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Age-related differences in cancer relative survival in the United States: A SEER-18 analysis

Diana R. Withrow[1] | Brian D. Nicholson[1] | Eva J. A. Morris[2] | Melisa L. Wong[3] | Sophie Pilleron[2,4]

[1]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

[2]Nuffield Department of Population Health, Big Data Institute, University of Oxford, Oxford, UK

[3]MAS Divisions of Hematology/Oncology and Geriatrics, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, California, USA

[4]Ageing, Cancer, and Disparities Research Unit, Department of Precision Health, Luxembourg Institute of Health, Strassen, Luxembourg

Correspondence
Sophie Pilleron, Luxembourg Institute of Health, 1A-B, rue Thomas Edison, 1445 Strassen, Luxembourg.
Email: sophie.pilleron@lih.lu

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Abstract

Cancer survival has improved since the 1990s, but to different extents across age groups, with a disadvantage for older adults. We aimed to quantify age-related differences in relative survival (RS—1-year and 1-year conditioning on surviving 1 year) for 10 common cancer types by stage at diagnosis. We used data from 18 United States Surveillance Epidemiology and End Results cancer registries and included cancers diagnosed in 2012 to 2016 followed until December 31, 2017. We estimated absolute differences in RS between the 50 to 64 age group and the 75 to 84 age group. The smallest differences were observed for prostate and breast cancers (1.8%-points [95% confidence interval (CI): 1.5-2.1] and 1.9%-points [95% CI: 1.5-2.3], respectively). The largest was for ovarian cancer (27%-points, 95% CI: 24-29). For other cancers, differences ranged between 7 (95% CI: 5-9, esophagus) and 18%-points (95% CI: 17-19, pancreas). Except for pancreatic cancer, cancer type and stage combinations with very high (>95%) or very low (<40%) 1-year RS tended to have smaller age-related differences in survival than those with mid-range prognoses. Age-related differences in 1-year survival conditioning on having survived 1-year were small for most cancer and stage combinations. The broad variation in survival differences by age across cancer types and stages, especially in the first year, age-related differences in survival are likely influenced by amenability to treatment. Future work to measure the extent of age-related differences that are avoidable, and identify how to narrow the survival gap, may have most benefit by prioritizing cancers with relatively large age-related differences in survival (eg, stomach, esophagus, liver and pancreas).

KEYWORDS
disparity, older adults, population-based cancer registries, survival

What's new?

While cancer survival has improved significantly, the gains have been uneven across age groups. The extent and pattern of age-related disparities in cancer survival, however, remain unclear. In

Abbreviations: CI, confidence interval; ICBP, International Cancer Benchmarking Partnership; RS, relative survival; SEER, Surveillance Epidemiology and End Results; SES, socioeconomic status.

this analysis of cancer registry data in the United States, age-related survival differences were investigated across 10 cancer sites in adults ages 50 to 64 and 75 to 84. Relative survival varied widely between the two age groups, ranging from small differences for breast and prostate cancer to large differences for pancreatic cancer. The variations may be due to ability to undergo treatment. Further research is warranted to better understand how to reduce age-related survival differences.

1 | INTRODUCTION

In the United States (US) in 2017, nearly half a million adults aged 75 and over were diagnosed with cancer,[1] and around 260 000 cancer deaths occurred in the same age group.[2] As the US population ages, more cancer cases and deaths will occur in older individuals.[3]

The International Cancer Benchmarking Partnership (ICBP) study in seven high-income countries with similar health care systems (excluding the US) recently showed that cancer survival has improved since the 1990s, but not similarly across age groups and cancer types.[4] Even after taking into consideration differences in life expectancy, older adults have experienced smaller improvements in survival than younger people resulting in widening differences in cancer survival across age groups. Outside ICBP countries, the magnitude and pattern of age-related differences in cancer survival are poorly documented.

Up-to-date information about the pattern of age-related gaps in cancer survival is required to motivate and direct efforts to understand and, hence, improve cancer outcomes for older adults. Stage is an important predictor of survival, but among those studies that have measured age-related differences in cancer survival,[4-10] those that have stratified by stage tend to be focused on a single cancer type.[7-10] Comparing patterns in age-related differences in relative survival by stage across multiple cancer types with different prognoses and treatment patterns; however, can provide insight and generate hypotheses as to how age-related differences in survival arise.

In our study, we describe age-related differences in 1-year relative survival (RS) and 1-year RS conditioning on surviving 1 year from diagnosis by stage across 10 cancer sites, namely, prostate, breast, rectum, colon, ovary, esophagus, stomach, liver, lung and pancreas in adults aged over 50 years. RS is a measure of net survival, that is a cancer survival in the absence of other causes of death. Together, these 10 cancer sites accounted for nearly 60% of all cancers diagnosed in US adults aged 50 and older in 2016.[11]

2 | METHODS

2.1 | Data source

We included all first primary prostate, breast, rectum, colon, ovary, esophagus, stomach, liver, lung and pancreas cancers diagnosed between 2012 and 2016 from 18 US Surveillance Epidemiology and End Results (SEER) cancer registries and followed for vital status through December 2017. The 18 SEER registries are located in California (San Francisco/Oakland, San Jose/Monterey, Los Angeles, Greater California), Connecticut, the Detroit metropolitan area, Hawaii, Iowa, New Mexico, Seattle, Utah, Georgia (Atlanta, rural Georgia and Greater Georgia), Alaska (restricted to Alaska Natives), Kentucky, Louisiana and New Jersey.[11] Together, these population-based registries cover nearly 30% of the US population.

Seven of the included cancer sites were chosen to be comparable with the ICBP study results.[12] Prostate, breast and liver cancers were added due to their high contribution to cancer incidence and mortality. Because of their high survival and use of surgery as a primary treatment modality, breast and prostate cancers also provide an interesting contrast to the other cancers included from which to generate hypotheses about drivers of age-related differences.

