

Premature Years of Life Lost Due to Cancer in the United States in 2017

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ABSTRACT

Background: Burden of cancer mortality is often measured by death counts or mortality rates, but potential years of life lost (PYLL) and PYLL per death may be more useful to estimate the impact of cancer-related deaths occurring at younger ages.

Methods: We used U.S. national death certificate data. A total of 45 categories of common cancers were grouped for cancer-specific calculations of PYLL and PYLL per death. PYLL was defined as the sum of the total years of life lost prior to age 75 years.

Results: The largest number of PYLL in 2017 was due to deaths from cancers of the lung/bronchus (891,313; 20.8%), colon/rectum (409,538; 9.6%), and breast (400,643; 9.4%). Cancers with the highest PYLLs generally also caused the largest number of deaths and had the highest mortality rates, with the exception of prostate

cancer (5.1% of deaths, 2.0% of PYLL). In contrast, PYLLs per death were greatest for deaths due to cancers of testis (mean = 34.0 years), bones/joints (26.4), and other endocrine sites including thymus (25.2).

Conclusions: Although PYLLs generally reflect mortality rates, they more heavily weigh cancers that occur at younger ages. In contrast, PYLL per death, which is an average quantification of life years lost for individual patients with cancer, shows a different pattern.

Impact: Mortality rates, PYLL, and PYLL per death are complementary measures of the burden of deaths due to cancer that should be considered in tandem to prioritize public health interventions focused on preventing premature mortality.

Introduction

Cancer is the second leading cause of death after heart disease in the United States with almost 600,000 deaths in 2017 (1). The greatest number of cancer-related deaths are due to cancers of the lung (21%), prostate (10%), and colorectum (9%) in men and the lung (24%), breast (15%), and colorectum (9%) in women. Cancer-related death rates increase with age with 30% of all cancer-related deaths occurring among ≥ 80 -year-olds. Moreover, cancer is the leading cause of death in individuals < 80 years old (1, 2).

Cancer mortality rates provide critical information on the absolute burden of cancer and progress in cancer prevention and control over time. However, these estimates are disproportionately weighted toward deaths occurring at very old ages, the age range where cancer mortality is the greatest. Other metrics of mortality can be used to estimate the impact of cancer on deaths occurring at younger ages (i.e., premature deaths), such as potential years of life lost (PYLL), an estimate of the average years a person would have lived if he or she had not died prematurely. This metric more heavily weights deaths at younger ages, indirectly highlighting loss of economic productivity, social contribution, and family stability (3). In addition, PYLL per cancer-related death is a metric that highlights the enormous loss of life due to deaths from certain cancers that occur at younger ages, even if they occur infrequently.

These metrics are important for quantifying the impact of premature cancer-related deaths in the U.S. population and should be considered in parallel with cancer-related death rates. In this study, we estimated PYLL and PYLL per death by cancer site in 2017 using nationwide death certificate data, and also examined these estimates by sex, race/ethnicity, and calendar year.

Materials and Methods

Data sources

We utilized U.S. mortality and racial/ethnic data for years 1990 and 2017 from death certificates from the U.S. National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC). Causes of death were defined according to the International Classification of Diseases, 10th Revision, and categorized by the Surveillance, Epidemiology, and End Results (SEER) Cause of Death Recode (4). Of the 85 causes of cancer-related deaths of all ages, less common cancers were grouped by organ site and 45 categories were chosen for presentation (Supplementary Table S1). Calculations for all 82 causes of cancer-related deaths are also provided in Supplementary Table S2. Population data were from the U.S. Census Bureau. Estimates for American Indians and Alaska Natives were restricted to counties in Purchased/Referred Care Delivery Areas to reduce racial misclassification (5).

Statistical analysis

Absolute death counts, mortality rates, PYLLs, and PYLL per death are presented. The 2000 U.S. standard population was used to estimate age-standardized cancer-related death rates. We estimated PYLL for each cancer type and population [i.e., sex (male and female), race/ethnicity (non-Hispanic Whites, NHW; Hispanics; non-Hispanic Blacks, NHB; Asian or Pacific Islanders, API; and American Indians/Alaska Natives, AIAN), and years (2017 and 1990)] by using the following formula:

$$PYLL = \sum_{i=0}^{age\ 75} (\text{number of deaths at age}_i) * (75 - i)$$

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

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PYLL was defined as the number of years of life lost prior to age 75 years, a commonly used reference age for many studies. Calculations using a set age allow for a uniform comparison across sex, race/ethnicity, and calendar year. In addition, PYLL per death for age less than 75 was calculated by dividing PYLL by the total number of deaths for each cancer type. As a sensitivity analysis, we have also used age 78.6 years as the reference age, which is the current, as of year 2017, average life expectancy in the United States (6).

Results

In 2017, there were 599,099 cancer-related deaths in the United States (age-standardized rate of 152.7 per 100,000 across all age

groups). The highest cancer mortality rates were due to cancers in the lung/bronchus, colon/rectum, pancreas, breast, and prostate (Table 1).

