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Estimation of the Number of Individuals Living With Metastatic Cancer in the United States

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Abstract

Background: The purpose of this study was to estimate the number of individuals living with metastatic breast, prostate, lung, colorectal, or bladder cancer or metastatic melanoma in the United States using population-based data. **Methods:** A back-calculation method was used to estimate the number of individuals living with metastatic cancer for each cancer type from US cancer mortality and survival statistics from the Surveillance, Epidemiology, and End Results registries. The percentages of those living with metastatic cancer who advanced to metastatic disease from early stage cancer vs who were diagnosed with metastatic cancer de novo were calculated. One- and 5-year relative survival rates for de novo metastatic cancer were compared by year of diagnosis to assess time trends in survival. **Results:** It is estimated that, in 2018, 623 405 individuals were living with metastatic breast, prostate, lung, colorectal, or bladder cancer, or metastatic melanoma in the United States. This number is expected to increase to 693 452 in 2025. In 2018, the percentage of metastatic cancer survivors who were initially diagnosed with early stage cancer and advanced to metastatic cancer ranged from 30% for lung cancer to 72% for bladder cancer. **Conclusions:** This study demonstrates increasing numbers of individuals living with metastatic cancer of the 6 most common cancer types in the United States. This information is critical for informing the allocation of research efforts and healthcare infrastructure needed to address the needs of these individuals.

As of January 2022, it was estimated that more than 18 million individuals in the United States were living with a history of cancer (1). Because of the growth of the aging population alone, this number is projected to reach more than 22.1 million by 2030 (2). These estimates include cancer survivors at all disease stages and treatment phases of the cancer survivorship continuum, including survivors who are newly diagnosed and undergoing treatment as well as those who are long-term survivors and living without evidence of disease.

One understudied group of cancer survivors is those who have been diagnosed with or have progressed to metastatic cancer, the most advanced form of the disease. The needs of this subpopulation likely differ from the group of cancer survivors diagnosed with and treated for early stage disease. However, there remains a paucity of knowledge related to the needs, and ways to effectively address these needs, of individuals living with advanced or metastatic cancer (3).

Equally as important to addressing the evidence gaps related to the needs of those with metastatic cancer is better understanding the number of individuals living with metastatic cancer in the United States, as this information is critical to informing the allocation of research efforts and healthcare infrastructure needed to address the needs of these individuals (3). Cancer registry data can be used to estimate the number of survivors who were initially diagnosed with metastatic cancer (de novo), however, registries do not collect longitudinal data on recurrence or progression to metastatic disease. Thus, estimating the number of individuals who were initially diagnosed with early stage disease and who later have a recurrence (after being disease free) or progress (after never being disease free) to metastatic disease is challenging. With the number of cancer survivors increasing overall (2), as well as survival rates improving for many cancers (4), it is likely that the number of individuals who are living with metastatic cancer is also growing, as shown

previously for breast cancer (5). However, data on the number of cancer survivors living with metastatic disease for cancer types other than breast are lacking.

Therefore, to better understand the current burden of metastatic cancer in the United States, we updated and extended the analysis by Mariotto et al. (5) to estimate the number of individuals living with metastatic disease (ie, the prevalence of metastatic cancer) for the 6 most common cancer types: breast, prostate, lung and bronchus (hereafter referred to as lung), colon and rectum (hereafter referred to as colorectal), bladder, and melanoma. We used national data on site-specific cancer mortality and distant stage site-specific survival from the Surveillance, Epidemiology, and End Results (SEER) registries to estimate the prevalence of metastatic cancer by cancer type, including those diagnosed with de novo metastatic cancer and those who are diagnosed with early stage cancer and experience a recurrence or progression to metastatic disease. From this point forward, we use the term *metastatic recurrence* to encompass a recurrence to metastatic disease after an early stage diagnosis (and disease-free period) and progression to metastatic disease after an early stage diagnosis (with no disease-free period). The term *recurrence* in this analysis does not include local or regional recurrence after an early stage diagnosis.

Methods

Back-Calculation Method to Estimate the Prevalence of Metastatic Disease

As in Mariotto et al. (5), we used the Mortality Incidence Approach Model (MIAMOD) to estimate prevalence of metastatic disease (6,7) (see Figure 1). MIAMOD assumes that each observed cancer death is the result of metastatic disease, either initially diagnosed as metastatic or a recurrence to metastatic disease after an early stage diagnosis. The main inputs to MIAMOD are US cancer deaths and cancer survival from metastatic disease. Other inputs include US all-cause deaths, to estimate overall survival, and US population counts. MIAMOD was applied by sex to each cancer type: breast [female only, to update Mariotto et al. (5)], prostate (male only), lung, colorectal, melanoma, and bladder. The MIAMOD software is available at www.eurocare.it/MiamodPiamod/tabid/60/Default.aspx.

