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Original Contribution

Pancreatic Cancer Risk After Loss of a Child: A Register-based Study in Sweden During 1991–2009

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The potential role of psychological stress in pancreatic cancer has rarely been investigated in epidemiologic studies. During 1991–2009, we conducted a nested case-control study based on Swedish national population and health registers to investigate whether severe psychological stress induced by the death of a child was associated with subsequent risk of pancreatic cancer. The study included 16,522 cases and 82,107 controls who were matched to the cases on sex and year of birth. Conditional logistic regression was used to estimate odds ratios and 95% confidence intervals. Overall, loss of a child was associated with an odds ratio of 1.09 for pancreatic cancer (95% confidence interval (CI): 1.02, 1.17). The risk elevation was mainly seen during the first 5 years after the loss (odds ratio (OR) = 1.27, 95% CI: 1.12, 1.45) and for loss of a child due to suicide (OR = 1.23, 95% CI: 1.03, 1.46). The association was statistically significant among women but not among men, and it appeared stronger for early-onset pancreatic cancer. Persons with a history of psychiatric illness had the greatest risk increase after child loss (OR = 1.43, 95% CI: 1.17, 1.76). Although other explanations are possible, our findings provide some evidence that psychological stress may be associated with pancreatic cancer.

case-control studies; pancreatic neoplasms; stress, psychological

Abbreviations: BMI, body mass index; CI, confidence interval; DCO, death certificate only; FAP, familial adenomatous polyposis; HBOC, hereditary breast-ovarian cancer; HNPCC, hereditary nonpolyposis colorectal cancer; MEN1, multiple endocrine neoplasia type 1; OR, odds ratio.

Pancreatic cancer is one of the most lethal malignancies. In Europe, it is the fifth most common cause of cancer-related death for men and the sixth most common for women (1). Well-established risk factors for pancreatic cancer include advanced age, male sex, tobacco smoking, hereditary pancreatitis, type 2 diabetes, and a family history of pancreatic cancer (2). However, these factors account for only a portion of pancreatic cancer risk, and despite the urgent need for primary prevention, the etiology of pancreatic cancer is not well understood.

There has been a long-standing interest in the potential link between psychological stress and cancer development in general. Possible underlying mechanisms for such a link include the altered release of stress-induced hormones, modified immune responses, and stress-mediated behavioral changes (3). However, results from human studies are largely inconsistent (4). On the other hand, studying psychological stress in the human setting is inherently difficult given the broad definition of stress exposures, varying perceptions of stress, and varying physiological responses across individuals, in addition to various methodological limitations (5).

The death of a child is one of the most stressful life events a person may encounter. Several studies have used the loss of a child due to death as a paradigm for exposure to severe psychological stress and have investigated the associations between such traumatic events and cancer. Levav et al. (6) observed an association between loss of a child and a higher risk of lymphatic and hematopoietic malignancies among Jewish Israelis. Li et al. (7) showed a slightly higher risk of lung cancer among bereaved mothers more than 10 years

after child loss in Denmark. In Sweden, a higher risk of human papillomavirus-related cancers (8), but not breast cancer (9), was observed after loss of a child.

Given the variable biology of different cancers, stress effects are likely to vary across different cancer types. Therefore, investigation of specific cancers is warranted. Because of the low incidence of pancreatic cancer, the association between a severely stressful life event and pancreatic cancer has never been examined in epidemiologic studies. However, overexpression of the stress-associated neurotransmitter noradrenaline has been demonstrated in pancreatic tumor tissue (10), and recently Schuller et al. (11) proposed that neurotransmitter responses to psychological stress may negatively affect clinical outcomes for pancreatic cancer, supporting the notion that psychological stress may play a role in the initiation and progression of pancreatic cancer. Therefore, leveraging the nationwide registration of population and health data in Sweden, we aimed to investigate whether the severe psychological stress induced by loss of a child results in an altered risk of pancreatic cancer.

