original reports abstract

Chronic Comorbidities Among Survivors of Adolescent and Young Adult Cancer

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PURPOSE To describe the incidence, relative risk, and risk factors for chronic comorbidities in survivors of adolescent and young adult (AYA) cancer.

METHODS This retrospective cohort study included 2-year survivors of AYA cancer diagnosed between age 15 and 39 years at Kaiser Permanente Southern California from 2000 to 2012. A comparison cohort without cancer was individually matched (13:1) to survivors of cancer on age, sex, and calendar year. Using electronic medical records, all participants were followed through December 31, 2014, for chronic comorbidity diagnoses. Poisson regression was used to evaluate the association between cancer survivor status and risk of developing each comorbidity. The associations between cumulative exposure to chemotherapy and radiation therapy and selected comorbidities were examined for survivors of cancer.

RESULTS The cohort included 6,778 survivors of AYA cancer and 87,737 persons without a history of cancer. The incidence rate ratio (IRR) for survivors of cancer was significantly increased for nearly all comorbidities examined. IRR ranged from 1.3 (95% CI, 1.2 to 1.4) for dyslipidemia to 8.3 (95% CI, 4.6 to 14.9) for avascular necrosis. Survivors of AYA cancer had a 2- to 3-fold increased risk for cardiomyopathy, stroke, premature ovarian failure, chronic liver disease, and renal failure. Among survivors of cancer, significant associations between chemotherapy and radiation therapy exposures and late effects of cardiomyopathy, hearing loss, stroke, thyroid disorders, and diabetes were observed from the multivariable analyses. Forty percent of survivors of AYA cancer had multiple (≥ 2) comorbidities at 10 years after index date, compared with 20% of those without cancer.

CONCLUSION Risk of developing comorbidities is increased in survivors of AYA cancer compared with the general population. Specific cancer treatment exposures were associated with risk of developing different comorbidities. These findings have important implications for survivorship care planning and patient education.

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INTRODUCTION

The incidence of cancer in adolescents and young adults (AYAs) has been increasing over the past 25 years.[1,2] With an annual incidence of > 70,000 cases[3] and 5-year survival exceeding 80%,[4,5] the number of survivors of AYA cancer living in the United States is estimated to be > 633,000 and will continue to grow.[6] Like survivors of childhood cancer, survivors of AYA cancer are at risk for late effects of cancer treatments; the detrimental impact of these late effects on years and quality of life lost can be substantial.[7-10]

Although extensive research has described the risk of chronic comorbidities among survivors of childhood cancer,[11-13] these data may not be applicable to survivors of cancers diagnosed later in life. The risk and risk factors for comorbidities may vary across age groups as a result of differences in primary cancers, treatment exposures, age at exposures, and background incidence.[14] There is a paucity of longitudinal data on the absolute and relative magnitude of risk for chronic health problems in survivors of AYA cancer. Moreover, there have been no studies to describe the specific risks to subgroups of survivors defined by demographic characteristics and cancer treatment exposures. This lack of high-quality data for AYAs with cancer has impeded the development of evidence-based early screening recommendations and interventions to limit the adverse impact of cancer and its treatment in these survivors.

To address these gaps in the literature, we evaluated the development of chronic comorbidities in survivors of AYA cancer who were members of Kaiser Permanente Southern California (KPSC) using a matched cohort design. We used an internal noncancer comparison cohort with similar demographics, socioeconomic

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

The number of survivors of adolescent and young adult (AYA) cancer, defined as cancer diagnosed in a person between age 15 and 39 years, is estimated to be > 633,000 in the United States and will continue to grow. Although extensive research has described the risk of chronic comorbidities among survivors of childhood cancer, such data on survivors of AYA cancer remain sparse. This study characterized the incidence, relative risk, and risk factors for chronic comorbidities in survivors of AYA cancer.

Knowledge Generated

Survivors of AYA cancer have increased risk of developing a wide array of chronic comorbidities compared with matched individuals without a history of cancer. Specific treatment exposures, including chemotherapy and radiation therapy, are associated with increased risk of late effects in multiple organ systems among survivors of AYA cancer.

Relevance

Data from this study may help provide much-needed information for the development of personalized survivorship care plans for survivors of AYA cancer.

status, and access to health care and took advantage of detailed treatment and diagnosis data from electronic medical records.

METHODS

Study Setting and Study Population

KPSC is an integrated health care organization that provides comprehensive health services to > 4.4 million racially, ethnically, and socioeconomically diverse members who are broadly representative of residents in southern California.[15] KPSC has high membership retention; we have shown that among AYAs diagnosed with cancer, 77% and 62% remain KPSC members 5 and 10 years after diagnosis, respectively.[16]

We identified survivors of AYA cancer using KPSC's SEER-affiliated cancer registry. KPSC members who met the following criteria were included in the cohort of survivors of AYA cancer: diagnosed with invasive cancer at age 15-39 years between 2000 and 2012 at KPSC; survived ≥ 2 years (index date) after cancer diagnosis (being cancer free at 2 years was not required); and retained KPSC membership at index date. We used 2-year survival as the cutoff for study inclusion because our goal was to characterize health outcomes after the completion of active treatment, and the majority (> 90%) of our AYA cancer cohort completed treatment within 2 years. In addition, the 2-year time point represented a junction whereby survivors are most likely transitioned from active therapy to long-term follow-up programs or to their primary care providers. Survivors diagnosed with another primary cancer before the index date were excluded.

KPSC members without a history of cancer were included as a reference group and individually matched 13:1 to survivors of AYA cancer by age (yearly), sex, and calendar year (age of the noncancer participants had to match the cancer survivor's age in the same calendar year of the cancer survivor's index date). Each noncancer participant was subsequently assigned an index date that was the index date of the survivor of cancer to which he or she was matched. Individuals in the noncancer comparison cohort were identified from KPSC members in the year of the corresponding cancer diagnosis for a survivor of cancer and remained a KPSC member 2 years thereafter (ie, at index date or later). Additional record linkage with the California Cancer Registry was performed to exclude the comparison participants who had a history of cancer before their KPSC enrollment. This study was approved and the requirement of informed consent was waived by KPSC's Institutional Review Board.

Data Collection

All study participants were followed from index date to KPSC disenrollment, death, or end of 2014, whichever came first. Comorbidities that are known late effects of cancer treatments or common in this age group were included for examination. The presence of these comorbidities before or after the index date was captured using previously validated or published approaches whenever possible[17-22] (Data Supplement). Covariates of interest included demographics, cancer characteristics, chemotherapy exposures (agent, cumulative dose), radiation therapy (anatomic site, cumulative dose), and death information. All covariate data were collected using KPSC's electronic health records and cancer registries, except for information on death, which was supplemented by outside claims, California State death files, and national Social Security death files.

