Research Article

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Differences in Cancer Survival with Relative versus Cause-Specific Approaches: An Update Using More Accurate Life Tables

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Abstract

Background: We investigated differences in net cancer survival (survival observed if the only possible cause of death was the cancer under study) estimated using new approaches for relative survival (RS) and cause-specific survival (CSS).

Methods: We used SEER data for patients diagnosed in 2000 to 2013, followed-up through December 31, 2014. For RS, we used new life tables accounting for geography and socio-economic status. For CSS, we used the SEER cause of death algorithm for attributing cancer-specific death. Estimates were compared by site, age, stage, race, and time since diagnosis.

Results: Differences between 5-year RS and CSS were generally small. RS was always higher in screen-detectable cancers, for example, female breast (89.2% vs. 87.8%) and prostate (98.5% vs. 93.7%) cancers; differences increased with age or time since diagnosis. CSS was usually higher in the remaining cancer sites, particularly those related to specific risk factors, for example, cervix (70.9% vs. 68.3%) and liver (20.7% vs. 17.1%) cancers. For most cancer sites, the gap between estimates was smaller with more advanced stage.

Conclusion: RS is the preferred approach to report cancer survival from registry data because cause of death may be inaccurate, particularly for older patients and long-term survivors as comorbidities increase challenges in determining cause of death. However, CSS proved to be more reliable in patients diagnosed with localized disease or cancers related to specific risk factors as general population life tables may not capture other causes of mortality.

Impact: Different approaches for net survival estimation should be considered depending on cancer under study.

Introduction

Information on survival has long been recognized as an important component in cancer surveillance. Cancer researchers and policy makers are usually interested in net survival (i.e., the survival that would be observed if the only possible underlying cause of death was the cancer under study; ref. 1). Net survival is a useful measure of cancer prognosis for tracking survival over time, comparing populations with different socio-demographic and socio-economic characteristics, and evaluating the progress in cancer control at the population level (2). Relative survival (RS) and cause-specific survival (CSS) are two distinct frameworks that have been used to estimate net survival and which rely on different assumptions (3).

Because patients with cancer can also die from competing causes (e.g., heart disease, diabetes, etc.), crude survival measures are more relevant survival statistics for cancer patients and the clinicians treating them as it captures these non-cancer deaths. Nonetheless, net survival can still provide some useful information to patients and physicians as it reflects a "cancer prognosis" measure not affected by changes in other causes mortality (4). It can also provide information on "cure" by identifying when the net survival curve levels off, and cancer patients are no longer at risk of dying from their cancer.

In brief, RS is defined as the ratio of the observed survival (i.e., the likelihood of surviving all causes of death) in a cohort of cancer patients to the expected survival in a comparable population, usually matched for age, sex, race, and calendar year, and considered to be free of cancer (5). Expected survival is estimated using general population life tables with the assumption that cancer deaths are a negligible proportion of all deaths in the general population and that cancer and non-cancer are independent competing causes of death (6). This approach removes the effect of mortality due to other causes (background mortality), providing a measure of the excess mortality experienced by patients with cancer, and dispenses the need of relying on information about cause of death, which in many settings is either unavailable or unreliable. For these reasons, RS has been the most frequently reported survival statistic when using data from population-based cancer registries, not least when the goal is to compare different populations or registries with diverse access to cause of death information. The main bias associated with RS is when life tables used to estimate expected survival are not representative of the other causes of mortality the cohort of patients with cancer would experience in the absence of a cancer diagnosis (Fig. 1).

In contrast, the cause-specific framework uses cause of death information and standard survival methods to estimate net survival (7). Here, deaths due to the disease being studied are treated

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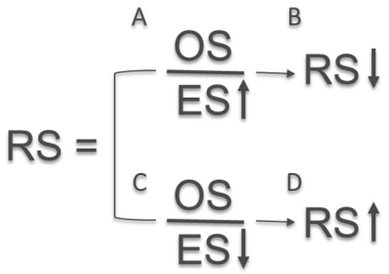

Figure 1.
Main bias impacting estimates of net survival in a RS setting. An overestimation of expected survival (**A**) would lead to an underestimation of RS (**B**), while an underestimation of expected survival (**C**) would result in an overestimation of RS (**D**). ES, expected survival; OS, observed survival. Adapted from Schaffar et al. (2015).

as events and deaths from other causes are treated as censored observations. The assumption is that by removing from the group at risk patients that died of other causes of death, the result would represent a "net" survival of the disease under study. Cancer-specific analyses have been most often used in clinical studies, where detailed clinical information is available, which in turn is used to more accurately identify and assign cause of death. However, in population-based cancer registries, cause of death information is often unavailable and if available ascertained only from death certificates. As cause-specific survival relies on the accuracy of causes of death, if these are misclassified it could lead to biased estimates (Fig. 2).

To account for potential misclassification in the cause of death, the U.S. National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program has developed an algorithm to improve the assignment of causes of death to a cancer (8). Several studies have been using the SEER cause of death classification in cause-specific survival calculations, either because life tables did not represent well the cohort of patients with cancer being studied (9) or because of their improved accuracy in estimating cause-specific survival (10–12). More recently, the SEER Program introduced new life tables that account for geography, race, ethnicity, and county level socio-economic differences in life expectancy (13).

The aim of our study is to address the question of "which framework one should use for estimating net cancer survival" by quantifying differences in cancer survival estimates through relative and cause-specific survival approaches using the new life tables and the SEER cause of death classification. Several studies have addressed this topic (7, 14–16), but to our knowledge, this is the first comparison after the new life tables have been introduced.

