Hypothesis/Commentary

Risk of Cancer among the Offspring of Women Who Experienced Parental Death during Pregnancy

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The causal link between psychological stress and cancer, if any, remains unclear (1-4). It has been hypothesized that stressors, such as dramatic life events, might result in an impairment of the immune response, thus increasing the risk of malignancies (e.g., those associated with viral infections; refs. 1, 4). On the other hand, studies in monozygotic twins, in archived neonatal blood spots of patients, and in normal newborn cord bloods suggest that most pediatric leukemias are initiated *in utero*. Postnatal secondary genetic changes, usually triggered by abnormal immune responses to infections, seem to be additionally required for leukemia development (5-7). Although epidemiologic studies have been conducted to investigate the relationship between stress and cancer, their small size and the inadequate ascertainment of the cases have been considered important limitations for the interpretation of the results (2). Another criticism has been the vagueness of the formulated hypotheses, which does not permit to distinguish between cancer initiation, cancer progression, and health behavior after a negative episode in life (3). A novel approach was used here to address this controversial topic: we investigated the risk of cancer among individuals born to women who experience death of a family member during pregnancy.

The Swedish Family-Cancer Database includes persons born in Sweden after 1931 with their biological parents, totaling more than 11.5 million persons and more than 1.2 million tumor notifications (for a detailed description of the Database and its last update, see refs. 8, 9). Diagnostic codes according to the International Classification of Diseases are available since 1961, as well as histopathologic codes according to the Systemized Nomenclature of Medicine after 1992. Standardized incidence ratios (SIR) with 95% confidence intervals and P values were used to compare the risk of cancer in offspring of mothers whose parents died during pregnancy with the risk of cancer in the general offspring population. Individuals were followed from birth, immigration date (the updated Database includes 0.4 million foreign-born offspring linked to parents; ref. 10), or first year of the study (1993 for histology specific testicular tumors, 1961 for any other cancer type), whichever came latest, until diagnosis of any cancer, death, emigration, or December 31, 2004, whichever came first. The estimated incidences were adjusted for the covariates age (5-year groups), sex, socioeconomic index of the offspring (six groups), region (four groups), mother's age at delivery (<20, 20-24, 25-29,. . ., 50-54, >55 years), and calendar year (before 1965, 1965-1969, 1970-1974,. . ., 1995-1999, 2000-2004).

We identified 39,002 offspring born to women who experienced parental death during pregnancy; 1.7% of them were siblings. The median birth year was 1982 (range, 1952-2003) for the offspring and 1952 (range, 1932-1985) for the mothers. Among the offspring, 217 were affected by cancer at any site within 0 to 43 years of follow-up (median length of follow-up, 22 years). The estimated SIRs are shown in Table 1. The offspring showed an increased risk of leukemia (SIR, 1.49; $P = 0.004$) and, more specifically, of acute lymphoblastic leukemia (SIR, 1.69; $P = 0.002$). The age of onset of the 31 acute lymphoblastic leukemias varied from 2 to 32 years (median age, 6 years), with >80% of the malignancies diagnosed before age 15 years (SIR, 1.58; $P = 0.01$). The incidence of Hodgkin's disease was also increased (SIR, 1.71; $P = 0.009$). The age at onset of the 20 Hodgkin's lymphomas was 6 to 35 years (median age, 20 years). An increased risk of testicular cancer was also noted (SIR, 1.80; $P = 0.02$), which was entirely explained by the morphology of embryonal carcinoma (SIR, 3.54; $P = 0.006$; 4 cases; median age of onset, 28 years). When the parental death occurred in the first trimester of pregnancy, the SIR of testicular embryonal carcinoma was 1.67 (1 case); it was 1.57 (1 case) for the second trimester and 8.87 (2 cases; 95% confidence interval, 2.21-35.6; $P = 0.001$) for the third trimester. With this exception, the trimester of pregnancy at which the women experienced parental loss seemed to have no influence on the observed associations. The offspring were at an increased risk of colon cancer before age 15 years (SIR, 3.95; $P = 0.003$). Interestingly, the four daughters were diagnosed with carcinoid tumors located in the appendix (SIR, 4.13; $P = 0.003$; median age of onset 11 years).

This study is the first to epidemiologically relate tragic events during pregnancy with cancer development in the offspring. A major limitation was that the mechanisms of

Cancer Epidemiol Biomarkers Prev 2007;16(11):2204–6

Received 7/16/07; revised 8/22/07; accepted 9/7/07.

Grant support: Deutsche Krebshilfe, the Swedish Cancer Society, The Swedish Council for Working Life and Social Research and the EU, LSHC-CT-2004-503465.

