Trends in the Proportion of Second or Later Primaries Among All Newly Diagnosed Malignant Cancers

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BACKGROUND: Improvements in cancer survival mean that an increasing number of survivors may live long enough beyond their initial cancer to be diagnosed with additional independent primary cancers. The proportion of newly diagnosed cancers that are second- or higher-order primaries and how this proportion has changed over the past several decades were examined. **METHODS:** Data from the Surveillance, Epidemiology, and End Results (SEER) program were used to identify incident malignant primaries diagnosed between 1975 and 2017. Using the SEER sequence number, the authors tabulated the proportion of all cancers in each calendar year that were second- or higher-order primaries. The average annual percent change (AAPC) was then calculated to assess how this proportion has changed over time. **RESULTS:** Analyses included nearly 4.9 million incident cancers diagnosed during 1975-2017. The proportion of all cancers that were second- or higher-order increased steadily from 9.77% during 1975-1984 to 21.03% during 2015-2017, reflecting an AAPC of 2.41% (95% CI, 2.16%-2.65%). In 2015-2017, second- or higher-order cancers were most prevalent among cancers of the bladder (28.79%), followed by lung and bronchus (28.07%), melanoma (27.88%), and leukemia (26.10%). The highest AAPCs over the study period were observed for melanoma (4.05%), leukemia (3.51%), and lung and bronchus (3.36%). **CONCLUSIONS:** The proportion of newly diagnosed cancers that are second- or higher-order has grown rapidly over the past several decades and currently exceeds 20%. Continued monitoring of second and later primaries will be critical for anticipating the future impact on cancer treatment and survivorship care.
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KEYWORDS: cancer survivors, second primary cancers, trends.

INTRODUCTION

Advances in early detection and treatment, combined with the aging of the population, have led to a rapid growth in the number of cancer survivors in the United States, with a projected increase from roughly 17 million in 2019 to over 22 million by the year 2030.[1] Importantly, approximately two-thirds of US survivors were diagnosed with cancer at least 5 years ago, and 18% were diagnosed at least 20 years ago.[1] Improvements in cancer survival mean that an increasing number of survivors may live long enough beyond their initial cancer to be diagnosed with additional independent primary cancers.

An increase in the prevalence of the second or later cancer diagnoses may be consequential for several reasons. Some studies have suggested that, for certain cancer types, overall survival may be significantly lower for patients whose diagnosis is a second- or higher-order primary, relative to those with a first primary cancer diagnosis.[2-5] As a result, patients with a second or later primary cancer are often excluded from cancer clinical trials on the basis of their cancer history.[6] An increase in the proportion of second- or higher-order primaries among new diagnoses of a particular cancer type could therefore decrease the eligible pool of potential participants for a given trial and limit the generalizability of trial results. Other research has suggested that individuals with a history of multiple primaries may have lower quality of life and poorer physical health than those with a history of only 1 primary cancer,[7-12] which may pose additional challenges for the delivery of treatment and survivorship care for these patients. These unique health and survival implications of a second- or higher-order primary suggest the need to investigate and monitor patterns of a cancer history among newly diagnosed cancer cases.

A report using data from the Surveillance, Epidemiology, and End Results (SEER) program found that 18.4% of all incident cancers during 2009-2013 were second- or higher-order.[13] In this study, we aimed to update these results (with SEER data through 2017), and to examine how this proportion has changed over time since the 1970s. Understanding historical trends will be important for anticipating future growth in the number of individuals with a history of multiple primaries, and predicting their impact on the future of cancer survival and survivorship care.

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MATERIALS AND METHODS

Incident cancers diagnosed between 1975 and 2017 were identified using data from the SEER 9 registries (Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco–Oakland, Seattle–Puget Sound, and Utah).[14] Only those with malignant behavior and known age were included. We excluded those whose malignancy was only defined as reportable by the individual state/province registry (<0.01% of all cases). A total of 4,870,113 incident cancers were included in analyses.

Cancer history was defined using SEER sequence numbers, or the sequence of all reportable primary neoplasms over an individual's lifetime. A sequence number of "00" indicates that the individual has had only one in situ or malignant neoplasm as defined by the Federal reportable list. Sequence number "01" represents the first of 2 or more neoplasms, "02" represents the second of 2 or more, and so on. Reportable neoplasms that occur outside the registry catchment area or were diagnosed before the registry's initiation are assigned a sequence number but are not included within the SEER database. Using the sequence number, we categorized incident cancers as first/only primary or second/higher-order primary.

