# Death of a Child and Mortality after Cancer: A Nationwide Cohort Study in Sweden

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## ABSTRACT

**Background:** The death of a child is a traumatic life event that may influence mortality in patients with cancer. Only a few studies investigated this association and their findings have been mixed. We analyzed whether the death of a child is associated with mortality in patients with cancer.

**Methods:** We conducted a cohort study of 371,673 parents who were diagnosed with cancer in Sweden during 1973 to 2014 by linking several population-based registers. We analyzed the association between the death of a child after the diagnosis of cancer and mortality using Cox proportional hazards models with time-varying exposure.

**Results:** The death of a child was associated with an increased risk of mortality [HR, 1.27; 95% confidence intervals (CI), 1.17–1.39]. The association was present not only in case of children's death due to cancer or other natural deaths, but also in case of unnatural deaths. Mortality was increased only in the long-term follow-up period (HR, 1.42; 95% CI, 1.29–1.56), but not in the short-term (HR, 0.95; 95% CI, 0.78–1.15). The association was most pronounced following loss of an adult child and for patients with reproductive cancers.

**Conclusions:** Death of a child is associated with increased risks of overall and long-term mortality in patients with cancer. The findings that the association was present not only in case of natural but also in case of unnatural deaths suggests that stress-related mechanisms may also operate.

**Impact:** Our findings highlight the importance of psychosocial support for patients with cancer experiencing severe stress.


## Introduction

The death of a close relative is one of the most stressful life events and is associated with increased risks of psychiatric and somatic morbidity and mortality (1). Bereavement may induce adverse changes in health behaviors and in neuroendocrine and immune activity, which in turn may influence cancer development and prognosis (2, 3). Increasing evidence suggests that bereavement, particularly following the loss of a child, may increase cancer incidence (4–6). However, only a few studies have analyzed the association between loss of a child and mortality in patients with cancer. Levav and colleagues found that the death of a child (in war or in accident) after, but not before, a cancer diagnosis was associated with an increased risk of mortality (7). Li and colleagues found in a Danish population-based study that parents who lost a child prior to their cancer diagnosis had a modestly increased risk of death from cancer (8). In contrast, Kvikstad and Vatten in a sample of Norwegian women and Schorr and colleagues in an Israeli sample found no increased mortality risk among study participants exposed to death of a child before their cancer diagnosis (9, 10). Most of these studies included deaths of children before but not after the diagnosis of cancer in the definition of their exposure, which may have contributed to an underestimation of the studied effects. None of these studies investigated short- and long-term mortality. Furthermore, although cancer is the most common cause of death in patients with cancer, with improved cancer survival, they have also increased risks of dying due to cardiovascular diseases (CVD) or unnatural causes (11–15); these outcomes have been shown to be associated with the death of a child (10, 16, 17), eventually more strongly than cancer. To what extent an increased risk of overall mortality after cancer, if any, is due to cancer or to other causes, particularly CVD or unnatural deaths, was not previously examined.

In this large Swedish register-based study, we investigated whether loss of a child is associated with poor survival in patients with cancer and whether this association differs according to the length of follow-up, cause of the parent's death, and characteristics of the loss.

## Materials and Methods

### Study population and design

We conducted a cohort study by linking individual-level data from several Swedish population-based registers, using the unique personal identification number that is assigned to all Swedish residents (18). We studied parents of children born during 1973 to 2014 and recorded in the Swedish Medical Birth Register. We identified parents of these children through the Multi-generation Register. We had information on mothers for 99.9% and on fathers for 83% of the children, resulting in 3,924,237 parents. Besides the children recorded in the Medical Birth Register during 1973 to 2014, we also identified parents' children who did not appear in the register during this period either because they were born before 1973 when the register was established, or because they were born abroad and were registered later. We obtained information on parents' cancer diagnosis from the Cancer Register that contains information on virtually all cancers in the country since 1958. In total, 371,676 of the above parents had at least one type of cancer. In case the parent had several cancers, we considered the cancer that occurred first after becoming a parent. After excluding three parents whose recorded date of death was before the date of the cancer

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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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Cancer Epidemiol Biomarkers Prev 2021;30:150–7