Cancer-Specific Mortality, All-Cause Mortality, and Population Data for the Back-Calculation Method

This analysis used US mortality data from the National Center for Health Statistics and US Census Bureau populations through 2018, both of which are available in the SEER*Stat software. We obtained US cancer-specific deaths for each cancer type, all-cause deaths, and populations from 1990-2018 by sex, single calendar year, single ages 0-84 years, and age group of 85 years or older. To project metastatic cancer prevalence into the future (2019-2025), we used the US Census Bureau July 1, 2016, population projections derived from the 2010 Census (8).

Survival Time from Metastatic Cancer

Survival time from metastatic cancer should reflect the mixture of survival after 1) de novo metastatic cancer and 2) recurrence to metastatic disease. Whereas survival from de novo metastatic cancer can be estimated from cancer registry data,

survival after metastatic recurrence requires external data and assumptions.

To estimate survival from de novo metastatic cancer, we calculated relative survival for individuals diagnosed with distant stage cancer between 2000 and 2017 in the SEER-18 areas for each cancer type. Relative survival was calculated by age group (0-49, 50-64, 65-74, 75-84 years) and year of diagnosis (2000-2005, 2006-2011, 2012-2017). Distant stage at diagnosis for cancers diagnosed between 1998 and 2017 was defined using summary stage 2000. We included only invasive cancers that were the first primary tumor (sequence number 0 or 1) and excluded cancers diagnosed through death certificate or autopsy and cases lost to follow-up at the month of diagnosis. Joinpoint survival models were used to assess changes in relative survival over time (9).
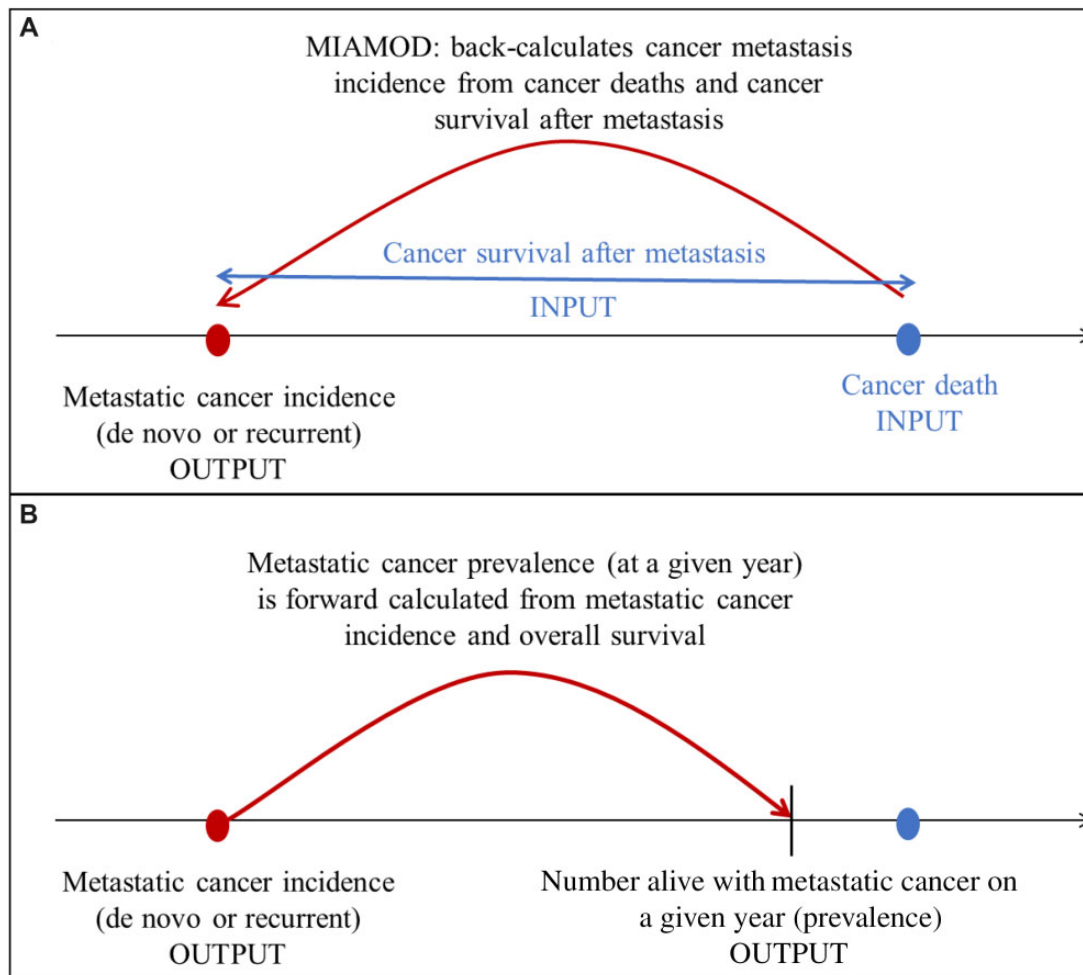
Data on survival after metastatic recurrence are largely unavailable for all cancer types considered except breast cancer. Thus, for bladder, colorectal, lung, melanoma, and prostate cancer, we assumed survival after metastatic recurrence following early stage diagnosis was equal to survival after de novo metastatic cancer. To estimate survival from breast cancer metastatic recurrence, we used an adjustment to de novo metastatic breast cancer survival reported in Mariotto et al. (5): recurrent metastatic survival = de novo metastatic survival$^{1.35}$. The adjustment was based on an MD Anderson Cancer Center study that showed, on average, the risk of death for recurrent relative to de novo metastatic breast cancer was 1.35 times higher (10). For breast cancer, survival from metastatic breast cancer was represented as a weighted sum of the de novo survival and recurrent survival: metastatic survival = w × (de novo metastic survival) + (1 − w) × (recurrent metastatic survival), with w = 0.2 (5). The weight was identified using the incidence-based mortality method, and further details can be found in Mariotto et al. (5).

