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Parental cancer diagnosis and child mortality - a population-based cohort study in Sweden

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Abstract

Objective: Cancer diagnosis is known to induce severe psychological stress for the diagnosed patients; however, how it affects the next-of-kin is less well documented. This study aimed to assess the impact of parental cancer on the risk of childhood death.

Methods: A population-based cohort study was conducted using the Swedish national registries, including 2,871,242 children followed during the period of 1991-2009. Parental cancer diagnosis was defined as a time-varying exposure. We used Cox proportional hazards regression to calculate the hazard ratio (HR) and its corresponding 95% confidence interval (CI) as an estimate of the association between parental cancer and childhood mortality. We adjusted for attained age, sex, gestational age, mode of delivery and birth weight of the child, maternal age at child's birth, as well as educational level and socio-economic classification of the parents in the analyses.

Results: Among 113,555 children with parental cancer, 127 deaths occurred during 561,198 person-years of follow-up. A parental cancer diagnosis was associated with an increased rate of death among children at the age of 1-18 (HR for all-cause death: 1.39; 95% CI: 1.16-1.66). For young children (aged 1-12), an increased rate was only noted for death due to cancer (HR: 2.06; 95% CI: 1.13-3.75) after parental cancer diagnosis. Among adolescents (aged 13-18), an increased rate was noted for all-cause death (HR: 1.52; 95% CI: 1.25-1.86), and for both non-cancer-related (HR: 1.43; 95% CI: 1.14-1.79) and cancer-related (HR: 2.07; 95% CI: 1.33-3.24) death in the exposed children.

Conclusion: Children have an increased rate of death if they have a parent diagnosed with cancer as compared to children without such experience; this association appears to be slightly stronger among adolescents.

Keywords: child of impaired parents, death, cancer, cohort study

1. Introduction

As the worldwide cancer cases have dramatically increased over the last few decades, the population of children exposed to a parent with cancer is expanding. For example, around 4% of the Norwegian population under the age of 25 years have or have had parents diagnosed with cancer [1]. A nationwide survey in the United States reported that 14% of cancer patients resided with their minor children [2].

A cancer diagnosis can cause considerable stress for patients and their partners, in terms of a higher risk for mental disorders, cardiovascular diseases and suicide [3-9]. Despite the potentially extensive public health impact of exposure to parental cancer, research on the well-being of children living with a parent with cancer has been largely overlooked. Early adversity may program the development of the hypothalamic-pituitary-adrenal axis, cause alterations of the neurochemical and immunologic activities, leading to both neurobehavioral symptoms and different somatic diseases [10, 11]. Previous studies have highlighted that children with a parent with cancer did appear to be at higher risks of psychological, behavioral and social problems, however these studies were usually cross-sectional and with small sample sizes [12-14]. A recent population-based cohort study from Sweden reported a higher risk of death due to perinatal and congenital conditions in children who were born around a cancer diagnosis of the mother [15]. This study specifically hypothesized that carcinogenesis itself or cancer treatment may bear harmful impact on childhood survival, especially during infancy [15]. However, whether the experience of having a parent (father or mother) with cancer is associated with the risk of death beyond infancy has not been investigated in population-based studies.

Therefore, we aimed to enrich the understanding on the impact of parental cancer on children's health by studying the risk of death among children at the age of 1-18 years subsequent to a parental cancer diagnosis, using data from several Swedish national registers. We hypothesized that a cancer diagnosis in a parent might be associated with a higher risk of death in their children at different stages of childhood above one year of age.

2. Materials and methods

This study is embedded in a population-based cohort. Using the unique national registration numbers that every Swedish resident is assigned, we collected information on children and their parents from the Swedish Multi-Generation Register, Cancer Register, Cause of Death Register, Register of Education, Medical Birth Register and several Swedish Population and Housing Censuses.