PYLL

In 2017, cancer-related deaths resulted in 4,280,128 PYLL prior to age 75 years in the United States (Table 1). The largest contributors to PYLLs were deaths due to cancers of the lung/bronchus (21%), colon/rectum (10%), breast (9%), pancreas (7%), and liver/intrahepatic bile duct (5%), totaling 52% of the overall PYLL. Rankings based on cancer mortality rates were similar to rankings based on PYLL, with a few exceptions, including prostate and urinary bladder cancers that are

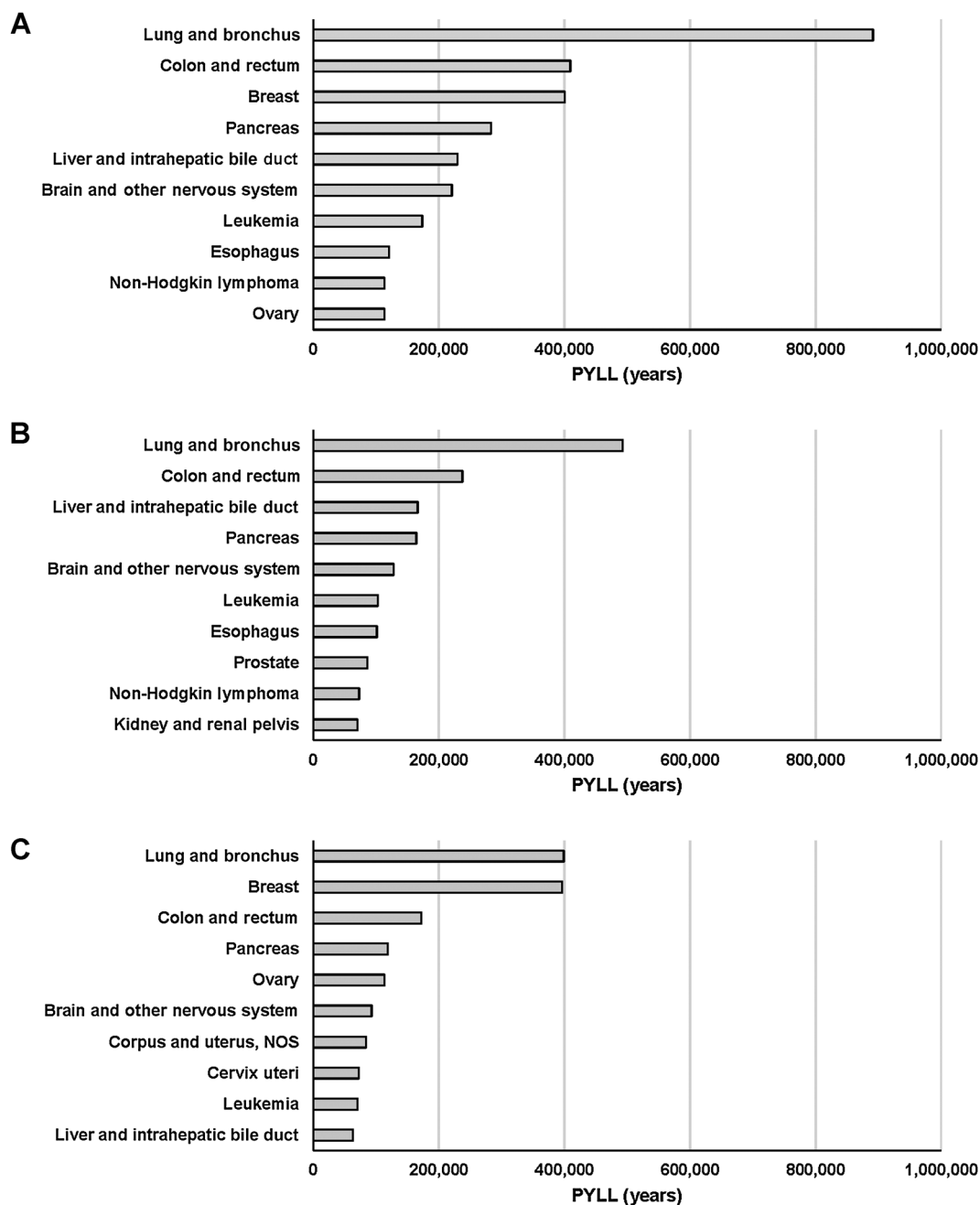
Table 1. Cancer-related deaths, rate, and PYLL in both men and women (year 2017).