MATERIALS AND METHODS

Study population

The study population was defined as all persons included in the Swedish Population and Housing Census in 1990 who were born in Sweden and had at least 1 child recorded in the Swedish Multi-Generation Register ($n = 4{,}865{,}150$). The Swedish Multi-Generation Register contains familial information for persons born in Sweden from 1932 onward, and familial linkages are complete for more than 90% of persons who were alive on January 1, 1990, or born afterward (12).

Follow-up

Using the unique Personal Identity Number assigned to all residents of Sweden, we followed the study population from January 1, 1991, to December 31, 2009, through cross-linkages with the Swedish Cancer Register, Cause-of-Death Register, and Migration Register. Follow-up was censored at the time of diagnosis of a first primary malignancy, death, or emigration out of Sweden, whichever occurred first. During cross-linkages, a total of 223,665 persons (4.6%) were excluded from follow-up given the fact that they had died ($n = 6{,}273$), had been diagnosed with a primary malignant cancer ($n = 168{,}322$, including 532 pancreatic cancer cases), or had emigrated out of Sweden ($n = 49{,}070$) before January 1, 1991. This left 4,641,485 persons in the study cohort.

Nested case-control study

A nested case-control study was conducted within the study base. During follow-up, we identified 11,465 cases of pancreatic cancer from the Swedish Cancer Register. Given the known possibility of death certificate only (DCO) cases of pancreatic cancer (13), we further identified 5,184 persons who died with pancreatic cancer as the underlying cause of death but did not have any record in the Swedish Cancer Register, leaving a total of 16,649 cases. Using the method of incidence density sampling (14), we randomly selected 5 controls per case who were matched to the case by sex and year of birth ($n = 83{,}245$). These were persons who had not yet died, emigrated out of Sweden, or been diagnosed with any primary malignancy at the time of index case diagnosis. The date of pancreatic cancer diagnosis or death for cases and the date of selection for controls was defined as the index date.

Exposure assessment

The exposure of interest was loss of a child due to death before the index date. From the Multi-Generation Register, we identified a total of 39,020 children for cases and 192,859 for controls who were born before the index date. Three cases and 21 controls had only children born after the index date and were therefore excluded, leaving 16,646 cases and 83,215 controls in the study. Given the matched design, the controls of the 3 cases were also excluded; since 5 controls were selected for each case, the matched case-control sets of the 21 controls were kept in the analysis. Through the Personal Identity Number, these children were linked to the Cause-of-Death Register to identify any death; information on age at death and cause of death was also retrieved. In the present analysis, we assessed such losses occurring from January 1, 1961, to the index date. A total of 1,232 cases and 5,551 controls had lost at least 1 child during this period.

A concern was that the death of a child may be associated with parental pancreatic cancer for reasons independent of severe psychological stress, such as shared genetic features, which may lead to both pancreatic cancer in a parent and pancreatic cancer or pancreatic cancer-related cancer syndromes among the children. For example, the multiple endocrine neoplasia type 1 (MEN1) syndrome is associated with neoplasm of the pituitary gland, the parathyroid gland, and endocrine pancreatic cancer. Hereditary breast-ovarian cancer (HBOC) syndrome is associated with germ-line mutations in the breast cancer 1, early-onset gene (*BRCA1*) and the breast cancer 2, early-onset gene (*BRCA2*), and previous studies have demonstrated that carriers of *BRCA1/BRCA2* mutations may have increased risk of pancreatic cancer (15). Similarly, hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) are 2 autosomal-dominant hereditary diseases with germ-line mutations that are potentially associated with higher risk of pancreatic cancer (16). Therefore, in the present analysis, we excluded cases and controls who had lost children who had pancreatic cancer, MEN1, HBOC syndrome, HNPCC, or FAP. Pancreatic cancer among the children was identified from both the Swedish Cancer Register and the Cause-of-Death Register, while MEN1, HBOC syndrome, HNPCC, and FAP were identified from the Cancer Register alone. These cancer syndromes included cancers of the pituitary gland and the parathyroid gland, as well as endocrine pancreatic cancer (MEN1); breast or ovarian cancer (HBOC syndrome); colon, rectal, endometrial, ovarian, bladder, or stomach cancer (HNPCC); and colorectal cancer (FAP). As a result, 124 cases and their matched controls ($n = 620$) and 481 controls were deleted.