Materials and Methods

We used data from the SEER 18 Registries Database (17) for patients diagnosed with a malignant tumor from January 1, 2000, through December 31, 2013, with follow-up through December 31, 2014. These registries cover approximately 28% of the U.S. population (based on 2010 census). We stratified cancer patients by age group (20–49, 50–64, 65–74, 75–84, 85+, all ages), summary stage (localized, regional, distant), race [Non-Hispanic white (NHW), non-Hispanic Black (NHB), non-Hispanic American Indian/Alaska Native (NHAIAN), non-Hispanic Asian or Pacific Islander (NHAPI), Hispanic], and time since diagnosis (1-, 2-, 3-, 4-, 5-, 10-year survival).

Cancer sites selected were based on SEER Site Recode (18) and represent the most common malignancies diagnosed in men and women: esophagus, stomach, colorectal, liver, pancreas, lung, melanoma, female breast, cervix uteri, ovary, prostate, thyroid, lymphoma. We excluded cases first diagnosed at autopsy, cases for which the death certificate was the only source of the cancer diagnosis, cases that were alive but with no survival time, and cases with unknown stage. We also excluded cases with missing or unknown cause of death, but only in the cause-specific setting. Finally, we age-standardized survival results by race as age structure of the cancer cases varies between different race populations. Analyses were limited to patients diagnosed with one primary only or with the first of multiple primaries.

We calculated RS estimates by actuarial method as the ratio of observed (all-cause) survival to expected survival. Estimates were calculated for patients with one or more cancer diagnoses, with analyses limited to first primary only (sequence number 0 or 1 in SEER*Stat software). Expected survival rates were calculated through the Ederer II method based on life expectancy tables that match the cohort of cancer patients for age, year, sex, race, ethnicity, and county-level SES index (13, 19). Although more recent methods exist (e.g., Pohar–Perme), Ederer II is the default to report survival using SEER data and software such as SEER*Stat (20) and has been shown to align well with the concept of net cancer survival, provided estimates are age-specific or age-standardized (21). Nevertheless, we provide supplemental tables showing cancer survival estimates calculated using both Ederer II and Pohar–Perme approaches.

To highlight differences between the frameworks and to better help interpret results, we decided to report unadjusted RS that is increasing or greater than 100%, even though the default calculation in SEER*Stat adjusts for this. It should be noted that for values of 100% or higher, a confidence interval could not be calculated.

We calculated CSS estimates by actuarial method in patients with one or more cancer diagnoses, with analyses limited to first primary only (sequence number 0 or 1 in SEER*Stat software). We used the SEER cause-specific death classification variable as the endpoint (8). According to this classification, deaths attributed to the incident cancer as well as deaths attributed to other cancers, AIDS, and/or site-related diseases are treated as events. All other

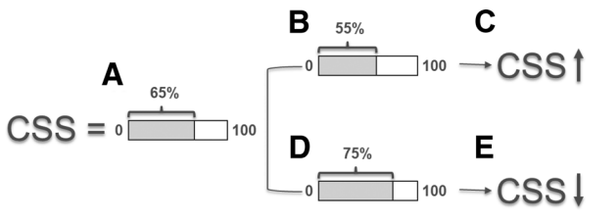

Figure 2.
Main bias impacting estimates of net survival in a cause-specific survival setting. In a hypothetical scenario, where the true proportion of deaths attributed to the cancer under study is known (e.g., 65%; **A**), cancer deaths that are misclassified as non-cancer deaths would lead to a decrease of the proportion of cancer deaths (e.g., 55%; **B**) and an overestimation of cause-specific survival (**C**), while noncancer deaths that are misclassified as cancer deaths would lead to an increase of the proportion of cancer deaths (e.g., 75%; **D**) and an under-estimation of cause-specific survival (**E**). Adapted from Schaffar et al. (2015).

deaths are censored. Survival times were censored at the date of lost to follow-up, the date of death from causes not considered as deaths due to the cancer according to our endpoint, or on December 31, 2014, whichever occurred first. We interpreted survival differences between RS and CSS of greater than 3% and no overlap between confidence as significant. All statistical analyses were performed using NCI's SEER*Stat software version 8.3.5 (22).

Results

The selected cancer sites accounted for more than 70% of all cancers diagnosed in 2000 to 2013 in the SEER 18 catchment area. There was a slightly lower number of cases for analysis in the CSS setting due to exclusion of cases with missing or unknown cause of death, e.g., 30,749 cases or 0.7% for all sites combined and all ages (Table 1). Differences in survival estimates calculated through the Ederer II and Pohar–Perme approaches were negligible, ranging between 0.0 and 0.7 survival points (Supplementary Tables S1–S3). Because there were no marked differences by sex, we reported results for both sexes combined except for sex-specific sites or when otherwise mentioned.

Differences by age

Overall 5-year RS and CSS survival were similar, for example, the five-year RS and CSS were 65.9% and 66.5%, respectively, for all cancer sites combined and for all ages (Table 1). The largest and statistically significant differences were observed among the oldest cancer patients, especially those aged 85 years and older diagnosed with prostate, breast, and thyroid cancers, with differences being over 10% survival points. Five-year CSS estimates were higher than 5-year RS estimates for most cancer sites (all ages) except for female breast (87.8% and 89.2%, respectively), melanoma (89.6% and 91.2%), prostate (93.7% and 98.5%), and thyroid (96.9% and 97.6%) and the differences increased with age. For most of the remaining cancer sites, differences were in the opposite direction, that is, CSS estimates were higher than RS estimates. However, the differences were not statistically significant, except for cervical cancer at age groups 50–64 (65.2% vs. 61.9%) and 65–74 (60.7% vs. 56.1%), and liver cancer at age groups 20–49 (26.4% vs. 21.7%) and 50–64 (24.3% vs. 19.5%).

Differences by stage

Similar patterns were observed for patients diagnosed with localized disease. Here, RS estimates were always higher than CSS estimates for female breast, melanoma, prostate, and thyroid, with the last two presenting values that even surpassed 100% (102.9% and 100.7%, respectively; Table 2). Conversely, higher CSS estimates were observed in patients with localized disease for cervix uteri, esophagus, liver, lung, pancreas, and stomach cancers. The differences between the two frameworks was smaller with more advanced stage. A notable exception were patients with colorectal cancer, who consistently presented similar estimates in both approaches across all stages.