Cancer sites	Death counts			Mortality rate			PYLL			PYLL per death	
	Count	%count	Rank	ASR ^a	ASR%	Rank	Years	%	Rank	Years	Rank
Lung and bronchus	145,849	24.3	1	36.7	24.0	1	891,313	20.8	1	9.9	39
Colon and rectum	52,547	8.8	2	13.5	8.8	2	409,538	9.6	2	13.3	17
Pancreas	44,011	7.3	3	11.1	7.3	3	282,886	6.6	4	10.6	37
Breast	42,510	7.1	4	11	7.2	4	400,643	9.4	3	14.5	11
Prostate	30,486	5.1	5	7.8	5.1	5	85,979	2.0	14	7.6	45
Liver and intrahepatic bile duct	27,104	4.5	6	6.6	4.3	6	229,777	5.4	5	11.9	26
Leukemia	23,527	3.9	7	6.2	4.1	7	173,629	4.1	7	14.7	9
Non-Hodgkin lymphoma	20,459	3.4	8	5.3	3.5	8	113,792	2.7	9	11.5	27
Brain and other nervous system	16,804	2.8	9	4.4	2.9	9	221,026	5.2	6	17.3	7
Urinary bladder	16,657	2.8	10	4.3	2.8	10	59,566	1.4	20	9.1	42
Esophagus	15,321	2.6	11	3.8	2.5	11	120,895	2.8	8	11.4	29
Ovary	14,193	2.4	12	3.6	2.4	12	113,695	2.7	10	12.4	21
Kidney and renal pelvis	13,959	2.3	13	3.6	2.4	13	101,928	2.4	11	12.0	25
Myeloma	12,322	2.1	14	3.2	2.1	14	60,873	1.4	19	9.6	40
Stomach	11,158	1.9	15	2.9	1.9	15	95,950	2.2	12	14.0	15
Corpus and uterus, NOS	10,994	1.8	16	2.7	1.8	16	83,930	2.0	15	11.3	31
Oral cavity and pharynx	10,126	1.7	17	2.5	1.6	17	90,344	2.1	13	12.8	18
Melanoma of the skin	8,056	1.3	18	2.1	1.4	18	69,183	1.6	17	14.1	13
Soft tissue including heart	4,970	0.8	19	1.3	0.9	19	68,555	1.6	18	19.4	5
Cervix uteri	4,207	0.7	20	1.2	0.8	20	73,014	1.7	16	20.7	4
Nonmelanoma skin	4,042	0.7	21	1	0.7	21	21,457	0.5	23	11.5	28
Larynx	3,708	0.6	22	0.9	0.6	22	29,742	0.7	22	11.4	30
Gallbladder	2,195	0.4	23	0.6	0.4	23	14,212	0.3	25	11.1	33
Thyroid	1,892	0.3	24	0.5	0.3	24	12,818	0.3	27	12.1	23
Other biliary	1,843	0.3	25	0.5	0.3	25	10,863	0.3	31	10.7	36
Bones and joints	1,725	0.3	26	0.5	0.3	26	31,193	0.7	21	26.4	2
Small intestine	1,682	0.3	27	0.4	0.3	27	12,238	0.3	28	12.5	20
Other digestive organs	1,471	0.2	28	0.4	0.3	28	10,257	0.2	32	12.2	22
Vulva	1,262	0.2	29	0.3	0.2	29	6,738	0.2	34	11.3	32
Anus, anal canal, and anorectum	1,169	0.2	30	0.3	0.2	30	11,671	0.3	29	13.9	16
Other endocrine including thymus	1,076	0.2	31	0.3	0.2	31	20,971	0.5	24	25.2	3
Hodgkin lymphoma	1,009	0.2	32	0.3	0.2	32	11,580	0.3	30	18.1	6
Peritoneum, omentum, and mesentery	1,008	0.2	33	0.3	0.2	33	6,268	0.1	35	11.0	34
Other female genital organs	897	0.1	34	0.2	0.1	34	7,031	0.2	33	12.1	24
Nose, nasal cavity, and middle ear	579	0.1	35	0.2	0.1	35	5,428	0.1	36	14.6	10
Other urinary organs	493	0.1	36	0.1	0.1	36	2,020	0.0	42	9.5	41
Ureter	435	0.1	37	0.1	0.1	37	1,215	0.0	43	8.0	44
Testis	425	0.1	38	0.1	0.1	38	13,448	0.3	26	34.0	1
Vagina	411	0.1	39	0.1	0.1	39	2,157	0.1	41	10.9	35
Penis	352	0.1	40	0.1	0.1	40	2,828	0.1	38	14.1	14
Eye and orbit	331	0.1	41	0.1	0.1	41	3,096	0.1	37	14.2	12
Pleura	319	0.1	42	0.1	0.1	42	1,102	0.0	44	8.0	43
Trachea, mediastinum, and other respiratory organs	291	0.0	43	0.1	0.1	43	2,760	0.1	39	15.2	8
Retroperitoneum	289	0.0	44	0.1	0.1	44	2,464	0.1	40	12.8	19
Other male genital organs	68	0.0	45	0.0	0.0	45	416	0.0	45	10.1	38

Note: Cancer sites sorted by largest to smallest counts in total death counts in men and women.

Abbreviations: ASR, age-standardized rate; NOS, not otherwise specified.

^aMortality rate: per 100,000.

**Figure 1.**

Top 10 PYLL cancers in each population group, overall (A), in men (B), and in women (C; year 2017). NOS, not otherwise specified.

common causes of cancer-related deaths (rank 5 and 10, respectively), but result in fewer PYLL relative to other cancer sites (rank 14 and 20, respectively; Supplementary Fig. S1).