Statistical Analysis

The distribution of demographic, cancer, and treatment characteristics and the incidence rate of each comorbidity were calculated. For each comorbidity, those with a diagnosis date that preceded the index date (prevalent cases) were excluded from the calculation of incidence rate and

TABLE 1. Demographic and Clinical Characteristics of the Study Population

Characteristic	No. of Participants (%)[a]		P
	Survivors of Cancer (n = 6,778)	Noncancer Comparison Cohort (n = 87,737)	
Age at cancer diagnosis, mean (SD)	31.3 (6.5)	31.3 (6.5)	.95
Range	15.0-39.0	15.0-39.0	
Age by group, years			
15-19	521 (7.7)	6,746 (7.7)	
20-29	1,706 (25.2)	22,093 (25.2)	
30-39	4,551 (67.1)	58,898 (67.1)	
Female sex	4,427 (65.3)	57,230 (65.2)	.89
Race or ethnicity			< .0001
Non-Hispanic White	2,819 (41.6)	24,059 (27.4)	
Non-Hispanic Black	534 (7.9)	8,022 (9.1)	
Hispanic	2,698 (39.8)	35,647 (40.6)	
Asian or Pacific Islander	696 (10.3)	8,595 (9.8)	
Other or unknown	31 (0.5)	11,414 (13.0)	
Years of membership before index date, mean (SD)	7.6 (6.4)	7.4 (6.2)	.14
Years of follow-up after cancer diagnosis, mean (SD)	6.1 (3.5)	5.9 (3.4)	< .0001
Median	5.1	4.9	
Range	2.0-15.0	2.0-15.0	
Cancer type			
Thyroid	1,082 (16.0)		
Breast	1,067 (15.7)		
Lymphoma	735 (10.8)		
Melanoma	663 (9.8)		
Male genital/urinary	601 (8.9)		
Female genital/urinary	518 (7.6)		
GI	373 (5.5)		
Ovary	278 (4.1)		
Brain	268 (4.0)		
Leukemia and myeloma	228 (3.4)		
Renal	197 (2.9)		
Oropharynx	158 (2.3)		
Sarcoma	142 (2.1)		
Bone	69 (1.0)		
Lung	69 (1.0)		
Other	330 (4.9)		
TNM stage			
Not applicable	925 (13.7)[b]		
I	3,318 (49.0)		
II	1,315 (19.4)		
III	644 (9.5)		
IV	296 (4.4)		
Unknown	280 (4.1)		

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TABLE 1. Demographic and Clinical Characteristics of the Study Population (continued)

Characteristic	No. of Participants (%)[a] Survivors of Cancer (n = 6,778)	Noncancer Comparison Cohort (n = 87,737)	*P*
Radiation therapy in 2 years			
Abdominal radiation	153 (2.3)		
Chest radiation	722 (10.7)		
Head/brain/neck radiation	619 (9.1)		
Head/brain radiation	534 (7.9)		
Pelvis radiation	233 (3.4)		
Chemotherapy in 2 years			
Alkylating agents	1,336 (19.7)		
Platinum agents	793 (11.7)		
Antimetabolite agents	229 (3.4)		
Methotrexate	220 (3.3)		
Anthracyclines agents	1,585 (23.4)		
Antitumor antibiotic	599 (8.8)		
Monoclonal antibody	223 (3.3)		
Corticosteroids	3,291 (48.6)		

Abbreviation: SD, standard deviation.

[a]Values are numbers and percentages unless otherwise noted.

[b]Include brain cancer, leukemia, other hematopoietic malignancies, ill-defined, other skin cancer, and others.

incidence rate ratios (IRRs) because we were primarily interested in late effects of treatment to inform screening guidelines after cancer treatment. The crude and adjusted IRRs of each comorbidity associated with being a survivor of AYA cancer compared with those in the noncancer cohort were estimated using bivariable and multivariable Poisson regression adjusting for age, sex, and race and ethnicity. The Bayesian Improved Surname Geocoding imputation method was used to impute for the missing (approximately 13%) race and ethnicity information in the noncancer comparison participants.[23] The cumulative incidence of each comorbidity and of ≥ 2 comorbidities was calculated using nonparametric methods accounting for competing risk.[24] Differences in cumulative incidence were tested using the Gray's test.[25] The trend for prevalence of ≥ 2 comorbidities over time was also plotted.

Among survivors of AYA cancer, Poisson regression was performed to evaluate the association between treatment and risk of selected comorbidities with a known or suspected association with these exposures. Because the vast majority of survivors ($> 90\%$) received all their cancer treatment within 2 years after diagnosis, treatment exposure was considered a time-fixed variable representing the cumulative exposure before the index date. A potential dose-response relationship was evaluated in crude Poisson regression; appropriate cutoff for the cumulative dose of a chemotherapy agent was determined based on its dose distribution (ie, tertile). A similar analytical strategy was used to evaluate the relationship for radiation therapy.

Multivariable Poisson regressions were performed to evaluate the effects of cancer treatment on common health outcomes, adjusting for age, sex, and race and ethnicity. When applicable, the joint effect of chemotherapy and radiation therapy was evaluated by creating mutually exclusive exposure categories of the combined exposure (eg, anthracycline and chest radiation for cardiomyopathy, platinum agents and head radiation for hearing loss). Sensitivity analyses were conducted to eliminate potential confounding by the initial diagnosis; for premature ovarian failure, avascular necrosis, and thyroid disorders, the sensitivity analyses excluded survivors of ovarian cancer, bone cancer, and thyroid cancer, respectively. All analyses were carried out using SAS Version 9.3 (SAS Institute, Cary, NC).