**doi:** 10.1158/1055-9965.EPI-20-0842

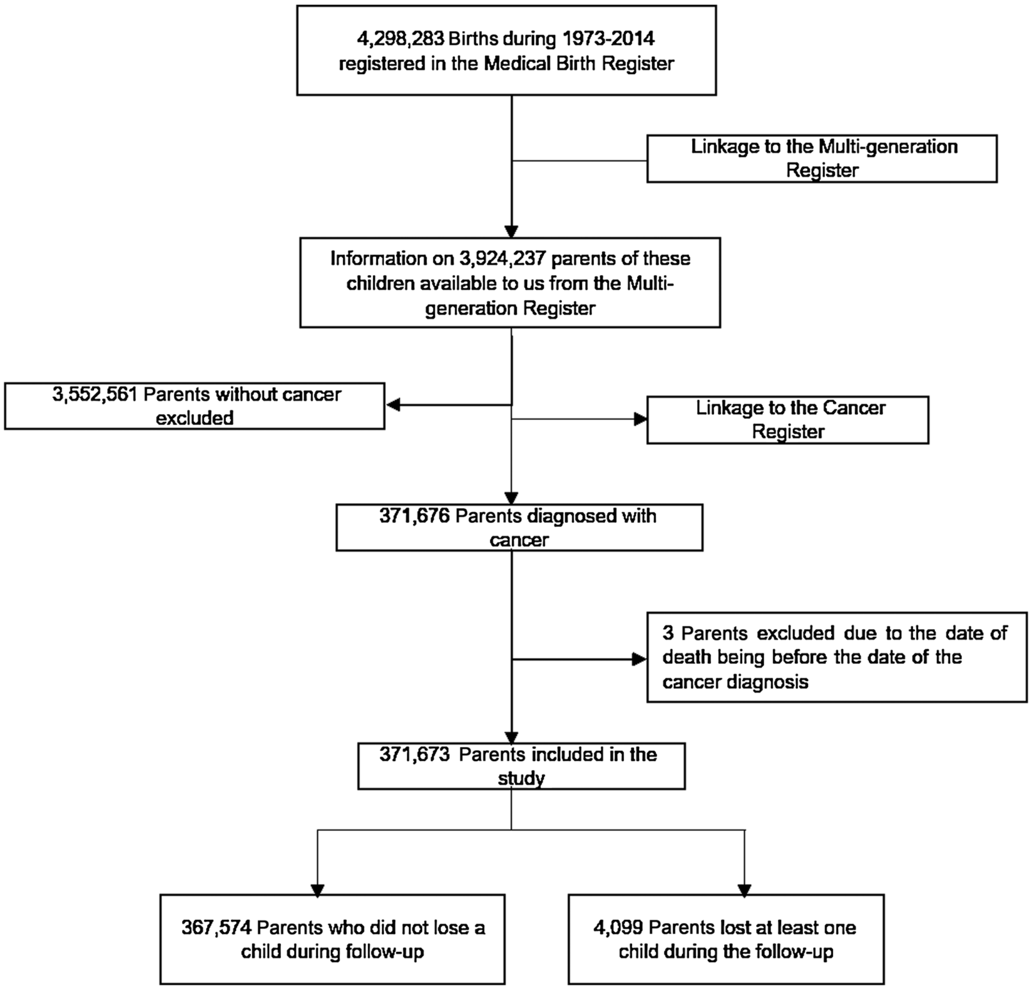


**Figure 1.**
The flowchart of the study population.

diagnosis, our study population consisted of 371,673 parents (**Fig. 1**).

The study was approved by the Regional Ethics Review Board in Stockholm.

## Measures

### Exposure

Information on children's date and cause of death was obtained from the Cause of Death Register. We defined exposure as loss of a live born child after the date of the index cancer diagnosis. We treated exposure as a time-varying variable; the person-years of each parent were calculated from the date of the cancer diagnosis. Parents who experienced the loss of a child contributed person-years to the unexposed group until the date of the child's death and to the exposed group afterwards, whereas parents without loss of a child contributed all person-years to the unexposed period. In case a parent lost several children after the index cancer, we considered the first loss in the analyses. We classified exposed parents according to the deceased child's age at the time of loss (0–5, 6–12, 13–18, and ≥18 years), the cause of the child's death (cancer, other natural causes, and unnatural causes), the number of the parents' live children at the time of loss (0 and ≥1), and the child's gender (male and female). Children's causes of death were classified as unnatural death, death due to cancer, and other natural death based on the International Classification of Diseases (ICD) codes presented in Supplementary Table S1.

### Outcome and follow-up

Information on parent's death after the diagnosis of cancer was obtained from the Cause of Death Register. Follow-up started on the date of cancer diagnosis and ended on the date of death, emigration, or December 31, 2014. We analyzed total mortality and cause-specific mortality, classified as death due to cancer, CVD, other natural causes, and unnatural deaths using the ICD codes in Supplementary Table S1.

