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ORIGINAL PAPER

Loss of a parent and the risk of cancer in early life: a nationwide cohort study

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Abstract
Background While early-life exposure to stress has been associated with subsequent psychiatric and cardiovascular morbidity, little is known regarding its potential role in cancer development. We hypothesized that severe emotional stress, such as the loss of a parent through death during childhood, may increase the risk of cancer in early life.
Method Based on the Swedish Multi-Generation Register, we identified a cohort of 4,219,691 individuals who had both parents identifiable in the same register and followed the cohort from birth to the age of 40 years between 1961 and 2006. Through information retrieved from the Swedish Causes of Death and Cancer Registers, we ascertained death among the parents and cancer diagnosis among the cohort individuals. We used Poisson regression to calculate the relative risks (RRs) and 95 % confidence intervals (CIs).
Results Parental death was not associated with total cancer risk. However, parental death during childhood was associated with a higher risk of human papillomavirus (HPV) infection-related cancers (RR 1.4; 95 % CI 1.2–1.7), and loss during early adulthood (>18 years) entailed a higher risk of cancers of the stomach (RR 1.8; 95 % CI 1.3–2.6), lung (RR 1.7; 95 % CI 1.1–2.4), rectum (RR 1.4; 95 % CI 1.0–2.0), and breast (RR 1.1; 95 % CI 1.0–1.3). A significant association was observed for pancreatic cancer for both loss during childhood (RR 2.6; 95 % CI 1.6–4.2) and afterward (RR 2.8; 95 % CI 1.9–4.3).
Conclusion Our results suggest that severe psychological stress in early life may be associated with premature development of certain malignancies, particularly cancers related to smoking and HPV infection.

Keywords Sweden/epidemiology · Cohort studies · Psychological stress · Neoplasms/epidemiology/etiology · HPV/infection · Risk

Introduction

Psychological stress is increasingly recognized as playing an important role for health in general, while the evidence for its possible direct influence on cancer development remains equivocal [1–4]. Methodological diversities across studies including varying assessment of stress exposure and evaluations of different cancer outcomes have undoubtedly contributed to the conflicting findings [2, 3, 5]. Proposed underlying biological mechanisms of stress-related cancer risks include neuroendocrine alterations in both the hypothalamic–pituitary–adrenal axis regulating glucocorticoid

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release and the sympathetic nervous system regulating catecholamine levels [6]. These modulations may alter the cellular immune response to malignant cells [7], affect tumor angiogenesis and inflammatory response [8], and increase the risk of tumor development and progression [9].

The influence of psychological stress may be of particular importance during childhood, given the developing neuroendocrine and immune systems. Childhood adversities and stress vulnerabilities have been associated with an increased risk of psychiatric disorders [10] and cardiovascular disease [11] later in life. Recent Scandinavian articles report an increased risk for childhood cancers among children who lost a close relative during their first 15 years of life [12] and also an increased risk of childhood cancers in children exposed to stress during the antenatal period [13]. In the present study, we assessed whether severe emotional stress indicated by the loss of a parent due to death during childhood (i.e., $\leq$18 years) increased the risk of cancer development beyond the teenage years into early adulthood (i.e., $\leq$ 40 years). Based on our previous findings of adulthood bereavement and a higher risk of infection, especially human papillomavirus (HPV)-related cancers [14], we were specifically interested in examining the association between loss of a parent in early life and HPV-related cancers.

Materials and methods

Study participants

We conducted a historical cohort study based on the Swedish Multi-Generation Register (MGR), which includes men and women born in 1932 or later (index persons) together with their parents. We included all individuals born in Sweden between 1961 and 2002 who had both parents identifiable in the MGR and both parents alive at the birth of the index individual. We further linked all the parents to the Swedish Population and Housing Censuses in 1960, 1970, 1980, and 1990 and only included individuals who had both parents registered in at least one of the censuses (n = 4,219,697).

Follow-up

Using individual national registration numbers (NRNs), the cohort was linked to the Swedish National Cancer Register, the Causes of Death Register, and the Emigration Register. The Cancer Register is based on mandatory reports from clinicians and pathologists, as required by Swedish law since cancer registration began in 1958, and has a very high overall completeness [15]. The Causes of Death Register was established in 1952, containing information on date of death as well as the underlying and contributory causes of death.