Cancers were originally coded using ICD-O-3 and grouped according to the SEER ICD-O-3/WHO 2008 definitions.[13] As our primary interest was in age-related differences in survival, we included only cases diagnosed in patients aged over 50. We excluded cancers that were registered based on death certificate or autopsy only (1.5%), were nonmalignant (6.4%), were missing age (0.04%) or with disagreement between vital status and survival time (0.4%).

2.2 | Statistical analysis

We extracted Ederer II estimates for 1-year RS and 1-year RS conditioning on surviving 1 year from diagnosis by age group (50-64, 65-74, 75-84 and 85-99 years) and stage (SEER Summary Stage, categorized as localized, regional, distant and unknown/unstaged) from SEER*Stat software.[14]

Relative survival is a metric of net survival, which estimates the probability of survival from cancer in the absence of other causes of death. It is especially useful for comparing survival between groups for whom background mortality differs since it is estimated based on the ratio of the observed survival to the expected survival of individuals of similar demographics in the general population.[15,16] One-year RS conditioned on surviving 1 year from diagnosis is the estimated likelihood of being alive at least 2 years after diagnosis, given surviving 1 year after diagnosis.

Expected mortality was estimated from life tables stratified by county, age, year, sex, race/ethnicity and county-level socioeconomic status (SES) index.[17] The SES index is a composite variable based on seven county-level SES attributes collected by the American Community Survey.[18]

We excluded patients aged 100+ as expected life tables extend only to age 99.[19] Age-related differences in 1-year RS were assessed using the absolute differences in RS between the 50 to 64 age group and the 75 to 84 age group. We estimated 95% confidence interval (CI) around differences of RS using Monte Carlo simulations assuming the complementary log-log transformed RS values to be normally distributed.[20] For each difference considered, the confidence limits were obtained by taking the 2.5 and 97.5 percentiles of the empirical RS difference distribution resulting from 100 000 random draws in the complementary log-log transformed RS values distribution.

The 75 to 84 age group was chosen as the comparison group because remaining life expectancy for this age group ranges from 6 years (for men aged 84) to 13 years (for women aged 75) years (https://www.ssa.gov/oact/STATS/table4c6.html) and therefore is an age group for whom improvement in cancer survival may be more achievable and impactful than among the oldest adults.

Data and relative survival estimates were retrieved through SEER*Stat software version 8.3.9 (National Cancer Institute). Data analysis was conducted between June and August 2021 by DW and SP. The estimation of confidence intervals around differences and plotting of results were performed using R statistical software (version 4.0.2; R Development Core Team, 2020).

3 | RESULTS

We included a total of 844 296 people diagnosed with cancer between the ages of 50 to 99 between 2012 and 2016. Figure 1 presents the distribution of stage at diagnosis by age group for the 10 cancer sites. Over half of prostate and breast cancers and about half of liver cancers were diagnosed at localized stage while less than 20% of ovarian, esophageal, lung and pancreatic cancers were diagnosed at an early stage. The proportion of cancers of unknown stage increased after the age of 75 and was largest in the group aged 85 to 99, with percentages ranging from 6% for breast cancer to 29% for esophageal cancer in this age group.

3.1 | Overall

One-year RS estimates were highest for prostate and breast cancers (>80% across age groups) and lowest for pancreatic cancer (43% in 50-64 age group and 25% in 75-84 age group, Table 1). Prostate, breast, colon, rectal and ovarian cancers all had relatively good prognosis in the youngest age group (1-year RS ≥86% in persons aged 50-64 years) whereas stomach, esophageal, liver, lung and pancreatic cancers had relatively poor prognosis (43%-63% in persons aged 50-64 years). For localized and regional prostate and breast cancers, 1-year RS remained high (>95%) until age 85, whereas survival for other cancer sites tended to decrease with increasing age. For unknown/unstaged cancers, 1-year RS fell between the RS observed for regional and distant stages, except for ovarian cancer for which unknown cancers had poorer RS than distant cancers.

The smallest absolute difference in 1-year RS between the 50 to 64 age group and 75 to 84 age group was observed for prostate and breast cancers with a difference of 1.8 percentage points (95% [CI] for prostate: 1.5-2.1) and 1.9 percentage points (95% CI breast: 1.6-2.3), respectively, and the largest was for ovarian cancer with a 27 percentage point difference (95% CI: 25-28, 1-year RS = 86% in the 50-64 age group vs 59% in the 75-84 age group). The age-related

