

Late mortality in people with cancer: a population-based Australian study

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The known: Data on late mortality in people with cancer, and the relative contributions of cancer and non-cancer causes to mortality, are limited.

The new: Long term mortality among people with cancer alive five years after diagnosis exceeds that of the general population. Cardiovascular disease is a major competing cause of death; from 13 years after diagnosis, the cumulative number of deaths exceed that of those attributed to cancer.

The implications: Cancer control systems should incorporate monitoring of long term outcomes, including non-cancer mortality. Mitigation of risk factors for premature death, particularly from cardiovascular disease, is needed.

Advances in the diagnosis and treatment of cancer have increased the number of cancer survivors, many of whom have comorbid chronic conditions.¹⁻³ Cancer and its treatment can exacerbate existing conditions and lead to new ones and competing mortality.^{4,5} In order to develop better models of care, it is important to understand the relative contribution of comorbidity to mortality, especially for long term survivors, whose survival ideally should approximate that of people without cancer.

Few studies have compared the relative contributions of cancer and non-cancer causes to mortality among people with cancer. In 2016, a study of death records from the United States Surveillance, Epidemiology and End Results (SEER) database indicated that the comparative risks of cancer and non-cancer death differed markedly by cancer type, and that more than 40% of non-cancer deaths were from cardiovascular disease.⁶ In Australia, an analysis of 1946 non-cancer deaths among 21 000 people with cancer found cardiovascular disease to be the most frequent cause of death, and that the standardised mortality ratio (SMR) for cardiovascular disease was higher than for people without cancer.⁷ Both studies found that SMRs were highest during the first year after diagnosis, probably reflecting the toxicity of anti-cancer treatment. In the Korean national cancer registry study, including nearly 3 million patients, 87% of the more than one million deaths were attributable to cancer, but cardiovascular disease increased 20-fold during 2000–2016 and the risk of suicide was higher than in the general population.⁸

These three studies raised awareness of competing causes of death among people with cancer. However, their inclusion of both early and later deaths made interpretation of their findings difficult. Acute treatment toxicity, rather than cancer itself, can contribute to early death, which may be attributed to cancer rather than organ failure. Patients with a comorbid condition may not be offered the most effective cancer treatment, leading to

Abstract

Objectives: To investigate causes of death of people with cancer alive five years after diagnosis, and to compare mortality rates for this group with those of the general population.

Design, setting, participants: Retrospective cohort study; analysis of South Australian Cancer Registry data for all people diagnosed with cancer during 1990–1999 and alive five years after diagnosis, with follow-up to 31 December 2016.

Main outcome measures: All-cause and cancer cause-specific mortality, by cancer diagnosis; standardised mortality ratios (study group v SA general population) by sex, age at diagnosis, follow-up period, and index cancer.

Results: Of 32 646 people with cancer alive five years after diagnosis, 30 309 were of European background (93%) and 16 400 were males (50%); the mean age at diagnosis was 60.3 years (SD, 15.7 years). The median follow-up time was 17 years (IQR, 11–21 years); 17 268 deaths were recorded (53% of patients; mean age, 80.6 years; SD, 11.4 years); 7845 attributed to cancer (45% of deaths) and 9423 attributed to non-cancer causes (55%). Ischaemic heart disease was the leading cause of death (2393 deaths), followed by prostate cancer (1424), cerebrovascular disease (1175), and breast cancer (1118). The overall standardised mortality ratio (adjusted for age, sex, and year of diagnosis) was 1.24 (95% CI, 1.22–1.25). The cumulative number of cardiovascular deaths exceeded that of cancer cause-specific deaths from 13 years after cancer diagnosis.

Conclusions: Mortality among people with cancer who are alive at least five years after diagnosis was higher than for the general population, particularly cardiovascular disease-related mortality. Survivorship care should include early recognition and management of risk factors for cardiovascular disease.

selection bias. Further, cancer-specific mortality for these patients may be higher because of less effective treatment, and they may be at greater risk of treatment toxicity and death because of their comorbid conditions.

Only one population-level study in the past 20 years has examined late mortality in adults with cancer, a Korean analysis of national cancer registry data (including 26 498 deaths). It found that the SMR for patients alive five years after diagnosis (median follow-up, 7.9 years) was 2.56; higher mortality was primarily driven by cancer-related deaths, but 24% of deaths were from causes other than cancer.⁹ The risks of non-cancer death (except for suicide) were lower than for the general population, and the cardiovascular death rate was similar to that for the general population.