By means of the record linkages, the cohort individuals were followed from their birth date to the date of cancer diagnosis, their 40th birthday, death, emigration out of Sweden, or the end of follow-up (31 December 2006), whichever came first. We censored the follow-up at 40 years of age representing the end of early adulthood. Six individuals were excluded due to inconsistencies discovered during register linkages (i.e., emigration or cancer diagnosis before entering to the cohort), leaving 4,219,691 individuals in the study population.

Exposure

The loss of a parent through death was used as an indicator of severe psychological stress. Via the NRNs, we linked all parents of the cohort individuals to the Causes of Death Register to identify parental death. During follow-up, a total of 486 858 individuals (11.5 %) lost a parent due to death. "Unexposed person-time" was accumulated from all person-years contributed by individuals who did not lose a parent during follow-up as well as person-years contributed before the loss of parent by individuals that did lose a parent during follow-up. Among individuals who lost a parent, "exposed person-time" was accrued after the date of the parental death. If a person lost more than one parent, loss of the first parent was counted.

Since our primary interest was to examine the role of loss of a parent during childhood, we separated all analyses by loss of a parent at $\leq$18 years (i.e., childhood) and $>$18 years (i.e., early adulthood).

Cancer outcome

The diagnosis of a first malignant cancer before the age of 40, as recorded in the Cancer Register, was defined as the follow-up outcome. To alleviate the potential influence of shared genetic features between children and parents on cancer development, we excluded all individuals from the cohort if they were diagnosed with the same cancer as any of their parents. Similarly, we further excluded individuals if they shared one of the three familial cancer syndromes (hereditary non-polyposis colon cancer syndrome, hereditary breast–ovarian cancer syndrome, or multiple endocrine neoplasia type 1 syndrome) with any of their parents. Accordingly, we excluded 626 individuals from the unexposed group (i.e., individuals that never lost a parent due to death during the study) and 281 from the exposed group (i.e., individuals that lost a parent due to death during the study), leaving 4,219,065 and 486,577 individuals in the unexposed and exposed groups for the final analyses, respectively. In total, 24,875 cases of cancer were

identified among the unexposed group and 2,811 cases among the exposed group during follow-up.

Given our previous findings on adult bereavement and HPV-related cancers [14], in the present study we specifically examined whether loss of a parent through death was associated with the early development of cancers with an established or suspected association with HPV infections, including cervical cancer, other male or female genital cancers (e.g., cancer in the vulva, vagina, or penis), anal cancer, non-melanoma skin cancer, lip cancer, oral cavity and pharynx cancer, esophageal cancer, laryngeal cancer, and eye cancer, as suggested by Grulich et al. [16].

Statistical analysis

We used log-linear Poisson regression models to calculate the relative risk (RR) and 95 % confidence interval (CI), as the ratio of the cancer incidence among the exposed group to that of the unexposed group. All models were adjusted for age at follow-up (5-year groups), sex, calendar period of follow-up (5-year groups), and socioeconomic status of the family (categorized as manual workers, non-manual workers, self-employed, or unclassified). We primarily used the socioeconomic status of the father as recorded in the most recent census following the birth of the index child; if information was missing for the father, the socioeconomic status of the mother was used. Pearson scale was used to correct for overdispersion if any.

We first calculated RRs separately for all major cancer sites. Given our primary interest in HPV-related cancers, we further explored whether the association between parental death and HPV-related cancers was modified by the characteristics of parental death such as paternal or maternal death, time since death, and cause of death. The underlying cause of death was classified as "unexpected" (i.e., suicide or other accidental death) and "expected" (i.e., deaths not classified as "unexpected": cancer or other disease). Since bereaved individuals may have different adherence to national cancer screening programs and proneness to actively seek medical attention, we compared the risk of cervical cancer in situ—a diagnosis often detected by screening—as recorded in the Cancer Register as well, between the exposed and unexposed groups. In this analysis, we only included cervical cancer in situ that was recorded in the Cancer Register as the first tumor.