RESULTS

A total of 9,173 KPSC members were diagnosed with an invasive cancer between 15 and 39 years of age from 2000 to 2012. Of these, 6,778 survivors met the inclusion criteria and were matched to 87,737 individuals without cancer (Appendix Fig A1, online only). Among survivors of AYA cancer, median age at initial cancer diagnosis was 31 years (15-19 years, 8%; 20-29 years, 25%; and 30-39 years, 67%). Approximately 65% of survivors were female, and 42% were non-Hispanic White. The most common cancer diagnoses were breast cancer (16%) and thyroid cancer (16%), followed by lymphoma (11%) and melanoma (10%). There was substantial heterogeneity of cancer type distribution by 5-year age groups (Appendix

TABLE 2. IR and IRR of Comorbidities Comparing Survivors of Adolescent and Young Adult Cancer to Matched Noncancer Comparison Cohort

	Survivors of Cancer			Noncancer Comparison Cohort			Adjusted[a]		
Comorbidity	No. of Events	IR[b]	Cumulative Incidence Through End of Study (%; 13 years after index date)	No. of Events	IR[b]	Cumulative Incidence Through End of Study (%; 13 years after index date)	IRR	95% CI	*P*
Any comorbidity	1,443	66.5	51.7	12,690	44.3	41.2	1.47	1.39 to 1.55	< .0001
Cardiovascular	111	4.2	6.0	530	1.6	2.7	2.54	2.07 to 3.12	< .0001
Cardiomyopathy/heart failure	36	1.3	1.5	165	0.5	0.6	2.64	1.84 to 3.79	< .0001
Coronary artery disease	34	1.3	2.6	250	0.8	1.3	1.63	1.14 to 2.34	.01
Stroke	56	2.1	2.9	209	0.6	1.3	3.19	2.37 to 4.29	< .0001
Dyslipidemia	502	22.4	26.0	4,996	17.1	21.7	1.31	1.20 to 1.44	< .0001
Hypertension	367	16.1	16.8	3,565	12.0	16.4	1.37	1.23 to 1.52	< .0001
Premature ovarian failure	13	1.4	1.3	54	0.5	0.6	2.87	1.56 to 5.28	.00
Other endocrine disease	364	18.8	22.1	3,322	11.1	14.8	1.72	1.54 to 1.92	< .0001
Diabetes	256	10.4	13.6	2,237	7.1	10.1	1.50	1.32 to 1.71	< .0001
Thyroid disorders	192	9.0	10.6	1,377	4.3	5.5	2.09	1.79 to 2.43	< .0001
Neurosensory	86	3.3	4.5	614	1.9	3.1	1.66	1.32 to 2.09	< .0001
Hearing loss	72	2.7	3.5	518	1.6	2.6	1.66	1.30 to 2.13	< .0001
Vision loss	14	0.5	1.0	106	0.3	0.5	1.48	0.83 to 2.63	.19
Pulmonary	132	5.5	4.8	1,278	4.1	4.4	1.29	1.08 to 1.54	.01
Asthma	117	4.9	3.7	1,230	4.0	4.2	1.18	0.98 to 1.43	.08
COPD/emphysema	13	0.5	1.0	65	0.2	0.3	2.30	1.26 to 4.20	.01
Pulmonary fibrosis	12	0.4	0.3	21	0.1	0.1	6.68	3.27 to 13.64	< .0001
Severe depression/anxiety	191	7.6	7.4	1,596	5.0	5.8	1.39	1.20 to 1.62	< .0001
Hepatic/renal disease	157	6.1	7.6	849	2.6	3.3	2.33	1.96 to 2.77	< .0001
Chronic liver disease	135	5.2	6.3	717	2.2	2.8	2.35	1.95 to 2.83	< .0001
Renal failure (GFR < 45 mL/min/173 m^2)	29	1.1	1.9	156	0.5	0.7	2.29	1.54 to 3.42	< .0001
Musculoskeletal	99	3.7	6.2	437	1.3	2.4	2.55	2.05 to 3.19	< .0001
Avascular necrosis	20	0.7	0.8	29	0.1	0.1	8.25	4.58 to 14.85	< .0001
Fractures (excluding vertebral fractures)	39	1.5	1.9	306	0.9	1.5	1.40	1.00 to 1.96	.05
Joint replacement	24	0.9	2.7	70	0.2	0.6	3.89	2.43 to 6.22	< .0001
Osteoporosis	30	1.1	1.3	61	0.2	0.3	5.75	3.71 to 8.93	< .0001

Abbreviations: COPD, chronic obstructive pulmonary disease; GFR, glomerular filtration rate; IR, Incidence rate; IRR, incidence rate ratio.
[a]Model adjusted for age, sex, and race and ethnicity. Crude estimates are not shown, but they are similar to the adjusted estimates.
[b]IR indicates number of events per 1,000 person-years at risk.

Fig A2, online only). Approximately a quarter of survivors of AYA cancer (23%) received external-beam radiation therapy. Exposure to selected chemotherapy agents ranged from 3% (epipodophyllotoxins) to 24% (anthracyclines; Table 1). The median follow-up time after cancer diagnosis was 5.1 years.

During the study follow-up, a total of 1,443 survivors of cancer (17%) developed ≥ 1 comorbidity, with an incidence rate of 66 per 1,000 person-years. The adjusted IRR of developing any comorbidity among survivors of cancer compared with the noncancer cohort was 1.47 (95% CI, 1.39 to 1.55; Table 2). The most common comorbidities among survivors of cancer were dyslipidemia (22 per 1,000 person-years), hypertension (16 per 1,000 person-years), diabetes (10 per 1,000 person-years), thyroid disorders (9 per 1000 person-years), and severe depression or anxiety (8 per 1,000 person-years; Table 2). With the exception of vision loss and asthma, survivors of cancer were significantly more likely to develop a comorbidity compared with the noncancer cohort. The IRR was highest for avascular

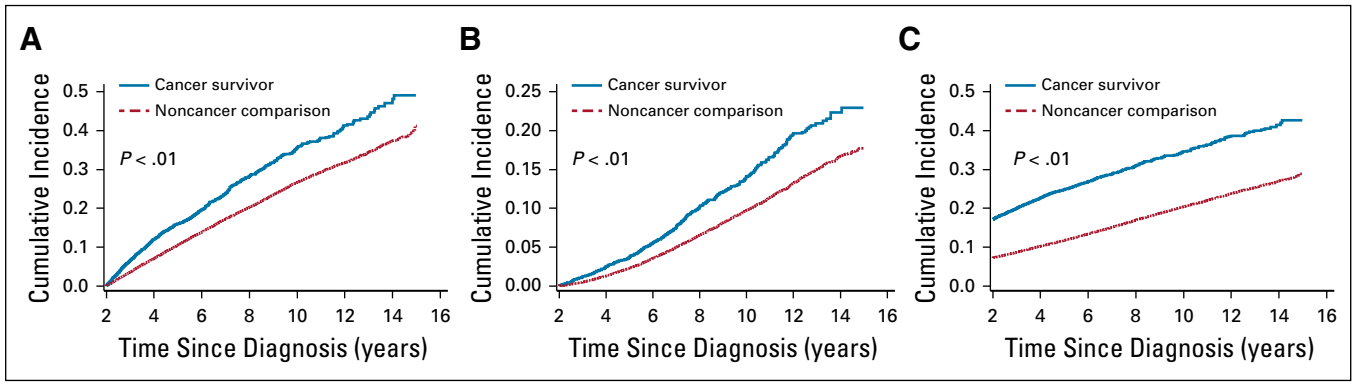

FIG 1. Incidence of (A) any comorbidity, (B) ≥ 2 new comorbidities, and (C) ≥ 2 comorbidities by cancer survivor status.