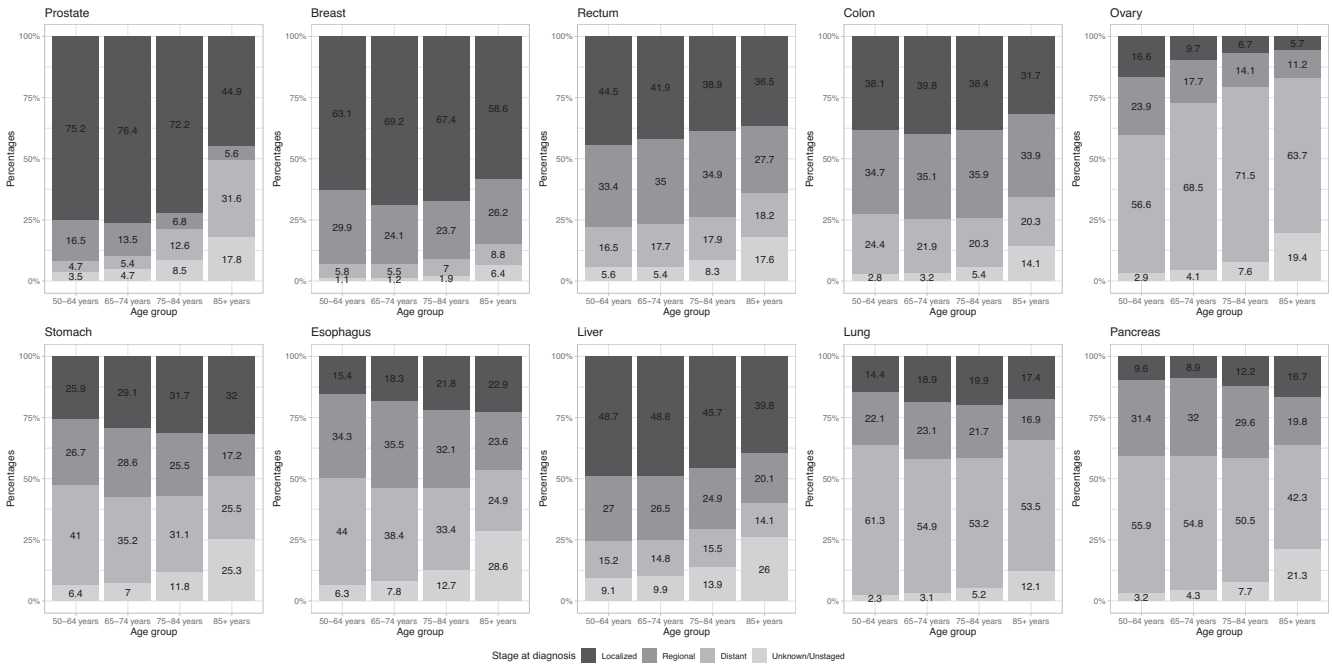

FIGURE 1 Distribution of stage at diagnosis by age group and cancer type.

TABLE 1 One-year relative survival from cancer by type, stage and age. Survival differences between those aged 75 to 84 and aged 50 to 64. SEER18 registries, diagnosed 2012 to 2016.

	Prostate		Breast		Rectum	
Age group	n	Relative survival% (95% CI)	n	Relative survival% (95% CI)	n	Relative survival% (95% CI)
Overall						
50-64 years	91 559	99.7% (99.6-99.8)	100 570	98.0% (97.9-98.1)	16 043	92.3% (91.8-92.7)
65-74 years	89 079	100.0% (—-—)[a]	61 655	97.8% (97.7-98.0)	7653	87.6% (86.8-88.4)
75-84 years	31 104	97.9% (97.6-98.2)	30 629	96.1% (95.8-96.4)	4233	78.9% (77.5-80.3)
85+years	7381	82.9% (81.7-84.1)	11 588	90.8% (89.9-91.6)	1814	65.0% (62.3-67.5)
Survival difference		1.8 (1.5-2.1)		1.9 (1.6-2.3)		13.3 (11.9-14.8)
Localized						
50-64 years	68 897	100.5% (—-—)[a]	63 467	100.0% (92.0-100.0)	7134	98.5% (98.1-98.8)
65-74 years	68 047	101.2% (—-—)[a]	42 676	100.3% (—-—)[a]	3208	96.6% (95.7-97.3)
75-84 years	22 444	102.4% (—-—)[a]	20 636	101.0% (—-—)[a]	1648	92.2% (90.4-93.7)
85+ years	3316	100.8% (—- —)[a]	6794	101.6% (—-—)[a]	662	84.3% (80.0-87.7)
Survival difference		−1.9 (—-—)[a]		−1.0 (—-—)[a]		6.3 (4.8-8.1)
Regional						
50-64 years	15 103	100.6% (—- —)[a]	30 093	98.7% (98.5-98.8)	5366	95.9% (95.2-96.4)
65-74 years	12 051	101.3% (—-—)[a]	14 878	98.3% (98.0-98.5)	2680	92.2% (90.9-93.2)
75-84 years	2102	99.9% (0-100.0)	7269	95.6% (94.8-96.2)	1479	86.9% (84.8-88.8)
85+ years	417	91.6% (85.6-95.2)	3035	91.2% (89.5-92.7)	502	77.7% (72.6-81.9)
Survival difference		0.7 (—-—)[a]		3.1 (2.5-3.9)		8.9 (7.0-11.2)
Distant						
50-64 years	4328	84.8% (83.7-85.9)	5875	74.7% (73.6-75.8)	2652	69.4% (67.6-71.2)
65-74 years	4797	82.4% (81.2-83.6)	3365	67.6% (65.9-69.1)	1352	60.7% (57.9-63.3)
75-84 years	3928	74.8% (73.3-76.3)	2150	58.2% (56.0-60.3)	756	42.6% (38.9-46.3)
85+ years	2334	63.0% (60.6-65.3)	1019	44.1% (40.8-47.5)	330	28.1% (22.9-33.4)
Survival difference		10.0 (8.1-11.9)		16.5 (14.1-19.0)		26.8 (22.7-30.9)
Unknown/unstaged						
50-64 years	3231	98.7% (98.1-99.1)	1135	89.3% (87.2-91.0)	891	89.0% (86.7-91.0)
65-74 years	4184	97.3% (96.6-97.9)	736	83.9% (80.9-86.5)	413	77.2% (72.6-81.1)
75-84 years	2630	92.3% (90.8-93.5)	574	68.7% (64.4-72.5)	350	60.8% (55.1-66.0)
85+ years	1314	70.3% (67.1-73.3)	740	54.0% (49.8-58.1)	320	43.0% (36.8-49.1)
Survival difference		6.4 (5.1-8)		20.6 (16.3-25.2)		28.2 (22.5-34.2)
	Colon		**Ovary**		**Stomach**	
Age group	**n**	**Relative survival% (95% CI)**	**n**	**Relative survival% (95% CI)**	**n**	**Relative survival% (95% CI)**
Overall						
50-64 years	30 171	87.9% (87.5-88.2)	8767	86.0% (85.2-86.7)	8671	63.4% (62.4-64.4)
65-74 years	21 822	83.7% (83.2-84.2)	5463	77.6% (76.4-78.7)	7068	61.4% (60.2-62.6)
75-84 years	16 264	74.9% (74.2-75.6)	3442	59.4% (57.7-61.1)	5442	52.2% (50.8-53.6)
85+ years	8626	60.2% (59.0-61.4)	1610	32.2% (29.7-34.6)	2564	34.8% (32.8-36.9)
Survival difference		13.0 (12.1-13.8)		26.5 (24.7-28.4)		11.2 (9.5-12.9)
Localized						
50-64 years	11 505	98.5% (98.2-98.8)	1457	98.4% (97.5-99.0)	2245	91.9% (90.6-93.0)
65-74 years	8681	96.6% (96.0-97.0)	528	96.0% (93.5-97.6)	2057	88.8% (87.2-90.2)
75-84 years	6251	92.3% (91.4-93.1)	231	93.7% (88.2-96.7)	1723	78.3% (76.0-80.3)
85+ years	2736	84.1% (82.1-85.9)	92	71.8% (58.9-81.3)	820	55.7% (51.8-59.5)
Survival difference		6.2 (5.3-7.1)		4.7 (1.6-10.2)		13.6 (11.2-16.1)