2.1. Participants

The Multi-Generation Register contains information on persons who were born in 1932 or later together with their parents [16]. To be included in the present analysis, a child must have both biological parents identifiable from the Multi-Generation Register and the parents had to be alive and free of cancer before the child turned one year of age. Familial linkage in the Multi-Generation Register is available for around 60% of those who died between 1968 and June 1991, and for more than 90% of those alive in July 1991 onwards, so we defined July 1991 to December 2009 as the study period. Since the present version of the Medical Birth Register was updated until the end of 2002, the youngest participants of the cohort was born in December 2002. Given the targeted age span and study period, we included all children recorded in the Multi-Generation Register that were born in Sweden between July 1973 and December 2002.

2.2. Exposure

Both parents of the children were linked to the Cancer Register to extract information on date of cancer diagnosis and cancer type; the latter being classified by the Swedish version of International Classification of Diseases (ICD) 7. A child became “exposed” when one parent had a cancer diagnosis according to the Cancer Register. Children without parental cancer contributed all person-time to the unexposed period, while children with parental cancer contributed person-time to the unexposed period before parental cancer diagnosis and afterwards to the exposed period. Children had a parental cancer diagnosed before July 1991 contributed all person-time to the exposed period. To further illustrate whether parental death subsequent to cancer was of any special importance on child’s mortality, we further linked the cancer parents to the Cause of Death Register to ascertain any death.

2.3. Follow-up

All children were linked to the Cause of Death Register for ascertainment of death. Follow-up started on July 1, 1991 or when the children turned one year of age. The end-point for follow-up was date of death, emigration, 18 years of age or December 31, 2009, whichever came first. As a result, 68,870 children who had died or emigrated before the start of follow-up were excluded, leaving 2,871,242 children in the final analyses.

Child and parental characteristics may serve as potential confounders for the studied association, since they may be associated with both the risk of cancer among parents and the risk of death among children [17-23]. We further obtained information on gestational age, mode of delivery and birth weight of the child, maternal smoking during early pregnancy (available since 1983), maternal age at child's birth, as well as the highest educational level and socio-economic classification of the parents (Table 1). Information on child and maternal characteristics at birth was extracted from the Swedish Medical Birth Register [24]. Information on the educational level was obtained from the Swedish Register of Education, which annually updates data on the highest education and completion year [25]. The socio-economic classification system was based on occupation and developed by Statistics Sweden [26]. This information for the parents was obtained from the Swedish Population and Housing Census in 1990. If data was missing in the 1990 Census, we obtained relevant information from the 1980 Census (N=3,966).

2.4. Statistical analysis

We used Pearson's χ^2 test to compare categorical variables. We used Cox proportional hazards regression to assess the association between parental cancer diagnosis and all-cause and cause-specific death of children. Hazard ratio (HR) with 95% confidence interval (CI) was estimated, comparing the exposed children to the unexposed. No statistically significant violation of the proportional hazards assumption was detected from the test based on Schoenfeld residuals ($P>0.05$). Since parental cancer might be associated with a child's risk of death due to different reasons, we conducted separate analyses for child's death due to non-cancer-related causes (ICD 9: all codes except 140-208 and 230-239, ICD 10: all codes except C00-D09 and D37-D48), especially external causes (ICD 9: E800-E999, ICD 10: V01-Y98; including accidents, suicide, assault, etc.), and death due to cancer (ICD 9: 140-208 and 230-239, ICD 10: C00-D09 and D37-D48). Time since one year of age was used as the underlying time scale, with the parental cancer diagnosis included as a time-varying variable. We further split the time scale at parental death among the children with parental cancer to assess the separate impact of parental death after cancer. Stratification in two age groups was used to assess the associations among young children and adolescents, and the potential difference of the associations between these two age groups was assessed by testing the interaction between parental cancer and attained age of child. Stratification analysis was done by analyzing two cohorts independently. The young children cohort was composed of children at the age of 1-12 and censored by the age of 12, while the adolescents cohort was composed of children between the age of 13 and 18 and those from the young children cohort who had attained 12 years of age.