Statistical Analysis

For each calendar year, we identified the proportion of all incident cancers that were second- or higher-order. Joinpoint software[15] was used to estimate the average annual percent change (AAPC) in this proportion over the full range of diagnosis years. The AAPC is a summary measure of the trend and is computed as a weighted average of the annual percent changes from the joinpoint regression model. It is valid even if the joinpoint model suggests there were changes in trends during the specified interval.[16,17] Confidence intervals for AAPCs were also calculated using Joinpoint.[17] Analyses were performed for all cancer sites combined and for the 12 most common cancer sites, which account for more than three-quarters of all new cancer cases.[18]

RESULTS

Analyses included nearly 4.9 million incident cancers diagnosed between 1975 and 2017. The proportion of all cancers that were second- or higher-order increased steadily from 9.77% during 1975-1984 to 21.03% during 2015-2017, reflecting an AAPC of 2.41% (95% CI, 2.16%-2.65%) (Fig. 1 and Table 1). In the earliest decade of 1975-1984, the proportion of second- or higher-order cancers was highest among colon and rectum (12.53%), followed by kidney and renal pelvis (11.83%), and bladder (11.29%). In contrast, in the 3 most recent years of data (2015-2017), second- or higher-order cancers were most prevalent among cancers of the bladder (28.79%), followed by lung and bronchus (28.07%), melanoma (27.88%), and leukemia (26.10%). The highest AAPCs over the study period were observed for melanoma (4.05%; 95% CI, 3.74%-4.36%), leukemia (3.51%; 95% CI, 2.48%-4.54%), and lung and bronchus (3.36%; 95% CI, 2.93%-3.80%) (Figs. 2 and 3 and Table 1). In 2015-2017, the cancer types with the lowest proportion of second- or higher-order diagnoses included prostate (10.69%), thyroid (14.09%), and endometrial (14.50%). The AAPC was also lowest for prostate cancer (0.64%; 95% CI, 0.31%-0.97%).

Between 1975 to 1984 and 2015 to 2017, the proportion of second- or higher-order cancers increased from 7.08% to 12.69% among cancers diagnosed at ages younger than 65 years (AAPC = 1.83%; 95% CI, 1.63%-2.03%) and from 12.07% to 27.93% among those 65 and older (AAPC = 2.60%; 95% CI, 2.23%-2.98%) (Fig. 1 and Supporting Table 1). The AAPC was significantly greater among those 65 and older both overall and for all cancer types other than lung and bronchus, uterus, kidney and renal pelvis, melanoma, thyroid, non-Hodgkin lymphoma, and leukemia, where AAPCs were similar by age. Consistently over the range of diagnosis years, a slightly higher proportion of cancers among women than among men were second- or higher-order, although the AAPC was similar (women: 2.31%, men: 2.51%; $P = .276$) (Fig. 1 and Supporting Table 2). Only melanoma and cancers of the lung and bronchus and bladder demonstrated significant differences according to sex, all with a higher AAPC among men. In analyses according to race, the proportion of second- or higher-order cancers was generally highest for incident cancers among White patients, compared to that among Black patients or those of other race (Fig. 1 and Supporting Table 3). However, the AAPC for all cancer types combined did not significantly differ between cancers among White and Black patients (2.49% vs 2.77%; $P = .206$) but was significantly lower for cancers among patients of other race (AAPC = 2.01%) than White ($P = .004$) or Black ($P < .001$).