Differences by race

In general, survival differences between the two approaches were very small when stratifying by race. RS estimates were higher than CSS estimates in NHW, NHB, and NHAIAN patients diagnosed with prostate cancer as well as in NHW patients diagnosed with thyroid cancer (Table 3). The opposite was observed in NHW and NHB patients diagnosed with cervix uteri cancer, and in NHAPI and Hispanic with liver cancer and lymphoma.

Differences from time since diagnosis

Figure 3 presents the differences between 5-year RS and 5-year CSS in survival points by time since diagnosis. Patterns varied by cancer site. For all sites combined as well as for colorectal and ovary, the gap between frameworks was smaller with increasing time since diagnosis, with differences varying between −1.4% and −0.5% (colorectal) and −0.9% and −0.1% (ovary) survival points, at 1 year and 10 years after diagnosis, respectively (Fig. 3A). For liver and pancreas, that gap was relatively stable, although in the former the difference was always high throughout the follow-up period, varying between −3.4% and −3.9% survival points. For the remaining cancers, the gap became larger with increasing time since diagnosis, with cervix uteri, esophagus, lymphoma, and stomach presenting CSS estimates always higher than RS estimates, and female breast, melanoma, prostate, and thyroid showing the opposite pattern (Fig. 3B). The increasing gap was especially pronounced in patients diagnosed with prostate cancer.

Discussion

Our study shows that, in general, RS and CSS are reliable and provide similar estimates of net cancer survival, with discrepancies between the estimates being negligible for most cases. However, some important systematic differences have been observed, which underscore the need for continued improvements to these methods. For some cancer sites most commonly detected through screening (female breast, melanoma, prostate, thyroid), RS was consistently higher than CSS. For cancer sites usually associated with specific risk factors (cervix uteri, liver, lung) or that present poor prognosis (esophagus, pancreas), the opposite was observed, with CSS being higher than RS. In general, these patterns held even when survival was stratified by age, stage, and time since diagnosis. For colorectal cancer, the two approaches provided very similar estimates. Our discussion focuses on the source of biases related to the assumptions of each framework, that is, appropriateness of life tables in the RS setting and cause of death misclassification in the CSS setting.

For screen-detectable cancers, we found that RS was higher than CSS. Two explanations are possible. First, RS estimates might be overestimated due to the so-called healthy screener effect, where patients with cancer more commonly diagnosed through screening examination are more likely to be healthier and their other causes mortality lower than the general population's, as observed in a large cohort study in the United States (23). Thus, using general population life tables to estimate expected survival among patients with cancer that were either screened or diagnosed with localized disease would underestimate their expected survival and, therefore, overestimate their net survival using an RS approach.

Second, CSS estimates for screen-detectable cancers might be underestimated due to misclassification of cause of death. In this case, more deaths than those actually caused by the cancer under study would have been misclassified as cancer deaths (16). The largest differences were observed for patients diagnosed at older ages or for longer term survival, when cancer survivors age. Because older individuals are more prone to comorbidities, assigning a single underlying cause of death is challenging and

Table 1. Five-year RS and CSS, by cancer site and age group, 2000–2013[a]