Prevalence Projections and Estimates for All Ages

MIAMOD does not provide prevalence estimates for open age class intervals (eg, ages 85 years and older). To include survivors who are aged 85 years and older in the metastatic prevalence estimates, we assumed that the prevalence of metastatic cancer survivors aged 85 years and older is equal to the prevalence proportion among the oldest age category we are able to estimate (ages 80-84 years). The number of survivors aged 85 years and older living with metastatic cancer was calculated by multiplying the estimated prevalence proportion for ages 80-84 years and the number of individuals aged 85 years and older in the United States. This number was then added to the estimated number of metastatic cancer cases for those aged 0-84 years. Projections of the numbers of metastatic cancer cases from 2019 to 2025 assumed constant cancer mortality rates at 2018 levels, constant survival, and dynamic population size projections as estimated in the US Census Bureau population projections.

Prevalence of de Novo Metastatic Cancer Using the Counting Method

MIAMOD metastatic cancer prevalence estimates include both the prevalence of de novo and recurrent metastatic disease, and we are unable to distinguish them. To quantify how much of the total metastatic cancer prevalence represents survivors who had a recurrence to metastatic disease after an early stage

Figure 1. Illustration of MIAMOD back-calculation method. **A)** MIAMOD first back-calculates the incidence of metastatic cases (de novo or recurrent) diagnosed in a year from cancer deaths and cancer survival after metastasis. Cancer survival after metastasis is estimated from de novo metastatic survival and adjustments. **B)** The number of people living with metastatic cancer (ie, metastatic prevalence) is then estimated from the estimated metastatic cancer incidence and survival (overall) as Prevalence = ∑ Incidence × Survival. MIAMOD = Mortality Incidence Approach Model.

diagnosis, we also calculated the prevalence of de novo metastatic cancer using cancer registry data and the counting method. We first calculated 18-year limited duration prevalence on January 1, 2018, by race (White or Unknown, Black, and Other) and 5-year age groups using SEER*Stat for those diagnosed with distant stage cancer between 2000 and 2017 in SEER-18 areas. We then multiplied these prevalence proportions by the respective 2018 US populations by race and age and summed across race, age, and sex to obtain US de novo metastatic cancer prevalence for each cancer type.

Results

In 2018, the last year with observed SEER data, it is estimated that 623 405 individuals were living with metastatic breast, prostate, lung, colorectal, or bladder cancer, or metastatic melanoma, in the United States (Table 1). The percentage of metastatic cancer survivors initially diagnosed with early stage cancer who later experienced a metastatic recurrence ranged from 30% for lung cancer to 71.8% for bladder cancer (Figure 2). Most survivors with metastatic cancer of each type, except for melanoma, are estimated to have been living less than 5 years

with metastatic disease (range: 52.1% for melanoma to 78.8% for lung cancer). Almost 30% of individuals diagnosed with metastatic melanoma and one-fifth of individuals diagnosed with metastatic colorectal or metastatic breast cancer are estimated to have been living with metastatic disease for 10 or more years (Figure 3; Supplementary Table 1, available online).

