Cancer Incidence and Survival Following Bereavement

ABSTRACT

Objectives. This study investigated the effect of parental bereavement on cancer incidence and survival.

Methods. A cohort of 6284 Jewish Israelis who lost an adult son in the Yom Kippur War or in an accident between 1970 and 1977 was followed for 20 years. We compared the incidence of cancer in this cohort with that among nonbereaved members of the population by logistic regression analysis. The survival of bereaved parents with cancer was compared with that of matched controls with cancer.

Results. Increased incidence was found for lymphatic and hematopoietic malignancies among the parents of accident victims (odds ratio [OR]=2.01; 95% confidence interval [CI]=1.30, 3.11) and among war-bereaved parents (OR=1.47; 95% CI=1.13, 1.92), as well as for melanomas (OR=4.62 [95% CI=1.93, 11.06] and 1.71 [95% CI=1.06, 2.76], respectively). Accident-bereaved parents also had an increased risk of respiratory cancer (OR=1.50; 95% CI=1.07, 2.11). The survival study showed that the risk of death was increased by bereavement if the cancer had been diagnosed before the loss, but not after.

Conclusions. This study showed an effect of stress on the incidence of malignancies for selected sites and accelerated demise among parents bereaved following a diagnosis of cancer, but not among those bereaved before such a diagnosis. (*Am J Public Health.* 2000;90: 1601–1607)

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The association between the loss of a significant other and morbidity and mortality has been widely explored, and many of the studies have shown a positive association.[1] The evidence that the inception of cancer is triggered by stress, however, remains elusive.[2–4] First, studies on this topic are fraught with methodological problems—for example, biased samples, retrospective designs, small numbers of cases, and limited follow-up. Second, reviewers[2,5–7] have concluded that most case–control[8–10] as well as cohort studies,[11–14] with few exceptions,[15] have shown little or no association.

Biobehavioral research on cancer, including the effect of bereavement, continues nevertheless to attract investigators with regard to onset, course, and intervention.[16–21] Present studies focus on the existence of pathways involving the brain and the neuroendocrine and immune systems.[4] These pathways link emotions and cognitions with body functions and disorders.[4,22,23]

To explore the association between stress and cancer, we studied a major life event, the loss of an adult son, and its effect on cancer incidence and survival. Bereavement may play a role in the inception of certain malignancies that involve the neuroendocrine and immune systems. It may also play a role in tumors associated with risky health behaviors among survivors.[1] These mechanisms also could be involved in accelerated death from neoplasms diagnosed before and after the loss. In our study, bereavement occurred between 1970 and 1977. Follow-up was until 1991 for new diagnoses and through June 1994 for the survival of parents with cancer. The study had 2 components: for incidence, a comparison of the bereaved parents with the general population, and for survival, a comparison of the parents with cancer with individually matched controls. These inquiries recognized that stress might differentially affect cancer incidence and progression.[7]

The death of one's child was ranked by Israelis as the most stressful event in life, even more stressful than spousal death.[24] Investigators also have noted that the death of one's child is a paradigm for severe stress[25] and that the emotional effect of the death of an adult child might not lessen with time.[26]

The research advantages of examining parental bereavement resulting from war are manifold. First, there is a smaller probability of confounding by variables related to the loss or the environment than in studies of conjugal bereavement,[13,27] cancer in one's child,[14] or divorce.[9] Second, the status of the bereaved parent never ceases. Third, parental bereavement allows one to explore the effect of grief more adequately than does conjugal loss, where grief is intertwined with loss of social supports.[28] Fourth, the sudden and untimely event maximizes its stressfulness and clearly anchors the inception of the bereavement process.[29]

Deaths from war and accidents were considered independently, since their meaning may be different for the parents. War-bereaved parents have a special status in Israel, where they receive continuous instrumental support and social recognition, the loss being shrouded by the ethos of national sacrifice. For accident-

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bereaved parents, the loss may carry no meaning or even a negative meaning. Additionally, among the war-bereaved parents, no premorbid linkage is suspected between the loss and the outcome; soldiers in front units possess healthy profiles and therefore may be the offspring of healthier families. Thus, familial factors may rarely be conducive both to war injuries and to the course or occurrence of cancer in war-bereaved parents. On the other hand, there may be familial factors (e.g., smoking, which characterizes a risky lifestyle) that predispose family members to both accidents and some tumors.

Methods

The Bereaved

The bereaved comprised 6284 Jewish parents who lost 1 or 2 sons in either the Yom Kippur War (n=4469) or in accidents (n=1815). The year bereavement began determined the entrance date into the analyses. For those bereaved by accidents, losses occurred between 1970 and 1977 (for 1970, n=130; 1971, n=180; 1972, n=177; 1973, n=172; 1974, n=375; 1975, n=286; 1976, n=193; 1977, n=302). For those bereaved by war, 4371 deaths occurred in 1973 and 98 in 1974. Thirty-seven parents lost 2 sons; the first death determined the date and nature of the bereavement for the purpose of this study. The mean ages of the sons who died in accidents and war were 25.3±5.2 years (range=15–45 years) and 24.8±5.3 years (range=18–51 years), respectively.

Almost all parents were in Israel at the time of the loss. Thirty returned or immigrated after the event; parents residing abroad were excluded.

The war-bereaved parents were identified through multiple sources. The Ministry of Defense provided the soldier's full name, father's given name, and personal identification number. This roster was verified in a memorial book. For the accident-bereaved parents, the son's identification was extracted from the Central Bureau of Statistics. For both groups, we linked sons to parents through the Population Register. Additionally, we obtained the parent's birth date, country of origin, year of immigration when appropriate, and date and cause of death. Although these data were already available,[30] for reliability, the linkage and all information were confirmed.