Note: The Family-Cancer Database was created by linking registers maintained at Statistics Sweden and the Swedish Cancer Registry.

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doi:10.1158/1055-9965.EPI-07-0638

Table 1. SIR of cancer for the offspring of women who experienced death of father or mother during pregnancy

Cancer site	Age at cancer diagnosis			
	Any age		<15 y	
	n	SIR* (95% CI)	*n*	SIR* (95% CI)
Leukemia	44	1.49 (1.11-2.01)	32	1.51 (1.07-2.14)
Acute lymphoblastic leukemia	31	1.69 (1.19-2.42)	25	1.58 (1.06-2.34)
Nervous system	34	0.97 (0.70-1.36)	15	0.82 (0.49-1.36)
Brain	30	1.04 (0.73-1.49)	14	0.93 (0.55-1.57)
Melanoma	23	0.91 (0.60-1.37)		
Hodgkin's disease	20	1.71 (1.10-2.66)	2	1.39 (0.35-5.61)
Non-Hodgkin's lymphoma	15	1.33 (0.80-2.21)	6	1.26 (0.56-2.81)
Testis	13	1.80 (1.04-3.10)		
Embryonal carcinoma	4	3.54 (1.32-9.48)		
Seminoma	3	0.48 (0.15-1.48)		
Teratoma	3	0.94 (0.30-2.93)		
Breast	12	0.77 (0.44-1.36)		
Colon	10	1.12 (0.60-2.10)	4	3.95 (1.46-10.7)
Appendix (carcinoid)	7	1.34 (0.63-2.82)	4	4.13 (1.52-11.2)

Abbreviation: 95% CI, 95% confidence interval.
*Adjusted for age, sex, period, socioeconomic index, region, and age of the mother at delivery.

the possible oncogenic effects of psychosocial stress have not been established (1, 3, 4, 11). Moreover, these are likely to be highly variable because individuals react and cope differentially with major stressors (12). The present sources of data were based on national registries of complete coverage, thus minimizing biases due to recall and ascertainment (8, 9, 13). However, associations due to chance cannot be excluded, in particular for testicular cancer and appendiceal carcinoid tumors. The adjustment for socioeconomic status was motivated by the likely dependence of the early parental death and the prevalence of viral infections on social conditions (14-16). Increased risks were noted for four tumor types: childhood acute lymphoblastic leukemia (median diagnostic age 6 years), Hodgkin's disease (20 years), embryonal carcinoma of the testis (30 years), and appendiceal carcinoid tumors (11 years). The results were consistent in that all these tumors were of early onset and histologically defined, as would be anticipated for exposures taking place during pregnancy. The age of onset of the four tumor types was below the median follow-up time of the offspring population (22 years), except for embryonal tumors. Additionally, acute lymphoblastic leukemia and Hodgkin's disease are suggested to be related to an infectious etiology, the former by unknown microbial agents and the latter by EBV (6, 17, 18). Another consistency is that testicular tumors (embryonal tumors are usually mixed with other histologic types) seem to be associated with prenatal estrogenic exposure, and appendiceal carcinoids are neuroendocrine tumors producing serotonin and bioactive peptides (19-21). Appendiceal carcinoids are usually asymptomatic, more frequent in females than in males, and often diagnosed at appendectomies (20). In the present study, all appendiceal carcinoid patients were female and they were diagnosed at a considerably younger age (11 years) than the mean diagnostic age reported in the literature (32-43 years); we have no data on whether the present tumors were diagnosed at appendectomies.

There are many lines of evidence showing that glucocorticoids and cathecolamines, released in chronic stress and depression, influence adversely immune function and increase risk of infection in adults (1-4). The immune system develops during the intrauterine period, and it may be sensitive to maternal stress hormones (22). Hormonal changes due to stressful events during pregnancy may activate viruses, such as the EBV or latent human T-cell lymphotropic viruses, or they could intervene with the development of the immune system of the fetus (4, 23). The proposed models for early-onset leukemia/lymphoma development invoke prenatal viral infections as the initial trigger with considerable supporting data (16). Our findings on leukemia and Hodgkin's disease have a reasonable biological rationale. However, for testicular embryonal tumors and appendiceal carcinoids, the only biological clue may be that they originate from an embryonic tissue that is hormone responsive. Practically nothing is known about the etiology of these tumors. Thus, even if we can only speculate about the biological mechanisms, the epidemiologically consistent findings bridge a challenging link between stress during pregnancy and cancer risk in the developing offspring.

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Cancer Epidemiol Biomarkers Prev 2007;16:2204-2206.