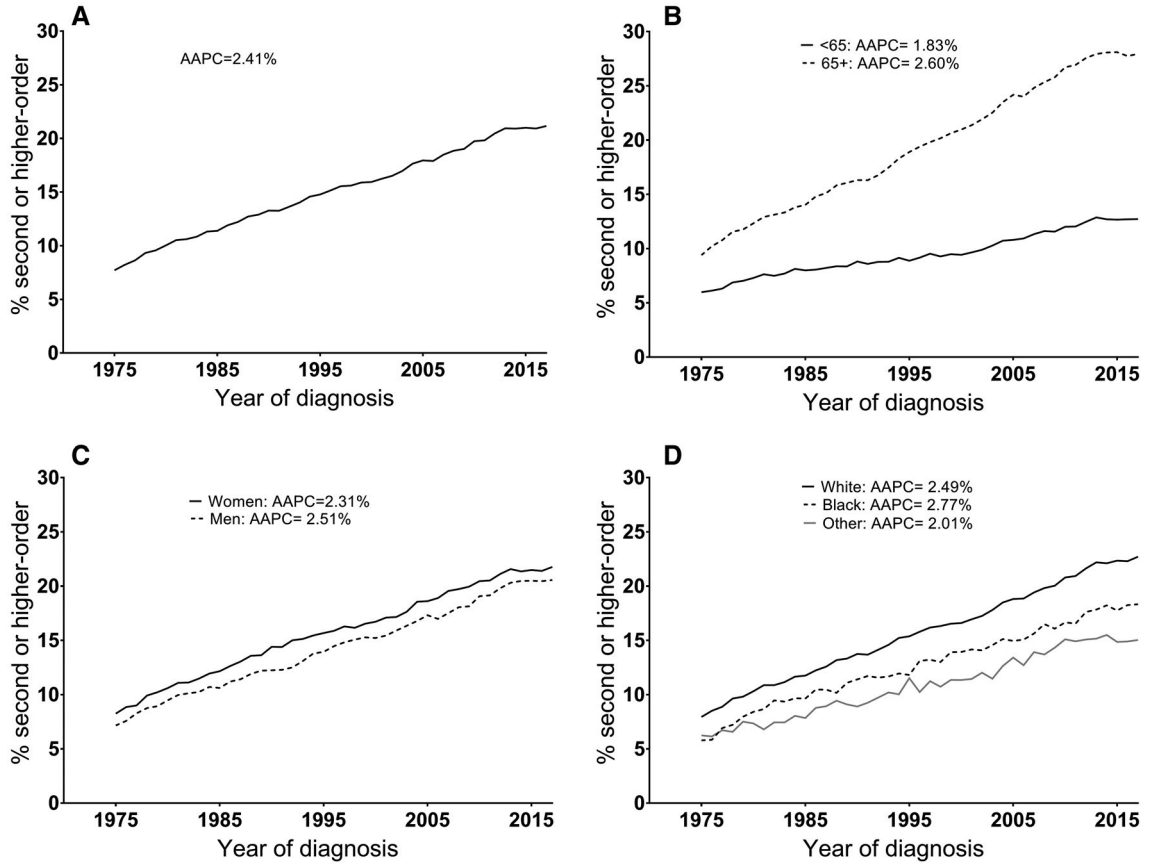

Figure 1. Trends in the proportion of second- or higher-order cancers among incident cancers (A) overall, (B) according to age at diagnosis, (C) according to sex, and (D) according to race. AAPC indicates average annual percent change.

DISCUSSION

Using population-based data from the SEER registries we examined the prevalence of second- or higher-order primaries among all newly diagnosed malignant cancers, and how this proportion has changed over the past several decades. Our findings indicate that more than one-fifth of incident cancer diagnoses during 2015-2017 occurred among individuals with a prior cancer history, and this figure has increased by an average of over 2% per year since the mid-1970s. Of the individual cancer types examined, second- or higher-order primaries were most common among incident cancers of the bladder and lung and bronchus, followed by and melanoma and leukemia, cancer types that also exhibited some of the most rapid increases over time. These increases may add to the challenges of cancer treatment and survivorship care in the coming years.

The steep rise in the proportion of second or later cancers over the past 4 decades may be explained by a combination of interrelated factors. Aside from the likely contributions of increases in life expectancy and the overall aging of the US population, there have also been substantial improvements in survival for several common cancer types (eg, breast and colorectal)[19] since the initiation of the SEER program in the 1970s. Improved prognosis for first cancers means more survivors may live long enough to develop a second primary cancer. Additionally, some of the largest drivers of improvements in cancer survival, namely early detection through screening and advances in cancer treatment, may also impact the incidence of second or later cancers. The implementation and expansion of screening programs, such as for breast and colorectal cancers, has likely contributed to an increase in the detection of additional cancers among cancer survivors, who may be encouraged to get screened for these malignancies as part of their survivorship care. For survivors whose first cancer was treated with carcinogenic therapies, including radiation and certain chemotherapies, exposure to these therapies can also contribute to incidence of second cancers.[20]

TABLE 1. Proportion of Incident Cases and AAPC in Second or Later Cancers, SEER 9, 1975-2017