At the end, a total of 16,522 cases ($n = 1{,}108$ exposed) and 82,107 controls ($n = 5{,}015$ exposed) remained in the final analysis.

Covariates

Sociodemographic factors may be associated with both one's likelihood of child loss and the risk of pancreatic cancer. Accordingly, information on attained educational level at the index date was obtained from the Swedish Education Register, and information on socioeconomic status and region of residence was obtained from the 1990 Swedish Population and Housing Census. Educational level was categorized as high (≥9 years), low (<9 years), or unknown. Socioeconomic status was categorized as blue-collar, white-collar, self-employed, or unclassified. Region of residence was classified as southern, central, or northern Sweden. If respective information from the 1990 Census was missing, information from the 1980 Census was used.

Statistical analysis

Odds ratios and their 95% confidence intervals were estimated for loss of a child using conditional logistic regression models. Multivariable models included adjustment for education, socioeconomic status, and region of residence. A person's total number of children may be associated with both the risk of child loss and the risk of pancreatic cancer (17–19); therefore, we adjusted in all models for total number of children before the index date, classified as 1, 2, or more than 2.

We further conducted analyses to examine the modifying effect of the cause of child loss and time since the loss (≤5 years or >5 years) on the studied association. The cause of child loss was classified as either "injury-related" (self-inflicted or non-self-inflicted) or "chronic disease" (not injury-related—i.e., cancer or other disease). For the analyses of time since loss and cause of loss, we used the information on the last loss for persons with more than 1 child death identified. Since coexisting psychiatric illness might modify the association between child loss and pancreatic cancer risk, we further classified the exposed group as persons with or without a history of psychiatric illness before the index date. History of psychiatric illness was obtained through linkage of the case-control study participants with the Swedish Patient Register, which includes information on hospital discharges for psychiatric diseases from 1973 onward (20). Since the Patient Register obtained complete nationwide coverage in 1987, we used information on psychiatric illnesses from 1987 to the index date.

The association between child loss and cancer risk may differ between men and women (7); therefore, we stratified the analyses by the sex of the parent. Psychological stress may be especially relevant for early-onset pancreatic cancer; thus, we specifically studied the association among persons who were aged 55 years or younger on the index date. Similarly, to examine the potentially differing effect of multiple child losses, among persons with more than 1 child we conducted analysis for loss of more than 1 child as compared with loss of 1 child. Among these persons, 77 cases and 325 controls had lost more than 1 child before the index date.

Finally, we conducted a few sensitivity analyses to check the soundness of our results. First, since we included DCO cases in the main analysis and a proportion of DCO cases may have been misclassified as pancreatic cancer cases (21), we performed a subanalysis by excluding all DCO cases ($n = 5,121$) and their matched controls ($n = 25,360$). Second, since diabetes and pancreatic cancer might share etiological factors (22), in another subanalysis we excluded all persons who had lost a child whose underlying cause of death was diabetes (23 cases together with their matched controls and 85 controls of other cases). Similarly, congenital malformations may be associated with different cancers (23), so in another subanalysis persons with children who died from congenital malformations were excluded (5 controls). Finally, since the potential impact of psychological stress might be different for endocrine pancreatic cancer compared with other pancreatic cancer, we performed different analyses for

Table 1. Characteristics of Pancreatic Cancer Patients and Matched[a] Controls in a Nested Case-Control Study, Sweden, 1991–2009

