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Original article

Mortality, cancer incidence, and survival in parents after bereavement

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ABSTRACT

Purpose: The study objective was to investigate whether child loss is related to mortality, cancer incidence, and cancer survival in parents.
Methods: We used a population-based birth cohort (1964–1976) in Jerusalem and ascertained mortality (average follow-up of 39.1 years) and any cancer (average follow-up of 35.6 years) among parents who lost a child (2838 mothers and 2532 fathers) and among nonbereaved parents (38,212 mothers and 36,433 fathers). We also assessed mortality among parents with cancer. Time-dependent Cox models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs).
Results: Overall mortality rates among bereaved parents were modestly increased when compared with nonbereaved parents (HR = 1.18, 95% CI: 1.05–1.32 in mothers; HR = 1.10, 95% CI: 1.01–1.20 in fathers). Hazard models indicated a significant relationship between bereavement and deaths from coronary heart disease in mothers (HR = 1.90, 95% CI: 1.23–2.95) and circulatory causes in both parents (HR = 1.69; 95% CI: 1.22–2.34 in mothers and HR = 1.25; 95% CI: 1.02–1.54 in fathers). Bereavement was not associated with parental risk of cancer disease and with survival from cancer. The association between bereavement and parental overall mortality was similar in the different parental sociodemographic characteristics. We observed a decrease in HRs for parental mortality associated with bereavement, with increasing time since the death of the child (HRs = 9–10, 0–3 years; HRs = 0.9–1.0, 9+ years; $P_{heterogeneity} \leq 3 \times 10^{-32}$). A similar decrease in HRs was observed for parental survival from cancer (HRs = 6.7–8.7, 0–3 years; HRs = 0.9–1.0, 9+ years).
Conclusions: Our study suggests that child loss was associated with slightly increased risk of all-cause and circulatory mortality in parents but not with incidence of cancer and cancer survival. The considerable increased parental mortality during a short period after child loss support the involvement of pathways related to psychological stress.

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Introduction

Growing evidence suggests that chronic diseases and mortality are influenced by psychological stress [1,2]. Bereavement, an acute life event and its association with mortality and disease morbidity, has been studied in various populations, and a number of studies demonstrate excess mortality among widowers [3,4]. Child loss is a particularly stressful life event [5,6], even more so than the death of a spouse [7–9].

Stressful events affect various physiological systems, such as the sympathetic nervous system, the hypothalamic-pituitary-adrenal axis, the neuroendocrine systems, and the immune systems [10]; we, therefore, predict that child loss may be associated with diseases such as cardiovascular and cancer and/or mortality in parents. Stressful life events raise the risk of various psychological disorders, which may lead to adverse lifestyle behaviors [11,12] and affect unnatural and natural deaths [13,14].

A study in Israel examined mortality in a group of bereaved parents of soldiers 18–40 years of age who were killed at war in 1973 and parents of offspring 18–30 years of age who died in accidents compared with the general population [15]. The 10-year follow-up indicated no excess mortality among bereaved parents;

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however, when the follow-up was extended to 20 years, the findings showed an effect of stress on incidence of malignancies for selected sites and accelerated demise among parents bereaved after a cancer diagnosis, but not among those bereaved before such a diagnosis [16]. Other investigations, however, indicate an overall association between child loss and mortality in parents [17].

The Jerusalem Perinatal Study (JPS) provides a unique opportunity to explore the relation between child loss and all-cause— and cause-specific mortality, cancer morbidity, and survival in parents.

Methods

The JPS is a prospective population-based birth cohort of 92,408 infants born (1964–1976) to residents of Jerusalem and their parents. Through the Israeli Population Registry (IPR), we verified identities of 41,050 mothers and 38,965 fathers (96.2% and 92.5%, respectively) in the original cohort and updated their vital status. We undertook a long follow-up study to determine the association between parental bereavement and mortality and cancer morbidity and survival. Non-Jewish parents, comprising 2.3% of the cohort, were included in analyses.

Study variables

Data included demographic and socioeconomic characteristics of parents and information on offspring including sex and birth date. Information was abstracted from birth certificates or maternity ward logbooks.

Primary outcomes in parents were risk of all-cause mortality and cause-specific mortality, including mortality due to coronary heart disease (CHD), circulatory disorders, cancer, unnatural and other causes, incidence of any cancer and mortality in parents with cancer diagnosis. The underlying cause of death was categorized according to *International Classification of Diseases, Ninth Revision* (ICD-9), codes until 1997 and in 1998 according to ICD-10 codes [18,19]. Causes of deaths were categorized into the following groups: CHD (ICD-9 codes: 410–414, 427.4, and 427.5; ICD-10 codes: I20–I25, I46, and I49); all circulatory conditions (ICD-9 codes: 390–459; ICD-10 codes: I0–I99); all neoplasms (ICD-9: 140–239; ICD-10: C0–C99 and D0–D48); death due to unnatural causes (ICD-9: 80–99; ICD-10: S0–T88, V0–Y99); and death due to all other causes taken together.