### Covariates

Parents were linked to the Register of the Total Population, the Register of Incomes and Taxes, and the Education Register to obtain information on year of birth, country of birth (Sweden or other), marital status, personal income, and education, respectively. We calculated age at the time of cancer diagnosis by subtracting the year of birth from the year of the cancer diagnosis. Information on marital status, personal income, and education was retrieved for the year

Published OnlineFirst October 20, 2020; DOI: 10.1158/1055-9965.EPI-20-0842



before the cancer diagnosis to ensure that it preceded both exposure and outcome. In case this information was missing, we used information on these variables up to 5 years before the date of diagnosis, from the year with available data that was closest to the date of cancer diagnosis. As the information on marital status was available to us from 1973, if the cancer was diagnosed before or during 1974, we categorized marital status using information from 1973. The marital status was classified as single, widowed, divorced/separated, and married/living in registered partnership. Likewise, if the cancer occurred before or in 1991, we defined education based on the level from 1990. We classified education as primary (≤9 years), secondary or postsecondary education (10–14 years), and college or university (≥15 years). To account for inflation during the study period, we classified personal income based on the tertile distribution of each 10-year interval during 1973 to 2014. The upper value of the first and the second tertile were 10,920 and 23,200 SEK for the period 1973 to 1979, 41,900 and 68,900 SEK for 1980 to 1989, 105,597 and 143,100 SEK for 1990 to 1999, 147,518 and 209,088 SEK for 2000 to 2009, and 181,868 and 272,612 SEK for ≥2010, respectively. Cancers were classified according to their ICD-7 code, as recorded in the Cancer Register since 1958, into 11 types as shown in Supplementary Table S2.

### Statistical analyses

We analyzed the association between loss of a child and mortality after cancer using Cox proportional hazard models with exposure treated as a time-varying variable, as described earlier; we compared the number of events/person-time after loss of a child to the number of events/person-time during unexposed periods (i.e., the reference). We tested the proportional hazards assumption by means of log–log curves and tests of interaction with time and the log of time. Because the 5-year survival rate is an important index to evaluate the prognosis of patients with cancer (19, 20) and because we observed some differences in the studied association according to the time since cancer, we present results with the total follow-up and with the follow-up split as the first 5 years versus the rest of the follow-up. In analyses with the first 5 years after the cancer, we censored parents alive at the 5-year follow-up. We restricted analyses concerning the link between death of a child and mortality after 5 years to study participants who were alive and did not emigrate from Sweden in the first 5 years after the cancer. We performed analyses with the exposure categorized according to the child's cause of death, the number of other children at the time loss, the child's age at loss, and the deceased child's gender; the events/person-time corresponding to each of these exposure categories was compared with unexposed events/person-time. We adjusted for the following potential confounders in our main models: age at cancer diagnosis, calendar year of the cancer diagnosis, education, personal income, type of cancer, and country of birth. As marital status is likely to be a further confounder, but because 101,766 (27.4%) participants lacked information on this measure, we adjusted for marital status in models restricted to participants with data on this variable. Confounders were chosen based on their known or possible association with death of a child and mortality after cancer, and not being on the pathway between exposure and outcome.

To study whether the investigated associations differ according to demographic and socioeconomic factors, we conducted stratified analyses with gender (father and mother), educational attainment (primary, secondary/postsecondary, and tertiary), age at cancer diagnosis (≤30, 31–40, 41–50, 51–60, and ≥61 years), and year of the index cancer (≤1979, 1980–1989, 1990–1999, 2000–2009, and ≥2010; indicative of available diagnostic procedures and treatment after cancer); we compared the number of events/person-time after loss of a child to the number of events/person-time during unexposed periods (i.e., the reference) within each strata. We repeated our main models with cause-specific mortality.

As some of the parents (both in the exposed and the unexposed group) are likely to have lost a child before their diagnosis of cancer and as for some of them the emotional impact of this event may have persisted after the cancer diagnosis, to investigate whether such a previous experience influenced our results, we rerun our main models after excluding parents who lost a child before the index cancer. As mortality in the early years after the cancer is high and time-on-study may be the appropriate time scale for the follow-up, long-term age-at-follow-up as a time scale may be increasingly important (21). Thus, to investigate the importance of the choice of the timescale for our results, we performed analyses also with age-at-follow-up as the underlying timescale. To investigate whether the association between the death of a child and mortality after cancer differs after a new cancer (possibly indicative of higher vulnerability to death), we performed analyses among those with a recorded second cancer in the Cancer Register. We also investigated whether the association differs according to number of deceased children.