	Cases ($n = 16,522$)		Controls ($n = 82,107$)	
	No.	%	No.	%
Sex				
Men	7,523	45.5	37,455	45.6
Women	8,999	54.5	44,652	54.4
Age at index date, years				
≤55	1,092	6.6	5,432	6.6
56–65	2,787	16.9	13,955	17.0
66–75	4,775	28.9	23,859	29.1
≥76	7,868	47.6	38,861	47.3
Calendar period of index date				
1991–1995	4,273	25.9	21,264	25.9
1996–2000	4,149	25.1	20,631	25.1
2001–2005	4,362	26.4	21,663	26.4
2006–2009	3,738	22.6	18,549	22.6
Education, years				
<9	6,658	43.8	34,359	45.5
≥9	8,535	56.2	41,221	54.5
Unknown	1,329		6,527	
Socioeconomic status				
Blue-collar	5,244	46.5	25,165	44.1
White-collar	4,801	42.6	25,465	44.7
Self-employed	1,235	11.0	6,392	11.2
Unclassified	5,242		25,085	
Region of residence				
Southern Sweden	3,903	23.6	20,076	24.4
Central Sweden	8,747	52.9	43,369	52.8
Northern Sweden	3,872	23.4	18,662	22.7
Total no. of children				
1	4,075	24.7	19,748	24.1
2	6,576	39.8	33,910	41.3
>2	5,871	35.5	28,449	34.7

[a] Controls were matched to cases by sex and year of birth.

cases with endocrine pancreatic cancer (77 cases) and cases with other pancreatic cancers.

Analyses were carried out using SAS, version 9.3, software (SAS Institute, Inc., Cary, North Carolina). All *P* values reported are 2-sided.

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

RESULTS

Compared with controls, more cases had an education of 9 years or more ($P = 0.001$; χ^2 test) (Table 1). An overall different pattern of socioeconomic status was observed between cases and controls ($P < 0.001$). Cases were also more likely to be residing in the northern part of Sweden than controls ($P = 0.03$).

Overall, there was a slightly increased risk of pancreatic cancer associated with the death of a child (odds ratio (OR) = 1.09, 95% confidence interval (CI): 1.02, 1.17) (Table 2). A statistically significant association was observed only during the first 5 years after child loss (OR = 1.27, 95% CI: 1.12, 1.45), for loss of a child due to suicide (OR = 1.23, 95% CI: 1.03, 1.46), and among persons with a history of psychiatric illness before the index date (OR = 1.43, 95% CI: 1.17, 1.76) (Table 2).

A statistically significant association between child loss and pancreatic cancer risk was noted among women but not men (Table 3); however, a statistically significant interaction between child loss and parent's sex was not detected ($P = 0.60$). Similar to the overall analysis, among women, the association was clear only during the first 5 years after the loss (OR = 1.37, 95% CI: 1.17, 1.60) and for child loss due to suicide (OR = 1.31, 95% CI: 1.05, 1.62). Focusing on early-onset pancreatic cancer, a slightly stronger association was observed (Table 4). Again, the first 5 years after the loss and loss due to injury-related causes largely explained the overall increased risk of pancreatic cancer in this group. Among persons with more than 1 child, no difference was observed between a single loss (OR = 1.08, 95% CI: 0.81, 1.43) and multiple losses (OR = 1.09, 95% CI: 1.00, 1.17).

The exclusion of DCO cases and their controls did not alter the results appreciably (OR = 1.08, 95% CI: 0.99, 1.18). Excluding persons who had lost a child due to diabetes (OR = 1.08, 95% CI: 1.01, 1.16) or congenital malformations (OR = 1.09, 95% CI: 1.02, 1.17) did not change the results either. Since only 1 out of the 77 endocrine pancreatic cancer cases had lost a child before the index date, we only calculated the child-loss odds ratio for other types of pancreatic cancer (OR = 1.09, 95% CI: 1.02, 1.17).