In both men and women, lung cancer-related deaths resulted in the greatest number of PYLL before age 75 in 2017 (Fig. 1; Supplementary Table S3A and S3B). PYLLs were generally higher in men compared with women with the exception of cancers of the gallbladder (4,743 in males vs. 9,469 in females), anus/anal canal and anorectum (5,002 vs. 6,669), and peritoneum/omentum and mesentery (1,545 vs. 4,723). PYLL ranks were also similar between men and women. Compared

with women, men had a higher proportion of PYLL due to deaths from cancers of the liver/intrahepatic bile duct (8% in males vs. 3% in females), esophagus (5% vs. 1%), and lung/bronchus (21% vs. 19%). Deaths due to female-specific cancers (female breast, cervix uteri, corpus/uterus, ovary, vagina, vulva, and other female organs) accounted for 33% of PYLL in women, and deaths due to male-specific cancers (prostate, testis, penis, and other male genital organs) accounted for 5% of PYLL in men.

While 78% of all cancer-related deaths occurred among NHW in 2017, a smaller fraction (70%) of all PYLL due to cancer occurred

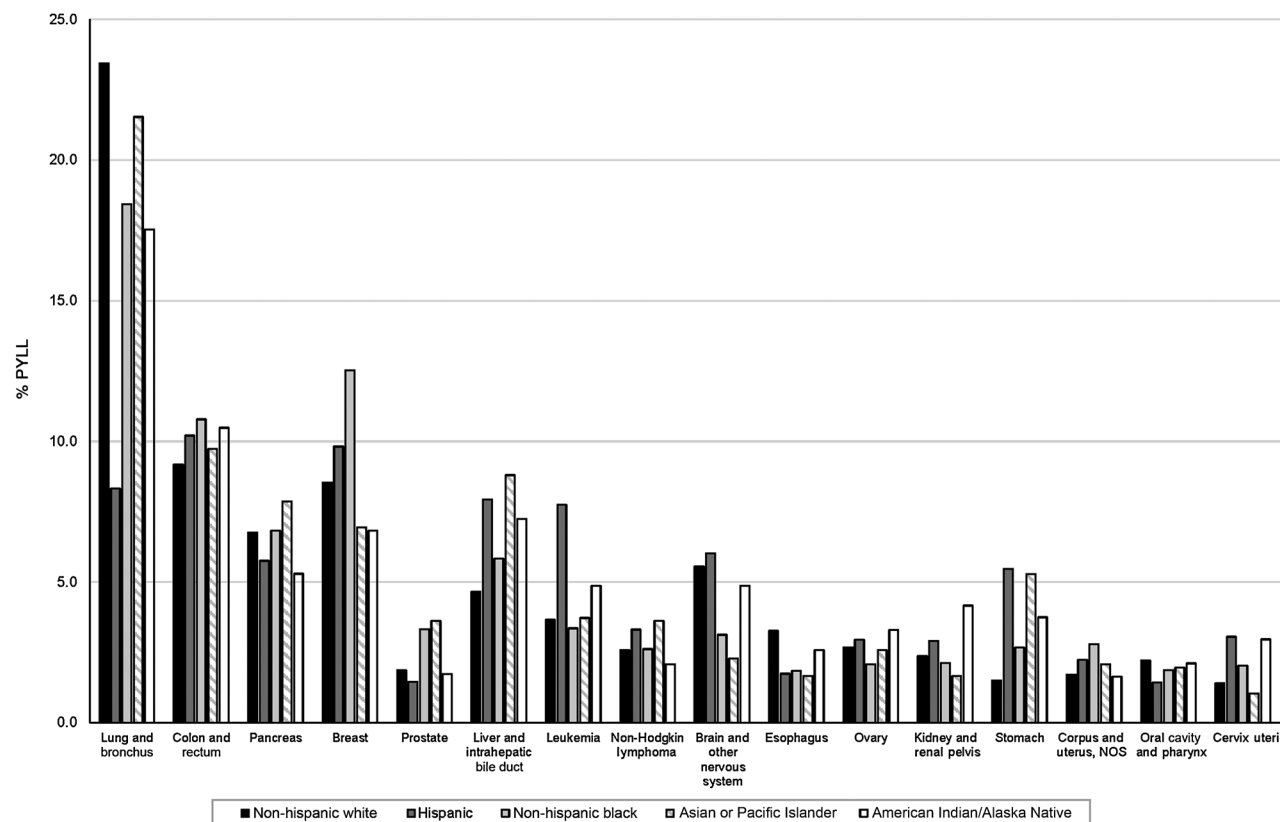


Figure 2.