By January 1, 2025, the following numbers of individuals are projected to be living with metastatic cancer in the United States: breast, 169 347; lung, 160 743; prostate, 156 812; colorectal, 149 840; melanoma, 38 691; and bladder, 18 019 (Table 2; Figure 4). For all cancer types except prostate, the metastatic cancer prevalence has increased linearly from 1990 to 2018, with the greatest percentage increase observed for melanoma (258%) and bladder cancer (62%) (Figure 4). The number of individuals living with metastatic cancer is projected to increase from 2019 to 2025 for breast, bladder, colorectal, and prostate cancer; conversely, the number of individuals living with metastatic cancer is projected to decrease for lung and melanoma over these 7 years.

One- and 5-year relative survival estimates and corresponding joinpoint survival model fits by cancer type for individuals diagnosed with de novo metastatic cancer in the SEER-18 areas are shown in Figure 5. Increases in 1- and 5-year relative survival are observed over time for all cancer types except bladder

Table 1. Estimates of deaths and incidence and prevalence of metastatic cancer including de novo and recurrent metastatic disease in the United States for 2018[a]

Cancer type	Number in US population in 2018	Number of cancer deaths		Number of new metastatic cancer cases (incidence)		Number of individuals living with metastatic disease on January 1, 2018 (prevalence)	
		Observed	Estimated	De novo (observed)	De novo and recurrence (estimated)	De novo (observed)	De novo and recurrence (estimated)
Lung and bronchus	326 687 501	142 211	142 069	95 723	148 533	121 943	174 090
Breast (female)	165 801 767	39 974	40 029	15 800	46 666	54 117	140 230
Colon and rectum	326 687 501	48 154	47 857	32 015	55 162	74 784	133 234
Prostate (male)	160 885 734	26 172	25 881	18 469	40 388	54 207	120 368
Melanoma	326 687 501	7693	7586	3928	9468	11 979	39 716
Bladder	326 687 501	14 193	14 140	4070	15 874	4446	15 767

[a]Estimates are presented for males and females together (all ages) unless otherwise specified.
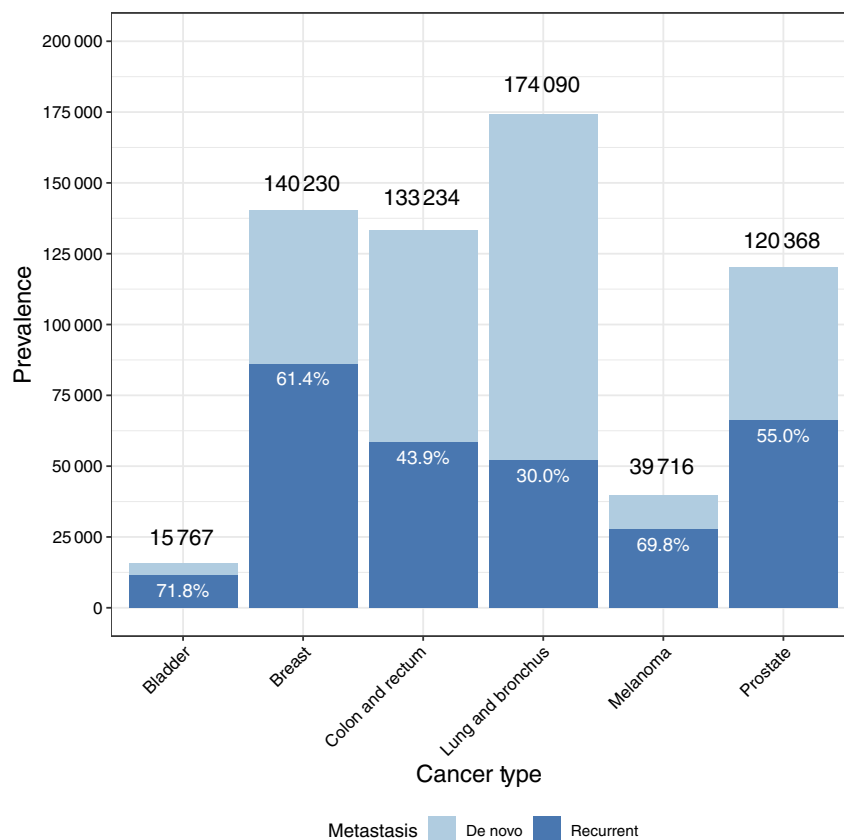
Figure 2. Percentages of estimated metastatic cancer cases (on January 1, 2018) who were initially diagnosed with metastasis (de novo) or who experienced recurrent metastatic disease after being initially diagnosed with early stage disease. Numbers above each bar represent total estimated metastatic prevalence for each cancer type.

cancer. For melanoma in particular, 1-year relative survival increased approximately 10% from 2000 to 2017, and 5-year relative survival increased almost 15% over the same period. One- and 5-year relative survival for the diagnosis periods 2000-2005, 2006-2011, and 2012-2017 are presented in Supplementary Tables 2 and 3 (available online), respectively.