	RS		CSS		Abs. Dif.		RS		CSS		Abs. Dif.
	N	5-y (95% CI)	*N*	5-y (95% CI)	(%)		*N*	5-y (95% CI)	*N*	5-y (95% CI)	(%)
Esophagus						**Breast**					
20–49	3,329	19.7 (18.3–21.2)	3,299	21.8 (20.3–23.3)	−2.1	20–49	158,585	88.8 (88.6–88.9)	158,005	89.1 (88.9–89.3)	−0.3
50–64	15,114	19.7 (19.0–20.4)	14,998	22.1 (21.4–22.9)	−2.4	50–64	243,843	89.9 (89.8–90.1)	242,910	89.6 (89.4–89.7)	0.3
65–74	11,423	19.4 (18.6–20.3)	11,324	22.3 (21.4–23.2)	−2.9	65–74	131,276	90.9 (90.6–91.1)	130,592	89.3 (89.1–89.5)	1.6
75–84	8,300	13.7 (12.7–14.7)	8,223	15.2 (14.3–16.1)	−1.5	75–84	88,889	88.2 (87.8–88.7)	88,190	83.9 (83.7–84.2)	4.3[b]
85+	2,789	5.8 (4.5–7.4)	2,770	6.5 (5.3–7.8)	−0.7	85+	30,515	80.3 (79.0–81.5)	30,261	69.9 (69.3–70.5)	10.4[b]
All ages	40,960	17.6 (17.2–18.1)	40,619	19.8 (19.4–20.3)	−2.2	All ages	653,181	89.2 (89.1–89.3)	650,031	87.8 (87.8–87.9)	1.4
Stomach						**Cervix uteri**					
20–49	9,091	32.4 (31.3–33.4)	8,906	34.0 (32.9–35.1)	−1.6	20–49	24,736	77.8 (77.2–78.3)	24,591	79.1 (78.5–79.6)	−1.3
50–64	20,313	31.1 (30.4–31.8)	20,034	33.7 (33.0–34.4)	−2.6	50–64	12,282	61.9 (61.0–62.9)	12,167	65.2 (64.3–66.1)	−3.3[b]
65–74	17,688	30.5 (29.7–31.3)	17,433	33.0 (32.2–33.8)	−2.5	65–74	4,523	56.1 (54.3–57.8)	4,444	60.7 (59.1–62.3)	−4.6[b]
75–84	16,626	24.6 (23.7–25.4)	16,415	26.2 (25.4–27.0)	−1.6	75–84	2,503	40.4 (37.9–42.9)	2,459	44.8 (42.6–47.0)	−4.4
85+	7,423	16.1 (14.8–17.5)	7,368	16.4 (15.4–17.5)	−0.3	85+	966	24.2 (19.9–28.6)	957	28.1 (24.6–31.7)	−3.9
All ages	71,223	28.1 (27.8–28.5)	70,238	30.2 (29.8–30.6)	−2.1	All ages	45,082	68.3 (67.8–68.8)	44,690	70.9 (70.4–71.3)	−2.6
Colon and rectum						**Ovary**					
20–49	48,471	67.4 (67.0–67.9)	48,096	68.8 (68.3–69.2)	−1.4	20–49	13,824	67.9 (67.0–68.7)	13,727	69.3 (68.4–70.1)	−1.4
50–64	133,070	69.0 (68.7–69.3)	132,212	70.2 (69.9–70.5)	−1.2	50–64	23,241	50.7 (50.0–51.5)	23,055	51.6 (50.9–52.3)	−0.9
65–74	103,897	66.7 (66.4–67.1)	103,123	67.9 (67.6–68.3)	−1.2	65–74	13,864	37.4 (36.4–38.3)	13,755	37.5 (36.5–38.4)	−0.1
75–84	96,744	60.2 (59.8–60.7)	95,937	59.9 (59.6–60.2)	0.3	75–84	11,452	23.9 (22.9–24.9)	11,364	22.2 (21.4–23.1)	1.7
85+	43,882	50.5 (49.6–51.4)	43,547	44.2 (43.6–44.7)	6.3[b]	85+	4,723	12.7 (11.2–14.3)	4,701	10.7 (9.7–11.8)	2.0
All ages	426,388	64.4 (64.2–64.5)	423,235	64.7 (64.6–64.9)	−0.3	All ages	68,107	45.3 (44.9–45.8)	67,604	45.6 (45.2–46.0)	−0.3
Liver						**Prostate**					
20–49	6,998	21.7 (20.7–22.8)	6,860	26.4 (25.3–27.6)	−4.7[b]	20–49	21,758	97.3 (97.0–97.6)	21,711	96.6 (96.3–96.9)	0.7
50–64	31,450	19.5 (19.0–20.0)	30,955	24.3 (23.7–24.9)	−4.8[b]	50–64	276,792	98.9 (98.8–99.0)	275,721	96.7 (96.6–96.7)	2.2
65–74	15,192	14.7 (14.0–15.4)	14,886	17.5 (16.8–18.3)	−2.8	65–74	261,579	100.3	259,828	95.3 (95.2–95.4)	5.0
75–84	10,283	7.9 (7.2–8.6)	10,142	9.2 (8.5–10.0)	−1.3	75–84	127,944	97.7 (97.3–98.1)	126,540	88.2 (88.0–88.4)	9.5[b]
85+	3,013	4.4 (3.2–5.8)	2,989	5.2 (4.1–6.4)	−0.8	85+	25,588	77.7 (76.2–79.1)	25,303	64.5 (63.8–65.2)	13.2[b]
All ages	67,786	17.1 (16.7–17.4)	66,674	20.7 (20.4–21.1)	−3.6[b]	All ages	713,710	98.5 (98.4–98.6)	709,152	93.7 (93.6–93.8)	4.8[b]
Pancreas						**Thyroid**					
20–49	7,748	18.0 (17.0–18.9)	7,651	19.2 (18.2–20.1)	−1.2	20–49	60,554	99.4 (99.3–99.5)	60,489	99.4 (99.4–99.5)	0.0
50–64	32,116	8.7 (8.3–9.1)	31,772	9.4 (9.0–9.7)	−0.7	50–64	34,732	97.8 (97.5–98.0)	34,644	97.1 (96.9–97.3)	0.7
65–74	29,637	6.3 (6.0–6.7)	29,352	6.7 (6.4–7.1)	−0.4	65–74	12,093	94.6 (93.8–95.4)	12,024	92.3 (91.7–92.8)	2.3
75–84	27,823	4.0 (3.7–4.3)	27,616	4.3 (4.0–4.5)	−0.3	75–84	5,227	88.3 (86.3–90.0)	5,175	82.3 (81.1–83.4)	6.0[b]
85+	12,544	2.4 (2.0–2.9)	12,463	2.0 (1.7–2.3)	0.4	85+	1,173	69.8 (63.3–75.4)	1,164	57.6 (54.3–60.8)	12.2[b]
All ages	109,944	6.9 (6.8–7.1)	108,930	7.4 (7.2–7.5)	−0.5	All ages	116,193	97.6 (97.5–97.8)	115,909	96.9 (96.8–97.0)	0.7
Lung						**Lymphoma**					
20–49	30,167	23.0 (22.5–23.5)	29,876	24.8 (24.2–25.3)	−1.8	20–49	51,247	82.4 (82.0–82.7)	50,988	84.1 (83.8–84.5)	−1.7
50–64	160,257	19.1 (18.9–19.3)	158,884	21.2 (21.0–21.4)	−2.1	50–64	58,899	75.8 (75.4–76.2)	58,534	78.2 (77.9–78.6)	−2.4
65–74	171,025	17.7 (17.4–17.9)	169,590	20.2 (19.9–20.4)	−2.5	65–74	43,012	68.4 (67.9–69.0)	42,692	70.5 (70.0–71.0)	−2.1
75–84	136,239	13.4 (13.2–13.7)	135,168	15.1 (14.9–15.4)	−1.7	75–84	37,579	55.8 (55.1–56.5)	37,234	55.9 (55.3–56.5)	−0.1
85+	38,075	7.6 (7.2–8.1)	37,844	8.2 (7.9–8.6)	−0.6	85+	13,990	41.4 (39.8–42.9)	13,857	37.5 (36.5–38.5)	3.9[b]
All ages	535,963	16.8 (16.6–16.9)	531,562	18.8 (18.7–18.9)	−2.0	All ages	212,410	71.0 (70.8–71.3)	210,949	72.5 (72.3–72.7)	−1.5
Melanoma						**All sites**					
20–49	56,518	93.8 (93.6–94.0)	56,409	93.7 (93.5–93.9)	0.1	20–49	686,354	78.1 (78.0–78.2)	682,669	79.4 (79.3–79.5)	−1.3
50–64	60,673	91.5 (91.2–91.8)	60,497	90.6 (90.4–90.9)	0.9	50–64	1,464,683	70.0 (70.0–70.1)	1,455,838	71.3 (71.2–71.4)	−1.3
65–74	33,335	90.9 (90.4–91.4)	33,171	87.9 (87.5–88.3)	3.0	65–74	1,104,756	65.4 (65.3–65.5)	1,096,155	66.0 (65.9–66.1)	−0.6
75–84	23,964	86.6 (85.6–87.5)	23,790	82.5 (82.0–83.1)	4.1[b]	75–84	802,420	54.7 (54.6–54.9)	795,307	54.2 (54.0–54.3)	0.5
85+	8,908	79.5 (76.8–82.0)	8,826	74.7 (73.5–75.9)	4.8[b]	85+	278,456	41.8 (41.5–42.2)	276,247	38.6 (38.3–38.8)	3.2[b]
All ages	184,971	91.2 (91.0–91.4)	184,263	89.6 (89.4–89.7)	1.6	All ages	4,392,176	65.9 (65.8–65.9)	4,361,427	66.5 (66.5–66.5)	−0.6