No other studies of late mortality have included adult patients with cancers of diverse tumour types. We therefore examined the causes of death among South Australians with cancer alive five years after diagnosis, and to compare mortality rates for this group with those of the general population.

1 Characteristics of people alive 5 years after being diagnosed with invasive cancer during 1990–1999 and followed until 31 December 2016

	Status, 31 December 2016			
	Total	Alive	Cancer death	Non-cancer death
Number of people	32 646	15 378	7845	9423
Age at index diagnosis (years)				
Mean (SD)	60.3 (15.7)	51.2 (15.1)	64.6 (12.1)	71.5 (9.4)
0–14	314	290 (92.4%)	15 (4.8%)	9 (3%)
15–40	3172	2826 (89.1%)	278 (8.8%)	68 (2.1%)
40–49	4120	3309 (80.3%)	630 (15.3%)	181 (4.4%)
50–59	5835	3977 (68.2%)	1313 (22.5%)	545 (9.3%)
60–69	8838	3583 (40.6%)	2600 (29.5%)	2645 (30.0%)
70–79	7971	1245 (15.6%)	2424 (30.4%)	4302 (54.0%)
≥ 80	2406	148 (6.2%)	585 (24.3%)	1673 (69.5%)
Follow-up time (years), median (IQR)	17 (11–21)	20 (18–23)	10 (7–14)	12 (8–16)
Sex				
Female	16 246	8884 (54.7%)	3277 (20.2%)	4085 (25.1%)
Male	16 400	6494 (39.6%)	4568 (27.9%)	5338 (32.6%)
Ethnic background				
European	30 309	13 429 (44.3%)	7719 (25.5%)	9161 (30.3%)
Asian	212	150 (70.8%)	35 (16%)	27 (13%)
Aboriginal and Torres Strait Islander Australians	119	50 (42%)	37 (31%)	32 (27%)
Unknown	2006	1749 (87.2%)	54 (2.7%)	203 (10.1%)
Socio-economic status (IRSD quintile)				
1 (most disadvantaged)	6356	2907 (45.7%)	1581 (24.9%)	1868 (29.4%)
2	6461	3058 (47.3%)	1587 (24.6%)	1816 (28.1%)
3	7609	3420 (45.0%)	1852 (24.3%)	2337 (30.7%)
4	5842	2744 (47.0%)	1416 (24.2%)	1682 (28.8%)
5 (least disadvantaged)	6378	3249 (50.9%)	1409 (22.1%)	1720 (27.0%)
Multiple cancers				
Yes	1572	293 (18.6%)	791 (50.3%)	488 (31.0%)
No	31 074	15 085 (48.5%)	7054 (22.7%)	8935 (28.8%)
Index cancer site				
Breast	6259	3516 (56.2%)	1439 (23.0%)	1304 (20.8%)
Prostate	5976	1539 (25.8%)	2005 (33.6%)	2432 (40.7%)
Skin	5185	3389 (65.4%)	677 (13.1%)	1119 (21.6%)
Gastrointestinal	5033	1979 (39.3%)	1119 (22.2%)	1935 (38.5%)
Lymphoma/other haematological	2686	1098 (40.9%)	958 (35.7%)	630 (23.4%)
Head/neck	1784	811 (45.5%)	377 (21.1%)	596 (33.4%)
Renal/testicular/bladder	1848	907 (49.1%)	420 (22.7%)	521 (28.2%)
Lung	654	206 (31.5%)	247 (37.8%)	201 (30.7%)
Gynaecological	1613	977 (60.6%)	261 (16.2%)	375 (23.2%)
Other	1475	913 (61.9%)	306 (20.8%)	256 (17.3%)
Unknown	133	43 (32%)	36 (27%)	54 (41%)

IQR = interquartile range; IRSD = Index of Relative Socio-economic Disadvantage; SD = standard deviation.

Methods

In our retrospective cohort study, we analysed data from the South Australian Cancer Registry (SACR). Data for all patients with invasive cancers diagnosed during 1 January 1990 – 31 December 1999 and alive five years after their index cancer diagnosis were included, with follow-up data until death or 31 December 2016 (final censoring date), whichever occurred first.