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

Results

The characteristics of participants who lost a parent due to death during follow-up are shown in Table 1. Over 70 % of the parental deaths occurred among the fathers; the pattern was similar among those who experienced loss during childhood and young adulthood. A higher proportion of "unexpected" parental deaths were observed for loss during childhood compared with early adulthood (32.2 vs. 8.9 %).

Table 1 Characteristics of participants who lost a parent due to death during follow-up, a cohort study in Sweden during 1961–2006

Characteristics	Lost a parent at ≤18 years (n = 140,695)	Lost a parent at >18 years (n = 345,882)
Mean age of the individual at loss, years (SD)	10.7 (4.9)	29.2 (6.1)
Loss of a father (%)	99,773 (70.9)	243,588 (70.4)
Mean age of father at death, years (SD)	45.0 (10.2)	63.1 (9.6)
Mean age of mother at death, years (SD)	45.0 (12.8)	59.9 (9.6)
Cause of death (%)		
"Expected"	95 388 (67.8)	315,179 (91.1)
Cancer	42,796 (30.4)	136,786 (39.6)
Non-cancer	52,592 (37.4)	178,393 (51.6)
"Unexpected"	45 307 (32.2)	30,703 (8.9)
Suicide	19,535 (13.9)	12,137 (3.5)
Non-suicide	25,772 (18.3)	18,566 (5.4)

Parental death was not associated with the overall risk of early cancer regardless of child age at loss (Figs. 1a, b). However, among those who experienced parental death during childhood (≤18 years), we observed higher risks of cervical cancer (RR 1.4; 95 % CI 1.1–1.7) and non-melanoma skin cancer (RR 1.8; 95 % CI 1.1–2.8). A borderline significant association was noted for other female genital cancers (RR 2.5; 95 % CI 1.0–5.5). Among those who experienced parental death after the age of 18, we found a higher risk of stomach cancer (RR 1.8; 95 % CI 1.3–2.6), lung cancer (RR 1.7; 95 % CI 1.1–2.4), rectal cancer (RR 1.4; 95 % CI 1.0–2.0), and breast cancer (RR 1.15; 95 % CI 1.02–1.29). Loss of a parent due to death during childhood or later was related to an excess risk of pancreatic cancer (RR 2.6; 95 % CI 1.6–4.3 for loss at ≤18 years and RR 2.8; 95 % CI 1.9–4.3 for loss at >18 years).

Since the association between parental death and some of the major HPV-related cancers was only noted for loss at ≤18 years, we performed additional analyses on parental death during childhood for all HPV-related cancers. As one group, the overall risk of HPV-related cancers was elevated after childhood parental loss and was similar for loss of mother and father (Table 2). The association was not modified by the time since loss or cause of parental death.

