Appendix SA2). Of 15

diagnoses whose mortality risk trend was nonsignificant, 3 (20.0 percent) had a significantly *increased* death risk over time after accounting for population survival. Diagnoses whose significance “flipped” after accounting for population life expectancy either had 95 percent confidence intervals for their IRR that were very close to 1.00 or a 1-year death risk that was very small (i.e., less than 2 percent).

Differences in the values of mortality trends between models that did or did not account for population survival varied extensively by admission urgency (Figure 2). In urgent hospitalizations, both absolute and relative differences in the incidence rate ratio (IRR) were all below 0.125, with approximately 60 percent being below 0.025 (Figure 2A). Differences were larger in elective hospitalizations (Figure 2B), but approximately 70 percent of absolute and relative differences were less than 0.1.

DISCUSSION

Disease-specific survival trend analyses are important tools for determining whether patient outcomes change over time. They help evaluate the impact of new interventions in health on patient mortality. This analysis found that the statistical significance of survival trends changed in 16 percent of diagnoses after adjusting for changes in population mortality risk. These results highlight the importance of accounting for changes in population life expectancy when conducting survival trend analyses. Results of survival trend analyses that do not account for changes in population life expectancy should be interpreted with caution.

Two factors can cause the significance of survival trend analyses to change when accounting for population life expectancy with relative survival models. First, the overall mortality rate for a patient disease group is the sum of the population mortality rate (from all causes of death) and the mortality rate due to the disease itself. Trends in disease-specific overall mortality rates can occur via changes in either population mortality or disease-specific mortality. If changes in overall mortality death rates in a particular disease group are due primarily to changes in population life expectancy, the relative survival model can cause previously significant survival trends to become insignificant. Second, changes over time in population survival can vary notably between particular age strata (Appendix SA3). As a result, significant changes over time in the age distribution of a particular disease cohort can also influence trend analyses in relative survival models.

Figure 2: Distribution of Absolute and Relative Differences in Adjusted Incidence Rate Ratio for Temporal Trend with and without Accounting for Population Survival

Notes. The incidence rate ratio (IRR) describes changes in adjusted 1-year death rate associated with each 5-year increase in time; for example, an IRR of 1.1 indicates that 1-year death rate increased 10 percent for each 5-year increase in time. These histograms present, for urgent hospitalizations (top) and elective hospitalizations (bottom), values for the absolute and relative differences in the IRR for temporal trend from models that did not account for population survival (“Crude IRR”) and did account for population survival (“Relative Survival IRR”). Absolute differences were calculated as the absolute value of $IRR[\text{crude}] - IRR[\text{relative survival}]$ and are plotted in light red. Relative differences were calculated as the absolute difference/ $IRR[\text{relative survival}]$ and are plotted in blue. Overlapping areas in the histogram are purple. Note the large differences in values presented on the horizontal axis for urgent hospitalizations (maximum value of 0.125) and elective hospitalizations (maximum value of 3.5).

Other studies provide examples of important changes to conclusions when relative survival analyses are used. Nelson et al. (2008) found that survival following a first myocardial infarction—which initially appeared to worsen throughout observation after an immediate, precipitous drop—actually leveled off a month post-event after accounting for population life expectancy. Lee et al. (2014) found that the rather grim 5-year survival in patients with osteoporotic hip fractures of 63 percent was primarily a function of the elderly age of this cohort, which had a much less alarming 5-year *relative* survival of 94 percent. Mitry et al. (2005) found that trends in 5-year survival risk in colorectal cancer patients older than 75 years changed from improved survival to no change when relative survival analyses were used. Each of these studies, along with the current data, shows the potential importance of relative survival analyses to conclusions regarding epidemiological studies of survival.

Several factors should be considered when interpreting these results. First, this study was limited to a single province in Canada. However, the fact that conclusions about mortality risk trends changed in a notable proportion of diseases in our study indicates that this can indeed occur. Second, this study put an inordinate amount of emphasis on the p-value for trend. This is, of course, inappropriate since many other factors should be examined when deciding whether trends in death risk are significant. However, the p-value is frequently given a great deal of attention when research is evaluated (Rennie 1978; Chia 1997) and its use as a summary statistic simplified the evaluation of a complex concept. Third, relative survival models can potentially either under estimate or over estimate death risk attributable to a particular disease. Deaths due to a particular disease contribute to population death risk

estimates; when these are used to calculate expected death rates, disease-specific death risk will be artificially decreased. However, this introduces negligible biases in even common diseases (Ederer, Axtell, and Cutler 1961). Also, relative survival models can *overestimate* disease-specific death risk when the expected death rates from life-tables are inaccurate. Consider patients with lung cancer who have a higher exposure to cigarettes than the population. Their risk of death from cardiovascular disease and other tobacco-associated deaths, therefore, is higher than the population. Expected death rates for these people will therefore be *underestimated* and disease-specific death risk will be biased upwards. However, these issues would be concerning to the current study only if they changed significantly over time.

This study found that conclusions regarding survival trend analyses can change importantly after accounting for life expectancy of the population. The results of survival trend analyses that do not account for changes in population life expectancy should be interpreted with caution.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Appendix SA1: A Description of Medline-Indexed, English-Language Disease-Specific Survival Studies Published between January and April 2014.

Appendix SA2: Description of Fifty Most Common Urgent and Elective Admissions in Ontario 1994, 1999, 2004, and 2009.

Appendix SA3: Annual Mortality Risk of Adults in Ontario, 1994–2009.