[a]All estimates are for both sexes except those for breast (women only) and sex-specific cancers. Estimates are for the first cancer diagnosed.
[b]Survival differences of greater than 3 percentage points and no overlap between confidence intervals.

physicians may be more prone to assign death to cancer than to other causes, given a diagnosis of cancer in this cohort of patients. This assumption may vary by cancer site, although our results suggest that for screen-detectable cancers, there might be an increase in the number of deaths erroneously attributed to cancer with advancing age. The same rationale may apply to long-term cancer survivors, with CSS estimates becoming progressively lower as time since diagnosis increases (15). Misclassification of causes of death may thus be the driving force behind the differences observed both in older patients and long-term survivors.

For cancers associated with specific risk factors or presenting poor prognosis, we found that CSS was usually higher than RS.

Table 2. Five-year RS and CSS, by cancer site and stage at diagnosis, 2000–2013[a]

	RS		CSS		Abs.		RS		CSS		Abs.
	N	5-y (95% CI)	*N*	5-y (95% CI)	Dif. (%)		*N*	5-y (95% CI)	*N*	5-y (95% CI)	Dif. (%)
Esophagus						**Breast**					
Localized	8,709	38.9 (37.7–40.2)	8,651	43.6 (42.4–44.8)	−4.7[b]	Localized	397,404	98.4 (98.3–98.5)	395,965	95.9 (95.8–96.0)	2.5
Regional	12,479	21.0 (20.2–21.9)	12,377	23.3 (22.4–24.1)	−2.3	Regional	208,154	84.2 (84.0–84.4)	207,057	84.0 (83.8–84.1)	0.2
Distant	14,731	4.0 (3.6–4.4)	14,608	4.5 (4.1–4.9)	−0.5	Distant	34,646	25.1 (24.6–25.6)	34,345	26.1 (25.6–26.7)	−1.0
Stomach						**Cervix uteri**					
Localized	18,056	63.9 (63.0–64.8)	17,903	67.4 (66.6–68.1)	−3.5[b]	Localized	21,285	91.1 (90.6–91.6)	21,179	92.5 (92.1–92.8)	−1.4
Regional	20,978	28.4 (27.7–29.2)	20,657	30.0 (29.3–30.7)	−1.6	Regional	16,022	57.5 (56.6–58.3)	15,862	60.7 (59.8–61.5)	−3.2[b]
Distant	24,539	4.4 (4.1–4.7)	24,165	4.8 (4.5–5.1)	−0.4	Distant	5,681	17.0 (16.0–18.2)	5,597	18.8 (17.6–19.9)	−1.8
Colon and rectum						**Ovary**					
Localized	166,299	89.6 (89.4–89.9)	165,406	89.4 (89.2–89.6)	0.2	Localized	9,950	92.7 (91.9–93.4)	9,910	92.4 (91.8–92.9)	0.3
Regional	153,806	69.8 (69.4–70.1)	152,793	69.3 (69.0–69.5)	0.5	Regional	12,419	72.5 (71.6–73.5)	12,350	71.9 (71.0–72.7)	0.6
Distant	85,924	12.5 (12.2–12.7)	85,083	12.9 (12.7–13.2)	−0.4	Distant	41,153	27.8 (27.3–28.3)	40,812	27.9 (27.4–28.4)	−0.1
Liver						**Prostate**					
Localized	29,122	29.9 (29.2–30.5)	28,685	35.8 (35.1–36.4)	−5.9[b]	Localized	570,072	102.9	566,718	97.3 (97.2–97.3)	5.6
Regional	17,948	10.6 (10.0–11.1)	17,600	13.0 (12.4–13.6)	−2.4	Regional	84,723	99.9 (99.1–100)	84,286	95.3 (95.1–95.4)	4.6[b]
Distant	11,421	2.9 (2.5–3.2)	11,212	3.5 (3.1–3.9)	−0.6	Distant	31,848	29.3 (28.7–30.0)	31,442	30.9 (30.3–31.5)	−1.6
Pancreas						**Thyroid**					
Localized	9,823	27.3 (26.3–28.4)	9,752	28.6 (27.6–29.6)	−1.3	Localized	78,753	100.7	78,633	99.5 (99.5–99.6)	1.2
Regional	30,449	10.1 (9.7–10.5)	30,136	10.5 (10.1–11.0)	−0.4	Regional	29,810	97.4 (97.1–97.7)	29,738	97.0 (96.8–97.2)	0.4
Distant	57,661	2.3 (2.1–2.4)	57,159	2.4 (2.3–2.6)	−0.1	Distant	5,098	55.2 (53.7–56.8)	5,031	57.2 (55.7–58.6)	−2.0
Lung						**Lymphoma**					
Localized	82,328	53.4 (53.0–53.9)	81,694	58.4 (58.0–58.7)	−5.0[b]	Localized	56,862	82.3 (81.9–82.7)	56,539	82.3 (82.0–82.7)	0.0
Regional	118,592	26.0 (25.7–26.3)	117,715	28.6 (28.3–28.9)	−2.6	Regional	39,072	78.0 (77.5–78.5)	38,875	79.1 (78.7–79.6)	−1.1
Distant	301,629	4.0 (3.9–4.1)	299,112	4.6 (4.5–4.7)	−0.6	Distant	99,633	62.3 (61.9–62.6)	98,912	64.4 (64.1–64.7)	−2.1
Melanoma						**All sites**					
Localized	154,801	98.0 (97.8–98.2)	154,346	95.7 (95.6–95.8)	2.3	Localized	1,992,651	91.2 (91.1–91.2)	1,982,451	89.6 (89.6–89.7)	1.6
Regional	15,922	62.4 (61.5–63.4)	15,825	63.6 (62.8–64.5)	−1.2	Regional	890,389	64.6 (64.5–64.7)	884,322	65.4 (65.3–65.5)	−0.8
Distant	7,008	17.7 (16.7–18.8)	6,962	18.9 (17.9–20.0)	−1.2	Distant	849,123	19.2 (19.1–19.3)	841,383	20.6 (20.5–20.7)	−1.4