Patients' index cancer diagnoses and demographic data — age, sex, ethnic background, Socio-Economic Indexes for Areas (SEIFA) Index of Relative Socio-economic Disadvantage (IRSD) category for area of residence¹⁰ — were provided by the SACR. The SA–Northern Territory DataLink (SA-NT DataLink) provided linked death data from Australian birth, death and marriage registries.

The outcomes of interest were time and cause of death. International Classification of Diseases (ICD)-9 codes were provided for deaths prior to 2007, and ICD-10 codes for deaths from 2007. ICD-9 codes were converted to ICD-10 codes using the SEER program conversion tables.¹¹ Given the small numbers in some categories, the 73 ICD cancer categories were collapsed to ten categories. Causes of death were classified according to World Health Organization recommendations.¹²

Statistical analysis

All-cause and cancer-specific mortality were calculated for each cancer group. Overall mortality and mortality by index cancer diagnosis topography were estimated in survival analyses. Patient study time was calculated from their index cancer diagnosis until death or 31 December 2016, whichever occurred first. The cumulative incidence function for mortality is reported, using a competing risks model to explore cancer cause-specific mortality, adjusted for other causes of death. The cumulative incidence function applies an overall survival function that counts deaths from competing events as well as the event of interest, thereby

reducing the risk of overestimating the probability of death from the event type of interest.¹³ The impact on survival (all-cause and cancer cause-specific mortality) of patients' characteristics was examined in multivariable Cox regression models; adjusted hazard ratios are reported with 95% confidence intervals (CIs).

Overall mortality rates were compared with those for the SA population using standard cohort techniques.^{14,15} As the life table for SA was available only for 1995–2015,^{16–18} data for patients diagnosed during 1995–1999 (about half the study population) were used to compare overall all-cause mortality with that of the SA population; the censoring date was accordingly set to 31 December 2015 for this analysis, and the number of person-years at risk calculated from five years after first diagnosis to the censoring date. The 429 people in the 1995–2015 study subsample with multiple cancers (2.4%) were excluded from this analysis.

The SMR was defined as the ratio of deaths in the study group to the estimated number of deaths in the corresponding component of the general population, calculated from the number of person-years at risk for each specific sex, 5-year age group, and one-year calendar period stratum and the corresponding population mortality rate. Cardiovascular disease was defined by the ICD-10 codes I10–I15, I20–I25, I26–I28, I34–I38, I42, I47–I49, I50–I51, I60–I71.

All analyses were conducted in Stata SE 15.0 or R 4.0.2.

Ethics approval

Our investigation was approved by the Human Research Ethics Committee of the South Australian Department for Health and Wellbeing (reference, HREC/16/SAH/72).

Results

A total of 32 646 people, including 314 children under 14 years of age at diagnosis, were diagnosed with invasive cancers

2 All-cause, cancer-specific, and non-cancer mortality (per 1000 person-years) for people alive 5 years after being diagnosed with invasive cancer during 1990–1999 and followed until 31 December 2016, by index cancer diagnosis

Index cancer at diagnosis	Patients at risk	Time at risk (years)	All-cause deaths	All-cause mortality (95% CI)	Cancer deaths*	Cancer-specific mortality* (95% CI)	Non-cancer deaths	Non-cancer mortality (95% CI)
Breast	6259	106 231	2743	25.8 (24.9–26.8)	1439	13.5 (12.9–14.3)	1304	12.3 (11.6–13.0)
Prostate	5976	81 053	4437	54.7 (53.2–56.4)	2005	24.7 (23.7–25.8)	2432	30.0 (28.8–31.2)
Skin	5185	93 764	1796	19.2 (18.3–20.1)	677	7.2 (6.7–7.8)	1119	11.9 (11.3–12.7)
Gastrointestinal	5033	77 384	3054	39.5 (38.1–40.9)	1119	14.5 (13.6–15.3)	1935	25.0 (23.9–26.1)
Lymphoma/other haematological	2686	40 374	1588	39.3 (37.4–41.3)	958	23.7 (22.3–25.3)	630	15.6 (14.4–16.9)
Head/neck	1784	29 017	973	33.5 (31.5–35.7)	377	13.0 (11.7–14.4)	596	20.5 (19.0–22.3)
Renal/testicular/bladder	1848	29 976	941	31.4 (29.4–33.5)	420	14.0 (12.7–15.4)	521	17.4 (16.0–18.9)
Lung	654	9045	448	49.5 (45.1–54.3)	247	27.3 (24.1–30.9)	201	22.2 (19.4–25.5)
Gynaecological	1613	28 507	636	22.3 (20.6–24.1)	261	9.2 (8.1–10.3)	375	13.2 (11.9–14.6)
Other/unknown	1608	27 333	652	23.9 (22.1–25.8)	342	12.5 (11.3–13.9)	310	11.3 (10.1–12.7)
Total	32 646	522 680	17 268	33.0 (32.5–33.5)	7845	15.0 (14.7–15.3)	9423	18.0 (17.7–18.4)

CI = confidence interval. * Death caused by any cancer, but not necessarily the index cancer.