For the first model, additional adjustment was made for sex of child alone, whereas the second model further encompassed gestational age, mode of delivery and birth weight of the child, maternal age at child's birth, highest educational level and socio-economic classification of the parents. In sub-analyses among children born since 1983, we further extended the second model by adjusting for maternal smoking during early pregnancy. To compare the impacts of paternal and maternal cancer, we first broke down the exposed group by sex of parent with cancer. We also assessed the possible modifying effect of parental cancer type and predicted survival for parental cancer on the studied association, as they might be good proxies for the nature and severity of cancer. The predicted survival for parental cancer was indexed as the predicted 5-year relative survival rates for different cancers [27, 28]. The Wald test was performed to compare the effects of different parental cancer characteristics listed above on risk of childhood death. Within-cluster correlation of children with the same biological parents was also adjusted for in all models, by using “clustered” (sandwich) standard errors.

Statistical analyses were conducted using Stata version 12.1 (Stata Corporation LP, College Station, Texas, USA).

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

3. Results

In the study, 113,555 children had experienced a parental cancer diagnosis, of which 127 died during a total of 561,198 person-years of follow-up. A total of 4379 of the unexposed children died during a total of 28,867,589 person-years of follow-up. The exposed children had higher proportion of caesarean section at birth, shorter gestational age, and higher proportion of both low birth weight (<2500 g) and high birth weight (≥4500 g), than the unexposed children. A higher percentage of maternal smoking in early pregnancy was also seen for the exposed children among those born since 1983. The exposed children had higher maternal age at birth, higher parental educational level and socio-economic classification than the unexposed children (Table 1).

Among all children, the exposed children had a higher crude mortality rate for any causes than the unexposed children. Among children at the age of 13-18 years, the exposed children had higher crude mortality rates for all-cause, non-cancer-related and cancer-related causes than the unexposed children regardless of sex; similar pattern was however not shown for children aged 1-12 years except for cancer-related mortality (Table 2).

The analysis from the Cox proportional hazards regression showed that, the exposed children had a 39% higher rate of all-cause death than the unexposed children (fully adjusted HR: 1.39, 95% CI: 1.16, 1.66). A parental cancer was associated with an increased rate of non-cancer-related death (fully adjusted HR: 1.25, 95% CI: 1.01, 1.54), especially death due to external causes (fully adjusted HR: 1.33, 95% CI: 1.02, 1.73), among all children. We also observed more cancer-related deaths in the exposed children (fully adjusted HR: 2.04; 95% CI: 1.43, 2.92) (Table 3). In the age range of 1-12 years, the exposed children had no difference in rates of all-cause death or non-cancer-related death from the unexposed children, although they did have a higher rate of death from cancers (fully adjusted HR: 2.06, 95% CI: 1.13, 3.75) (Table 3). For children at the age of 13-18 years, we found higher rates of all-cause (fully adjusted HR: 1.52, 95% CI: 1.25, 1.86), non-cancer-related (fully adjusted HR: 1.43, 95% CI: 1.14, 1.79) and cancer-related (fully adjusted HR: 2.07, 95% CI: 1.33, 3.24) death among the exposed children (Table 3). The interactions between parental cancer and child's attained age were not statistically significant regarding causes of death except non-cancer-related death (*P*= 0.021). Additional adjustment for maternal smoking during early pregnancy did not further change these estimates (data not shown).

A total of 33 parents with cancer deceased before their children's death. When comparing children whose parent had a cancer diagnosis and was alive with the unexposed children, the fully adjusted HR (95%CI) was 1.31 (1.06-1.61) for all-cause death. When comparing children whose parent with cancer deceased with the unexposed children, the fully adjusted HR (95%CI) was 1.68 (1.18-2.39) for all-cause death. No statistically significant difference was noted between these two HRs (*P*= 0.232; Wald test).