Analyses were performed using SAS 9.4.

## Results

Compared with unexposed parents, exposed parents were younger at the time of the cancer diagnosis, more likely to be women, also more likely to be diagnosed with cancer in the earlier years of the follow-up, less likely to be married/in registered partnership, and more likely to have lower education and a higher personal income; they were more likely to have cancers of the female reproductive system, but less likely to have breast cancer, cancers of the digestive and respiratory system, male reproductive cancers, skin cancers, and hematologic malignancies (**Table 1**).

Death of a child was associated with an increased risk of overall mortality [adjusted HR, 1.27; 95% confidence interval (CI), 1.17–1.39; **Table 2**]. The association was present regardless of the cause of the child's death (cancer, other natural causes, or unnatural causes). The association was more pronounced in case of losses of adult children than in children aged <18 years and if the deceased was the only child. The association did not differ by the deceased child's gender.

When we split the follow-up at 5 years, we found an association between the loss of a child and mortality only after 5 years; the adjusted HR, 95% CIs were 0.95, 0.78–1.15 in the first 5 years and 1.42, 1.29–1.56 after 5 years of follow-up. There was no association between the death of a child and 5-year mortality when exposure was classified according to the child's cause of death, number of children at the time of loss, or age or gender of the deceased child. In contrast, the risk of death after 5 years was generally comparable, although somewhat stronger, with those in the analyses with the total follow-up (**Table 3**).

Death of a child was associated with an increased risk of death due to cancer only in the long-term follow-up and with increased risks of death due to CVD and due to other natural causes both in the total and in the long-term follow-up. Increased mortality rates due to unnatural causes in bereaved parents were seen in all studied follow-up periods, that is, overall, short-, and long-term (**Table 4**).

We found no strong evidence for differences in the association between death of a child and the risk of mortality by sociodemographic factors (Supplementary Table S3). In analyses stratified by cancer type, we observed an association between loss of a child and mortality in parents with breast cancer and cancers of the reproductive systems,

**Table 1.** Characteristics of the study participants according to exposure to death of a child.

| Variables | Unexposed ($n$ = 367,574) | Exposed ($n$ = 4,099) | $P$ value |
|---|---|---|---|
| Gender | | | <0.0001 |
| Male | 139,070 (37.8) | 1,089 (26.6) | |
| Female | 228,504 (62.2) | 3,010 (73.4) | |
| Education | | | <0.0001 |
| Primary (≤9 years) | 81,394 (22.1) | 1,361 (33.2) | |
| Secondary or postsecondary (10–14 years) | 214,742 (58.4) | 2,198 (53.6) | |
| College or university (≥15 years) | 64,045 (17.4) | 481 (11.7) | |
| Missing | 7,393 (2.0) | 59 (1.4) | |
| Personal income | | | <0.0001 |
| Low tertile | 122,130 (33.2) | 1,552 (37.9) | |
| Middle tertile | 122,360 (33.3) | 1,308 (31.9) | |
| High tertile | 122,481 (33.3) | 1,210 (29.5) | |
| Missing | 603 (0.2) | 29 (0.7) | |
| Marital status | | | <0.0001 |
| Single | 58,978 (16.1) | 741 (18.1) | |
| Widowed | 5,528 (1.5) | 63 (1.5) | |
| Divorced or separated | 49,726 (13.5) | 768 (18.7) | |
| Married or in registered partnership | 152,168 (41.4) | 1,935 (47.2) | |
| Missing | 101,174 (27.5) | 592 (14.4) | |
| Year of the index cancer | | | <0.0001 |
| ≤1979 | 11,676 (3.2) | 567 (13.8) | |
| 1980–1989 | 34,329 (9.3) | 1,009 (24.6) | |
| 1990–1999 | 62,903 (17.1) | 1,048 (25.6) | |
| 2000–2009 | 137,601 (37.4) | 1,179 (28.8) | |
| ≥2010 | 121,065 (32.9) | 296 (7.2) | |
| Age at the time of the index cancer (in years) | | | <0.0001 |
| ≤30 | 32,335 (8.8) | 790 (19.3) | |
| 31–40 | 66,414 (18.1) | 1,016 (24.8) | |
| 41–50 | 74,384 (20.2) | 805 (19.6) | |
| 51–60 | 91,466 (24.9) | 755 (18.4) | |
| ≥61 | 102,975 (28.0) | 733 (17.9) | |
| Country of birth | | | 0.0004 |
| Sweden | 331,142 (90.1) | 3,625 (88.4) | |
| Other country | 36,396 (9.9) | 474 (11.6) | |
| Type of cancer | | | <0.0001 |
| Cancer of the digestive system | 39,820 (10.8) | 281 (6.9) | |
| Cancer of the respiratory system | 13,772 (3.8) | 44 (1.2) | |
| Breast cancer | 55,500 (15.1) | 477 (11.6) | |
| Cancer of the female reproductive system | 98,867 (26.9) | 1,957 (47.7) | |
| Cancer of the male reproductive system | 46,572 (12. 7) | 382 (9.3) | |
| Cancer of the urinary tract system | 9,369 (2.6) | 104 (2.5) | |
| Skin cancer (including melanoma) | 42,333 (11.5) | 348 (8.5) | |
| Head and neck cancer | 7,245 (2.0) | 74 (1.8) | |
| Cancer of the nervous and endocrine system | 21,623 (5.9) | 213 (5.2) | |
| Hematologic malignancies | 18,900 (5.1) | 127 (3.1) | |
| Other cancers | 13,573 (3.7) | 92 (2.2) | |