Discussion

To our knowledge, this is the first study to report on the prevalence of individuals living in the United States with metastatic

cancer of the prostate, lung, colon and rectum, and bladder as well as metastatic melanoma; it also provides an update on the number of women living with metastatic breast cancer in the United States (5). Our study presents not only the overall number of metastatic cases for each cancer type but also the proportion of cases that arise from either de novo metastatic cancer or early stage cancer that later metastasizes. The prevalence counts for breast cancer differ slightly from those reported in Mariotto et al. (5). Mariotto et al. (5) calibrated the de novo metastatic prevalence estimated via MIAMOD to the de novo metastatic prevalence estimated via the counting method by
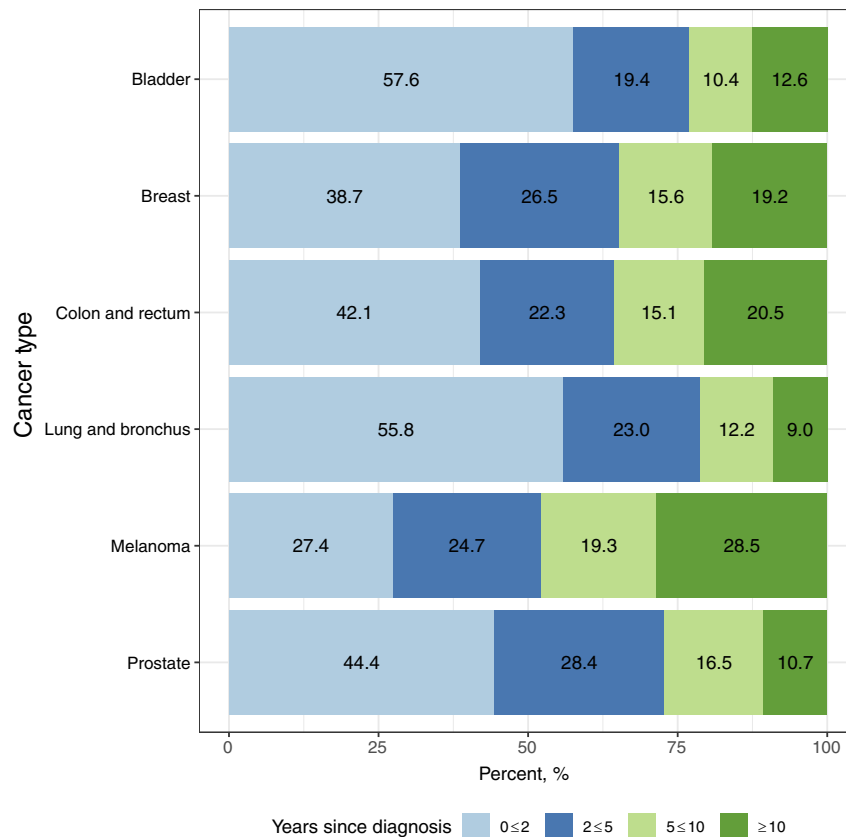
Figure 3. Percentage of estimated metastatic prevalence (on January 1, 2018) by years since diagnosis for each cancer type.

Table 2. Projections of deaths and incidence and prevalence of metastatic cancer including de novo and recurrent metastatic disease in the United States for 2025[a]

| Cancer type	Projected number in US population in 2025	Projected number of cancer deaths	Projected number of new metastatic (de novo and recurrence) cancer cases (incidence)	Projected number of individuals living with metastatic disease (de novo and recurrence) on January 1, 2025 (prevalence)
Lung and bronchus	344 114 571	104 363	110 132	160 743
Breast (female)	174 407 303	41 434	52 126	169 347
Colon and rectum	344 114 571	47 355	56 227	149 840
Prostate (male)	169 707 268	29 567	50 055	156 812
Melanoma	344 114 571	3900	4810	38 691
Bladder	344 114 571	14 826	16 720	18 019

[a]Estimates are presented for males and females together (all ages) unless otherwise specified.

adjusting metastatic survival in an ad hoc way. In our analysis, we did not calibrate the de novo metastatic prevalence estimate in this same way; the metastatic breast cancer prevalence estimate is based on the raw survival data.

Our findings indicate that, in general, the number of metastatic cancer survivors of the 6 cancer types examined have increased substantially since 1990, with the greatest percentage increases in melanoma and bladder cancer. For metastatic bladder cancer, the increase appears to be primarily because of an increased incidence of de novo metastatic diagnoses. For metastatic melanoma, the increase is likely due, in part, to the improvement in relative survival. In addition, the results show that a large percentage of cancer survivors living with metastatic disease were diagnosed with early stage cancer and later

experienced a recurrence or progression to metastatic disease. This finding highlights the need to identify methods to capture individuals diagnosed with early stage cancers who have a recurrence or progression to metastatic disease in cancer registries and electronic medical records. These types of methods would enable accurate counts of this unique group of cancer survivors as well as advance research pertaining to metastatic cancer survivorship.