Top 10 PYLL cancers by race/ethnicity (year 2017). %PYLL calculated within each race/ethnic group. Top 10 PYLL cancers of each race/ethnicity were combined for a total list of 16 cancer types (sorted by largest to smallest counts in total death counts in men and women). NOS, not otherwise specified.

among NHW, whereas other racial/ethnic groups contributed a higher fraction of PYLL than deaths: Hispanics (10% of all PYLL vs. 7% of all cancer-related deaths), NHB (15% vs. 12%), API (4% vs. 3%), and AIAN (0.55% vs. 0.39%). Within each race/ethnic group, lung/bronchus cancer-related deaths caused the largest number of PYLLs, with the exception of Hispanics (rank 3), where colorectal cancer-related deaths caused the largest number of PYLLs (Fig. 2; Supplementary Table S4; Supplementary Fig. S2). Lung/bronchus cancers caused 23% of cancer-related PYLLs in NHW, 18% in NHBs, 18% in AIANs, 16% in APIs, and 8% in Hispanics. The largest fraction of PYLL due to colorectal cancer was observed among NHB (11% of all PYLL in NHB) and the smallest in NHW (9%), and the largest fraction of PYLL due to breast cancer was observed among NHB (13%) and the smallest in AIAN (7%). For PYLL due to pancreatic cancer, the fraction was largest in NHW (7%) and smallest in AIAN (5%).

Overall, PYLL for all cancer-related deaths increased from 4,262,397 in 1990 (20.5% of all PYLL) to 4,280,128 in 2017 (19.3% of all PYLL; Fig. 3; Table 1; Supplementary Tables S5–S7; Supplementary Fig. S3). As the concurrent cancer mortality rates decreased from 214.9 to 152.7 per 100,000, the increase in PYLLs is driven by the growth of the U.S. population. The proportion of total PYLLs caused by cancer-related deaths decreased among men, women, and NHWs, indicating that PYLLs due to other causes grew more rapidly over this time period. However, the fraction of total PYLLs due to cancer increased in other racial/ethnic groups (Supplementary Table S8).

The largest increases in the number of PYLL between 1990 and 2017 were for deaths due to cancers of the liver/intrahepatic bile duct (72,873 to 229,777; 1.7% to 5.4% of total PYLLs due to cancer), pancreas (166,039 to 282,886; 3.9% to 6.6%), and colon/rectum (347,317 to 408,754; 8.1% to 9.4%), whereas the largest PYLL decreases were for deaths due to cancers of the lung/bronchus (1,176,860 to 891,313; 27.6% to 21.4%), breast (489,491 to 400,643; 11.5% to 9.4%), and non-Hodgkin lymphoma (174,224 to 113,792; 4.1% to 2.7%).

PYLL per death

In 2017, an average of 12 years of life before age 75 was lost per cancer-related death (mean = 11.6 years for men and 12.5 years for women; Fig. 4; Table 1). Cancer sites with the largest number of PYLL per death differed from those with the largest overall number of PYLL before age 75. The highest PYLLs per death were for cancers of the testis (mean = 34.0 years), bones/joints (26.4 years), other endocrine sites including thymus (25.2), cervix uteri (20.7), and soft tissue including heart (19.4 years/death).

Overall ranks of PYLL per death for sex nonspecific cancers were similar among men and women (Supplementary Table S3; Supplementary Fig. S1). Largest differences of PYLL per death by sex were observed for trachea/mediastinum/other respiratory organs (difference = 2.7 years; mean = 16.1 in men vs. 13.4 in women), anus/anal canal/anorectum (1.7; 14.9 vs. 13.3), and peritoneum/omentum/mesentery (1.6; 12.3 vs. 10.6).

PYLL per death for all cancers was highest in Hispanics (mean = 15.9 years), followed by API (14.3), AIAN (13.8), NHB (13.4), and