DISCUSSION

In this large nested case-control study, we found a slightly increased risk of pancreatic cancer among women who had previously lost a child. The risk increment was noted only

Table 2. Risk of Pancreatic Cancer According to the Death of a Child in a Nested Case-Control Study, Sweden, 1991–2009

	Cases ($n = 16,522$)		Controls[a] ($n = 82,107$)		OR[b]	95% CI
	No.	% of All Cases	No.	% of All Controls		
Death of a child						
No loss	15,414	93.3	77,092	93.9	1.00	
Loss	1,108	6.7	5,015	6.1	1.09	1.02, 1.17
Time since last loss, years						
≤5	302	1.8	1,168	1.4	1.27	1.12, 1.45
>5	806	4.9	3,847	4.7	1.03	0.96, 1.12
Cause of last loss						
Injury-related	411	2.5	1,832	2.2	1.10	0.99, 1.23
Self-inflicted	158	1.0	634	0.8	1.23	1.03, 1.46
Non-self-inflicted	253	1.5	1,198	1.5	1.04	0.91, 1.19
Chronic illness-related	697	4.2	3,183	3.9	1.08	0.99, 1.18
Cancer	200	1.2	866	1.1	1.14	0.98, 1.33
Noncancer	497	3.0	2,317	2.8	1.06	0.96, 1.17
Psychiatric illness in parent						
No	987	6.0	4,604	5.6	1.06	0.98, 1.14
Yes	121	0.7	411	0.5	1.43	1.17, 1.76

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Controls were matched to cases by sex and year of birth.

[b] In addition to matching, odds ratios were adjusted for education (<9 years, ≥9 years, or unknown), socioeconomic status (blue-collar, white-collar, self-employed, or unknown), region of residence (southern, central, or northern Sweden), and total number of children (1, 2, or >2).

Table 3. Risk of Pancreatic Cancer According to the Death of a Child Among Men and Women in a Nested Case-Control Study, Sweden, 1991–2009

	Men						Women					
	Cases (n = 7,523)		Controls[a] (n = 37,455)		OR[b]	95% CI	Cases (n = 8,999)		Controls[a] (n = 44,652)		OR[b]	95% CI
	No.	% of All Cases	No.	% of All Controls			No.	% of All Cases	No.	% of All Controls		
Death of a child												
No loss	7,106	94.5	35,517	94.8	1.00		8,308	92.3	41,575	93.1	1.00	
Loss	417	5.5	1,938	5.2	1.06	0.95, 1.18	691	7.7	3,077	6.9	1.10	1.01, 1.20
Time since last loss, years												
≤5	96	1.3	427	1.1	1.10	0.88, 1.38	206	2.3	741	1.7	1.37	1.17, 1.60
>5	321	4.3	1,511	4.0	1.05	0.93, 1.19	485	5.4	2,336	5.2	1.02	0.92, 1.13
Cause of last loss												
Injury-related												
Self-inflicted	53	0.7	239	0.6	1.10	0.82, 1.48	105	1.2	395	0.9	1.31	1.05, 1.62
Non-self-inflicted	106	1.4	518	1.4	1.01	0.82, 1.24	147	1.6	680	1.5	1.06	0.89, 1.27
Chronic illness-related												
Cancer	67	0.9	283	0.8	1.18	0.90, 1.54	133	1.5	583	1.3	1.12	0.93, 1.36
Noncancer	191	2.5	898	2.4	1.05	0.89, 1.23	306	3.4	1,419	3.2	1.06	0.93, 1.20
Psychiatric illness in parent												
No	364	4.8	1,817	4.9	0.99	0.88, 1.11	623	6.9	2,787	6.2	1.10	1.00, 1.20
Yes	53	0.7	121	0.3	2.10	1.52, 2.91	68	0.8	290	0.6	1.15	0.88, 1.50

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Controls were matched to cases by sex and year of birth.
[b] In addition to matching, odds ratios were adjusted for education (<9 years, ≥9 years, or unknown), socioeconomic status (blue-collar, white-collar, self-employed, or unknown), region of residence (southern, central, or northern Sweden), and total number of children (1, 2, or >2).