TABLE 1 (Continued)

Age group	Colon		Ovary		Stomach	
	n	Relative survival% (95% CI)	n	Relative survival% (95% CI)	n	Relative survival% (95% CI)
Regional						
50-64 years	10 463	95.5% (95.0-95.9)	2092	94.3% (93.2-95.3)	2315	78.5% (76.7-80.1)
65-74 years	7661	91.3% (90.6-92.0)	968	88.6% (86.3-90.6)	2023	72.4% (70.3-74.4)
75-84 years	5832	84.6% (83.4-85.6)	487	74.2% (69.7-78.1)	1386	62.3% (59.5-64.9)
85+ years	2923	75.2% (73.2-77.1)	180	52.6% (44.2-60.4)	442	48.1% (42.9-53.2)
Survival difference		10.9 (9.8-12.1)		20.2 (16.1-24.8)		16.2 (13.0-19.5)
Distant						
50-64 years	7368	61.9% (60.8-63.0)	4961	79.9% (78.8-81.0)	3558	35.5% (33.9-37.1)
65-74 years	4775	51.4% (49.9-52.8)	3741	73.5% (72.0-74.9)	2491	32.1% (30.2-34.0)
75-84 years	3303	34.2% (32.6-35.9)	2461	56.8% (54.7-58.8)	1691	23.7% (21.6-25.8)
85+ years	1749	19.9% (17.9-21.9)	1026	29.5% (26.5-32.5)	654	10.1% (7.8-12.8)
Survival difference		27.7 (25.7-29.7)		23.2 (20.8-25.5)		11.8 (9.1-14.4)
Unknown/unstaged						
50-64 years	835	77.0% (73.9-79.8)	257	64.9% (58.6-70.4)	553	64.8% (60.5-68.7)
65-74 years	705	63.0% (59.2-66.5)	226	55.2% (48.3-61.5)	497	50.3% (45.7-54.8)
75-84 years	878	40.2% (36.8-43.5)	263	27.3% (21.8-33.0)	642	35.5% (31.7-39.4)
85+ years	1218	28.9% (26.1-31.7)	312	17.6% (13.3-22.4)	648	24.1% (20.6-27.8)
Survival difference		36.8 (32.2-41.2)		37.6 (29.2-45.4)		29.2 (23.5-34.7)

Age group	Esophagus		Liver		Lung		Pancreas	
	n	Relative survival% (95% CI)	n	Relative survival% (95% CI)	n	Relative survival% (95% CI)	n	Relative survival% (95% CI)
Overall								
50-64 years	5870	52.0% (50.7-53.3)	16 863	51.7% (50.9-52.5)	56 724	51.1% (50.7-51.5)	14 936	42.8% (41.9-43.5)
65-74 years	4918	53.9% (52.4-55.3)	8871	51.2% (50.2-52.3)	63 421	49.9% (49.5-50.3)	14 082	35.9% (35.1-36.8)
75-84 years	2848	45.1% (43.1-47.0)	4340	41.1% (39.5-42.6)	44 942	42.8% (42.4-43.3)	10 454	25.1% (24.2-25.9)
85+ years	1071	27.4% (24.5-30.4)	1391	26.8% (24.3-29.3)	15 068	30.3% (29.5-31.1)	5279	12.4% (11.5-13.4)
Survival difference		6.9 (4.6-9.2)		10.6 (9.0-12.4)		8.3 (7.6-8.9)		17.7 (16.5-18.9)
Localized								
50-64 years	906	80.0% (77.1-82.5)	8217	72.9% (71.9-73.9)	8151	90.7% (90.-91.3)	1427	78.4% (76.1-80.5)
65-74 years	900	76.8% (73.8-79.6)	4326	71.8% (70.3-73.1)	11 976	88.0% (87.4-88.7)	1251	65.5% (62.7-68.1)
75-84 years	621	64.1% (59.9-68.0)	1983	60.0% (57.6-62.2)	8944	82.3% (81.4-83.2)	1279	43.0% (40.2-45.8)
85+ years	245	45.0% (37.9-51.9)	553	47.3% (42.7-51.9)	2629	71.7% (69.6-73.7)	879	26.8% (23.6-30.0)
Survival difference		15.9 (11.1-20.8)		12.9 (10.5-15.5)		8.4 (7.3-9.5)		35.4 (31.8-39.0)
Regional								
50-64 years	2011	67.3% (65.2-69.3)	4547	41.5% (40.0-43.0)	12 510	73.0% (72.2-73.8)	4689	64.0% (62.6-65.4)
65-74 years	1747	66.9% (64.6-69.2)	2354	41.0% (39.0-43.0)	14 646	69.0% (68.2-69.7)	4506	56.3% (54.8-57.8)
75-84 years	915	57.9% (54.4-61.2)	1081	32.7% (29.8-35.6)	9755	59.1% (58.1-60.1)	3090	42.9% (41.1-44.8)
85+ years	253	39.0% (32.3-45.5)	280	16.0% (11.7-20.8)	2549	41.5% (39.3-43.6)	1043	19.7% (17.1-22.3)
Survival difference		9.4 (5.5-13.4)		8.8 (5.5-12.0)		13.9 (12.6-15.2)		21.1 (18.8-23.4)
Distant								
50-64 years	2585	31.7% (29.9-33.5)	2569	14.1% (12.8-15.5)	34 761	34.3% (33.8-34.8)	8348	25.2% (24.3-26.2)
65-74 years	1889	32.9% (30.8-35.1)	1313	16.3% (14.3-18.4)	34 824	29.6% (29.1-30.1)	7719	20.3% (19.4-21.2)