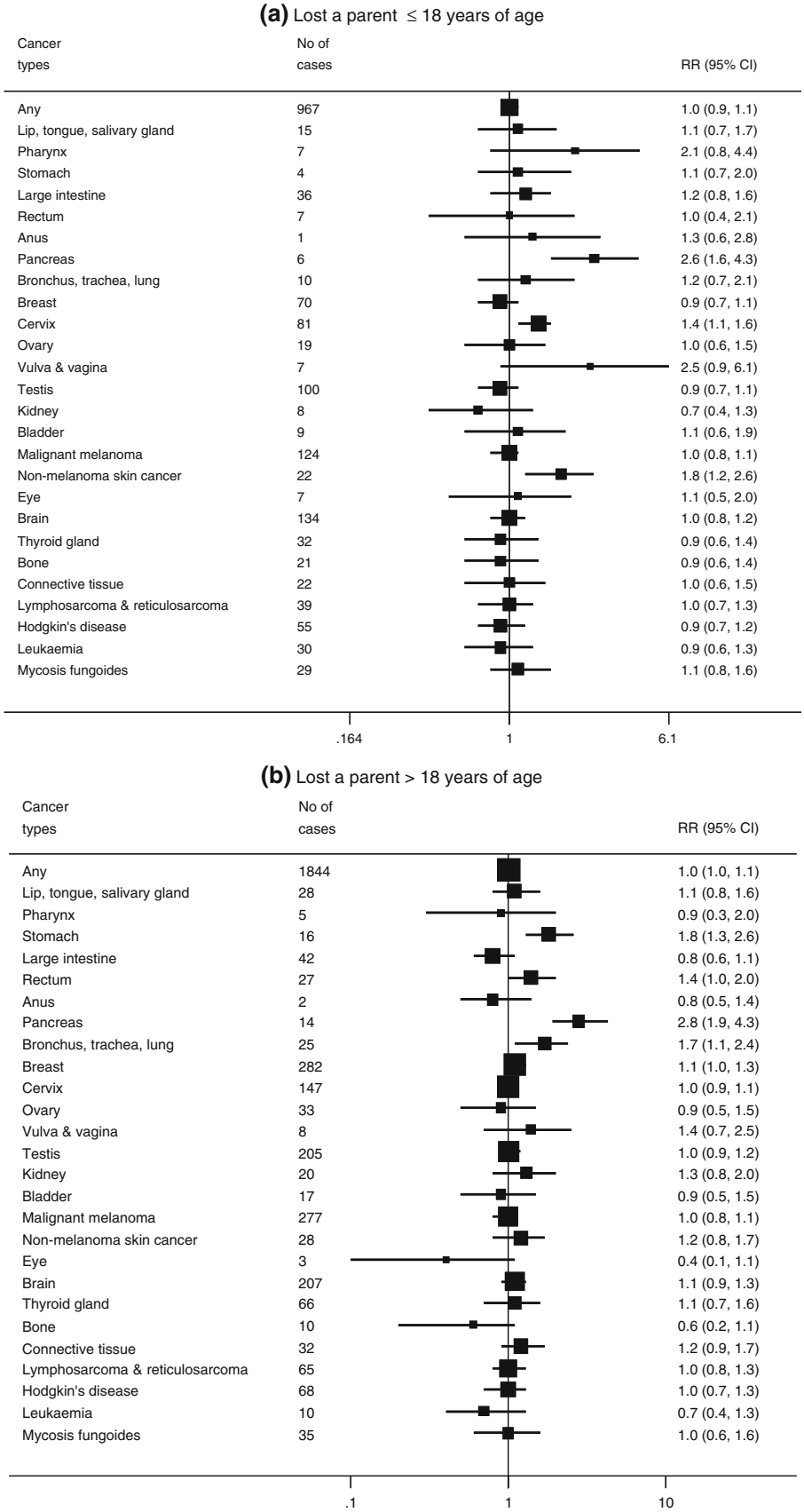

Fig. 1 **a** Loss of a parent due to death before or at the age of 18 and relative risks of cancer before the age of 40—a cohort study in Sweden during 1961–2006. **b** Loss of a parent due to death after the age of 18 and relative risks of cancer before the age of 40—a cohort study in Sweden during 1961–2006

Table 2 Loss of a parent due to death during childhood and the risk of human papillomavirus-related cancers before the age of 40—a cohort study in Sweden during 1961–2006

	No. of cancer	RR (95 % CI)[a]
Never lost a parent	1,749	1.0
Lost a parent	110	1.4 (1.2–1.7)
Sex of the parent		
Lost a mother	30	1.4 (0.9–1.9)
Lost a father	80	1.4 (1.1–1.8)
Time since loss, years		
<10	12	1.4 (0.6–2.7)
10–19	46	1.5 (1.0–2.2)
≥20	52	1.3 (0.9–1.9)
Cause of parent death		
Unexpected		
Suicide	22	2.2 (1.4–3.3)
Non-suicide	23	1.6 (1.0–2.3)
Expected		
Cancer	35	1.6 (1.1–2.2)
Non-cancer	30	1.0 (0.6–1.3)

HPV-related or possibly related cancers: cervical cancer, other male or female genital cancers, anal cancer, non-melanoma skin cancer, lip cancer, oral cavity and pharynx cancer, esophageal cancer, laryngeal cancer, and eye cancer

[a] RR = relative risk; CI = confidence interval; RRs are adjusted for age at follow-up, sex, calendar period at follow-up, and socioeconomic status of the family

However, there was no excess risk of HPV-related cancers after a parental death due to "expected" causes that were not related to cancer (Table 2).