[a]All estimates are for both sexes except those for breast (women only) and sex-specific cancers. Estimates are for the first cancer diagnosed.
[b]Survival differences of greater than 3 percentage points and no overlap between confidence intervals.

The largest differences were observed for cervical cancer (age groups 50–64 and 65–74) and liver cancer (age groups 20–49 and 50–64), and for localized esophagus, liver, and lung cancers. The most plausible explanation is that expected survival might be overestimated due to inadequacy of general life tables to represent the background mortality of patients that have an increased risk of dying from causes of death associated with common risk factors. For example, Cho and colleagues (2013) showed that other causes mortality for patients diagnosed with lung cancer were much higher than the general population mortality (24). As the majority of patients with lung cancer are smokers, and therefore carry a higher risk of dying from other smoking-related causes, their other causes mortality is not comparable with the mortality of the general population (25).

Interestingly, with the exception of older patients (≥85 years), 5-year colorectal survival estimates using the two approaches did not differ significantly. Cho and colleagues also showed that noncancer mortality for colorectal patients was similar to the mortality of the general population, and thus life tables represent their other causes mortality accurately. We have also shown that the only two cancer sites presenting statistically significantly higher CSS estimates by age are those caused by infectious agents, namely human papillomavirus in cervical cancer and hepatitis B and C viruses in liver cancer (26). Future research focused on these two cancer sites is warranted to further elucidate these results.

To what extent discrepancies between estimates reflect bias from either the RS approach or the CSS approach is difficult to assess, as both frameworks are vulnerable to error, that is, neither can be used as the "gold standard" by which to measure the other (27). However, the small differences observed confirm that both can reliably estimate net survival in most situations, although findings are not directly generalizable outside the SEER setting. As the largest differences were observed for patients aged 85 years or older, we recommend exercising caution when interpreting results. Large differences were also more easily observable when survival was high. When survival was very low, with patients dying quickly from their cancer (e.g., pancreatic cancer), the approaches provided similar estimates and were less affected by biases.

Strengths of this study include the quality of the registry data and the availability of a large number of cases from a representative population in the U.S. However, this study has several limitations. First, we compared results by age, stage, race, and time since diagnosis, but did not compare estimates for other factors that are also known to play an important role in survival differences, such as geography. Second, we only included first primary cancers because the algorithm that improved the classification of cause of death was only developed for first cancers. We are working to improve this algorithm and to include second or later primary cancers, which in some populations may now range between 3.5% to 36.9%, depending on the cancer site and age at diagnosis (28). Third, although the life tables are an improvement to the previous general U.S. life tables, because they include mortality data at the county level by detailed race-ethnicities and socio-economic status, they still do not take into account general health status of cancer patients or risk factors such as infectious agents, smoking or obesity. For particular studies, researchers have constructed tailored life tables for estimation of RS in specific cohorts of cancer patients, like patients diagnosed with a common cancer (e.g., prostate cancer; ref. 29) or tobacco-related

Table 3. Five-year RS and CSS, by cancer site and race/ethnicity, 2000–2013[a]