(Continues)

TABLE 1 (Continued)

Age group	Esophagus n	Esophagus Relative survival% (95% CI)	Liver n	Liver Relative survival% (95% CI)	Lung n	Lung Relative survival% (95% CI)	Pancreas n	Pancreas Relative survival% (95% CI)
75-84 years	951	24.7% (21.9-27.6)	673	14.3% (11.7-17.2)	23 923	23.1% (22.6-23.6)	5282	11.7% (10.8-12.6)
85+ years	267	12.0% (8.2-16.6)	196	10.9% (6.8-16.1)	8060	15.3% (14.5-16.2)	2235	4.7% (3.8-5.7)
Survival difference		7.0 (3.6-10.3)		−0.2 (−3.3-2.8)		11.2 (10.4-11.9)		13.6 (12.3-14.8)
Unknown/ unstaged								
50-64 years	368	42.0% (36.9-47.1)	1530	30.9% (28.5-33.2)	1302	43.2% (40.5-45.9)	472	33.9% (29.6-38.2)
65-74 years	382	43.9% (38.8-49.0)	878	29.8% (26.8-33.0)	1975	34.3% (32.2-36.4)	606	23.0% (19.7-26.5)
75-84 years	361	33.7% (28.6-38.8)	603	23.6% (20.1-27.1)	2320	26.0% (24.1-27.9)	803	15.6% (13.1-18.3)
85+ years	306	17.2% (12.8-22.0)	362	12.5% (9.2-16.4)	1830	21.1% (19.1-23.2)	1122	9.8% (8.0-11.8)
Survival difference		8.4 (1.1-15.5)		7.3 (3.1-11.5)		17.2 (13.9-20.5)		18.3 (13.2-23.3)

[a]Confidence intervals could not be computed because relative survival estimates are above 100%.
Abbreviation: CI, confidence interval.

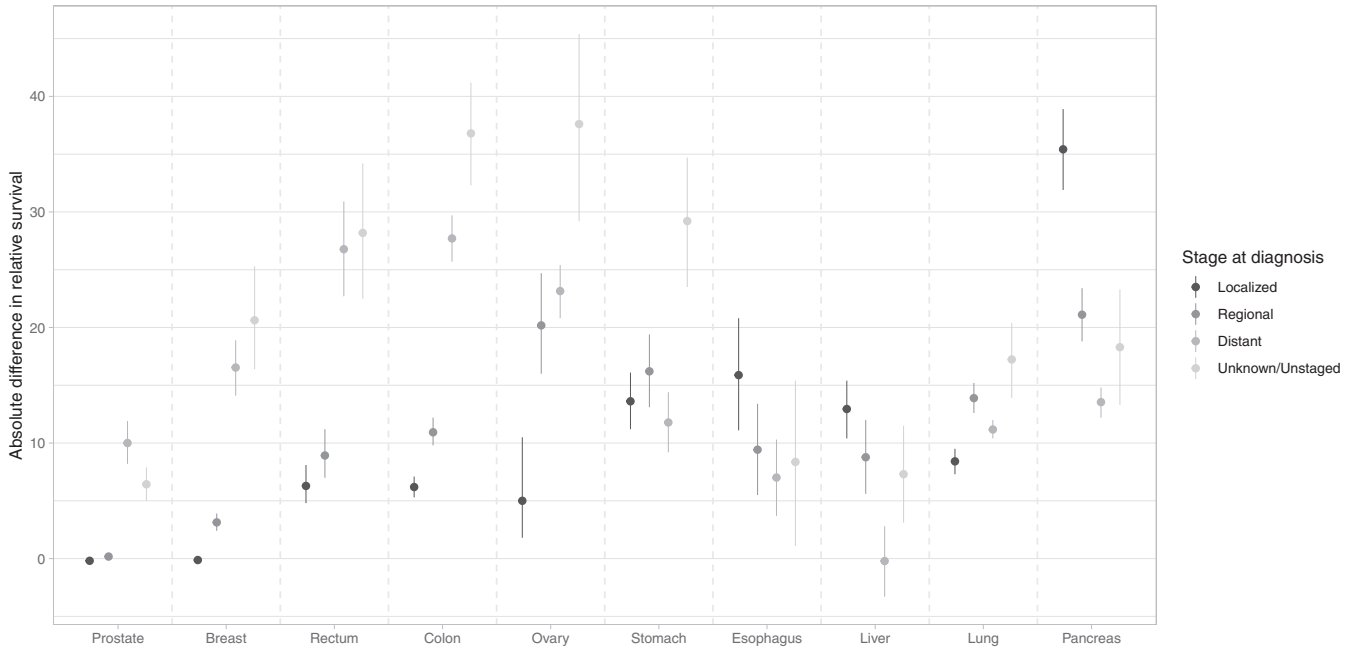

FIGURE 2 Absolute difference in relative survival between 50 to 64 year olds and 75 to 84 year olds by cancer site and stage. Capped lines are 95% confidence intervals around difference.

differences in 1-year RS for other cancers ranged from 7 percentage points for esophageal cancer (95% CI: 5-9) to 18 percentage points for pancreatic cancer (95% CI: 17-19).