3 All-cause and cancer cause-specific mortality for people alive 5 years after being diagnosed with invasive cancer during 1990–1999 and followed until 31 December 2016: Cox regression analyses

	All-cause mortality	Cancer cause-specific mortality*
Sex		
Female	1	1
Male	1.28 (1.23–1.34)	1.36 (1.28–1.45)
Age at diagnosis, years		
< 40	1	1
40–49	2.07 (1.83–2.34)	2.00 (1.74–2.30)
50–59	3.47 (3.10–3.88)	2.87 (2.52–3.26)
60–69	7.26 (6.52–8.08)	3.98 (3.52–4.51)
70–79	14.7 (13.2–16.3)	5.36 (4.73–6.08)
≥ 80	26.2 (23.4–29.4)	6.50 (5.62–7.52)
Ethnic background		
European	1	1
Asian	0.59 (0.46–0.76)	0.71 (0.51–0.99)
Aboriginal and Torres Strait Islander Australians	1.46 (1.15–1.85)	1.53 (1.11–2.11)
Unknown	0.20 (0.18–0.23)	0.09 (0.07–0.12)
Socio-economic status (IRSD quintile)		
1 (most disadvantaged)	1	1
2	0.96 (0.92–1.01)	0.98 (0.91–1.05)
3	0.90 (0.86–0.94)	0.91 (0.85–0.97)
4	0.94 (0.90–0.99)	0.95 (0.88–1.02)
5 (least disadvantaged)	0.86 (0.82–0.90)	0.87 (0.81–0.94)
Multiple cancer diagnosis		
No	1	1
Yes	1.53 (1.44–1.62)	2.32 (2.15–2.50)
Diagnosis year		
1990–1991	1	1
1992–1993	0.97 (0.93–1.02)	0.93 (0.86–0.997)
1994–1995	0.96 (0.91–1.00)	0.94 (0.87–1.01)
1996–1997	0.93 (0.88–0.97)	0.91 (0.85–0.98)
1998–1999	0.95 (0.90–0.995)	0.93 (0.86–0.998)
Index cancer diagnosis group		
Breast	1	1
Prostate	1.11 (1.04–1.18)	1.08 (0.98–1.19)
Skin	0.80 (0.75–0.85)	0.54 (0.49–0.60)
Gastrointestinal	0.95 (0.90–1.00)	0.73 (0.67–0.79)
Lymphoma/other haematological	1.49 (1.40–1.59)	1.66 (1.52–1.82)
Head/neck	1.16 (1.07–1.26)	0.85 (0.75–0.96)
Renal/testicular/bladder	1.01 (0.93–1.09)	0.83 (0.74–0.94)
Lung	1.55 (1.40–1.72)	1.53 (1.33–1.77)
Gynaecological	0.95 (0.87–1.03)	0.73 (0.64–0.83)
Other/unknown	1.25 (1.15–1.37)	1.13 (1.002–1.28)

CI = confidence interval. *Death caused by any cancer, but not necessarily the index cancer. † The multivariable Cox regression models include all variables reported in the table.

during 1990–1999 and were alive five years after the index cancer diagnosis. Most patients were of European ancestry (30 309, 93%), and 16 400 were male (50%); the mean age at diagnosis was 60.3 years (standard deviation [SD], 15.7 years). The most frequent cancer types were breast (6259, 19.2%), prostate (5976, 18.3%), skin (5185, 15.9%), and gastrointestinal cancers (5033, 15.4%); 1572 people (4.8%) had multiple cancer types (Box 1).

By the end of 2016, median follow-up time was 17 years (range, 5–26 years; interquartile range, 11–21 years). A total of 17 268 deaths were recorded (53% of patients): 7845 attributed to cancer (24% of patients, 45% of deaths) and 9423 attributed to non-cancer causes (29% of patients, 55% of deaths). The mean age at death was 80.6 years (SD, 11.4 years). Cause of death information was missing in 2025 cases (11.7%); these cases were included in the total death count for our analyses, but were excluded from calculations of proportions for leading causes of death.

