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LETTER TO THE EDITOR

Risk of cardiovascular disease among parents of children diagnosed with cancer: a population-based study from Denmark and Sweden

Dear Editor,

Receiving a cancer diagnosis is a traumatic life event that impacts not only the patients but also their families [1]. Parents of patients with a cancer diagnosed in early life might experience a life crisis with various negative emotions, including the difficult decision-making in cancer treatment, concerns related to the side effects of the treatment and comorbidities, the worry for progression and relapse of the cancer and the risk of loss of the child due to death, as well as the physical demand of caregiving [2, 3]. Accumulating evidence has indeed shown that the diagnosis of cancer in a child can lead to severe psychological distress for parents [1]. Previous studies have suggested that psychological distress plays an important role in the triggering, maintenance, and progression of cardiovascular disease (CVD) through biological or behavioral changes [4, 5]. Little is known, however, about the risk of CVD among parents of children with cancer.

To this end, we performed a cohort study using Danish (during 1978-2016) and Swedish (during 1987-2014) nationwide registers to assess the association between cancer diagnosis of a child and subsequent risk of CVD among their parents, using both population- and sibling-based comparisons. The study included 79,158 parents who had a child diagnosed with cancer during 1978-2016 in Denmark or 1987-2014 in Sweden, 791,580 parents without such an experience who were randomly selected from the general populations of the two countries and individually matched to the exposed parents by birth year, sex, and country of residence (population comparison), and 45,007 unaffected full siblings of the exposed parents (sibling comparison). Detailed methods are described in Supplementary Methods.

In population comparison, the baseline characteristics of parents who had a child with cancer were similar to the unexposed parents, apart from having slightly lower educational levels (Supplementary Table S1). The median follow-up time for the whole cohort was 6.7 years (interquartile range: 3.1 - 12.8 years). During follow-up, we identified 18,977 cases of first-onset CVD among the exposed parents (incidence rate [IR], 27.2 per 1000 person-years) and 177,295 cases among unexposed parents (IR, 25.5 per 1000 person-years) (Table 1). Parents of children with a cancer diagnosis had a statistically significantly increased risk of CVD compared with unexposed parents (Supplementary Figure S1). The risk increase was found immediately after cancer diagnosis and persisted during the entire 38-year follow-up. The mean hazard ratio (HR) for first-onset CVD during the entire follow-up was 1.06 (95% confidence interval [CI] 1.05 to 1.08) (Table 1). The association was slightly more pronounced among women than men (HR 1.08, 95% CI 1.06 to 1.11 vs. HR 1.05, 95% CI 1.02 to 1.07; P for difference = 0.02). In sibling comparison, exposed parents had a slightly higher risk than their unexposed siblings (HR 1.04, 95% CI 1.00 to 1.08) (data not shown).

When studying specific types of CVD, we observed a positive association for ischemic heart disease (HR 1.05, 95% CI 1.02 to 1.09), acute myocardial infarction (HR 1.05, 95% CI 1.00 to 1.11), atrial fibrillation (HR 1.06, 95% CI 1.01 to 1.11), and pulmonary embolism or deep venous thrombosis (HR 1.10, 95% CI 1.05 to 1.16) (Supplementary Figure S2). A positive association was observed for most studied cancer types (Supplementary Table S2). The increased risk of CVD in relation to cancer diagnosis of a child was primarily limited to parents of children with cancer diagnosed at regional spread or advanced stage or unknown stage (P for difference = 0.03) (Supplementary Table S3). The increased risk of CVD related to cancer diagnosis of a child was more pronounced for parents of children with cancer diagnosed at >18 years (Supplementary Table S4). Other results of sensitivity analyses were shown in Supplementary Results. Finally, in the separate cohort of parents with

Abbreviations: CVD, cardiovascular disease; IR, incidence rate; HR, hazard ratio; CI, confidence interval; BMI, body mass index.

TABLE 1 IRs (per 1000 person-years) and HRs with 95% CIs for the association between cancer diagnosis of a child and risk of first-onset CVD.