	1975-1984			1985-1994			1995-2004			2005-2014			2015-2017			
	Total Cases, No.	Second or Later, No.	Second or Later, %	Total Cases, No.	Second or Later, No.	Second or Later, %	Total Cases, No.	Second or Later, No.	Second or Later, %	Total Cases, No.	Second or Later, No.	Second or Later, %	Total Cases, No.	Second or Later, No.	Second or Later, %	AAPC (95% CI)
All cancers	758,602	74,081	9.77	1,025,500	133,968	13.06	1,220,358	195,988	16.06	1,407,276	273,628	19.44	458,377	96,376	21.03	2.41 (2.16%-2.65%)
Female breast	104,117	11,482	11.03	151,654	21,232	14.00	186,504	29,591	15.87	210,394	41,641	19.79	71,514	14,798	20.69	1.84 (1.51%-2.16%)
Prostate	71,314	6377	8.94	146,908	13,804	9.40	190,605	17,036	8.94	201,386	18,732	9.30	57,402	6138	10.69	0.64 (0.31%-0.97%)
Lung and bronchus	111,547	10,996	9.86	145,697	21,712	14.90	162,149	32,777	20.21	173,484	44,749	25.79	53,377	14,982	28.07	3.36 (2.93%-3.80%)
Endometrial	30,522	2051	6.72	29,307	3141	10.72	34,645	4725	13.64	44,609	6393	14.33	16,161	2343	14.50	2.37 (2.05%-2.68%)
Colon and rectum	110,193	13,808	12.53	127,194	21,043	16.54	134,518	26,601	19.78	127,787	26,441	20.69	38,404	7755	20.19	1.68 (1.39%-1.97%)
Bladder	35,555	4015	11.29	44,675	7397	16.56	53,319	12,214	22.91	62,824	17,538	27.92	20,293	5842	28.79	2.68 (2.50%-2.86%)
Kidney and renal pelvis	15,037	1779	11.83	22,035	3707	16.82	30,881	6387	20.68	46,703	11,164	23.90	16,484	4017	24.37	2.16 (1.83%-2.48%)
Pancreas	20,836	1813	8.70	24,157	3123	12.93	28,604	4722	16.51	38,506	7812	20.29	13,750	3004	21.85	2.79 (2.50%-3.09%)
Melanoma	18,727	1306	6.97	30,963	3562	11.50	48,163	8669	18.00	70,365	17,114	24.32	26,253	7319	27.88	4.05 (3.74%-4.36%)
Thyroid	9345	699	7.48	12,457	1028	8.25	20,978	2044	9.74	40,723	5511	13.53	13,892	1958	14.09	1.68 (1.26%-2.11%)
Non-Hodgkin lymphoma	23,250	1871	8.05	38,412	4735	12.33	51,047	8078	15.82	61,732	12,881	20.87	20,142	4657	23.12	3.05 (2.63%-3.46%)
Leukemia	22,719	1923	8.46	27,295	3071	11.25	33,296	5196	15.61	41,582	9358	22.50	13,947	3640	26.10	3.51 (2.48%-4.54%)

Abbreviations: AAPC, average annual percent change; SEER, Surveillance, Epidemiology, and End Results.