Table 4. Risk of Early-Onset Pancreatic Cancer (Age at Diagnosis ≤55 Years) According to the Death of a Child in a Nested Case-Control Study, Sweden, 1991–2009

	Cases (n = 1,092)		Controls[a] (n = 5,432)		OR[b]	95% CI
	No.	% of All Cases	No.	% of All Controls		
Death of a child						
No loss	1,048	96.0	5,277	97.1	1.00	
Loss	44	4.0	155	2.9	1.41	0.99, 2.01
Time since last loss, years						
≤5	7	0.6	17	0.3	2.29	0.94, 5.57
>5	37	3.4	138	2.5	1.31	0.89, 1.92
Cause of last loss						
Injury-related	17	1.6	43	0.8	1.97	1.11, 3.49
Chronic illness-related	27	2.5	112	2.1	1.19	0.76, 1.86
Psychiatric illness in parent						
No	39	3.6	146	2.7	1.35	0.93, 1.96
Yes	5	0.5	9	0.2	2.30	0.76, 6.97

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Controls were matched to cases by sex and year of birth.
[b] In addition to matching, odds ratios were adjusted for education (<9 years, ≥9 years, or unknown), socioeconomic status (blue-collar, white-collar, self-employed, or unknown), region of residence (southern, central, or northern Sweden), and total number of children (1, 2, or >2).

within the first 5 years after the child's death. Loss due to suicide appeared to be most clearly associated with the risk increase. A stronger association was also suggested for early-onset pancreatic cancer and for persons with coexisting psychiatric illnesses.

The strengths of the present study include mainly the large sample size, the population-based design, and prospectively and independently collected data on child loss and pancreatic cancer. On the other hand, given the register-based nature of the data, the present analysis lacked information on potential confounders or mediators of the studied association, such as smoking, which is an established risk factor for pancreatic cancer (24) and a possible behavioral change associated with stressful life events (3). Confounding from body mass index (BMI; weight (kg)/height $(m)^2$) may have contributed to our findings similarly—parental obesity might be associated with the risk of child loss, while higher BMI has been shown to be associated with an increased risk of pancreatic cancer (25). However, the lack of association more than 5 years after loss helps to argue against a pure explanation by these factors, assuming a cumulative influence of such factors over time on pancreatic cancer. In addition, if smoking or BMI were to explain the observed association, we should have seen similar associations between child loss and pancreatic cancer among men and women, since smoking and BMI do not seem to have sex-specific relationships with pancreatic cancer risk (24–26). Furthermore, according to Walker's finding (27), the effect size of confounding is usually rather small, even when both the exposure-covariate relationship and the confounder-disease relationship are strong. For example, fully explaining a relative risk of 1.4 among women (as we observed for the first 5 years after child loss) by pure confounding from smoking or BMI would require that both the association between child loss and smoking/BMI and the association between smoking/BMI and pancreatic cancer be larger than 3. As we have seen from previous studies, smoking is probably associated with a 2-fold increased risk of pancreatic cancer (24, 26), while a 5-unit increase in BMI is associated with a 1.1-fold increased risk of pancreatic cancer (25). Thus, the increased risk of pancreatic cancer among bereaved parents may not be completely explained by confounding from smoking or BMI. Finally, although cases and controls clearly differed with regard to socioeconomic status, education, and region of residence in our study, adjusting for these factors in the analyses did not change the results largely (data not shown).

Another potential confounder of the studied association was shared etiology between pancreatic cancer in the parent and cancer in the deceased child. To allay this concern, we excluded all persons who had lost a child with pancreatic cancer or who had pancreatic cancer-related phenotypes, including MEN1, HBOC syndrome, HNPCC, and FAP. Such exclusions diminished the odds ratios to some extent (given the diminishing effect for loss of a child due to cancer), but associations between loss of a child for external reasons (i.e., suicide) remained unchanged. Furthermore, additional analyses excluding persons who had lost a child for other reasons that might be associated with pancreatic cancer in a parent (i.e., diabetes or congenital malformations) did not alter the results either.