Given the small number of outcomes among the exposed children at the age of 1-12 years, the possible modifying effects of parental cancer characteristics on the studied association were only presented for children at the age of 13-18 years (Table 4). Both paternal and maternal cancer diagnosis was associated with increased rates of all-cause, non-cancer-related and cancer-related death among children, but the associations did not differ by sex of the parent with cancer (all *P*>0.05). When examining different types of parental cancer, no statistically significant association was observed for non-cancer-related death among the exposed children. The predicted 5-year relative survival rate of parental cancer did not appear to modify the HRs for all-cause death (*P*= 0.769) or non-cancer-related death (*P*= 0.927), although a clear dose-response was seen for cancer-related death among the exposed children (*P* for trend, <0.001).

4. Discussion

To our knowledge, this is the first large population-based study to investigate the association between a parental (both paternal and maternal) cancer diagnosis and the risk of death among children. Our findings thus add to the existing literature suggesting considerable impact of parental cancer diagnosis on children [12, 14, 29-31]. We found that having a parent with cancer was associated with increased rates of all-cause, cancer-related and non-cancer-related death among children aged 1-18. Similar associations were seen among adolescents but only for cancer-related death among young children.

Verkooijen et al. previously reported in a Swedish population-based cohort study that offspring born over one year before their mother's cancer diagnosis had no significant increase in risk of all-cause death up to over 25 years of age [15]. In the present study, we concentrated on children (1-18 years of age) having either a father or a mother with cancer, aiming to first eliminate the potentially complicating effects of lifestyle and environmental factors on mortality beyond childhood and second to contrast the impact of paternal and maternal cancer. It has been reported that children may be more emotionally affected by maternal than paternal cancer [32]. However, our findings did not advocate for such a difference, at least in terms of childhood mortality. Plausible explanation may include the fact that Swedish parental leave policies encourage greater participation of fathers in childrearing, leading to larger gender equality in parenting and, therefore, a potentially equally strong bond between a mother and a father with their children [33].

To emphasize the potential impact of non-genetic factors such as psychological distress induced by a parental cancer, we specifically assessed death due to causes other than cancer, as cancer-related causes might reflect genetic similarity between parents and their children. Positive associations of parental cancer with non-cancer-related death and particularly death from external cause (including mainly accidents and suicides) support our hypothesis.

Whether younger children are differently affected by parental cancer from older children is not known [31, 34]. In our study, all exposed children showed a higher rate of cancer-related death; however, only adolescents demonstrated an increased rate of non-cancer-related death. Although chance cannot be ruled out completely, this finding may indicate that children's strategies of coping with parental cancer vary by age. Younger children may not be able to fully comprehend the significance and consequence of parental cancer [1, 35]. Parents may be more prone to share facts about the illness with their older children, who in turn might be more affected by such new reality [34].

The nature and severity of parental cancer may further modify the adverse experience among the parents as well as among the children. In our data, when focusing on the adolescents, no statistically significant association between cancer types and non-cancer-related death may suggest that the specific cancer type perhaps had a minor role in further modifying the non-genetic impact on child's death induced by parental cancer. Our analyses on the predicted 5-year relative survival of parental cancer did not indicate that a poorer predicted prognosis for parental cancer contributed more to a greater risk of non-cancer-related death among adolescent. Furthermore, no strong evidence suggested that the eventual death in parent with cancer further modify the association between parental cancer and childhood death.