Unlike HPV-related invasive cancers, the risk of cervical cancer in situ was slightly increased among all exposed individuals ($n = 4{,}841$ among the exposed group and $n = 28{,}920$ among the unexposed group; RR 1.11; 95 % CI 1.08–1.15), regardless of whether the parental death occurred during childhood ($n = 1{,}789$; RR 1.15; 95 % CI 1.10–1.21) or early adulthood ($n = 3{,}052$; RR 1.09; 95 % CI 1.05–1.13). The increased risk appeared to be clearer for parental death due to non-cancer-related causes ($n = 3{,}297$; RR 1.15; 95 % CI 1.11–1.20) than for cancer-related causes ($n = 1{,}544$; RR 1.03; 95 % CI 0.98–1.09).

Since similar associations were observed between parental death before and after 18 years of age and pancreatic cancer, we examined the influence of parental loss characteristics on pancreatic cancer by pooling parental loss during childhood and young adulthood (Table 3). We observed an increased risk for pancreatic cancer both during the first 5 years after loss (RR 3.3; 95 % CI 2.1–5.0) and thereafter (RR 2.3; 95 % CI 1.6–3.4) as well as for cancer-related (RR 3.4; 95 % CI 1.6–7.1) and non-cancer-related (RR 2.2; 95 % CI 1.1–4.4) parental death (Table 3).

Table 3 Loss of a parent due to death and the risk of pancreatic cancer before the age of 40—a cohort study in Sweden during 1961–2006

	No. of cancer	RR (95 % CI)[a]
Never lost a parent	42	1.0
Lost a parent	20	2.6 (1.9–3.7)
Time since loss, years		
<5	8	3.3 (2.1–5.0)
≥5	12	2.3 (1.6–3.4)
Cause of parent death		
Non-cancer	11	2.2 (1.1–4.4)
Cancer	9	3.4 (1.6–7.1)

[a] RR = relative risk; CI = confidence interval; RRs are adjusted for age at follow-up, sex, calendar period at follow-up, and socioeconomic status of the family

Discussion

In this nationwide historical cohort study, we found no overall association between loss of a parent through death and the risk of cancer before the age of 40. However, individuals who experienced parental death during childhood (i.e., up to the age of 18) had an increased risk for HPV-related cancers as well as pancreatic cancer, compared with individuals who had not lost a parent before the age of 40. A parental death during early adulthood (i.e., 19–40 years) was associated with higher risks of early-onset (<40 years) stomach, lung, rectal, pancreatic, and breast cancers. As of note, loss of a parent due to death was associated with a higher risk of pancreatic cancer, regardless of age at loss.

The strengths of the present study included a population-based design, the use of prospectively and independently collected data, and the virtually complete follow-up. The large sample size further allowed us to conduct subgroup analyses of individual cancer sites and explorative analyses of the gender of the deceased parent, time since loss, and cause of parental death. An important advantage of the study design was that we used an event of universally and unequivocally strong emotional stress. Furthermore, the death of a parent was both objectively assessed, independently of the outcome under study, and precisely dated.

A few limitations of the present study must be addressed. First, we studied the specific emotional stress induced by loss of a parent due to death, leaving unravelled other perhaps equally stressful life events such as loss of other family members due to death, non-fatal but critical diseases in the family, as well as severe familial dysfunctions (e.g., physical or mental abuse, and substance abuse). Second, due to the register-based study design, we lacked detailed information on individual behaviors such as smoking, physical activity, alcohol consumption, and diet. These

factors may lead to a spurious association between parental death and cancer, if they are both related to parental death and the cancer of the child; however, they may also mediate this association. For example, parental death after the age of 18 was associated with stomach, lung, and pancreatic cancers that are known to be associated with smoking, and smoking is a well-recognized lifestyle change after bereavement [17].