Overall, the highest estimated prevalence of the cancer types examined was for metastatic lung cancer. Interestingly, it appears that the prevalence of individuals living with metastatic lung cancer may have peaked around 2016 and is beginning to decrease. This decrease may be because overall lung cancer mortality has been declining since the late 1980s and
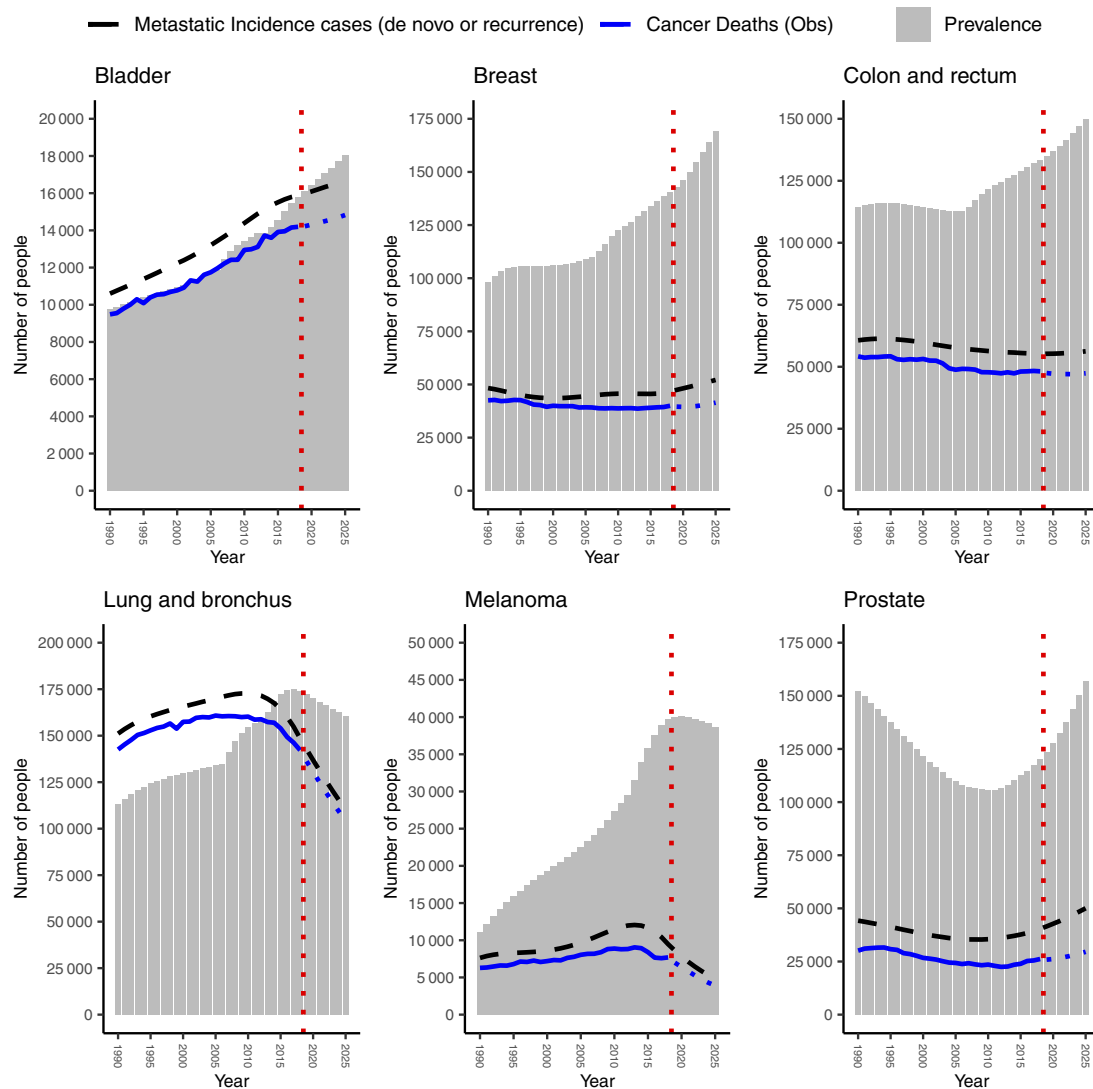
Figure 4. Estimates and projections of metastatic cancer incidence and prevalence for both sexes combined in the United States from 1990 to 2025 (**gray bars**) by cancer type. **Dashed black line** is estimated number of new incidence cases with metastatic cancer, including de novo and recurrent metastatic cancer. **Solid blue line** is observed number of cancer deaths (all stages) from 1990 to 2018. **Dotted blue line** is projected number of cancer deaths (all stages) from 2019 to 2025. **Dotted red line** indicates projections from 2019 to 2025.