Characteristics	Matched unexposed parents (N = 791,580)		Exposed parents (N = 79,158)				Absolute difference (95% CI) of IR
No. of parents with CVD*	Crude IR	HR (95% CI)#	No. of parents with CVD*	Crude IR	HR (95% CI)#	*P* for interaction	
Overall†	177,295	25.5	1.0	18,977	27.2	1.06 (1.05 to 1.08)	1.8 (1.4 to 2.2)
Sex						0.02	
Male	92,268	29.2	1.0	9,697	30.7	1.05 (1.02 to 1.07)	1.4 (0.8 to 2.1)
Female	85,027	22.3	1.0	9,280	24.4	1.08 (1.06 to 1.11)	2.1 (1.6 to 2.6)
Age at index date, years						0.75	
< 40	27,095	12.5	1.0	2,880	13.2	1.05 (1.01 to 1.09)	0.7 (0.2 to 1.2)
40-60	107,033	27.2	1.0	11,443	29.1	1.06 (1.04 to 1.08)	1.9 (1.4 to 2.5)
> 60	43,167	50.6	1.0	4,654	55.0	1.08 (1.04 to 1.11)	4.4 (2.8 to 6.1)
Calendar year						0.78	
< 1990	16,773	16.8	1.0	1,814	18.0	1.07 (1.02 to 1.13)	1.2 (0.4 to 2.1)
1990-1999	52,449	21.3	1.0	5,605	22.8	1.06 (1.03 to 1.09)	1.5 (0.8 to 2.1)
2000-2009	80,247	29.9	1.0	8,604	32.2	1.07 (1.04 to 1.09)	2.3 (1.5 to 3.0)
≥ 2010	27,826	33.9	1.0	2,954	36.0	1.05 (1.01 to 1.09)	2.1 (0.7 to 3.4)
Country of residence						0.41	
Sweden	90,833	24.9	1.0	9,731	26.8	1.07 (1.05 to 1.09)	1.8 (1.3 to 2.4)
Denmark	86,462	26.0	1.0	9,246	27.7	1.06 (1.03 to 1.08)	1.7 (1.1 to 2.3)
Educational level, years						0.20	
0-9	51,981	29.6	1.0	6,152	32.4	1.09 (1.06 to 1.11)	2.8 (1.9 to 3.6)
10-14	92,228	24.2	1.0	9,709	25.6	1.05 (1.03 to 1.07)	1.4 (0.9 to 1.9)
≥ 15	30,460	23.4	1.0	2,839	24.2	1.06 (1.02 to 1.10)	0.7 (-0.2 to 1.7)
Missing	2,626	26.2	1.0	277	28.5	-	2.3 (-1.2 to 5.8)
Household income						0.11	
Low	45,925	34.1	1.0	4,963	37.2	1.08 (1.05 to 1.11)	3.2 (2.1 to 4.3)
Middle	46,229	24.8	1.0	5,176	26.7	1.08 (1.05 to 1.11)	1.9 (1.1 to 2.6)
High	85,069	22.7	1.0	8,830	23.9	1.05 (1.02 to 1.07)	1.2 (0.7 to 1.8)
Missing	72	10.7	1.0	8	19.6	-	8.8 (-4.9 to 22.6)
Marital status						0.78	
Single, widowed or divorced	47,512	23.7	1.0	4,891	25.7	1.07 (1.04 to 1.10)	2.0 (1.3 to 2.8)
Married or in registered partnership	112,789	25.5	1.0	12,344	27.1	1.06 (1.04 to 1.08)	1.7 (1.2 to 2.2)
Missing	16,994	31.8	1.0	1,742	33.8	-	2.0 (0.3 to 3.6)
History of cancer						0.50	
Yes	8,679	43.8	1.0	1,189	46.9	1.08 (1.02 to 1.15)	3.1 (0.3 to 5.9)
No	168,616	24.9	1.0	17,788	26.5	1.06 (1.05 to 1.08)	1.6 (1.2 to 2.0)
Family history of CVD						0.66	
Yes	82,176	27.9	1.0	8,692	30.0	1.06 (1.04 to 1.08)	2.0 (1.4 to 2.7)
No	95,119	23.6	1.0	10,285	25.3	1.07 (1.05-1.09)	1.8 (1.2 to 2.2)
Family history of psychiatric disorders						0.82	
Yes	27,336	27.3	1.0	2,894	29.3	1.06 (1.02 to 1.10)	1.9 (0.7 to 3.0)
No	149,959	25.1	1.0	16,083	26.9	1.06 (1.04 to 1.08)	1.8 (1.4 to 2.2)

*Number of CVD events among studied parents.

#Cox models were adjusted for sex, age at index date, country of residence, calendar year at index date, marital status, highest attained education, personal income, history of cancer, family history of CVD, and family history of psychiatric disorders. Time since the index date was used as the underlying time scale. The analyses of Cox models were performed on five imputed datasets, and HRs were obtained from the combination of each dataset using Rubin's rule.