The increased rates of cancer-related death observed in our study on the other hand might be attributable to inherited susceptibility to specific cancer or cancer syndrome from parents to children. Among the exposed children, 1 case died from the same type of cancer with the parent, and 6 cases of cancer-related deaths were probably due to Lynch syndrome, Li-Fraumeni syndrome, Xeroderma pigmentosum syndrome or Gorlin syndrome [36]. After excluding these cases, we still found an increased rate of cancer-related death among the exposed children (HR=1.60, 95% CI: 1.07, 2.39). Therefore, it remains possible that other less frequent or yet unknown cancer syndromes, shared genetic or even non-genetic-factors between parents and children may further explain this association. Given the extremely small number of parent-child pairs in each cancer group, the concurrences could be due to chance alone. Finally, it has been shown for several cancer types that cancer prognosis might also be genetically inherited, independent of patient and tumor characteristics [37-39]. Our study appears to provide further evidence for such possibilities, as a dose-response relationship was noted between the predicted survival for parental cancer and cancer-related death among adolescent children.

The strengths of this study lie in its population-based design as well as long term and complete follow-up, allowing for adequately powered estimations for a rare outcome, such as childhood all-cause mortality. The fact that information on both the exposure and outcome was prospectively and independently collected minimized the possibility of information bias. Our study also has some limitations. First of all, the subgroup analyses lack sufficient statistical power because of the uncommon exposure (cancer diagnosis among parents of children at 1-18 years of age) and outcome. Parental smoking may potentially be an important confounder, and we had data on smoking for only mothers of children born since 1983. Although we excluded maternal smoking from the fully adjusted models, we obtained similar and reassuring results in additional analyses restricted to these children and further adjusted for maternal smoking. Socio-economic status has been reported to have independent impact on the risk of cancer [40]. For example, higher educational level is associated with higher risk of breast cancer and with lower risk of lung cancer [41, 42]. In our study, further adjustment for socio-economic classification and educational level did not appear to strongly modulate the association between parental cancer and childhood mortality. Although we made great efforts in adjusting for a handful of child and parental characteristics including gestational age, mode of delivery, birth weight and maternal age at child's birth, other unmeasured factors may explain our findings to some extent. For instance, information on family structure may be of great importance. A previous Swedish population-based study has shown that children with single parent had an increased risk of death including suicide as compared to children living with both parents [43]. And family support has been shown to play an important role in protecting children from hazards [44]. Furthermore, we had no information on tumor characteristics which may be important to define the severity of parental cancer; however, predicted relative survival rate should be seen as a good proxy for such characteristic and did not appear to modify the association between parental cancer and non-cancer-related childhood death. Given that we only enrolled children born in Sweden in the present analysis, our results are not generalizable to children with different cultural and socio-economic background.

5. Conclusion

This population-based cohort study shows that a parental cancer diagnosis was associated with an increased rate of death among children aged 1-18; this association appears to be slightly stronger among adolescents. Careful interpretation of the findings is needed because of the low absolute risk of death among these children and lack of information of other potential confounders.

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Conflict of interest statement

The authors have no conflict of interest to declare.

Authorship contribution

Ms. Ruoqing Chen had substantial contribution to study concept and design, analysis and interpretation of data, as well as drafting and revising the manuscript. Dr. Arvid Sjölander had substantial contribution to study concept and design, analysis and interpretation of data, and revising the manuscript. Prof. Unnur Valdimarsdóttir and Dr. Katja Fall had substantial contribution to study concept and design, and revising the manuscript. Ms. Catherine Varnum had substantial contribution to study concept and design, analysis of data and revising the manuscript. Prof. Catarina Almqvist, Prof. Weimin Ye and Prof. Kamila Czene had substantial contribution to study concept and design, acquisition of data and revising the manuscript. Dr. Fang Fang had substantial contribution to study concept and design, supervision of the study, analysis of data and revising the manuscript. All authors have seen and approved the final version of the manuscript.