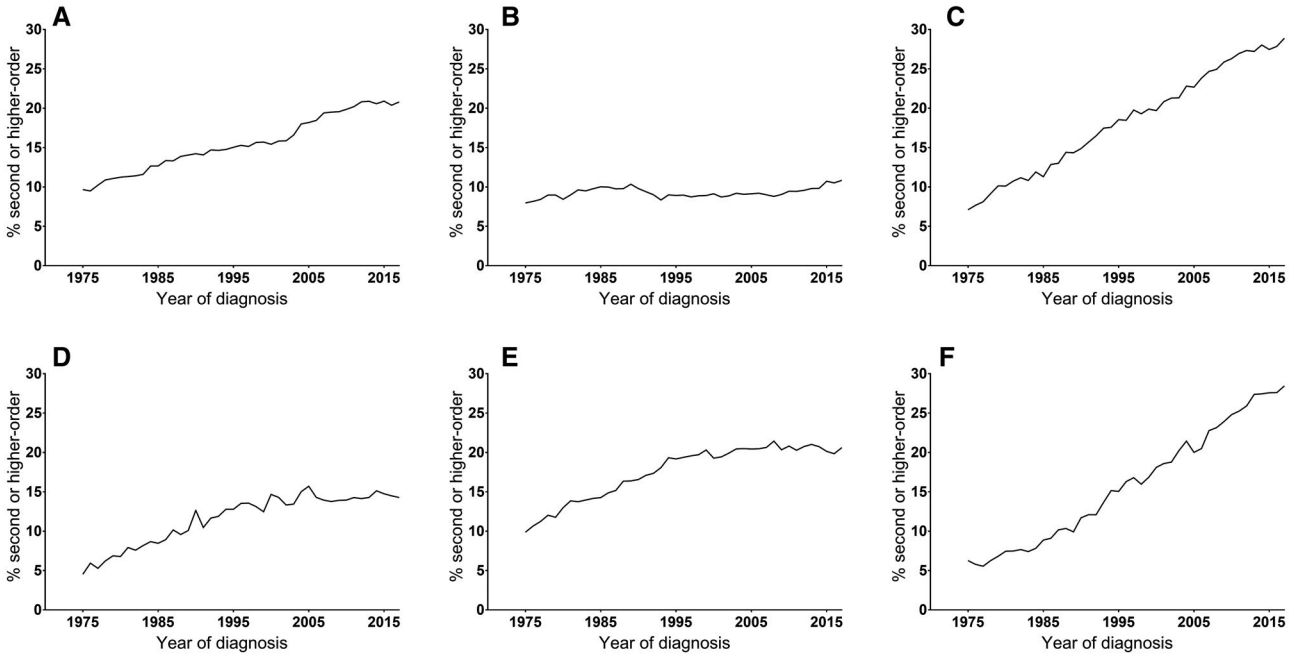

Figure 2. Trends in the proportion of second- or higher-order cancers among incident cancers of the following types: (A) female breast, (B) prostate, (C) lung and bronchus, (D) uterine, (E) colon and rectum, and (F) melanoma.

Our findings demonstrate considerable variability across cancer types in the proportion of newly diagnosed patients who have a prior cancer history, and in how rapidly this proportion has increased over the past several decades. Among incident cancers of the lung and bronchus and bladder, the high prevalence of second- or higher-order primaries may reflect the influence of shared risk factors (ie, smoking), which increase the likelihood for individuals with these cancer types to develop multiple unique cancers. For melanoma, which has increased in overall incidence in recent years,[21] a probable contributor is the relatively high frequency of a subsequent primary melanoma diagnosis after a first primary melanoma.[22,23] Trends in the use of carcinogenic cancer therapies for the first primary cancer may have contributed to the high prevalence and steep increase in second or later primaries among certain cancer types, particularly leukemias.[24] Our results also highlight some differences in prevalence and trends according to demographic characteristics, such as age, sex, and race. These differences are likely partially explained by differences in the underlying cancer type distribution according to these characteristics, but they may also reflect demographic variation in patterns of behavioral factors, health care access, and biological susceptibility to second or later cancers. Additional research may seek to better understand the drivers of the increase in the proportion of second- or higher-orders cancers among patients newly diagnosed with the cancer types and whether these trends will continue over the next several years.

The high prevalence of a cancer history among individuals with a new cancer diagnosis may have important implications for the delivery of cancer treatment and survivorship care. Some reports, including those conducted using SEER data, have documented inferior overall survival among patients with certain cancer types, including breast, prostate, colorectal, uterine, thyroid, melanoma, and bladder, who have a prior cancer diagnosis compared to those without, even after accounting for demographic and tumor characteristics.[2-5] For patients with these cancer types, prior cancer history may therefore influence decisions surrounding treatment for the newly diagnosed cancer. Additionally, given the high proportion of new diagnoses of these cancers that are second- or higher-order, exclusion of patients on the basis of cancer history may limit the generalizability of clinical trials and observational studies focused on new cancer therapies. The survivorship care of patients with a history of multiple cancers may also be complicated by the additional physical and psychological toll, as well as the additional treatment-related exposures, that