3.2 | Stage-specific differences

Overall, age-related differences in 1-year RS increased with worsening stage for the better prognosis cancer types (ie, those with overall 1-year RS exceeding 85%: prostate, breast, colon, rectum and ovary), while the opposite was observed for all the remaining cancers except stomach cancer and lung cancer (Table 1, Figure 2). For stomach cancer, age-related differences remained relatively consistent irrespective of stage and for lung cancer, age-related differences were similar in regional and distant cancers (11-14 percentage points).

For localized cancers, the biggest age-related difference in 1-year RS was seen for pancreatic cancer with a difference of over 35 percentage points (95% CI: 32-39) between RS in the 50 to 64 age group

(78%) and the 75 to 84 age group (43%). For localized prostate and breast cancers, the age-related difference was negligible.

For regional cancers, age-related differences in 1-year RS were greatest for pancreatic cancer (21 percentage-point-difference, 95% CI: 19-23) and ovarian cancer (20, 95% CI: 16-25). Differences ranged between 9 and 16 percentage points for rectal, colon, stomach, esophagus, liver and lung cancers.

For distant cancers, the greatest age-related differences in 1-year RS were observed for colon and rectal cancers with differences of 28 (95% CI: 26-30) and 27 (95% CI: 23-31) percentage points respectively, closely followed by ovarian cancer with a difference of 23 points (95% CI: 21-25). For distant liver cancer, there was no difference in survival by age (1-year RS = 14% in 50-64 age group and 75-84 age group).

For cancers of unknown stage, the age-related difference in 1-year RS ranged between 6 (prostate cancer, 95% CI: 5-8) and 37 percentage points (colon cancer, 95% CI: 32-41).

3.3 | Conditional relative survival

Overall, age-related differences in 1-year relative survival conditional on surviving 1 year were practically absent for colon, stomach, esophagus, lung cancers and were greatly reduced for ovarian (11%-points vs 27%-points in the first year), liver (5%-points vs 11% points) and pancreatic cancers (6% points vs 18% points; Table S1).

By stage, age-related differences remained relatively large for distant rectal, colon and ovarian cancers (9% to 13% points) as well as for cancers of rectum, colon, ovary, stomach, esophagus and pancreas that were of unknown stage (10%-27% points).

4 | DISCUSSION

Using high-quality data from 18 SEER population-based cancer registries, we described overall and stage-specific age-related differences in 1-year RS for 10 cancer types. For some cancers with overall very good prognosis (eg, localized breast and prostate cancers, 1-year RS >95% for adults aged 50-84) or very poor prognosis (distant stage esophageal and liver cancers, 1-year RS <40%), age-related differences in RS were negligible. Age-related differences were largest for localized pancreatic cancer and unknown stage rectal, colon and ovarian cancers. Age-related differences in survival diminished or were eliminated in the second year after diagnosis conditioning on 1-year survival, suggesting that differences arise in the first year after diagnosis. Broad age-related variation in survival by prognosis (ie, cancer type and/or stage) concentrated in the first year, suggests that the magnitude of age-related survival differences may depend on the extent to which cancers are amenable to treatment.

Our results add to the growing international body of work that describes age-related differences in cancer survival.[5,6,8,9] Whereas other studies commonly adjust for age at diagnosis, we considered age at diagnosis as an independent axis of investigation. Without measuring age-related differences directly, Zeng et al reported that improvements in cancer survival between 1990 and 2009 in the US were significantly larger for younger patients with cancer, and that this was particularly the case for colorectal, breast and early-stage liver cancers.[4] The magnitude of the differences reported here are smaller than those reported for cases diagnosed in France between 1989 and 1997,[5] but similar to those reported for a pooled European analysis of cases from 2000 to 2002.[6] The ICBP study compared survival among persons by age splitting at age 75 for all stages combined and, like our study in the US, found large age-related differences in cancer survival for ovarian and pancreatic cancers, but the rank order of cancers by age-related difference varied across countries. Age-related differences in lung cancer survival were high in New Zealand and Norway, for example, and age-related differences in esophageal cancer survival were higher in Ireland and Norway. With respect to stage, in New Zealand, authors found greater age-related differences in colon cancer survival with worsening stage at diagnosis,[16] and age-related differences in lung cancer survival were higher for regional vs advanced disease,[8] both patterns being consistent with our results. Given differences in health care systems internationally and potential differences in data quality, collection and analytical methods, the exact magnitude of age-related differences is difficult to compare.

We observed that when diagnosed early with relatively good prognosis cancers (eg, localized and regional stage prostate and breast cancers, and localized colorectal and ovarian cancers) or with late-stage poor prognosis cancer (eg, liver), older adults have similar survival probabilities (when considering differences in life expectancy) as their younger peers. If treatment is a primary driver of age-related differences in cancer survival as suggested by the smaller differences in RS observed in patients surviving the first year, our results would suggest equally tolerated treatment regimens across age groups for the cancers with better prognosis. For cancers with poorer prognosis, the small differences observed across age groups are likely to be explained by their high lethality regardless of patients' age.

Age-related differences in 1-year RS were greater in good prognosis cancers diagnosed at later stage (eg, colon or rectal cancers) and poor prognosis cancers diagnosed at early stage (eg, pancreatic, esophageal or liver cancers). This observation may be explained by several factors. First, different treatment strategies may be offered or accepted in younger and older patients because of differences in health status, such as the presence of comorbid conditions or frailty. Second, patients' preferences, such as valuing quality over quantity of life in the face of an uncertain prognosis may yield different treatment decisions.[21-28] Third, healthcare providers may not know which treatment strategy will most appropriately balance benefits and harms because there is poor evidence base on treatment strategies in older adults.[29]

Factors other than treatment could also contribute to the age-related differences in cancer survival reported here, such as tumor-specific factors. For example, age-related differences in lung cancer survival have been shown to vary by histology, and by subsite in colorectal cancer.[16] It is also possible that insurance status or more generally access to care may affect age-related differences in survival.