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Tables

Table 1
Characteristics of the participating children and their parents, a cohort study of parental cancer and childhood death in Sweden, 1991 - 2009

Characteristics	Children with parental cancer		Children without parental cancer		*P*
	N	%	N	%	
Characteristics of the children					
Sex					
Male	58,301	51.3	1,415,844	51.3	0.999
Female	55,254	48.7	1,341,843	48.7	
Gestational age (weeks)					
<35	2,457	2.2	54,149	2.0	<0.001
35 - 36	4,288	3.8	95,592	3.5	
37 - 38	20,794	18.3	47,747	17.3	
39 - 40	54,675	48.2	1,350,843	49.0	
41 - 42	27,946	24.6	688,829	25.0	
≥43	1,293	1.1	33,321	1.2	
Missing	2,102	1.9	57,483	2.1	
Mode of delivery					
Caesarean section	14,104	12.4	312,570	11.3	<0.001
Vaginal delivery	97,601	86.0	2,393,735	86.8	
Missing	1,850	1.6	51,382	1.9	
Birth weight (g)					
< 2500	4,811	4.2	107,059	3.9	<0.001
2500-2999	12,351	10.9	299,648	10.9	
3000-3499	34,461	30.3	869,831	31.5	
3500-3999	38,695	34.1	934,971	33.9	
4000-4499	16,941	14.9	396,542	14.4	
≥ 4500	4,144	3.7	90,422	3.3	
Missing	2,152	1.9	59,214	2.2	
Maternal smoking in early pregnancy [a]					
No	53,984	70.2	1,392,199	72.3	<0.001
Yes	16,714	21.7	373,513	19.4	
Missing	6,234	8.1	158,832	8.3	
Characteristics of the parents					
Maternal age at child's birth (years)					
< 20	1,703	1.5	94,175	3.4	<0.001
20-24	15,360	13.5	637,978	23.1	
25-29	35,148	30.9	1,017,450	36.9	
30-34	36,182	31.9	705,334	25.6	
≥ 35	25,162	22.2	302,750	11.0	
Highest educational level					
Primary school or lower	8,759	7.7	181,116	6.6	<0.001
Secondary education	51,733	45.6	1,374,004	49.8	
Tertiary education	50,328	44.3	1,150,257	41.7	
Postgraduate education	2,701	2.4	51,839	1.9	

missing	34	0.0	471	0.0	
Highest socio-economic status					
Blue-collar	34,531	30.4	957,678	34.7	<0.001
White-collar	58,983	51.9	1,264,481	45.9	
Self-employed including farmers	10,041	8.8	207,337	7.5	
Others	8,885	7.8	277,590	10.1	
Missing	1,115	1.0	50,601	1.8	

[a] Children born 1983-2002 (n=2,001,476)

Table 2

Mortality rate among the exposed children and unexposed children by sex and age at follow-up, a cohort study of parental cancer and childhood death in Sweden, 1991 - 2009

Causes of death	**Exposed children**			**Unexposed children**		
	No. of deaths	**Person-years**	**Mortality rate [No. of deaths per 1000 person-years (95% CI)]**	**No. of deaths**	**Person-years**	**Mortality rate [No. of deaths per 1000 person-years (95% CI)]**
All-cause						
All children	127	561,198	0.23 (0.19 - 0.27)	4,379	28,867,589	0.15 (0.15-0.16)
Male						
1 - 12 years	14	100,634	0.14 (0.08 - 0.23)	1,396	9,391,976	0.15 (0.14 - 0.16)
13 - 18 years	57	187,791	0.30 (0.23 - 0.39)	1,170	5,427,648	0.22 (0.20 - 0.23)
Female						
1 - 12 years	7	94,973	0.07 (0.04 - 0.15)	1,040	8,902,232	0.12 (0.11 - 0.12)
13 - 18 years	49	177,800	0.28 (0.21 - 0.36)	773	5,145,733	0.15 (0.14 - 0.16)
Non-cancer-related causes [a]						
All children	95	561,198	0.17 (0.14 - 0.21)	3,516	28,867,589	0.12 (0.12 - 0.13)
Male						
1 - 12 years	7	100,634	0.07 (0.03 - 0.15)	1,083	9,391,976	0.12 (0.11 - 0.12)
13 - 18 years	48	187,791	0.26 (0.19 - 0.34)	994	5,427,648	0.18 (0.17 - 0.19)
Female						
1 - 12 years	3	94,973	0.03 (0.01 - 0.10)	793	8,902,232	0.09 (0.08 - 0.10)
13 - 18 years	37	177,800	0.21 (0.15 - 0.29)	646	5,145,733	0.13 (0.12 - 0.14)
Cancer-related causes [b]						
All children	32	561,198	0.06 (0.04 - 0.08)	863	28,867,589	0.03 (0.03 - 0.03)
Male						
1 - 12 years	7	100,634	0.07 (0.03 - 0.15)	313	9,391,976	0.03 (0.03 - 0.04)
13 - 18 years	9	187,791	0.05 (0.02 - 0.09)	176	5,427,648	0.03 (0.03 - 0.04)
Female						
1 - 12 years	4	94,973	0.04 (0.02 - 0.11)	247	8,902,232	0.03 (0.02 - 0.03)
13 - 18 years	12	177,800	0.07 (0.04 - 0.12)	127	5,145,733	0.02 (0.02 - 0.03)