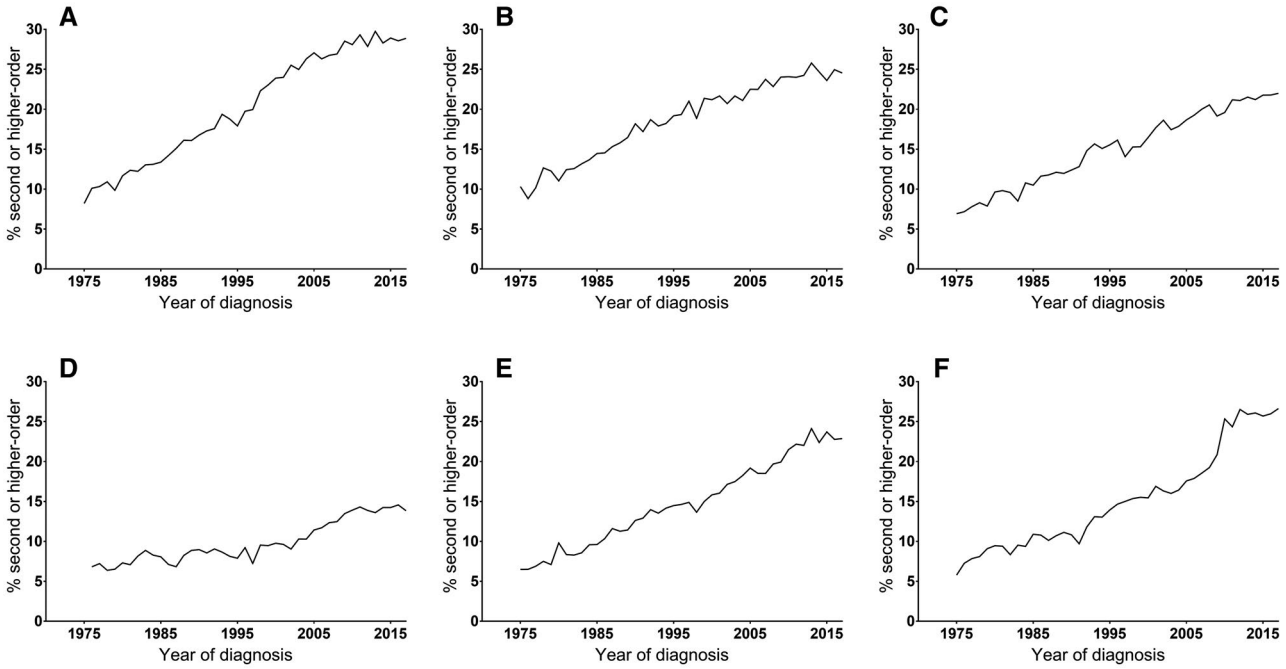

Figure 3. Trends in the proportion of second- or higher-order cancers among incident cancers of the following types: (A) bladder, (B) kidney and renal pelvis, (C) pancreas, (D) thyroid, (E) non-Hodgkin lymphoma, and (F) leukemia.

accompany each new cancer diagnosis. Accordingly, the potential for poorer quality of life[8-12] and poorer physical health[7] among multiple primary cancer survivors should be considered in planning for posttreatment care. Given our finding of a rapid increase in the prevalence of a cancer history among newly diagnosed patients in recent decades, there is a corresponding need for additional research to support the long-term survivorship care needs of patients with 2 or more primary cancer diagnoses. Efforts to ensure that newly diagnosed patients continue to receive recommended screenings for other cancers in the years following their initial cancer diagnosis also remain critical.

One limitation of our analysis is the possibility that the criteria used to define a primary malignancy for some cancer types may have changed at some point during the study period. However, we expect the impact of any such changes on our overall results would be small. Additionally, it is possible that sequence number may have been coded incorrectly in the SEER data, or that some recurrent cancers may have been misclassified as second- or higher-order primaries, although we believe that these errors would be relatively rare overall. Outmigration of cancer survivors from SEER registry areas could also lead some second- or higher-order primaries to be missed and not captured in the registry data. Increases in second- or higher-order primaries that we observed over time may include some diagnoses that would not have become clinically apparent (overdiagnosis) due to increases in cancer screening or use of imaging. However, these patients are still subjected to diagnostic procedures and cancer treatments that may have psychosocial and/or medical consequences, and therefore still reflect the burden of second- and higher-order primary cancers. We were also limited by small sample sizes in some cancer type–specific analyses according to race. Finally, because the SEER registries are located within specific geographic regions and do not cover the entire United States, our results are estimates and may not reflect the exact proportions of second- or higher-order cancers for the whole US population across all diagnosis years.

The proportion of newly diagnosed cancers that are second- or higher-order has grown rapidly over the past several decades and currently exceeds 20%. Because the challenges associated with 2 or more primary cancer diagnoses may be substantial and unique, continued monitoring of second- or higher-order cancers will be critical for anticipating the future impact on cancer treatment and survivorship care.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Chelsea Anderson: Conceptualization, formal analysis, writing–original draft, and writing–review and editing. **Deborah K. Mayer:** Writing–review and editing. **Hazel B. Nichols:** Supervision and writing–review and editing.

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