necrosis (IRR, 8.25; 95% CI, 4.58 to 14.85), followed by osteoporosis (IRR, 5.75; 95% CI, 3.71 to 8.93), joint replacement (IRR, 3.89; 95% CI, 2.43 to 6.22), stroke (IRR, 3.19; 95% CI, 2.37 to 4.29), premature ovarian failure (IRR, 2.87; 95% CI, 1.56 to 5.28), and cardiomyopathy or heart failure (IRR, 2.64; 95% CI, 1.84 to 3.79; Table 2). The adjusted IRR of developing ≥ 2 incident comorbidities was 1.63 (95% CI, 1.48 to 1.78).

The cumulative incidence curves for any comorbidity and for comorbidities by organ system are shown in Figure 1 and Appendix Figure A3 (online only). Fig 1 also shows the prevalence of ≥ 2 comorbidities over time. For survivors of AYA cancer, the prevalence of multiple comorbidities approached 40% at 10 years after the index date, compared with 20% for those without cancer ($P < .001$). The combinations of the first 2 incident comorbidities among survivors of cancer are shown in the Data Supplement.

Within Survivors of AYA Cancer

When we examined the crude association between exposure to selected chemotherapy agents and the development of specific comorbidities (Table 3), use of alkylating agents (IRR, 2.8 [95% CI, 1.2 to 6.2] for > 2,500 mg/m^2), anthracyclines (IRR, 3.3 [95% CI, 1.6 to 6.9] for > 240 mg/m^2), and trastuzumab (IRR, 9.1 [95% CI, 3.2 to 25.6] for > 4,000 mg/m^2) was significantly associated with risk of cardiomyopathy or heart failure. Use of alkylating agents (IRR, 4.5 [95% CI, 1.4 to 15.0] for > 2,500 mg/m^2) and platinum agents (IRR, 9.0 [95% CI, 2.8 to 29.2] for > 450 mg/m^2) was significantly associated with premature ovarian failure. Use of methotrexate (IRR, 21.6 [95% CI, 8.8 to 52.8] for any dose) and corticosteroids (IRR, 5.4 [95% CI, 1.8 to 16.0] for any dose) was significantly associated with avascular necrosis. Use of bleomycin was significantly associated with pulmonary fibrosis (IRR, 4.7 [95% CI, 1.0 to 21.7] for > 120 mg/m^2), and use of corticosteroids was significantly associated with osteoporosis (IRR, 2.3 [95% CI, 1.1 to 4.9] for any dose).

Table 4 lists the crude IRR estimates for selected comorbidities associated with radiation exposure (compared with no exposure). Radiation therapy to the head and neck area was significantly associated with risk of stroke (IRR, 3.1 [95% CI, 1.6 to 6.0] for ≥ 30 Gy), hearing loss (IRR, 3.0 [95% CI, 1.6 to 5.6] for ≥ 30 Gy [head only]), vision loss (IRR, 8.1 [95% CI, 2.7 to 24.2] for ≥ 30 Gy [head only]), thyroid disorders (IRR, 3.4 [95% CI, 2.4 to 4.7] for ≥ 30 Gy), and diabetes (IRR, 1.9 [95% CI, 1.3 to 2.8] for ≥ 30 Gy [head only]). Chest radiation therapy was associated with risk of cardiomyopathy or heart failure (IRR, 2.6 [95% CI, 1.2 to 5.7] for ≥ 30 Gy).

In multivariable analyses, the following agents were significantly and independently associated with risk of cardiomyopathy: anthracycline > 240 mg/m^2 (IRR, 3.3; 95% CI, 1.0 to 10.67) and trastuzumab > 4,000 mg/m^2 (IRR, 8.1; 95% CI, 2.5 to 25.5; Table 5). A combined exposure to platinum (> 450 mg/m^2) and radiation to the head (≥ 30 Gy) was associated with increased risk of hearing loss (IRR, 14.9; 95% CI, 5.9 to 37.2). Radiation therapy to the head and neck (≥ 30 Gy) was associated with risk of stroke (IRR, 3.5; 95% CI, 1.8 to 6.8). For thyroid disorders, significant risk factors included female sex and head and neck radiation (≥ 30 Gy; IRR, 3.1; 95% CI, 2.2 to 4.4). For diabetes, significant risk factors included older age at diagnosis (30-39 years); non-Hispanic Black, Hispanic, and Asian race/ethnicity; and head radiation (≥ 30 Gy; IRR, 1.9; 95% CI, 1.3 to 2.9). Similar results were obtained in sensitivity analyses that excluded survivors of ovarian cancer (premature ovarian failure), bone cancer (avascular necrosis), and thyroid cancer (thyroid disorders).

DISCUSSION

In this study, we describe the incidence and relative risk of development of chronic comorbidities among survivors of AYA cancer compared with controls without a history of cancer. We found that the risk of nearly all comorbidities was significantly elevated in survivors of cancer, with magnitudes of IRR ranging from 1.3 for dyslipidemia to 8.3 for avascular necrosis. Moreover, 2 in 5 survivors had multiple comorbidities just 10 years after the index date. Among survivors of AYA cancer, we observed significant

TABLE 3. Crude Associations Between Chemotherapy Exposure and Selected Comorbidity Outcomes