To alleviate the concern that the association found between parental death and child cancer was due to shared genetic or environmental factors between children and parents, we excluded all potential familial cancers (same cancer or cancer syndrome between the child and parent) in the main analyses. Clearly increased risks of HPV-related and pancreatic cancers were also observed for parental loss due to causes other than cancer. However, because hereditary cancers account only for a small proportion of cancer incidence overall, and cancer is one of the leading causes of death in Sweden regardless of family history, we have likely excluded cases that were not really due to familial factors and thus potentially underestimated the actual stress-associated cancer risk.

Previous studies have examined the risk of adulthood cancer after the loss of a child and have reported a slightly or no increased overall risk of cancer after bereavement [18, 19]. To our knowledge, no study so far has specifically focused on the influence of psychological stress in childhood on adult cancer. An Israeli study indicated that experiencing the holocaust early in life was related to an elevated cancer risk in general and increased risks of breast cancer and colon cancer in particular later in life [20]. However, because of the multitude of environmental and social traumas endured during the holocaust, it is difficult to discern the specific effect of psychological stress from other factors such as malnutrition in that study.

Evidence is mounting for an association between psychological stress and accelerated tumor growth in virally induced tumors, either by a direct effect of neuroendocrine pathways on viral oncogenesis and tumor metabolism or through downregulation of cellular immune responses [21, 22]. In support of a role of psychological stress in human tumorigenesis, our previous study showed an increased risk for infection-, especially HPV-, related cancers among parents who lost a child due to death [14]. Interestingly, in the present study, the risk for HPV-related cancers before the age of 40 was clearly associated with parental death during childhood/adolescence, although not during early adulthood. This may be supported by earlier findings that oncogenic HPV is most common at ages 16–20 [23] and that cervical cancer risk increases sharply as a result of younger age at, and therefore longer time since, first intercourse (i.e., presumed first HPV exposure) [24].

Besides the potential biological pathways directly imposed by psychological stress, behavioral changes among the bereaved individuals may offer an alternate or additional mechanism. Parental loss is related to psychological distress, depression, and alcohol or substance abuse among the bereaved children [25, 26]; these factors may in turn indicate a tendency toward sexual risk behavior [27–29]. A recent study did, however, not show increased risky health behaviors in general among the bereaved adolescents, although sexual risk habits were not specifically assessed [30]. The observed increased risk for cervical carcinoma in situ after parental death helps to argue against reduced health consciousness in this group. A lower uptake of cervical cancer screening among the bereaved children could theoretically have lead to a positive association between bereavement and invasive cervical cancer. Furthermore, detection of precancerous lesions should lead to surgical removal of the neoplastic tissue to prevent future invasive cancer. Given the context of higher risk of cervical carcinoma in situ among the bereaved individuals overall, the still increased risk for early-life invasive cervical cancer is intriguing and may lend support to earlier findings of stress-related impairment of HPV-specific immune response in cervical dysplasia [31].

Pancreatic cancer showed the strongest association with parental death, and the association was independent of age at loss. Although increased smoking may represent a possible intermediate factor in this association [32], as for stomach and lung cancers, results from recent animal studies did show that neuroendocrine transmitter responses to psychological stress affect proliferation, migration, angiogenesis, and apoptosis in both pancreatic cancer cells and non-small cell lung cancer cells [33, 34]. Furthermore, our data showed that the risk of pancreatic cancer rose rapidly after loss of parent (e.g., during the first 5 years after loss), again likely supporting direct influence of psychological stress on pancreatic cancer, assuming an accumulative effect of smoking on carcinogenesis. These findings are also congruent with another recent study on the incidence of pancreatic cancer after loss of child, where a risk elevation was discerned mainly the first 5 years after loss [35]. Finally, the similarly increased risk of pancreatic cancer after parental death due to both cancer- and non-cancer-related causes further supports the soundness of this observed association.

In conclusion, our findings suggest that severe psychological stress caused by parental death during childhood may increase the risk of HPV-related cancers and pancreatic cancer. Stress-induced modulations of the immune response to infections and of neuroendocrine functions may contribute to the observed associations, but the effects of behavioral changes following a stressful life event may also play a role.

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