	RS		CSS		Abs.		RS		CSS		Abs.
	N	5-y (95% CI)	*N*	5-y (95% CI)	Dif. (%)		*N*	5-y (95% CI)	*N*	5-y (95% CI)	Dif. (%)
Esophagus						**Breast**					
NHW	31,068	18.6 (18.1–19.1)	30,898	20.6 (20.1–21.1)	−2.0	NHW	466,726	90.6 (90.5–90.8)	464,861	87.8 (87.7–88.0)	2.8
NHB	4,823	11.2 (10.1–12.4)	4,780	13.7 (12.5–14.9)	−2.5	NHB	67,853	78.7 (78.1–79.3)	67,504	78.1 (77.7–78.6)	0.6
NHAIAN	227	20.5 (14.2–27.6)	225	17.9 (12.7–23.7)	2.6	NHAIAN	3,237	85.6 (82.5–88.2)	3,219	83.6 (81.6–85.5)	2.0
NHAPI	1,774	16.1 (14.2–18.2)	1,715	18.9 (16.8–21.1)	−2.8	NHAPI	47,784	89.6 (89.1–90.2)	47,419	90.0 (89.6–90.4)	−0.4
Hispanic	2,942	15.5 (14.0–17.1)	2,878	18.1 (16.5–19.8)	−2.6	Hispanic	64,373	85.6 (85.0–86.1)	63,861	86.0 (85.6–86.4)	−0.4
Stomach						**Cervix uteri**					
NHW	38,057	27.2 (26.6–27.7)	37,841	28.8 (28.3–29.3)	−1.6	NHW	24,094	54.3 (53.2–55.5)	23,972	57.7 (56.7–58.8)	−3.4[b]
NHB	9,736	27.2 (26.2–28.3)	9,656	30.2 (29.1–31.2)	−3.0	NHB	6,243	48.6 (46.4–50.7)	6,204	53.3 (51.3–55.2)	−4.7[b]
NHAIAN	602	21.5 (17.5–25.7)	597	23.3 (19.6–27.3)	−1.8	NHAIAN	346	42.0 (31.8–51.8)	343	44.9 (35.0–54.3)	−2.9
NHAPI	10,122	35.8 (34.7–36.9)	9,858	38.5 (37.4–39.5)	−2.7	NHAPI	3,888	62.6 (60.0–65.0)	3,819	66.7 (64.3–68.9)	−4.1
Hispanic	12,422	26.5 (25.6–27.5)	12,012	29.1 (28.2–30.1)	−2.6	Hispanic	10,171	62.2 (60.1–64.3)	10,019	66.2 (64.3–68.0)	−4.0
Colon and rectum						**Ovary**					
NHW	299,360	65.8 (65.5–66.0)	297,732	65.6 (65.4–65.8)	0.2	NHW	48,975	40.7 (40.2–41.2)	48,734	40.3 (39.8–40.7)	0.4
NHB	49,542	55.9 (55.4–56.5)	49,219	57.2 (56.7–57.7)	−1.3	NHB	5,452	30.2 (28.8–31.7)	5,411	31.1 (29.7–32.5)	−0.9
NHAIAN	2,497	62.8 (60.0–65.5)	2,479	61.0 (58.8–63.2)	1.8	NHAIAN	409	36.6 (30.9–42.3)	405	37.1 (31.7–42.5)	−0.5
NHAPI	32,202	66.1 (65.4–66.7)	31,647	68.2 (67.7–68.8)	−2.1	NHAPI	4,891	44.5 (42.7–46.4)	4,799	46.1 (44.2–47.9)	−1.6
Hispanic	40,205	61.7 (61.1–62.3)	39,607	63.7 (63.2–64.3)	−2.0	Hispanic	7,744	39.7 (38.3–41.1)	7,620	41.0 (39.6–42.4)	−1.3
Liver						**Prostate**					
NHW	33,540	14.4 (14.0–14.8)	33,268	17.4 (16.9–17.8)	−3.0	NHW	498,139	99.1 (99.0–99.3)	495,845	93.6 (93.5–93.7)	5.5[b]
NHB	8,511	10.6 (9.6–11.7)	8,415	13.4 (12.3–14.5)	−2.8	NHB	102,609	95.5 (95.1–95.9)	102,048	90.7 (90.4–90.9)	4.8[b]
NHAIAN	743	10.9 (8.3–14.0)	736	13.5 (10.5–16.9)	−2.6	NHAIAN	2,332	95.5 (92.1–97.4)	2,315	88.9 (87.3–90.3)	6.6[b]
NHAPI	11,530	21.5 (20.6–22.4)	11,098	25.0 (24.1–26.0)	−3.5[b]	NHAPI	32,642	96.0 (95.5–96.4)	32,108	94.4 (94.1–94.7)	1.6
Hispanic	12,524	12.5 (11.8–13.2)	12,237	16.0 (15.2–16.9)	−3.5[b]	Hispanic	61,707	94.8 (94.4–95.2)	60,724	92.5 (92.2–92.7)	2.3
Pancreas						**Thyroid**					
NHW	77,344	7.3 (7.0–7.5)	76,944	7.6 (7.4–7.8)	−0.3	NHW	77,534	94.9 (94.3–95.5)	77,426	91.4 (91.0–91.8)	3.5[b]
NHB	13,268	6.1 (5.7–6.6)	13,176	6.9 (6.4–7.4)	−0.8	NHB	7,521	91.4 (88.8–93.4)	7,501	89.8 (88.3–91.1)	1.6
NHAIAN	594	5.6 (3.8–7.8)	587	6.2 (4.3–8.6)	−0.6	NHAIAN	623	94.8 (68.2–99.2)	622	90.4 (82.4–94.8)	4.4
NHAPI	7,580	9.1 (8.3–9.9)	7,382	9.9 (9.1–10.8)	−0.8	NHAPI	11,590	89.1 (87.5–90.6)	11,512	89.1 (87.9–90.2)	0.0
Hispanic	10,903	7.5 (7.0–8.1)	10,591	8.2 (7.6–8.9)	−0.7	Hispanic	17,181	89.2 (87.5–90.7)	17,107	89.4 (88.2–90.4)	−0.2
Lung						**Lymphoma**					
NHW	413,723	17.4 (17.3–17.6)	411,518	19.4 (19.3–19.6)	−2.0	NHW	150,762	69.5 (69.2–69.8)	150,029	70.1 (69.9–70.4)	−0.6
NHB	59,520	13.6 (13.2–13.9)	59,057	15.5 (15.2–15.9)	−1.9	NHB	17,512	60.0 (58.7–61.3)	17,404	62.7 (61.6–63.7)	−2.7
NHAIAN	2,492	14.4 (12.8–16.0)	2,473	15.3 (13.7–17.0)	−0.9	NHAIAN	928	66.6 (61.3–71.3)	922	64.6 (60.6–68.3)	2.0
NHAPI	30,078	19.2 (18.6–19.7)	29,141	21.1 (20.6–21.7)	−1.9	NHAPI	12,555	62.4 (61.4–63.5)	12,391	65.9 (64.9–66.8)	−3.5[b]
Hispanic	29,146	16.5 (16.0–17.0)	28,406	18.6 (18.1–19.2)	−2.1	Hispanic	24,723	61.1 (60.3–62.0)	24,333	64.9 (64.1–65.6)	−3.8[b]
Melanoma						**All sites**					
NHW	168,152	90.0 (89.7–90.4)	167,604	87.4 (87.2–87.7)	2.6	NHW	3,145,182	65.6 (65.5–65.6)	3,130,029	65.5 (65.5–65.6)	0.1
NHB	873	65.7 (60.8–70.2)	867	66.5 (62.5–70.1)	−0.8	NHB	458,538	57.2 (57.0–57.4)	455,535	58.5 (58.3–58.6)	−1.3
NHAIAN	361	85.2 (73.6–91.9)	359	81.1 (74.2–86.3)	4.1	NHAIAN	21,592	55.9 (54.9–56.8)	21,436	55.7 (55.0–56.5)	0.2
NHAPI	1,157	70.9 (66.7–74.7)	1,130	73.5 (70.0–76.7)	−2.6	NHAPI	268,759	60.9 (60.7–61.2)	263,876	63.3 (63.0–63.5)	−2.4
Hispanic	5,826	75.4 (73.2–77.4)	5,743	78.8 (77.2–80.4)	−3.4	Hispanic	414,991	61.0 (60.8–61.2)	408,195	63.3 (63.1–63.4)	−2.3