Future research should continue to disentangle the role of these factors on age-related differences across a range of cancer types.

As is apparent from Figure 1, age is associated with higher likelihood of having an unstaged cancer.[30] We observed large age-related differences in cancer survival for colon, rectal, ovarian and stomach cancers of unknown stage. Cancers will have unknown stage if there were insufficient information for the registry to assign stage or may reflect a decision not to pursue a staging workup if the potential harms outweigh the benefits (ie, due to patient preference or if the patient is too frail for cancer treatment regardless of stage). In the absence of reasons for missingness and how they vary by age, it is difficult to explain age-related differences in cancer survival for cancer of unknown stage in our study. For example, if all younger patients had missing stage due to data collection errors and all older patients had cancer of unknown stage because it was not investigated (poor health status or patient preferences), the differences in survival between them would be inappropriate to interpret since they represent different types of patients or cancers. While the determinants of unstaged disease have been explored and age has been determined as a primary factor,[31-33] the determinants of missingness within age categories, and how they differ by age have not been documented and are worthy of future research to better interpret results of studies like this one.

Our study has limitations, largely as a consequence of its broad scope. Our multicancer approach and use of cancer registry data prohibited a detailed analysis of the influence of specific patient, tumor and/or healthcare system factors that could also explain age-related differences in survival. For example, because of the lack of information about comorbidity, frailty or other geriatric conditions, it was not possible to distinguish fit vs frail patients. Consequently, we were unable to disentangle which share of the age-related differences in survival observed may be avoidable vs arose as a consequence of differences in baseline health status. Despite these limitations, the article provides insight on the role of stage in age-related disparities and how this varies by cancer type, knowledge which can be mobilized to prioritize efforts to narrow age gaps in survival.

With respect to methods, the estimation of relative survival relies on background mortality rates obtained from lifetables and implies that in the absence of cancer, people in our study cohort would have the same mortality risk as the general population. While the US life tables account for differences in age, sex, ethnicity and county SES between cancer patients and the general population, they are not specific to other factors influencing prognosis and mortality (such as comorbidities and smoking), for which the prevalence may differ between cancer patients and the general population. Consequently, age-related differences in relative survival estimates may be underestimated.[34] In a recent study describing age-related differences in lung cancer survival, correction of life tables for smoking did change net survival estimates, but did not meaningfully change age-related differences in survival,[8] our main outcome of interest in the present study. Finally, as a consequence of using SEER-extracted RS estimates, we were unable to impute missing stages and observe how imputation might affect age-related differences in cancer survival.

In this population-based study, we confirmed that cancer survival in older adults tends to be poorer even after accounting for differences in background mortality for a range of common cancers and we illustrated that the patterns of age-related differences varied by cancer type and stage and aligned with prognosis. More detailed studies of the determinants of age-related differences in cancer survival, considering the characteristics of the patients, their cancers and their treatment, are necessary to achieve better outcomes in older adults.

AUTHOR CONTRIBUTIONS

The work reported in the article has been performed by the authors, unless clearly specified in the text. **Diana Withrow:** Conceptualization, methodology, formal analysis, writing - original draft, project administration. **Sophie Pilleron:** Conceptualization, methodology, formal analysis, writing - original draft, project administration. **Melisa Wong:** Interpretation, writing - review and editing. **Eva Morris:** Interpretation, writing - review and editing. **Brian Nicholson:** Interpretation, writing - review and editing.

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CONFLICT OF INTEREST STATEMENT

MLW reported conflicts of interest outside of the submitted work (an immediate family member is an employee of Genentech with stock ownership; royalties from UpToDate). The remaining authors have no conflicts to report.

DATA AVAILABILITY STATEMENT

Only publicly available data were used in our study and data sources and handling of these data are described in the Materials and Methods. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

Ethical approval was not required for our study.

ORCID

Sophie Pilleron https://orcid.org/0000-0001-7146-4740

TWITTER

Diana R. Withrow @d__with
Brian D. Nicholson @BrianDNicholson
Eva J. A. Morris @EJAMorris
Melisa L. Wong @melisawongmd
Sophie Pilleron @Spilleron

REFERENCES

1. United States Department of Health and Human Services. *United States Cancer Statistics - Incidence: 1999-2017, WONDER Online Database*. Washington, DC: Centers for Disease Control and Prevention and National Cancer Institute; 2020.