Among 9423 non-cancer cause deaths, 4612 were caused by cardiovascular diseases (14.1% of patients, 26.7% of deaths, 51.1% of non-cancer deaths); 338 deaths were attributed to cardiac failure (2.22% of deaths). Ischaemic heart disease was the leading cause of death (2393 deaths, 15.7%), followed by prostate cancer (1424, 9.3%), cerebrovascular disease (1175, 7.7%), and breast cancer (1118, 7.3%). Breast cancer was the leading cause of death in women (1112, 17.1%), followed by ischaemic heart disease (940, 14.5%) and cerebrovascular disease (546, 8.4%); ischaemic heart disease was the leading cause of death in men (1453, 16.6%), followed by prostate cancer (1424, 16.3%) and cerebrovascular disease (629, 7.2%) (Supporting Information, tables 1 and 2).

All-cause and cancer cause-specific mortality: by cancer type

The highest all-cause mortality rates were for patients with prostate cancer (54.7 per 1000 person-years) and lung cancer (49.5 per 1000 person-years). The highest cancer cause-specific mortality rates were for patients with lung cancer (27.3 per 1000 person-years) and prostate cancer (24.7 per 1000 person-years). For non-cancer deaths, the highest mortality rates were for people with prostate cancer (30.0 per 1000 person-years) and gastrointestinal cancer (25.0 per 1000 person-years) (Box 2).

All-cause and cancer cause-specific mortality: by patient characteristics

All-cause mortality risk was greater for male patients (adjusted hazard ratio [aHR], 1.28; 95% CI, 1.23–1.34), for people over 40 years of age at diagnosis, for Aboriginal and Torres Strait Islander Australians (v European background: aHR, 1.46; 95% CI, 1.15–1.85), and for patients with multiple tumours (aHR, 1.53; 95% CI, 1.44–1.62); risk was lower for patients of Asian background (v European: aHR, 0.59; 95% CI, 0.46–0.76) and for patients from

areas of lesser socio-economic disadvantage (IRSD quintiles 3–5). All-cause mortality risk for patients diagnosed during 1996–1997 (aHR, 0.93; 95% CI, 0.88–0.97) or 1998–1999 (aHR, 0.95; 95% CI, 0.90–1.00) was lower than for those diagnosed during 1990–1991. All-cause mortality risk was higher for patients with prostate cancer, lymphoma/other haematological cancer, head and neck cancer, or lung cancer than for those with breast cancer, and lower for those with skin cancer (Box 3).

Cancer cause-specific mortality risk was higher for male patients (aHR, 1.36; 95% CI, 1.28–1.45), for people over 40 years of age at diagnosis, for Aboriginal and Torres Strait Islander Australians (aHR, 1.53; 95% CI, 1.11–2.11), for patients with multiple tumours (aHR, 2.32; 95% CI, 2.15–2.50), and for patients from areas of greater socio-economic disadvantage. All-cause mortality risk for patients diagnosed during 1996–1997 was lower than for those diagnosed during 1990–1991 (aHR, 0.91; 95% CI, 0.85–0.98). Cancer cause-specific risk was higher for patients with lymphoma/other haematological cancer or lung cancer than for those with breast cancer, and lower for those with head and neck, renal/testicular/bladder, or gynaecological cancers (Box 3).

Standardised mortality ratios

The overall SMR for the study group was 1.24 (95% CI, 1.22–1.25); all-cause and cardiovascular death SMRs by sex, age at diagnosis, follow-up period, and index cancer are reported in the Supporting Information, table 3. The cumulative incidence of cardiovascular deaths exceeded that of cancer cause-specific deaths from 13 years after index cancer diagnosis (Box 4).