In Israel, nearly 100% of deaths are reported to the IPR, along with the date and cause of death. Linkage to the IPR occurred in 2011 at which point the registry had been fully updated through December 2010 for 89.6% of the mothers and 88.4% of the fathers. The remaining parents had updated information through April 30, 2005. Cancer incidence was ascertained via the Israel National Cancer Registry which was established in 1961 [20]. Linkage occurred in 2010 at which point the registry had been updated through July 31, 2008. For parents diagnosed with cancer, mortality was assessed via the IPR, and they were determined to have died from cancer regardless of the actual cause of death, that is, “cancer mortality.”

The following parental characteristics were included in the analyses: parents' ethnic origin—classified according to the parents' country of birth, or if born in Israel, that of the grandfather's birth country (categorized as Israel, other West Asia, North Africa, Europe or America or other industrialized countries, and non-Jewish), a social class scale (socioeconomic status [SES]: from 1 = highest to 3 = lowest) based on father's occupation, parity (number of children born before 1964, as reported by the mother, plus those born within the cohort [categorized as 1, 2, and ≥3]), having a stillbirth in the family (1, yes; 0, no), parents' age at child's birth (<30, 30–39, ≥40 years), parents' age at child's death (<30, ≥30 years), and parents' education level (0–4, 5–8, 9–12, ≥13, unknown).

In addition, we examined the following characteristics related to the deceased child: number of deceased children in the family (1, ≥2), child's age at death (<1, 1–17, ≥18 years), and time passed since child loss (0–3, 4–8, ≥9 years).

Statistical analysis

Time was counted from birth of the deceased child or earliest birth in the cohort when parents had multiple live offspring until death of parent or study closure (December 31, 2010 or April 30, 2005). The Cox proportional hazards regression model, with child's death as a time-dependent exposure variable, was used to evaluate associations between this life event and parental mortality after controlling for possible confounders. If a child died during the study period, the surviving parent(s) changed status from nonexposed (nonbereaved) to exposed (bereaved). All parents, even those who died before the child loss, were included in the mortality analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated, and competing hypotheses were tested by the likelihood ratio test.

For the investigation of cancer incidence, parents with cancer diagnosed within 5 years after child loss were eliminated from the analysis. However, we performed a series of sensitivity analyses to test the robustness of our cancer results: (1) by including parents with cancer diagnosed 3 or more years after bereavement and (2) by including parents diagnosed 1 year after bereavement. We also compared survival in parents whose cancer was diagnosed before their loss (and survived at least till after the child loss) and those whose cancer was diagnosed after their loss.

Adjustments for parents' education level, parents' age at child's birth and death, and child's age at death in all models were also assessed as continuous variables and yielded HRs similar to those obtained using age and education as categorical variables.

Analyses were stratified by characteristics of parents and the deceased child, which may modify parents' ability to cope with the acute life event. Owing to sample size limitations, stratification was not carried out on cause-specific mortality. We used heterogeneity tests for stratified data to test for interactions between the exposure and modifier variables. The significance of effect modification was assessed using Higgins and Thompson's heterogeneity index [21] which under the null hypothesis is distributed as $\chi^2_{(I-1)}$ where I indicates the number of strata. Most analyses were completed using Stata, version 12.0 (StataCorp, College Station, TX), and heterogeneity tests were calculated using WinPepi, version 11.42 (J.H. Abramson, Jerusalem, Israel) [22]. All tests were two-sided, and an alpha set at 0.05.

This study was approved by the Institutional Review Boards of Hadassah–Hebrew University Medical Center in Jerusalem.

Results

Table 1 shows baseline characteristics of bereaved (2838 mothers and 2532 fathers) and nonbereaved (38,212 mothers and 36,433 fathers) parents. There was no relation between bereavement and parents' age at birth. About 77% of mothers and 60% of fathers gave birth before the age of 30 years. Compared with the unexposed group, exposed Jewish parents tended to be of Asian and North African origin. Exposed parents were less educated, exhibited lower SES, and have more children. About 9.5% of parents were exposed to death of two children or more, and more than 50% of the deceased children died during their first year of life.

During the follow-up, mothers contributed 1,608,772 person-years (average: 39.1 person-years) for overall mortality and 1,451,323 person-years (average: 35.6 person-years) for cancer

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