both during the whole follow-up and 5 years after the cancer; an association in patients with digestive cancers and other cancers was observed only during the long-term follow-up. For most other types of cancers, the point estimates were comparable, but due to the low number of cases and events, the corresponding CIs were wide.

The association between death of a child and the total mortality risk did not change substantially after adjusting for marital status (adjusted HR, 1.25; 95% CI, 1.14–1.36; $n = 270,723$), excluding study participants who lost a child before their cancer diagnosis (adjusted HR, 1.25; 95% CI, 1.15–1.37; $n = 360,262$) or starting follow-up from the date of the second cancer among those with more than one cancer (adjusted HR, 1.30; 95% CI, 1.01–1.67; $n = 41,285$). The risk of mortality increased with the number of children deceased after the cancer; the adjusted HR and 95% CI corresponding to one and two or more losses were 1.23, 1.13–1.35 and 1.64, 0.82–3.29, respectively. Results were similar to those in the primary analyses, although the point estimates were slightly weaker, when we used age-at-follow-up as the underlying timescale (Supplementary Table S4).

## Discussion

We found that the death of a child is associated with an increased risk of overall mortality in patients with cancer, particularly after 5 years of follow-up. We observed an association not only in case of natural deaths of children, but also in case of unnatural deaths. The association was most pronounced if the parent lost their only child, if

Published OnlineFirst October 20, 2020; DOI: 10.1158/1055-9965.EPI-20-0842



**Table 2.** HRs and 95% CIs for mortality during the whole follow-up period according to death of a child.

| Category of exposure | Number of events/person-years | Mortality/$10^5$ person-years | Crude HR (95% CI) | Adjusted HR (95% CI)[a] |
|---|---|---|---|---|
| Unexposed | 80,048/3,505,008 | 2,284 | 1.00 | 1.00 |
| Exposed | 565/35,580 | 1,588 | 1.56 (1.44–1.70) | 1.27 (1.17–1.39) |
| Cause of the child's death | | | | |
| Death due to cancer | 128/5,599 | 2,286 | 2.18 (1.83–2.59) | 1.26 (1.05–1.50) |
| Death due to other natural causes | 247/19,955 | 1,238 | 1.25 (1.10–1.42) | 1.24 (1.08–1.41) |
| Death due to unnatural causes | 190/10,026 | 1,895 | 1.80 (1.56–2.08) | 1.32 (1.14–1.53) |
| Age of the child at loss | | | | |
| 0–5 years | 36/7,739 | 465 | 0.91 (0.33–0.64) | 1.02 (0.69–1.51) |
| 6–12 years | 17/2,048 | 830 | 0.85 (0.53–1.37) | 1.25 (0.65–2.41) |
| 13–18 years | 37/3,584 | 1,032 | 1.09 (0.79–1.50) | 1.10 (0.79–1.53) |
| ≥18 years | 475/22,210 | 2,139 | 2.07 (1.89–2.26) | 1.30 (1.19–1.43) |
| Number of alive children at the time of loss | | | | |
| 0 | 42/2,620 | 1,603 | 1.59 (1.18–2.15) | 1.90 (1.37–2.62) |
| ≥1 | 523/32,960 | 1,587 | 1.56 (1.43–1.70) | 1.24 (1.13–1.36) |
| Gender of the deceased child | | | | |
| Male | 357/22,530 | 1,585 | 1.56 (1.40–1.73) | 1.26 (1.13–1.41) |
| Female | 208/13,051 | 1,594 | 1.57 (1.37–1.80) | 1.29 (1.12–1.48) |

[a]Adjusted for age, calendar year of diagnosis, education, personal income, type of cancer, and country of birth.

the deceased child was an adult, and in patients with reproductive cancers. The increased risk of mortality after 5 years was not only due to cancer, but also deaths due to other natural causes and due to unnatural deaths.