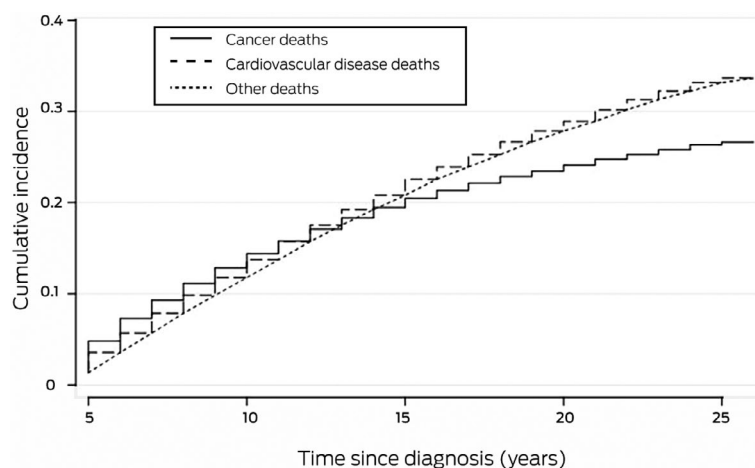
Discussion

In this large population-based study, long term mortality among people with cancer and alive five years after diagnosis exceeded that for the general SA population, with cardiovascular disease a major competing cause of death.

The deaths of 4612 people with cancer and alive five years after diagnosis were attributed to cardiovascular diseases; that is, 26.7% of all deaths and 56.1% of non-cancer deaths. These estimates are higher than those derived from a recent analysis of cardiovascular mortality data in the SEER database, in which 11% of all deaths and 43% of non-cancer deaths were attributed to cardiovascular diseases,¹⁹ and those of the 2010 Korean study (7.5% of all deaths, 31% of non-cancer deaths).⁹ Our finding is probably explained by our longer follow-up and our inclusion of long term survivors and a smaller number of early cancer-related deaths. We found that by 13 years after the index cancer diagnosis the cumulative number of cardiovascular deaths exceeded that of cancer cause-specific deaths, underscoring the importance of longer follow-up. Our findings are also consistent with the steady rise in cumulative cardiovascular mortality reported by an Australian study of early competing causes of death among patients with cancer.⁷

While the risks of cardiovascular disease in people with cancer have previously been reported, our study was unique in its focus on long term survivors and its longer follow-up period. Our findings may partly reflect the high prevalence of and mortality from

4 Cumulative incidence function of mortality among people alive 5 years after being diagnosed with invasive cancer during 1990–1999 and followed until 31 December 2016



cardiovascular disease in Australia,²⁰ but we also found that cardiovascular mortality was higher than in the general population, consistent with an earlier Australian study of non-cancer mortality among people with cancer.²¹ Our findings suggest an interaction between cancer or its treatment and cardiovascular risk factors. The interaction may reflect a biological phenomenon (such as a direct toxic effect of anti-cancer treatment on the heart or vascular system),²² or it may reflect lack of prioritisation of cardiovascular disease by patients, or health care focused on treating cancer.²³ It is notable that cardiac failure was a relatively infrequent cause of death (2.2% of all deaths), suggesting that treatment toxicity, which tends to cause cardiac failure, may lead to earlier mortality, but that later mortality from cardiovascular disease is driven more by existing risk factors and background population risk. The relative contributions of these factors in patients with different cancer types should be further examined.

Death from cardiovascular disease annuls any benefits of anti-cancer treatment, and identifying cancer survivors most at risk of cardiovascular disease is critical. Specific risk estimates have been reported for some cancers, such as Hodgkin disease,²⁴ but not for other cancer types. Managing cardiovascular disease risk factors and providing interventions for the people at greatest risk (men, older people, Indigenous patients with cancer and comorbid conditions), for whom outcomes are inferior to those of other patient groups,^{25,26} should be prioritised. Treating comorbid conditions has recently been identified as an important component of survivorship care,²⁷ but management of cardiovascular risk factors has not always been a routine part of cancer care; the emergence of cardio-oncology may change this situation.²⁸

Limitations

The long follow-up period and complete population data were strengths of our study. But it is possible that cancer had been incorrectly recorded as the cause of death for some people with histories of cancer, potentially leading to underestimation of non-cancer causes of death. Further, the estimated mortality rates for the general population are based on data that also include people with cancer, leading to underestimation of the difference between mortality rates for people with and without cancer. We had no information about comorbid conditions or prior cancer treatment for patients, and therefore could not assess their impact on

mortality and causality. These findings suggest that it would be useful to include data on these variables in the routine cancer registry dataset.

Conclusion

We found that mortality among long term cancer survivors exceeds that of the general population, with cardiovascular disease a major competing cause of death. Cancer control systems should incorporate monitoring of long term survivorship outcomes,

including non-cancer-related mortality, and manage risk factors for premature death from non-cancer causes.

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Supporting Information

Additional Supporting Information is included with the online version of this article.