Chemotherapy Agent and Dose and Comorbidity	IRR	95% CI	*P*
Alkylating agents			
Cardiomyopathy/congestive heart failure			
Any dose	2.20	1.12 to 4.35	.02
≤ 2,500 mg/m^2	1.66	0.63 to 4.36	.31
> 2,500 mg/m^2	2.78	1.24 to 6.22	.01
Premature ovarian failure			
Any dose	2.78	0.91 to 8.51	.07
≤ 2,500 mg/m^2	1.10	0.14 to 8.76	.93
> 2,500 mg/m^2	4.53	1.36 to 15.04	.01
Platinum			
Coronary artery disease/myocardial infraction			
No exposure	1.00		
Any dose	0.59	0.14 to 2.45	.47
≤ 450 mg/m^2	—[a]	—	—
> 450 mg/m^2	1.38	0.33 to 5.74	.66
Premature ovarian failure			
Any dose	4.93	1.52 to 16.00	.01
≤ 450 mg/m^2	—[a]	—	—
> 450 mg/m^2	9.00	2.77 to 29.24	< .001
Hearing loss			
Any dose	1.38	0.69 to 2.78	.36
≤ 450 mg/m^2	0.80	0.25 to 2.54	.70
> 450 mg/m^2	2.18	0.94 to 5.03	.07
Renal failure			
Any dose	0.70	0.17 to 2.96	.63
≤ 450 mg/m^2	—[a]	—	—
> 450 mg/m^2	1.66	0.39 to 6.97	.49
Dyslipidemia			
Any dose	0.94	0.70 to 1.28	.71
≤ 450 mg/m^2	0.76	0.50 to 1.17	.21
> 450 mg/m^2	1.21	0.80 to 1.82	.36
Antimetabolites			
Chronic liver disease			
Any dose	1.97	0.96 to 4.02	.06
≤ 9,000 mg/m^2	1.72	0.64 to 4.66	.28
> 9,000 mg/m^2	2.29	0.84 to 6.18	.10
Methotrexate			
Renal failure			
Any dose	2.30	0.55 to 9.69	.25
≤ 1,200 mg/m^2	2.11	0.29 to 15.55	.46
> 1,200 mg/m^2	2.54	0.34 to 18.66	.36
Fracture			
Any dose	1.66	0.40 to 6.90	.48

(continued on following page)

TABLE 3. Crude Associations Between Chemotherapy Exposure and Selected Comorbidity Outcomes (continued)

Chemotherapy Agent and Dose and Comorbidity	IRR	95% CI	*P*
≤ 1,200 mg/m^2	3.02	0.73 to 12.54	.13
> 1,200 mg/m^2	—[a]	—	—
Avascular necrosis			
Any dose	21.56	8.81 to 52.75	< .0001
≤ 1,200 mg/m^2	14.43	4.07 to 51.13	< .0001
> 1,200 mg/m^2	30.65	10.80 to 87.00	< .0001
Osteoporosis			
Any dose	2.23	0.53 to 9.34	.27
≤ 1,200 mg/m^2	2.02	0.28 to 14.88	.49
> 1,200 mg/m^2	2.47	0.34 to 18.17	.37
Pulmonary fibrosis			
Any dose	2.80	0.36 to 21.70	.32
≤ 1,200 mg/m^2	5.06	0.65 to 39.20	.12
> 1,200 mg/m^2	—[a]	—	—
Anthracyclines			
Cardiomyopathy/congestive heart failure			
Any dose	2.83	1.47 to 5.44	< .01
≤ 240 mg/m^2	2.25	0.90 to 5.64	.08
> 240 mg/m^2	3.28	1.56 to 6.90	< .01
Bleomycin			
Pulmonary fibrosis			
Any dose	3.58	0.97 to 13.24	.06
≤ 120 mg/m^2	2.44	0.31 to 19.24	.40
> 120 mg/m^2	4.69	1.01 to 21.70	.05
Corticosteroids			
No exposure	1.00		
Vision loss, any dose	1.78	0.62 to 5.12	.29
Fracture, any dose	1.14	0.61 to 2.13	.69
Avascular necrosis, any dose	5.35	1.79 to 16.01	< .01
Osteoporosis, any dose	2.32	1.10 to 4.87	.03
Antibody (trastuzumab)			
Cardiomyopathy/congestive heart failure			
Any dose	4.88	1.73 to 13.80	< .01
≤ 4000 mg/m^2	—[a]	—	—
> 4,000 mg/m^2	9.06	3.20 to 25.61	< .0001

NOTE. Reference group is no exposure.
Abbreviation: IRR, incidence rate ratio.
[a]IRR cannot be estimated as a result of no event in this exposure level.

associations between treatment exposures and certain comorbidities such as cardiomyopathy, hearing loss, stroke, thyroid disorders, and diabetes. These data highlight the burden of adverse long-term health outcomes of cancer and its treatment in survivors of AYA cancer and will facilitate the identification of high-risk survivors who may benefit from tailored surveillance and prevention strategies.

Long-term survival outcomes in AYAs with cancer has not improved to the extent seen in children with cancer.[5] Lack of data on long-term health outcomes and treatment late effects may be key knowledge gaps for improving outcomes in these patients. To our knowledge, this is the first study to systematically characterize the development of chronic comorbidities among survivors of AYA cancer in the United

TABLE 4. Crude Associations Between Radiation Exposure and Selected Comorbidity Outcomes

Radiation Site and Dose and Comorbidity	IRR	95% CI	*P*
Head and neck			
Stroke			
Any dose	2.76	1.43 to 5.34	< .01
< 30 Gy	—[a]	—	—
≥ 30 Gy	3.11	1.61 to 6.01	< .001
Premature ovarian failure[b]			
Any dose	2.56	0.57 to 11.56	.22
< 30 Gy	12.22	1.58 to 94.64	.02
≥ 30 Gy	1.43	0.18 to 11.09	.73
Hearing loss[b]			
Any dose	2.75	1.48 to 5.11	< .01
< 30 Gy	—[a]	—	—
≥ 30 Gy	3.02	1.62 to 5.61	< .001
Vision loss[b]			
Any dose	7.43	2.49 to 22.18	< .001
< 30 Gy	—[a]	—	—
≥ 30 Gy	8.12	2.72 to 24.22	< .001
Thyroid disorders			
Any dose	3.22	2.32 to 4.48	< .0001
< 30 Gy	1.89	0.60 to 5.92	.28
≥ 30 Gy	3.38	2.42 to 4.74	< .0001
Diabetes[b]			
Any dose	1.79	1.23 to 2.63	< .01
< 30 Gy	0.68	0.10 to 4.88	.71
≥ 30 Gy	1.90	1.29 to 2.80	< .01
Dyslipidemia[b]			
Any dose	1.13	0.82 to 1.56	.46
< 30 Gy	1.29	0.48 to 3.44	.62
≥ 30 Gy	1.12	0.79 to 1.57	.53
Hypertension[b]			
Any dose	1.20	0.83 to 1.73	.33
< 30 Gy	0.47	0.07 to 3.33	.45
≥ 30 Gy	1.26	0.87 to 1.84	.22
Severe depression/anxiety[b]			
Any dose	1.23	0.74 to 2.06	.42
< 30 Gy	0.92	0.13 to 6.57	.93
≥ 30 Gy	1.26	0.74 to 2.14	.39
Chest			
Pulmonary fibrosis			
Any dose	1.63	0.36 to 7.44	.53
< 30 Gy	—[a]	—	—
≥ 30 Gy	1.75	0.38 to 8.00	.47

(continued on following page)

States and to examine the relationship between these comorbidities and treatment exposures in this unique group. A few US-based studies have reported on the comorbidity burden among survivors of AYA cancer, although most are cross-sectional and subject to recall and participation bias as a result of the use of self-reported questionnaires and/or lack of a comparison group.[26-29] Longitudinal studies have described hospitalizations for survivors of AYA cancer in Denmark,[30-33] but these studies have not included more common health conditions that can be diagnosed and managed on an outpatient basis. As such, the current study represents an important and more comprehensive assessment of the long-term burden of comorbidities in survivors of AYA cancers.