[a] ICD codes (ICD 9: all except 140-208 and 230-239, ICD 10: all except C00-D09 and D37-D48)

[b] ICD codes (ICD 9: 140-208 and 230-239, ICD 10: C00-D09 and D37-D48)

CI: confidence interval, ICD: International Classification of Diseases.

Table 3

Hazard ratios for all-cause and cause-specific death among the exposed children vs. unexposed children, a cohort study of parental cancer and childhood death in Sweden, 1991 - 2009

Causes of death	Children at the age of 1-18 years			Children at the age of 1-12 years			Children at the age of 13-18 years		
	No. of deaths	HR (95%CI)[a]	HR (95%CI)[b]	No. of deaths	HR (95%CI)[a]	HR (95%CI)[b]	No. of deaths	HR (95%CI)[a]	HR (95%CI)[b]
All-cause									
Unexposed	4,379	1.00	1.00	2,436	1.00	1.00	1,943	1.00	1.00
Exposed	127	1.36 (1.13-1.62)	1.39 (1.16-1.66)	21	0.98 (0.64-1.51)	1.00 (0.64-1.56)	106	1.47 (1.21-1.79)	1.52 (1.25-1.86)
Non-cancer-related causes[c]									
Unexposed	3,516	1.00	1.00	1,876	1.00	1.00	1,640	1.00	1.00
Exposed	95	1.23 (1.00-1.51)[f]	1.25 (1.01-1.54)	10	0.63 (0.34-1.17)	0.62 (0.32-1.19)	85	1.39 (1.11-1.73)	1.43 (1.14-1.79)
External causes[d]									
Unexposed	1,723	1.00	1.00	680	1.00	1.00	1,043	1.00	1.00
Exposed	60 [g]	1.29 (0.99-1.68)	1.33 (1.02-1.73)	4	0.60 (0.22-1.60)	0.62 (0.23-1.66)	56	1.41 (1.07-1.85)	1.48 (1.12-1.95)
Cancer-related causes[e]									
Unexposed	863	1.00	1.00	560	1.00	1.00	303	1.00	1.00
Exposed	32	1.96 (1.37-2.80)	2.04 (1.43-2.92)	11	2.00 (1.10-3.65)	2.06 (1.13-3.75)	21	1.94 (1.25-3.02)	2.07 (1.33-3.24)

[a] Adjusted for attained age and sex of child.

[b] Adjusted for attained age, sex, gestational age, mode of delivery and birth weight of the child, maternal age at child's birth, highest educational level and socio-economic classification of the parents

[c] ICD codes (ICD 9: all except 140-208 and 230-239, ICD 10: all except C00-D09 and D37-D48)

[d] ICD codes (ICD 9: E800-E999, ICD 10: V01-Y98)

[e] ICD codes (ICD 9: 140-208 and 230-239, ICD 10: C00-D09 and D37-D48)

[f] $P<0.05$

[g] Including 41 accidents, 11 suicides, 3 assaults and 5 other causes.