Our findings that the death of a child was associated with a modestly increased risk of overall mortality corroborate those of Li and colleagues in a Danish population-based study (8) and of Levav and colleagues in an Israeli sample (10), both showing an association between the death of a child and poor survival after the cancer diagnosis. In contrast, Kvikstad and Vatten in a sample of Norwegian women and Schorr and colleagues in an Israeli sample found no increased risk of mortality among participants who lost a child before their cancer diagnosis (9, 10). Differences in the time frame for defining exposure (before versus after cancer), in statistical power or characteristics of the study population might have contributed to differences between our and these two later studies (9, 10). Our findings are also in line with the meta-analysis conducted by Chida and colleagues reporting that patients with cancer exposed to stress-related psychosocial factors had a 29% increased mortality risk (22, 23) and those of Falagas and colleagues who found that psychosocial factors were associated with poor survival in patients with breast cancer (24). The findings also corroborate those of several population-based studies, suggesting that parents who lost a child had an increased risk of total and cause-specific mortality (10, 16, 25) or of certain types of cancers (5, 7). Our study extends the results of the earlier studies regarding the association between death of a child and the risk of mortality after cancer by studying a very large sample that allowed to explore the association on the short- and the long-term, to perform subgroup analyses and to investigate cause-specific mortality.

**Table 3.** HRs and 95% CI for mortality during the first or after 5 years according to death of a child.

| | First 5 years | | | After 5 years | | |
|---|---|---|---|---|---|---|
| Category of exposure | Number of events/ person-years | Mortality/$10^5$ person-years | Adjusted HR (95% CI)[a] | Number of events/ person-years | Mortality/$10^5$ person-years | Adjusted HR (95% CI)[a] |
| Unexposed | 59,443/1,348,817 | 4,407 | 1.00 | 20,605/2,156,191 | 956 | 1.00 |
| Exposed | 116/3,095 | 3,748 | 0.95 (0.78–1.15) | 449/32,485 | 1,382 | 1.42 (1.29–1.56) |
| Cause of the child's death | | | | | | |
| Death due to cancer | 20/552 | 3,623 | 0.91 (0.68–1.22) | 108/5,047 | 2,140 | 1.54 (1.27–1.86) |
| Death due to other natural causes | 44/1,517 | 2,900 | 1.07 (0.88–1.31) | 203/18,438 | 1,101 | 1.34 (1.16–1.55) |
| Death due to unnatural causes | 52/1,026 | 5,068 | 1.21 (0.98–1.50) | 138/8,999 | 1,534 | 1.44 (1.22–1.71) |
| Age of the child at loss | | | | | | |
| 0–5 years | 11/642 | 1,713 | 0.91 (0.56–1.46) | 25/7,097 | 352 | 0.93 (0.61–1.42) |
| 6–12 years | 5/152 | 3,289 | 1.03 (0.43–2.48) | 12/1,896 | 633 | 1.01 (0.48–2.11) |
| 12–18 years | 6/214 | 2,804 | 0.75 (0.43–1.31) | 31/3,370 | 920 | 1.26 (0.88–1.82) |
| ≥18 years | 94/2,087 | 4,504 | 1.14 (0.99–1.31) | 381/20,122 | 1,893 | 1.49 (1.34–1.65) |
| Number of alive children at the time of loss | | | | | | |
| 0 | 7/235 | 2,979 | 1.61 (0.94–2.77) | 35/2,385 | 1,468 | 1.88 (1.33–2.66) |
| ≥1 | 109/2,681 | 4,066 | 1.06 (0.93–1.21) | 414/30,100 | 1,375 | 1.39 (1.26–1.54) |
| Gender of the deceased child | | | | | | |
| Male | 70/1,966 | 3,561 | 1.13 (0.97–1.33) | 287/20,564 | 1,396 | 1.41 (1.25–1.59) |
| Female | 46/1,130 | 4,071 | 0.99 (0.79–1.25) | 162/11,921 | 1,359 | 1.43 (1.22–1.68) |

[a]Adjusted for age, calendar year of diagnosis, education, personal income, type of cancer, and country of birth.