Compared with survivors of childhood cancer, the relative risk increase for survivors of AYA cancer appears to be smaller in magnitude across most comorbidities. Data from the Childhood Cancer Survivors Study (CCSS) showed that for grade 3 or 4 cardiac events, the IRR was 7.5 for survivors of childhood cancer. For grade 3 or 4 pulmonary disease, renal disease, disorders of hearing, speech, or vision, and musculoskeletal conditions, the IRRs were 3.1, 8.1, 5.8, and 77.1, respectively.[11] In comparison, in the current study, the IRRs for severe cardiovascular diseases, severe pulmonary diseases, renal failure, hearing loss, vision loss, and musculoskeletal conditions were 2.1, 2.3, 2.3, 1.7, 1.5, and 2.6, respectively. Although the definitions of comorbidities, study design, and follow-up time between our study and the CCSS are different, the differences may still reflect the intensity of cancer treatments, the effect of these treatments on developing organs versus mature organs, and background incidence in the general population. Importantly, these differences again highlight the need for age-appropriate survivorship guidelines for survivors of AYA cancer.

The examination of the relationship between treatment exposure and selected health outcomes was based on a priori knowledge about treatment-related late effects in survivors of childhood cancer,[34] as well as those reported in survivors of adult-onset cancers (eg, trastuzumab). Although we confirmed previously reported associations between anthracyclines and trastuzumab and cardiomyopathy, platinums and head and neck radiation and hearing loss, head and neck radiation and stroke, head and neck radiation and thyroid diseases, and head and neck radiation and diabetes, there were other instances where the association could not be confirmed. These included, for example, the association between platinum exposure and myocardial infarction, methotrexate and renal failure, and pelvic radiation and premature ovarian failure. There are several possible explanations for these null results, including a true lack of association, limited power for some analyses, or the need for longer follow-up for certain late effects (eg, myocardial infarction). Several other risk factors based on patient characteristics were also found, which vary for different comorbidities.

TABLE 4. Crude Associations Between Radiation Exposure and Selected Comorbidity Outcomes (continued)

Radiation Site and Dose and Comorbidity	IRR	95% CI	*P*
Cardiomyopathy/heart failure			
Any dose	2.73	1.28 to 5.80	.01
< 30 Gy	4.46	0.61 to 32.85	.14
≥ 30 Gy	2.60	1.18 to 5.72	.02
Coronary artery disease			
Any dose	0.50	0.12 to 2.10	.35
< 30 Gy	—[a]	—	—
≥ 30 Gy	0.54	0.13 to 2.26	.40
Pelvis			
Premature ovarian failure			
Any dose	3.03	0.39 to 23.32	.29
< 30 Gy	—[a]	—	—
≥ 30 Gy	3.24	0.42 to 24.95	.26

NOTE. Reference group is no exposure.

Abbreviation: IRR, incidence rate ratio.

[a]IRR cannot be estimated as a result of no event in this exposure level. We could not evaluate the association between abdominal radiation exposure and premature ovarian failure, between axial skeleton radiation exposure and fractures (excluding vertebral), and between axial skeleton radiation exposure and osteoporosis as a result of the lack of events in the exposed group.

[b]Except for stroke and thyroid disorders, for the other conditions, we assessed radiation to the head only (ie, radiation to the neck was not included in the total radiation assessment).

National guidelines specific for AYA oncology were not available until 2016.[35] For the survivorship care recommendations, the National Comprehensive Cancer Network (NCCN) AYA guidelines generally follow the Children's Oncology Group long-term follow-up guidelines, noting that these guidelines do not apply to survivors of common adult cancer types (eg, breast and colorectal cancer). There also remains room for clinical judgement for the survivorship screening tests recommend by the NCCN AYA oncology guidelines. For example, the recommendations for cardiomyopathy screening with echocardiography were for 2- to 5-year intervals for a range of anthracycline and chest radiation exposures, but the specific intervals of screening based on level of treatment exposure were not specified. A study by Barthel et al[36] found that, for AYA cancers, age-related recommendations from several survivorship care guidelines disagree on the link between treatment exposures and late effects, who should be screened, the screening intervals, and the screening test to be used.[35] Unique challenges for survivorship care for AYA cancer may stem from the heterogeneity of cancer type distributions and treatment variations for the same cancer (eg, pediatric *v* adult oncology) within the AYA age range. There is certainly a need for additional research to further inform guideline development and strategies to promote the adoption of these guidelines to help improve long-term outcomes for these survivors of cancer.

There are several limitations of this study that should be considered. First, for comorbidities that require medical management but are mostly asymptomatic (eg, dyslipidemia, hypertension, osteoporosis), there may be differential surveillance patterns; survivors of cancer likely have more frequent health care encounters and/or are more likely to be screened and diagnosed with these conditions. As a result, the findings for these comorbidities should be interpreted with caution. Second, the number of events for some comorbidities were small, which limited our ability to perform multivariable analyses for their risk factors. Third, our follow-up was limited to 14 years after diagnosis, with a median follow-up of 5 years after diagnosis. As a result, this study may not be representative of late-occurring (> 10-15 years) comorbidities in survivors of AYA cancer. Future studies should include longer follow-up to further inform the long-term trajectory of health risk. Finally, we did not have comprehensive data on lifestyle factors such as smoking, alcohol use, and exercise to evaluate whether they may have confounded the observed associations.

Despite the limitations, our study has several important strengths. We have longitudinal data on the development of health outcomes and a carefully matched internal comparison cohort, providing us with robust estimates for the IRR of health outcomes. We also included cancer treatment in our analyses, allowing us to examine the association between select exposures and more common comorbidities. Our racially and ethnically diverse survivor population made our findings uniquely relevant for populations in the United States compared with studies from Scandinavian countries. In addition, the relatively equal access to health care in our membership minimized the likelihood of confounding as a result of insurance coverage; previous studies have highlighted the challenges of conducting studies in survivors of AYA cancers as a result of inequities in access to care.[37] Leveraging the stable membership of KPSC, we were able to study the health outcomes of AYAs long after their cancer diagnosis, allowing us to address important gaps in the literature.