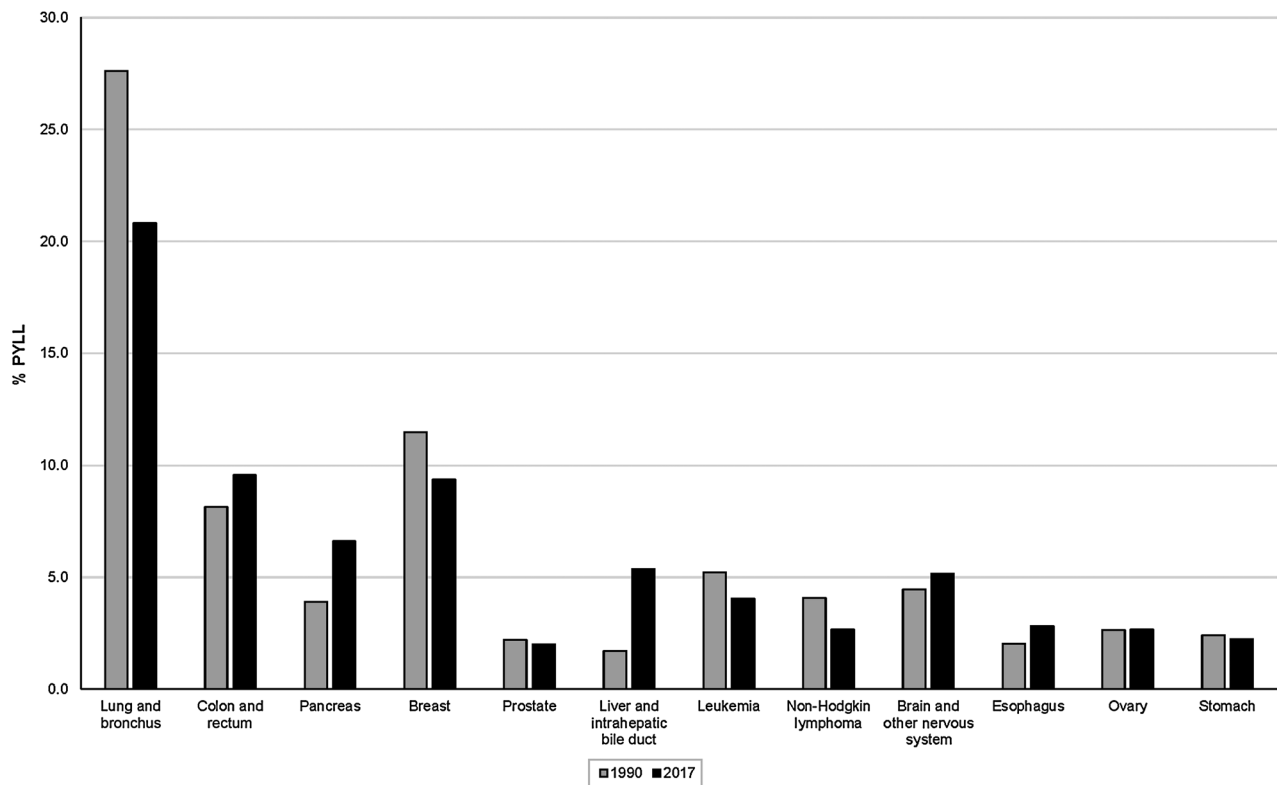


Figure 3.

Top 10 PYLL cancers in year 2017 versus 1990. %PYLL calculated within each year. Top 10 PYLL cancers of each year were combined for a total list of 12 cancer types (sorted by largest to smallest counts in total death counts in men and women).

NHW (11.2), reflecting a younger age at cancer-related death in some racial/ethnic groups (Fig. 2; Supplementary Table S9; Supplementary Fig. S2). The highest ranking cancer for PYLL per death was testis for all race/ethnic groups, except for AIAN, for which it was cancers of bones/joints. However, PYLL per death due to testicular cancer varied substantially across race/ethnicity, with the largest number of PYLL per death observed among APIs (47.1 years) and the lowest among NHW (30.7 years). In general, the PYLL per death has decreased for most cancer sites over time (mean = 12.8 years in 1990 to 12.0 in 2017; Table 1; Supplementary Table S5; Supplementary Fig. S3). Large decreases of PYLL per death were observed for cancers such as Hodgkin lymphoma (mean = 28.5 to 18.1 years), cancer in other endocrine sites including thymus (34.8 to 25.2), and eye/orbit (20.2 to 14.2).

From 1990 to 2017, a total of 10 cancers had increased PYLL per death, including deaths due to cancers of the colon/rectum (10.9 to 13.3 years per death), stomach (12.1 to 14.0), penis (12.4 to 14.1), other digestive tract (11.0 to 12.2), and corpus/uterus, not otherwise specified (NOS; 10.4 to 11.3; Table 1; Supplementary Table S5; Supplementary Fig. S3). PYLL and PYLL per death by sex and race/ethnicity for the year 1990 are presented in Supplementary Tables S7 and S10.

Sensitivity analysis with 78.6 as reference age

Recalculation using the current average life expectancy of 78.6 years in the United States for year 2017 data renders an increase of PYLL by 1,361,932 years (from 4,280,128 to 5,642,060 years) and an increase of PYLL per death by 1.9 (from 12.0 to 13.9). However, most of the cancer sites maintained rank within two places, with 30 of 45 cancers with no change in ranks (Supplementary Table S11).

Discussion

Using nationwide death certificate data, this study reported two measures of PYLL due to cancer in the United States, for 45 cancer types by sex, race/ethnicity, and calendar years. In 2017, the largest number of PYLL occurred in cancers of the lung/bronchus, colon/rectum, and breast, whereas the largest number of PYLL per death were in cancers of testis, bones/joints, and other endocrine sites including thymus. The total PYLLs before age 75 in the United States has increased despite decreasing cancer mortality rates between 1990 and 2017, reflecting population growth.

National estimates of cancer-related deaths and death rates are critical to assess progress in cancer prevention and control. However, PYLLs and PYLL per death are complementary metrics that emphasize the impact of cancer on premature deaths by more heavily weighting cancer-related deaths that occur at younger ages. The largest contributors to PYLL before age 75 in the United States are the same cancer sites that contribute the largest number of deaths, cancers in lung/bronchus, colon/rectum, breast, pancreas, and liver. However, not all cancer burden estimates are similar across different metrics. Some cancers like prostate cancer rank high in mortality rate, but lower in PYLL, whereas some cancers like testicular cancer rank low in mortality rate, but higher in PYLL. These discrepancies arise due to the differences in age at death. The median age at prostate cancer-related death is around 80 years (7), whereas the median age at testicular cancer-related death is around 42 years (8). The effect of age on cancer burden is accentuated in PYLL per death calculations, where testicular cancer ranks first and prostate cancer last.