more markedly in the most recent years (11). Distant stage incidence has also been declining (https://seer.cancer.gov/explorer/). These declines are not surprising, given the fact that low-dose computed tomography was endorsed by the US Preventive Services Task Force in 2013 for lung cancer screening among adults aged 55 to 80 years who have a 30 pack-year smoking history and are either currently smoking or have quit in the past 15 years (12). These recommendations were subsequently updated in 2021 (13). Use of low-dose computed tomography in this high-risk population has likely shifted the stage at diagnosis distribution, with more lung cancers being diagnosed at earlier stages (14). Treatments for metastatic lung cancer have also improved with the development and use of newer immunotherapies and targeted therapies (11), although findings from this study suggest that 5-year relative survival for individuals with metastatic lung cancer has improved only modestly, from 3% in 2000-2005 to 7% in 2012-2017.

For cancer of the breast, colon and rectum, prostate, and bladder, estimates for the number of individuals living with metastatic disease are projected to continue to rise, as they have been, for the most part, over the past 3 decades. In addition, many individuals with metastatic cancer of these types are living longer. For example, our findings show that approximately 30% of metastatic melanoma survivors and approximately one-fifth of metastatic breast and colorectal cancer survivors have lived 10 or more years postdiagnosis. Unfortunately, despite the growing numbers of individuals living with metastatic cancer and those living longer postdiagnosis, there remains a dearth of knowledge about the needs of these survivors (3). Knowledge gaps identified in a 2021 National Cancer Institute meeting on the topic of metastatic cancer survivorship include the trajectory and mechanisms of symptoms, particularly associated with newer therapies, experienced by individuals living with metastatic cancer; the

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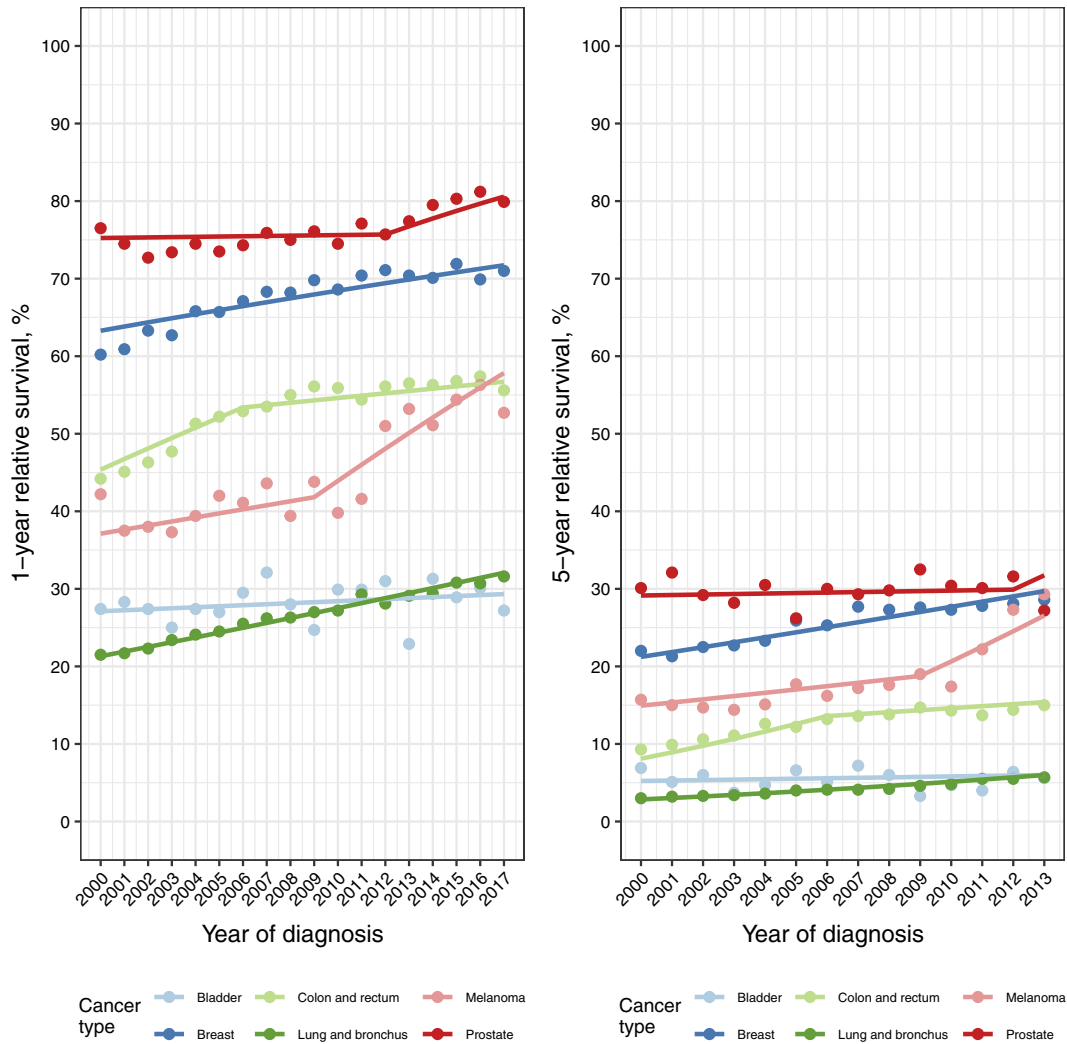
Figure 5. One-year and 5-year de novo metastatic relative survival (%) for each cancer type by year of diagnosis. **Solid points** correspond to cumulative relative survival. **Solid lines** correspond to predicted joinpoint survival model fits.