In conclusion, this study provided a comprehensive overview of the incidence and relative risk of chronic comorbidities in long-term survivors of AYA cancer compared with matched individuals without a history of cancer. We showed that the risk of developing chronic comorbidities was increased across nearly all outcomes examined and highlighted important treatment-related modifiers of risk in these survivors. These data may help provide much-needed information for the development of personalized survivorship care plans for survivors of AYA cancer, taking into consideration the unique phenotypes of comorbidities over time. Importantly, it may set the stage for prevention, early diagnosis, or intervention strategies to mitigate long-term comorbidity burden in this growing population of long-term survivors.

TABLE 5. Risk Factors for Comorbidity Outcomes Among Survivors of Adolescent and Young Adult Cancer in Adjusted Poisson Regression

Comorbidity and Risk Factor	IRR	95% CI	*P*
Cardiomyopathy/heart failure (n = 33)			
Age at cancer diagnosis, years			
15-19	1.00		
20-29	1.64	0.19 to 14.28	.65
30-39	2.51	0.33 to 19.10	.37
Race/ethnicity			
Non-Hispanic White	1.00		
Other	0.80	0.40 to 1.61	.54
Sex			
Male	1.00		
Female	0.78	0.34 to 1.75	.54
Alkylating agent			
No	1.00		
≤ 2,500 mg/m^2	0.53	0.12 to 2.25	.39
> 2,500 mg/m^2	1.21	0.35 to 4.19	.76
Anthracycline agent			
No	1.00		
≤ 240 mg/m^2	2.36	0.60 to 9.36	.22
> 240 mg/m^2	3.27	1.00 to 10.69	.05
Antibody (trastuzumab)			
No	1.00		
> 4,000 mg/m^2	8.06	2.54 to 25.52	< .001
Chest radiation			
No	1.00		
Yes	1.52	0.60 to 3.82	.38
Hearing loss (n = 69)			
Age at cancer diagnosis, years			
15-19	1.00		
20-29	2.62	0.61 to 11.24	.20
30-39	2.07	0.50 to 8.53	.32
Race/ethnicity			
Non-Hispanic White	1.00		
Other	0.92	0.57 to 1.48	.73
Sex			
Male	1.00		
Female	0.74	0.45 to 1.21	.23
Platinum; head/brain radiation			
Platinum ≤ 450 mg/m^2 or radiation 0-29.9 Gy	1.00		
Platinum > 450 mg/m^2 or radiation ≥ 30 Gy	14.87	5.94 to 37.20	< .0001
Stroke (n = 52)			
Age at cancer diagnosis, years			
15-19	1.00		
20-29	0.42	0.12 to 1.50	.18

(continued on following page)

TABLE 5. Risk Factors for Comorbidity Outcomes Among Survivors of Adolescent and Young Adult Cancer in Adjusted Poisson Regression (continued)

Comorbidity and Risk Factor	IRR	95% CI	*P*
30-39	0.96	0.34 to 2.68	.93
Race/ethnicity			
Non-Hispanic White	1.00		
Other	0.90	0.52 to 1.56	.70
Sex			
Male	1.00		
Female	0.74	0.42 to 1.30	.30
Head/brain/neck radiation			
0-29.9 Gy	1.00		
≥ 30 Gy	3.52	1.81 to 6.84	< .0001
Thyroid disorders (n = 175)			
Age at cancer diagnosis, years			
15-29	1.00		
30-39	1.10	0.78 to 1.56	.59
Race/ethnicity			
Non-Hispanic White	1.00		
Other	0.98	0.72 to 1.32	.88
Sex			
Male	1.00		
Female	2.07	1.44 to 2.99	< .0001
Head/brain/neck radiation			
0-29.9 Gy	1.00		
≥ 30 Gy	3.07	2.15 to 4.38	< .0001
Diabetes (n = 238)			
Age at cancer diagnosis, years			
15-29	1.00		
30-39	2.41	1.68 to 3.45	< .0001
Race/ethnicity			
Non-Hispanic White	1.00		
Non-Hispanic Black	2.25	1.43 to 3.54	< .001
Hispanic	2.21	1.63 to 3.00	< .0001
Asian/Pacific Islander	1.78	1.13 to 2.80	.01
Sex			
Male	1.00		
Female	1.06	0.79 to 1.41	.71
Head/brain radiation			
0-29.9 Gy	1.00		
≥ 30 Gy	1.94	1.31 to 2.86	< .001
Abdomen radiation			
0-29.9 Gy	1.00		
≥ 30 Gy	2.12	0.67 to 6.67	.20

Abbreviation: IRR, incidence rate ratio.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Chronic Comorbidities Among Survivors of Adolescent and Young Adult Cancer

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APPENDIX

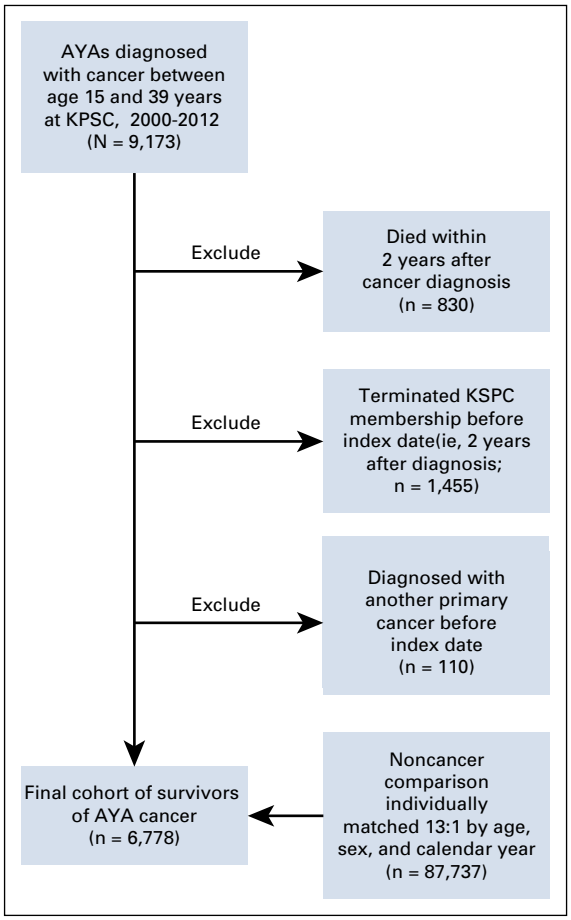

FIG A1. Study population flowchart. AYA, adolescent and young adult; KPSC, Kaiser Permanente Southern California.