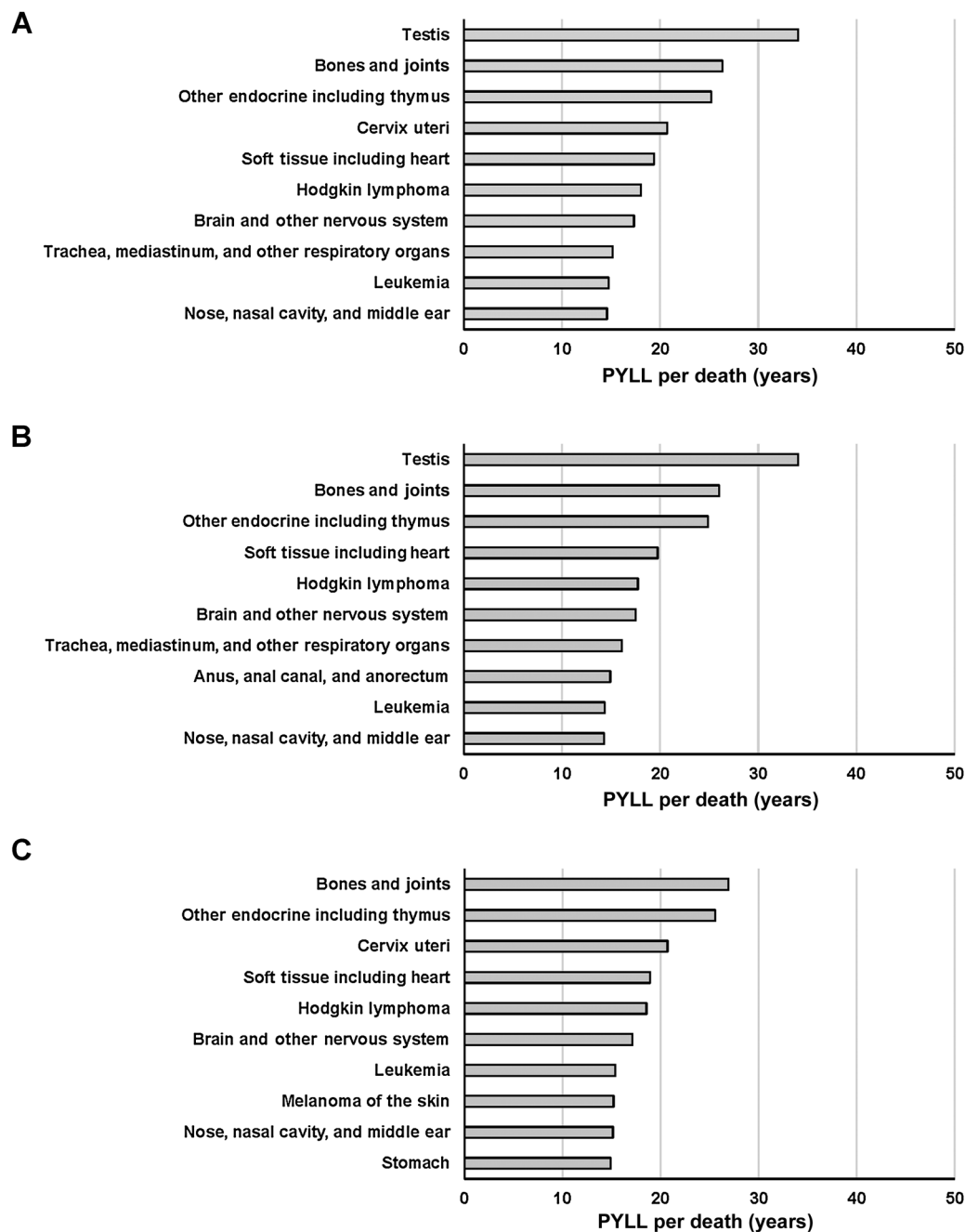


Figure 4. Top 10 PYLL per death cancers overall (A), in men (B), and in women (C; year 2017).

Cancer burden by sex shows some differences across metrics. While men have higher cancer mortality rates and PYLL due to cancer compared with women overall, women have an excess of almost 1 year of life lost due to a cancer of any type that occurred in 2017. The excess PYLL in women is partially driven by deaths due to female-specific cancers occurring at earlier ages. For example, female breast cancer-related deaths occur at median age of 68 years and cervical cancer-related deaths occur at a median of 58 years (9, 10). Moreover, some cancers show higher PYLL per death for one sex over the other despite the lower mortality rate and/or PYLL. An example is melanoma of the

skin, where mortality rate is more than double among men (3.1 per 100,000) as compared with women (1.3 per 100,000), but PYLL per death is almost 2 years higher in women (15.2 years) as compared with men (13.5).

