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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.

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

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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 ($N = 3966$).

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