HR: hazard ratio, CI: confidence interval

Table 4

Hazard ratios for all-cause and cause-specific death among the exposed children vs. unexposed children, after breaking down the exposed children by parental sex, cancer type and predicted survival for parental cancer, a cohort study of parental cancer and childhood death (13-18 years of age) in Sweden, 1991 - 2009

	Person-years	All-cause death			Non-cancer-related death			Cancer-related death		
		No. of deaths	%	HR (95%CI)[a]	No. of deaths	%	HR (95%CI)[a]	No. of deaths	%	HR (95%CI)[a]
Unexposed children	10,573,381	1943	-	1.00	1,640	-	1.00	303	-	1.00
Exposed children										
Sex of the parent with cancer										
Male	151,972	50	47.2	1.71 (1.28-2.28)	37	43.5	1.47 (1.05-2.07)	13	61.9	3.07 (1.76-5.37)
Female	213,620	56	52.8	1.39 (1.06-1.82)	48	56.5	1.40 (1.05-1.87)	8	38.1	1.35 (0.67-2.74)
Parental cancer type (ICD 7 codes)										
Digestive organs (150.0-157)	40,423	15	14.2	1.94 (1.13-3.33)	12	14.1	1.81 (0.98-3.35)	3	14.3	2.67 (0.85-8.36)
Respiratory system (160.0-165)	15,329	6	5.7	1.92 (0.86-4.30)	4	4.7	1.49 (0.56-3.97)	2	9.5	4.64 (1.14-18.91)
Breast (170.0-170.9)	85,340	20	18.9	1.31 (0.84-2.04)	19	22.4	1.47 (0.93-2.31)	1	4.8	0.43 (0.06-3.10)
Reproductive system (171-179.9)	58,447	18	17.0	1.61 (1.01-2.56)	14	16.5	1.47 (0.87-2.49)	4	19.0	2.42 (0.90-6.49)
Urinary tract (180.0-181.9)	16,278	8	7.5	2.20 (1.05-4.61)	5	5.9	1.46 (0.55-3.90)	3	14.3	6.57 (2.11-20.44)
Skin including melanoma (190.0-191.9)	44,333	10	9.4	1.25 (0.67-2.32)	7	8.2	1.03 (0.49-2.17)	3	14.3	2.43 (0.78-7.58)
Brain (193.0-193.9)	28,598	8	7.5	1.32 (0.63-2.77)	5	5.9	0.89 (0.33-2.37)	3	14.3	3.79 (1.22-11.79)
Others (140.0-148, 192, 194-199, 200.0-209)	76,842	21	19.8	1.46 (0.95-2.25)	19	22.4	1.55 (0.99-2.44)	2	9.5	0.93 (0.23-3.76)
Predicted 5-year relative survival rate of the parental cancer										
< 20% [b]	26,292	10	9.4	1.90 (1.02-3.54)	7	8.2	1.54 (0.73-3.24)	3	14.3	4.08 (1.29-12.92)
20-80%	167,112	50	47.2	1.51 (1.13-2.03)	39	45.9	1.37 (0.98-1.91)	11	52.4	2.36 (1.29-4.30)
≥ 80% [c]	172,188	46	43.4	1.48 (1.10-1.98)	39	45.9	1.48 (1.07-2.03)	7	33.3	1.48 (0.70-3.14)

[a] Adjusted for attained age, sex, gestational age, mode of delivery and birth weight of the child, maternal age at child's birth, highest educational level and socio-economic classification of the parents

[b] Including cancers in esophagus, liver, gall bladder, biliary tract, pancreas, lung and stomach.

[c] Including cancers in lip, breast, corpus uteri, testis, skin, thyroid and other endocrine glands, and Hodgkin’s lymphoma.

HR: hazard ratio, CI: confidence interval, ICD: International Classification of Diseases