Because of the missing familial links for approximately 40% of persons who died before 1990 in the Multi-Generation Register (12), a few persons who had lost a child before 1990 might have been misclassified as belonging to the reference group. Such misclassification could theoretically have led to underestimation of the studied association. Finally, although the coverage of the Cancer Register approaches 100% in general, over 20% of DCO pancreatic cancer cases were reported for the calendar period of 1959–2003 (13). In the present study, we found that 31% of pancreatic cancer cases were DCO cases. During the study period (1991–2009), 34% of pancreatic cancer cases were identified as DCO cases in the entire country when comparing the Cancer Register with the Cause-of-Death Register. The change in DCO cases might be explained by the declining autopsy rate in Sweden since the early 1990s, as the number of pancreatic cancers confirmed at autopsy diminished markedly (13). Reassuringly, excluding all DCO cases rendered the results largely unchanged.

Earlier studies demonstrated that psychiatric diseases might be associated with pancreatic cancer (28) and may therefore interact with the emotional stress of child loss. As shown in our data, persons who had been admitted to a hospital for psychiatric treatment at least once before the index date indeed had more increased risk of pancreatic cancer after a child loss compared with others. Given the incomplete coverage of the Patient Register before 1987, we were not able to disentangle whether the association would further differ between persons with psychiatric illness before the child loss and those with psychiatric illness after the child loss (29); in the latter case, psychiatric illness might serve as a mediator between child loss and pancreatic cancer.

Although chance cannot be ruled out, our finding of a positive association between loss of a child and pancreatic cancer among mothers but not among fathers does not stand alone in the literature. Previous studies have found that after the loss of a child, mothers are at higher risk than fathers of several different severe health outcomes, including hospitalization for psychiatric illness, cancer, and death (29–31). This may potentially indicate that bereaved mothers, as compared with bereaved fathers, are more influenced by the death of a child and more susceptible to physical consequences of stress as well.

Apart from all other alternative explanations, a direct biological mechanism between stress and carcinogenesis of the pancreas is plausible. Severe psychological stress may induce coactivation of the hypothalamic-pituitary-adrenal axis and the sympathetic-adrenal-medullary system (32), which in turn may result in the release of corticotropin-related hormones, glucocorticoids, adrenaline, and noradrenaline. A new hypothesis indicates that the central regulation of pancreatic cancer is mediated by neurotransmitter receptors (33). The stress-response-releasing neurotransmitters, adrenaline and noradrenaline, may lead to the activation of β-adrenergic receptor and may stimulate pancreatic cancer cell proliferation, migration, and invasion via a β-adrenergic receptor-dependent cyclic adenosine monophosphate-associated signaling transduction pathway (33, 34). Psychological stress may also promote the progression of pancreatic cancer xenografts via these neurotransmitter pathways (11). In line with these findings,

Chan et al. (35) showed that noradrenaline may dysregulate interleukin-6 and vascular endothelial growth factor, promoting proliferation of pancreatic duct epithelial cells. Furthermore, using a progression evolution model of pancreatic cancer, Yachida et al. (36) proposed that it takes more than 10 years from tumor initiation to diagnosis and approximately 20 years from initiation to death, a much longer time frame than the 5-year window in which we observed a significant effect of child loss on pancreatic cancer. Therefore, there are reasons to believe that the psychological stress of a child's death may tend to precipitate rather than trigger or initiate pancreatic carcinogenesis.

In summary, although chance or explanations by other factors could not be ruled out, in this nationwide population-based study, we found an overall increased risk of pancreatic cancer among parents who had lost a child, and the association was observed mostly during the first 5 years after the loss.

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