Differences in PYLL due to cancer and PYLL per cancer-related death were also observed by race/ethnicity. Overall, a disproportionately high number of PYLL occurred among minority populations compared with NHWs, and the PYLL per death was greatest among Hispanics and API, suggesting that non-NHW populations are dying from cancer at younger ages than NHWs in the United States. This

could reflect poorer survival among certain racial/ethnic groups (11, 12), as well as a higher burden of cancer types that occur at younger ages. Disparities in particular cancer sites were also observed, for instance, prostate cancer ranked similar in mortality rate across different race/ethnic groups, but NHB men had much higher proportion of PYLL due to prostate cancer compared with other groups, highlighting a younger age at death among this group (13).

The change in PYLL due to cancer between 1990 and 2017 is driven by a combination of changes in cancer-related death rates and increases in the size and changes in the demographics of the U.S. population. Therefore, there was an increase in the total PYLL due to cancer-related deaths, despite declining mortality rates, which is driven by the growth and aging of the U.S. population (14). Specifically, the population under age 75 years has grown from 239 to 304 million between 1990 and 2017 in the United States, with increase of 11 million in 65- to 74-year-old individuals (15). The largest reduction in PYLLs over time was observed for cancers of the lung/bronchus, reflecting strongly decreasing lung cancer-related death rates driven by declining smoking prevalence (16). The largest increase in PYLL was in cancers of liver/intrahepatic bile duct driven by a rising mortality rate for liver/intrahepatic bile duct cancers and the growth of the population (17). A notable increase in PYLL per death for cancers in colon/rectum and stomach between 1990 and 2017 is likely due to the increasing death rates at younger ages for these two cancer sites (18, 19).

Approaches for calculating PYLL vary across studies (3). A fixed age of 75 years was used as the life expectancy in this study to provide a consistent benchmark for defining premature death. Often PYLLs are calculated on the basis of demographic group, birth cohort, and year-specific life expectancy estimates; however, this approach would estimate fewer PYLLs in groups with lower life expectancy, deemphasizing the importance of premature cancer-related death in these groups. The SEER Cancer Statistics Review report estimated that approximately 9.3 million PYLLs due to cancer occurred in 2017 (20). This estimate is far higher, as it takes into account each individual's probability of surviving to a certain age based on age, race, and sex. By setting our benchmark at 75, we are more strongly focusing on premature deaths. In addition, age 75 is a benchmark for PYLL calculations that has been widely used by international health agencies, including the U.S. CDC (21), the United Kingdom National Health Service (22), and the Canadian government (23), allowing for a direct comparison with our work. Finally, using the average life expectancy in the United States in PYLL calculation resulted in little difference in ranking across cancer sites.

PYLL depends on many factors including risk factors, cancer screening, cancer treatment, and competing risks of other deaths. However, because our study is descriptive, we focused on the overall patterns. In addition, other components of disease burden, such as disability-adjusted life years, are not provided. This study relies on cause of death reported on death certificates, which are known to imperfectly capture cause of death. Death certificates are also known to have racial/ethnic misclassification (24), particularly for AIANs. To

mitigate this problem, we have restricted our analysis of AIANs to those living within Purchased/Referred Care Delivery Areas of the country. This approach limits misclassification, but also excludes AIANs living in other parts of the country. In addition, death certificate data available from NCHS combine Asians and Pacific Islanders, two groups with very different health profiles.

No single index may sufficiently quantify the social and economic impact of cancer mortality in a society. Many cancer-related deaths occur in the elderly, thus relying on the absolute counts may obscure the importance of cancer at younger ages. Age-standardized mortality rates incorporate age structure of the population, but fail to capture the magnitude of the impact stemming from the deaths at young ages. PYLL integrates age at death, emphasizing the "premature" component due to the death, and can be used as a public health goal to maximize the "natural" lifespan of those individuals (3). PYLL per death takes a step further and quantifies the burden of that specific cancer-related death at the individual level. Therefore, although both PYLL and PYLL per death give greater weight to cancers that affect younger populations, their measurements serve different purposes. PYLL is a public health metric that can be used to quantify premature cancer-related deaths at a population level (25). PYLL per death provides an average quantification of life years lost for individual patients with cancer.

When considering the burden of cancer mortality in the United States, it is important to consider not only the absolute number of cancer-related deaths, but also the age at which those deaths occur. Here, we observed that lung cancer contributed the largest number of PYLL and testicular cancers result in the largest number of PYLL per death. Mortality rates, PYLL, and PYLL per death are complementary measures of cancer-related death that should be considered in tandem. PYLL and PYLL per death provide quantification of premature mortality that can be utilized to prioritize public health interventions focused on preventing premature deaths.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

M. Song: Conceptualization, data curation, formal analysis, visualization, methodology, writing—original draft, writing—review and editing. **A. Hildesheim:** Conceptualization, supervision, methodology, writing—review and editing. **M.S. Shiels:** Conceptualization, data curation, supervision, visualization, methodology, project administration, writing—review and editing.

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