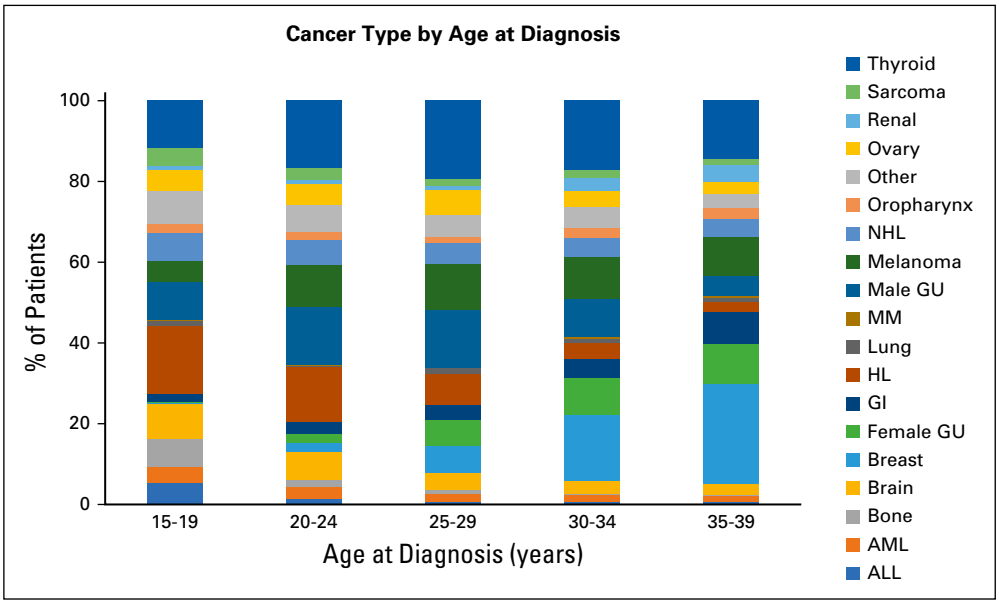

FIG A2. Distribution of cancer types by 5-year age groups within survivors of adolescent and young adult cancer. Cancer type shown in the same order (from top to bottom) in every age group as in the right text panel. ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; GU, genitourinary; HL, Hodgkin lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma.

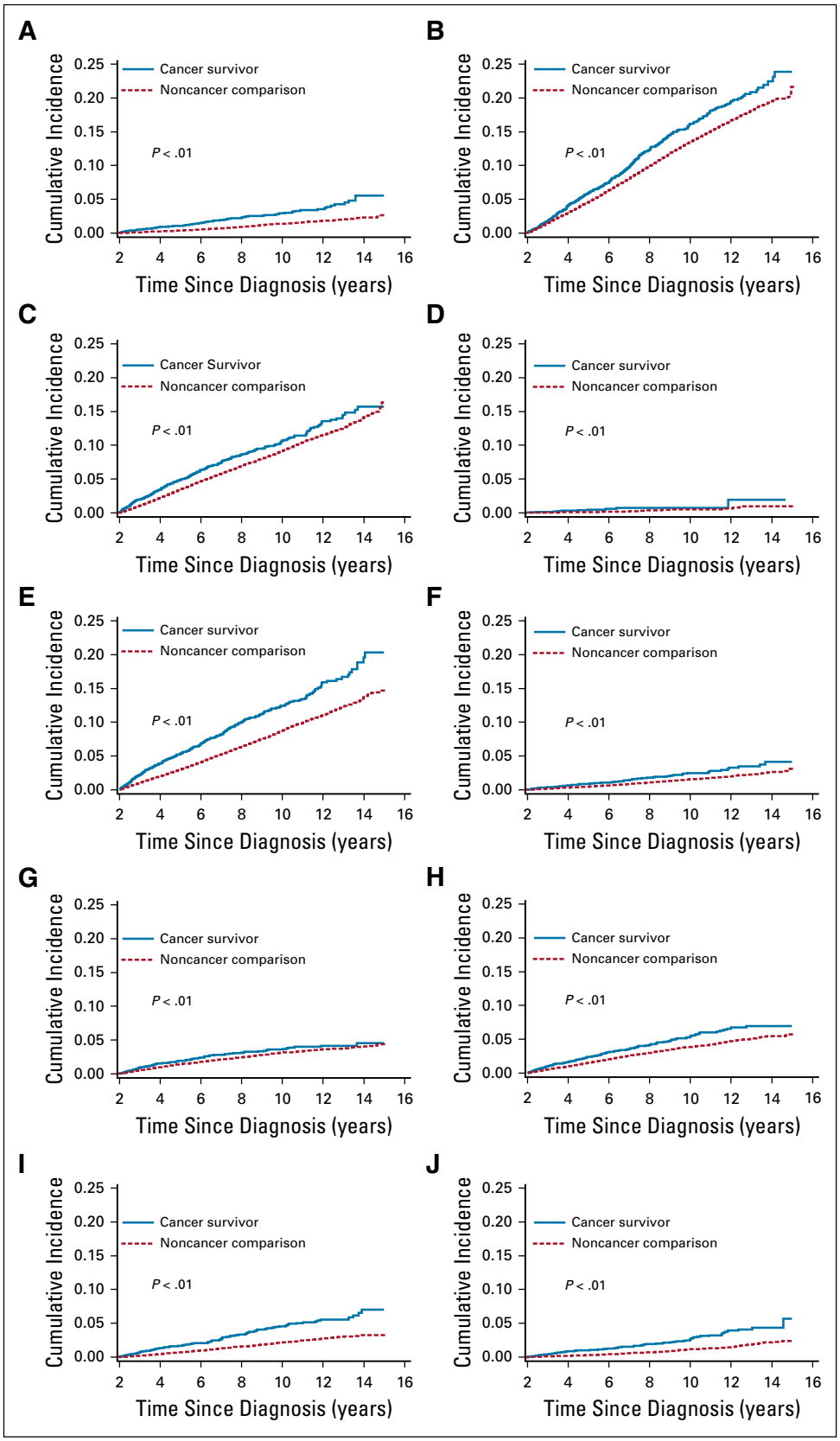

FIG A3. Incidence of condition by cancer survivor status: (A) cardiovascular, (B) dyslipidemia, (C) hypertension, (D) premature ovarian failure, (E) other endocrine disease, (F) neurosensory, (G) pulmonary, (H) severe depression or anxiety, (I) hepatic or renal disease, and (J) musculoskeletal.