psychosocial needs for individuals living with metastatic cancer; and care patterns throughout the care trajectory (3). Filling these knowledge gaps is critical for delivering high-quality healthcare that addresses the needs of individuals living with metastatic cancer.

Several strengths of this study should be noted. The dataset used in the analysis was large and population based and included a long follow-up period, with the ability to compare survival estimates across multiple time periods. Further, consistent definitions of staging and other variables were used across time. The main limitation of this study is the absence of population-based survival estimates following progression to metastatic disease. Duplicating the method used in Mariotto et al. (5), we used a 1.35 higher risk of cancer death for recurrent metastatic breast cancer relative to de novo disease; however, this estimate was based on a single institution study (10). Had we instead assumed equal risk for recurrent metastatic breast cancer, it is likely that our prevalence estimate for metastatic cancer would be markedly higher. To our knowledge, there are no other studies for the other cancer types examined in this study comparing survival among individuals diagnosed with de novo vs recurrent disease; therefore, it was assumed

in the analysis that survival was the same for both. Population-based studies estimating differences in survival between de novo and recurrent metastatic disease for the cancers analyzed in this study are needed and would improve the accuracy of the prevalence estimates. Prevalence estimates are impacted by model inputs (which can be affected by certain events such as the introduction of curative therapies); our estimates are based on the available data and do not reflect future changes in treatment or screening.

The methods described in this manuscript assume that before dying of cancer, patients were diagnosed or advanced to metastatic cancer. Progression to metastasis refers to a worsening of the cancer and progressing to a later stage without the patient being ever cancer free. Recurrence refers to the return of the cancer after treatment and a disease-free period. The cancer can return to the same organ (local recurrence), lymph nodes (regional recurrence), or distant organs (metastatic recurrence). In this paper, we do not distinguish between progression to metastasis or metastatic recurrence. Use of the counting method to estimate de novo metastatic prevalence in combination with MIAMOD allows us to quantify the proportions of patients who are de novo and recurrent metastatic. However,

because of the lack of recurrence information in the SEER registries, it is difficult to determine whether any metastatic patients are disease free.

This study demonstrates the growing burden of metastatic cancer in the United States. Despite this growing burden, little is known about the needs of these survivors. Leveraging existing resources can help address research gaps in this understudied population; these resources include cancer registry–based datasets (eg, SEER-Medicare), foundation-based registries and datasets (eg, Susan Love Foundation Health of Women study), and electronic health record–based databases (eg, Flatiron, American Society of Clinical Oncology's CancerLinq). Importantly, future studies, including those using existing resources, should account for the heterogeneity of individuals living with metastatic cancer, even within cancer type, by collecting detailed data on demographic characteristics including race and ethnicity, disease state, underlying comorbid conditions, treatments, and symptoms to help better identify needs. Further, engaging patients and advocates, as well as other stakeholders, can ensure that the issues and experiences most important to them are accurately reflected in research as well as implementation efforts in the healthcare setting. This study is a first step toward a more comprehensive understanding of an understudied, and often medically underserved, cancer survivor population.

Funding

Notes

Data Availability

The data underlying this article are available through the National Cancer Institute's Surveillance, Epidemiology, and End Results Program at https://seer.cancer.gov/data-software/datasets.html and the U.S. Census Bureau at https://www.census.gov/data/datasets/2017/demo/popproj/2017-popproj.html.

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