2. United States Department of Health and Human Services. *United States Cancer Statistics - Mortality: 1999-2017, WONDER Online Database*. Washington, DC: Centers for Disease Control and Prevention; 2020.
3. Colby S, Ortman JM. *Projections of the size and composition of the US population: 2014 to 2060*. Washington, DC: US Department of Commerce, Economics and Statistics Administration; 2015.
4. Zeng C, Wen W, Morgans AK, Pao W, Shu XO, Zheng W. Disparities by race, age, and sex in the improvement of survival for major cancers: results from the National Cancer Institute Surveillance, epidemiology, and end results (SEER) program in the United States, 1990 to 2010. *JAMA Oncol*. 2015;1:88-96.
5. Colonna M, Bossard N, Remontet L, Grosclaude P. Changes in the risk of death from cancer up to five years after diagnosis in elderly patients: a study of five common cancers. *Int J Cancer*. 2010;127:924-931.
6. Quaglia A, Tavilla A, Shack L, et al. The cancer survival gap between elderly and middle-aged patients in Europe is widening. *Eur J Cancer*. 2009;45:1006-1016.
7. Pilleron S, Charvat H, Araghi M, et al. Age disparities in stage-specific colon cancer survival across seven countries: an international cancer benchmarking partnership SURVMARK-2 population-based study. *Int J Cancer*. 2021;148:1575-1585.
8. Pilleron S, Maringe C, Charvat H, Atkinson J, Morris E, Sarfati D. Age disparities in lung cancer survival in New Zealand: the role of patient and clinical factors. *Lung Cancer*. 2021;157:92-99.
9. Pilleron S, Maringe C, Charvat H, Atkinson J, Morris EJA, Sarfati D. The impact of timely cancer diagnosis on age disparities in colon cancer survival. *J Geriatr Oncol*. 2021;12:1044-1051.
10. DeSantis CE, Miller KD, Dale W, et al. Cancer statistics for adults aged 85 years and older, 2019. *CA Cancer J Clin*. 2019;69:452-467.
11. Surveillance Epidemiology and End Results Program. *SEER*Stat Databases: November 2018 Submission*. Vol 2019. Rockville, MD: National Cancer Institute; 2019.
12. Arnold M, Rutherford MJ, Bardot A, et al. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995-2014 (ICBP SURVMARK-2): a population-based study. *Lancet Oncol*. 2019;20:1493-1505.
13. National Cancer Institute. *In: Surveillance, Epidemiology, and End Results (SEER) Program*. NCI. https://seer.cancer.gov/iccc/iccc-who2008.html
14. SEER. *Localized/Regional/Distant Stage Adjustments*. US National Cancer Institute; 2020. https://seer.cancer.gov/seerstat/variables/seer/lrd-stage/
15. Sarfati D, Blakely T, Pearce N. Measuring cancer survival in populations: relative survival vs cancer-specific survival. *Int J Epidemiol*. 2010;39:598-610.
16. Pilleron S, Gower H, Janssen-Heijnen M, et al. Patterns of age disparities in colon and lung cancer survival: a systematic narrative literature review. *BMJ Open*. 2021;11:e044239.
17. Mariotto AB, Zou Z, Johnson CJ, Scoppa S, Weir HK, Huang B. Geographical, racial and socio-economic variation in life expectancy in the US and their impact on cancer relative survival. *PLoS One*. 2018;13:e0201034.
18. Yu M, Tatalovich Z, Gibson JT, Cronin KA. Using a composite index of socioeconomic status to investigate health disparities while protecting the confidentiality of cancer registry data. *Cancer Causes Control*. 2014;25:81-92.
19. US National Cancer Institute SEaERP. *Expected Survival Life Tables*. US National Cancer Institute SEaERP: Rockville; 2018.
20. Buckland ST. Monte Carlo confidence intervals. *Biometrics*. 1984;40:811-817.
21. Sarasqueta C, Perales A, Escobar A, et al. Impact of age on the use of adjuvant treatments in patients undergoing surgery for colorectal cancer: patients with stage III colon or stage II/III rectal cancer. *BMC Cancer*. 2019;19:1-15.
22. Pettersson A, Robinson D, Garmo H, Holmberg L, Stattin P. Age at diagnosis and prostate cancer treatment and prognosis: a population-based cohort study. *Ann Oncol*. 2018;29:377-385.
23. Limonnik V, Abel S, Finley GG, Long GS, Wegner RE. Factors associated with treatment receipt and overall survival for patients with locally advanced large cell neuroendocrine carcinoma of the lung: a National Cancer Database analysis. *Lung Cancer*. 2020;150:107-113.
24. Belot A, Fowler H, Njagi EN, et al. Association between age, deprivation and specific comorbid conditions and the receipt of major surgery in patients with non-small cell lung cancer in England: a population-based study. *Thorax*. 2019;74:51-59.
25. Gooiker GA, Dekker JWT, Bastiaannet E, et al. Risk factors for excess mortality in the first year after curative surgery for colorectal cancer. *Ann Surg Oncol*. 2012;19:2428-2434.
26. Dekker JWT, van den Broek CB, Bastiaannet E, van de Geest LG, Tollenaar RA, Liefers G-J. Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. *Ann Surg Oncol*. 2011;18:1533-1539.
27. Majano SB, Di Girolamo C, Rachet B, et al. Surgical treatment and survival from colorectal cancer in Denmark, England, Norway, and Sweden: a population-based study. *Lancet Oncol*. 2019;20:74-87.
28. Seghers PA, Wiersma A, Festen S, et al. Patient preferences for treatment outcomes in oncology with a focus on the older patient—a systematic review. *Cancer*. 2022;14:1147.
29. Sedrak MS, Freedman RA, Cohen HJ, et al. Older adult participation in cancer clinical trials: a systematic review of barriers and interventions. *CA Cancer J Clin*. 2021;71:78-92.
30. Herget K, Stroup A, Smith K, Wen M, Sweeney C. Unstaged cancer: long-term decline in incidence by site and by demographic and socioeconomic characteristics. *Cancer Causes Control*. 2017;28:341-349.
31. Merrill RM, Sloan A, Anderson AE, Ryker K. Unstaged cancer in the United States: a population-based study. *BMC Cancer*. 2011;11:1-10.
32. Koroukian SM, Xu F, Beaird H, Diaz M, Murray P, Rose JH. Complexity of care needs and unstaged cancer in elders: a population-based study. *Cancer Detect Prev*. 2007;31:199-206.
33. Di Girolamo C, Walters S, Benitez Majano S, et al. Characteristics of patients with missing information on stage: a population-based study of patients diagnosed with colon, lung or breast cancer in England in 2013. *BMC Cancer*. 2018;18:1-10.
34. Blakely T, Soeberg M, Carter K, Costilla R, Atkinson J, Sarfati D. Bias in relative survival methods when using incorrect life-tables: lung and bladder cancer by smoking status and ethnicity in New Zealand. *Int J Cancer*. 2012;131:E974-E982.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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