†Analysis of the overall population comparison.

IR: incidence rate; HR: hazard ratio; CI: confidence interval; CVD: cardiovascular disease. N: total number of parents in the exposed group or unexposed group.

a history of CVD, we observed a more pronounced risk increase of any CVD (HR 1.14, 95% CI 1.12 to 1.16) as well as most specific CVDs in relation to a child cancer diagnosis (Supplementary Figure S3 and Supplementary Table S5).

To the best of our knowledge, our study is the first to systematically investigate the association between a child's cancer diagnosis and the subsequent risk of CVD in parents. Our finding of a modestly increased risk of CVD, particularly in the cases of advanced cancer stage, provides complementary data on the negative health impact of a child's cancer diagnosis on parents. Further, this finding corroborates and extends the documented link between traumatic and stressful events, including the bereavement of a child [6], having a child with congenital anomaly [7], receiving a diagnosis of cancer [8], and job strain [9], and increased risk of CVD.

A cancer diagnosis in a child and the resultant psychological distress might immediately trigger acute cardiovascular events, such as myocardial ischemia and abnormality of cardiac rhythm, through disturbance of inflammatory process or autonomic response [5]. In addition, psychological stress could also induce a series of chronic biological changes, including dysfunction of the hypothalamic-pituitary-adrenal axis, abnormal hormone levels, and adverse changes in metabolic activity [4, 5]. These biological changes could further contribute to diverse pathophysiological alterations of the cardiovascular system, such as endothelial dysfunction, increased blood pressure, changes in heart rate variability, hypercoagulation, atherosclerosis, stress cardiomyopathy, myocardial ischemia, abnormal ventricular wall motion, and arrhythmias [4, 5]. In addition to biological alterations, stress-related behavioral changes (e.g., smoking, inactivity, unhealthy diet, and sleep problems) [10], reduced income, and marital status change subsequent to cancer diagnosis of a child could also play a role in the association between cancer diagnosis of a child and parental CVD.

The association was stronger for mothers than fathers, which might be due to the closer emotional bond between child and mother and potentially greater caregiving burden among mothers. Our finding indicates that the risk elevation of CVD is limited to parents of children with cancer diagnosed at regional spread or advanced stage or unknown stage, compared with parents of children with a lower stage cancer, suggesting a greater level of psychological distress associated with receiving a diagnosis of cancer with adverse prognosis. Further, although the difference was not statistically significant, our study also suggested a slightly higher risk increase of CVD among parents who lost their child due to cancer compared to parents whose cancer child was still alive. Finally, parents with a previous history of CVD were at a higher risk of new CVD event than parents without such.

The strengths of our study include the population-based and sibling-controlled design, the large sample size, the long and complete follow-up, and the prospective and independent collection of information on cancer and CVD. Potential limitations of the study include residual confounding (e.g., due to genetics or lifestyle factors not shared between siblings) and surveillance bias (e.g., different health-seeking behaviors of the parents after a cancer diagnosis of their child). For instance, given the register-based nature of the study, we had limited information on potential confounders (e.g., body mass index [BMI], smoking and alcohol consumption). Therefore, future studies with detailed information on such factors are needed to validate our findings.

In conclusion, we observed a modestly increased risk of CVD among parents who had a child with cancer, especially when the cancer was diagnosed at an advanced stage. The risk increase was evident for several decades after the event and was robust in subgroup and sensitivity analyses.

DECLARATIONS

AUTHOR CONTRIBUTIONS

Qianwei Liu, Krisztina D László and Fang Fang conceived the idea for the study. Qianwei Liu, Krisztina D László, Jiong Li, and Fang Fang designed the study. Qianwei Liu had full access to all the data and performed the analysis. Qianwei Liu prepared the manuscript draft. All authors interpreted data and revised and completed the final version of the manuscript for submission.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by Danish Protection Agency in Denmark (J nr. 2013–41-2569) and the Regional Ethical Review Board in Stockholm, Sweden (DNR 2016/288-31/1). Informed consent of the study participants was waived by the ethical committees.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data underlying this article were provided by Statistics Denmark, the Swedish National Board of Health and Welfare, and Statistics Sweden. The data cannot be shared publicly due to the regulations of the above data holder authorities and ethical reasons. Similar data might

be requested from these holder authorities for research purposes by researchers who fulfill specific requirements.

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SUPPORTING INFORMATION

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