[a]All estimates are for both sexes except those for breast (women only) and sex-specific cancers. Estimates are for the first cancer diagnosed.
[b]Survival differences of greater than 3 percentage points and no overlap between confidence intervals.

cancers (25, 30, 31). However, given the challenges in making these life tables up to date [e.g., by single calendar year, gender, geography, detailed race-ethnicities, SES, or an important clinical factor (e.g., cancer patient's health status)], we do not anticipate that these tailored life tables will be readily available for users of SEER*stat software or become part of routine reports of cancer survival statistics (e.g., the Cancer Statistics Review). Another and more recent example would concern survival in cancer patients that are opioid-dependent (CPOD). This specific cohort of patients is now part of an increasing proportion of people in the U.S., as the opioid epidemic has been escalating in this country (32). Finally, a bootstrap analysis might be applied to generate a single confidence interval of the difference between RS and CSS estimates, for each cancer site. This would bring more assurance when interpreting differences between approaches.

Estimating net survival through a RS framework still holds the great advantage of independence from potential miscoding of the underlying cause of death, which may vary considerably among jurisdictions, as many cancer registries may not have cause of death information or its accuracy is variable (8). This makes RS the gold standard approach for international comparisons. RS may also be the best approach when including patients with multiple tumors, as the assessment of cause of death for these patients is challenging. However, as the cohorts of patients with cancer become more and more specific in this era of increasing interest for minorities and smaller groups, the RS framework might lose some of its potential to estimate net survival due to inadequacy of life tables to represent the patients' background mortality. When accurate information on cause of death is available, cause-specific survival estimates are thus likely to provide less biased net survival rates than RS estimates, although this may be limited to patients diagnosed with screen-detectable cancers, namely those with localized disease, and patients that have been heavily exposed to specific risk factors, such as certain types of infectious agents or smoking.

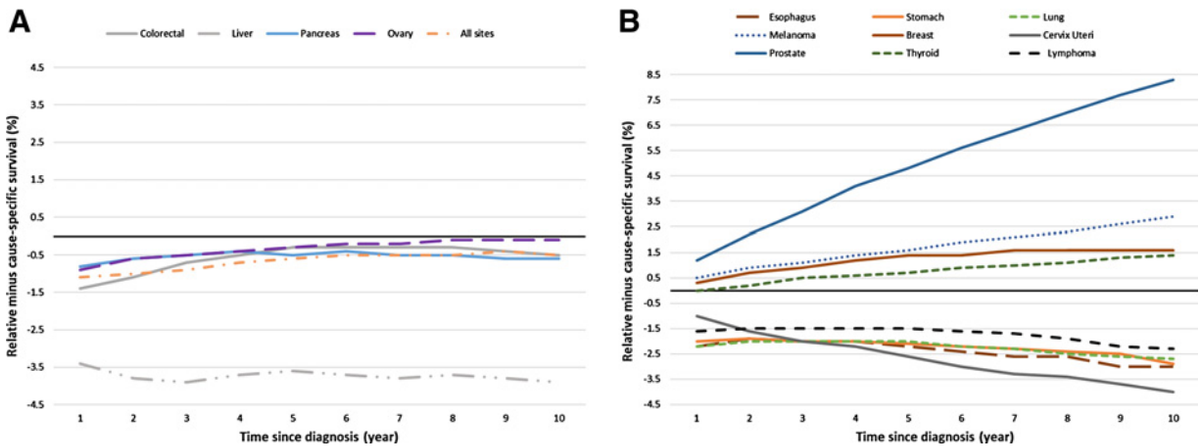

Figure 3.
The difference in percentage points between 5-year RS and 5-year CSS estimates by time since diagnosis for selected sites and all sites combined. **A,** Cancers that showed a stable or decreasing gap between methods. **B,** Cancers that showed an increasing gap between methods.

In conclusion, our study emphasizes that the choice of the framework to estimate net survival may depend on the specific cancer and on the nature of the study. This is important to keep providing researchers, patients, and policy makers with accurate and up-to-date cancer survival figures.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: G.F. de Lacerda, N. Howlader, A.B. Mariotto
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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G.F. de Lacerda, N. Howlader, A.B. Mariotto
Writing, review, and/or revision of the manuscript: G.F. de Lacerda, N. Howlader, A.B. Mariotto
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): G.F. de Lacerda

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