**Table 4.** HRs and 95% CIs for cause-specific mortality in the total follow-up and with the follow-up split at 5 years.

| | Overall | | First 5 years | | After 5 years | |
|---|---|---|---|---|---|---|
| Cause of death | Mortality/$10^5$ person-years | HR (95% CI)[a] | Mortality/$10^5$ person-years | HR (95% CI)[a] | Mortality/$10^5$ person-years | HR (95% CI)[a] |
| Cancer | 1,953 | 1.07 (0.96–1.19) | 3,995 | 0.86 (0.70–1.07) | 693 | 1.21 (1.06–1.37) |
| Unnatural death | 27 | 2.44 (1.62–3.68) | 30 | 3.27 (1.05–10.21) | 25 | 2.33 (1.50–3.63) |
| CVD | 148 | 1.39 (1.12–1.72) | 185 | 0.79 (0.35–1.75) | 124 | 1.46 (1.17–1.83) |
| Other natural death | 149 | 1.68 (1.37–2.06) | 195 | 1.38 (0.72–2.66) | 120 | 1.65 (1.33–2.06) |

[a]Adjusted for age, calendar year of diagnosis, education, personal income, type of cancer, and country of birth.

To our knowledge, our study is the first to systematically investigate the association between the death of a child and survival in parents with cancer by the length of follow-up. We found an increased mortality risk only in the long-term follow-up period (after 5 years from cancer diagnosis), but not in the short-term (in the first 5 years from cancer diagnosis). As many patients with cancer experience high stress after the cancer diagnosis, relative differences in mortality between the exposure groups may not be apparent during the early follow-up. Furthermore, it is well known that the 5-year survival after cancer is strongly influenced by factors such as the type of cancer, pathology, clinical stage, and treatment (26–29); psychologic stress, even if severe, may play a less important role during this period (23). However, in a relatively more stable phase after the diagnosis of cancer (i.e., after 5 years), psychosocial factors, as suggested also by the meta-analysis of Chida and colleagues (23), may have a more important contribution to mortality than in the first 5 years.

In an attempt to disentangle causal mechanisms and to identify groups at the highest risk of mortality after bereavement, we performed analyses with several exposure categories. Our finding that the association was present not only in case of deaths due to cancer or other natural deaths, but also in case of unnatural deaths suggest that stress-related mechanisms may also contribute to the observed association. Compared with natural deaths, unnatural deaths of children are less likely to be influenced by genetic or environmental factors (e.g., socioeconomic, lifestyle-, or housing-related) that increase the risk of mortality after cancer; thus, the effect of unnatural deaths on mortality after cancer is less likely to be confounded by such characteristics shared by family members. We found, as did Schorr and colleagues (10), that patients who lost their only child had a higher risk of mortality than those with at least one more child, suggesting that having a child may alleviate parents' grief (16, 30). When investigating the importance of the child's age at loss, we found that only death of an adult child is associated with mortality after cancer, a finding in line with those of Schorr and colleagues and Fang and colleagues (5, 10). Besides differences in parents' age and stronger emotional bonds to their adult than to minor children, differences in statistical power may have contributed to these findings as the number of parents who lost an adult child was substantially larger than that of parents who lost a minor child. A further possible explanation is that in case of losses of adult children, the patient may have met extra requirements in the care and the emotional support of their grandchildren.

An increasing number of studies suggest that adverse psychosocial factors are involved in the causation of breast, digestive, hematologic, and immune- and hormone-related malignancies (23, 31, 32). This is also supported by our results that an association between the death of a child and an increased mortality risk is observed in case of patients with breast and reproductive cancers during the whole follow-up and for digestive and other cancers in the long-term follow-up. Reproductive cancers often deprive the patients of the possibility of a new pregnancy, indicating that these patients, in particular those who lost their only child, are unable to compensate for the loss (33, 34). Their loss of fertility is likely to be an additional important source of grief. Furthermore, the better statistical power in case of reproductive cancers may have also contributed to the associations observed in case of these cancers.

The findings that the death of a child was associated not only with an increased cancer mortality in the long-term follow-up, but also with parents' risk of death due to CVD, other natural causes, and of unnatural causes is in line with earlier findings showing increased risks of coronary heart disease, cardiovascular mortality (10, 17), and deaths due to unnatural causes (16) in bereaved parents. The main mechanisms linking stress to total and cancer mortality involve the prolonged activation and the dysregulation of the hypothalamic–pituitary–adrenal axis and the autonomic nervous system, poor mental health, and adverse changes in lifestyle and in metabolic and endocrine activity. These in turn may modulate the activity of multiple components of the tumor microenvironment (35) and accelerate tumor cell proliferation by altering glucose uptake rate (23).

Our study has several strengths. First, given the prospective design and that information on exposure was registered before and independently of the outcome, reverse causation and recall bias are not likely to explain our findings. Furthermore, as registration of death in Sweden is of high quality, misclassification of exposure or outcome is likely to be minimal, if at all present; the death of a child is an objective source of stress that is likely to induce physiologic changes for almost all individuals. The large sample size allowed us to analyze cancer survival not only during the whole follow-up but also after splitting it at 5 years, to perform analyses with cause-specific mortality, several subtypes of exposure, several potential effect modifiers, and to adjust for several confounders.

Our study also has several limitations. First, although we adjusted for several confounders, we cannot exclude the possibility of residual confounding from, for example, genetic factors, mental health, lifestyle, etc. (36, 37). Second, we had no information on predictors of survival after cancer such as clinical stage at cancer diagnosis, pathology, and treatment (38, 39). To substantially confound the investigated associations, these factors would have to be not only predictors of cancer survival, but also to be strongly associated with exposure to the death of a child (which is not likely) and to be unrelated to the confounders we already adjusted for. Instead, clinical stage at cancer diagnosis and treatment are likely to act as effect modifiers of the studied association; thus, not including them in our analyses would prevent identifying the particularly vulnerable groups or the factors that may buffer the effect of severe stress on mortality after cancer.

Similarly, we did not have information on psychosocial resources such as religion or spirituality (40), social support, or participation in psychological interventions related to cancer (e.g., cognitive behavioral therapy, relaxation therapy, support expressive groups, psychoeducational programs, etc.; refs. 41, 42), which may influence parents' ability to adjust to a severe life event such as the loss of a child and a diagnosis of cancer, and which may buffer the effect of these events on mortality. We hope that our findings may inspire others with further clinical and psychologic data to investigate in more depth the association between severe stress and mortality after cancer. Third, although our sample size was very large, the power in some of the subanalyses may have been limited. Fourth, it is not clear whether our findings may be generalized to countries with health care systems and sociocultural contexts (e.g., in terms of cancer screening and treatment, psychiatric care, child mortality, religion, social support, or socioeconomic resources) substantially different from that of Sweden.

### Conclusions

We found that patients who experienced the loss of a child after a cancer diagnosis have a higher risk of total and cause-specific mortality, particularly in the long-term follow-up period. The increased mortality risk was observed not only for offspring deaths due to cancers and for other natural deaths, but also for unnatural deaths, the effect of which is less likely to be due to confounding by shared familial factors. The association was more pronounced for patients who lost their only child, an adult child, and for patients with reproductive cancers. Our findings highlight the importance of psychosocial support for patients with cancer experiencing severe stress. Further studies are needed to elucidate the mechanisms underlying the observed association.

## Authors' Disclosures

K.D. László reports grants from Swedish Council for Working Life and Social Research during the conduct of the study, as well as grants from KI Research Foundation, Swedish Heart and Lung Foundation, Clas Groschinsky Foundation, and Swedish Society of Medicine and other from Karolinska Institutet (salary) outside the submitted work. No disclosures were reported by the other authors.

## Authors' Contributions

**Y. Wang:** Data curation, formal analysis, investigation, methodology, writing–original draft, project administration. **D. Wei:** Data curation, formal analysis, validation, investigation, methodology, writing–review and editing. **H. Chen:** Data curation, methodology. **B. Chen:** Supervision, methodology. **J. Li:** Conceptualization, methodology, writing–review and editing. **K.D. László:** Conceptualization, resources, data curation, supervision, funding acquisition, methodology, project administration, writing–review and editing.

## Acknowledgments

Financial support for the study was obtained from the Swedish Council for Working Life and Social Research granted to K.D. László (grant no. 2015-00837) and from the China Scholarship Council granted to Y. Wang (grant no. 201806090228), to D. Wei (grant no. 201700260276), and to H. Chen (grant no. 201700260296). J. Li is supported by the Novo Nordisk Foundation (grant no. NNF18OC0052029), the Danish Council for Independent Research (grant no. DDF-6110-00019B and 9039-00010B), and the Karen Elise Jensens Fond (grant no. 2016).

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Received June 3, 2020; revised August 27, 2020; accepted October 13, 2020; published first October 20, 2020.

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Published OnlineFirst October 20, 2020; DOI: 10.1158/1055-9965.EPI-20-0842

Cancer Epidemiology, Biomarkers & Prevention

American Association for Cancer Research

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*Cancer Epidemiol Biomarkers Prev* 2021;30:150-157. Published OnlineFirst October 20, 2020.