Comparison Population

The Jewish population used for comparison in the incidence study comprised individuals who were born before 1945, resided in Israel before 1972, and were not among the bereaved group. Relying on information from the Central Bureau of Statistics, we reconstructed the midyear population for the years 1970 to 1991 by sex, year of birth, region of origin (Israel, Asia, Africa, or Europe-America-Oceania), and period of immigration (born in Israel, pre-1948, 1948–1954, 1955–1960, 1961–1964, 1965–1971). By the end of the war (midyear 1974), this population was 1 019 255.

Cancer Cases

The Israel Cancer Registry (ICR) provided the information on cancer occurrence. The ICR records all incident cases, except nonmelanoma skin cancer, according to the *International Classification of Diseases for Oncology*.[31] Data completeness is over 95%. Five percent of the registrations rely only on death certificates; all others have confirmation of pathology. The ICR has less than a 5% rate of cases in which the primary site of a tumor is uncertain.[32] The proportion of histologically verified diagnoses from 1961 through 1981 was 81.3% for males and 85.2% for females.[32] Cases receive a unique number, enabling cumulative entries and linkage to other national databases.

We linked the Population Register information and names of the bereaved parents to the ICR to identify who had developed cancer and whether they were currently alive or dead. The algorithm included a search according to the pronunciation of the parent's name to make the linkage as accurate as possible. To confirm the matching, the procedure was conducted twice, weighting key identifiers differently. A total of 947 parents with cancer were found; 768 were diagnosed with cancer following bereavement.

Beginning in 1970, 131 493 cancer cases were identified in the comparison population from the ICR. Cases were included in the incidence study only if the diagnosis was made before the end of 1991. Except for Kaposi's sarcoma (*International Classification of Diseases, Ninth Revision* [*ICD-9*] morphology: M9140/3) and nonmelanoma skin cancers (*ICD-9* topography: 173.0–173.9; morphology: M8050/3–M8110/3, M8247/3, M8390/3–M8420/3, M8832/3–M8833/3), all malignancies and nonpituitary central nervous system tumors were included (*ICD-9* topography: 140.0–165.9, 170.0–172.9, 174.0–208.9, 225.0–225.9, 237.5–237.7, 239.6).

For the survival study, all 808 of the bereaved parents identified in the ICR as having cancer at a single primary site diagnosed before the end of 1994 were included. Patients with Kaposi's sarcoma were included, but the 58 parents with tumors of an unknown primary site were omitted, because the tumors were too heterogeneous for suitable matched controls. The 58 parents with multiple primary malignancies were excluded from the survival study owing to the difficulty of finding controls for each primary malignancy.

Matched Controls

For the survival study, individually matched controls with a single primary site were selected from all Jewish patients in the ICR residing in Israel before the corresponding parent's date of bereavement. An exact match was required for sex and primary tumor site (first 3 digits in the *ICD-9* number). Additionally, the following were minimum requirements: age at diagnosis±7 years, year of diagnosis±7 years, broad morphology group (clustered into 32 groups), and region of birth. For best matching, weights were calculated on the basis of closeness of the match for age at diagnosis, year of diagnosis, morphology, and country of origin, in decreasing importance. Country of birth is strongly associated with ethnicity and is a proxy for social class, enabling some degree of matching for the latter. The maximum score required exact matches on each variable. Each variable was matched as closely as possible, but the direction of the disparity was disregarded. If there were ties, a random choice was made. Matching resulted in 67% of cases and controls having the same country of origin, 45.1% having the same period of immigration, 70.4% having been born within 2 years of each other, 71.1% having been diagnosed within 2 years of each other, and 83.7% having the same 5-digit *ICD-9* morphology. Suitable matches were unavailable for 77 parents, yielding 54 whose diagnosis preceded bereavement and 677 whose diagnosis followed bereavement. For the latter, the date of diagnosis for the potential control had to follow the bereavement date for the relevant case.

Variables

Demographic information was verified in the Population Register for all parents, the comparison population with cancer, and the matched cancer cases. This information included sex, year of birth, country of origin, year of immigration, and, except for the comparison population, date of death. The countries of origin were categorized by the abovementioned regions of birth. Age was divided into 10-year groups. Period of immigration was categorized as follows: before 1948, 1948–1954, 1955–1960, 1961–1964, 1965–1971, 1972–1979, 1980–1989, Israel born, and unknown. For each primary neoplasm, the following variables were extracted: *ICD-9* code, date of diagnosis, and histologic morphology.

Incidence Analyses

We contrasted the bereaved group with the comparison population. The associations were appraised by multiple logistic regression analysis; the independent variables were bereavement and 4 confounders: age group, sex, period of immigration, and region of birth. All these confounders are associated with cancer incidence in Israel.[32,33] Because of the ongoing changes in the size and composition of the groups as a result of bereavement, death, or emigration and possible confounding effects connected with time, separate analyses were conducted for each calendar year. Post hoc tests for sex and cancer subgroups large enough to warrant separate consideration were conducted. The Hosmer–Lemeshow statistic showed that the fit of the individual logistic regression models was satisfactory.[34]

The logistic regression coefficient estimate for a given year was weighted (W= weight) in proportion to the reciprocal of the square of the standard error for each year, by the equation $W=(1/se^2_{year})/(\Sigma 1/se^2_{year})$. The weighted coefficients were summed across each year to obtain a summary odds ratio (OR), by the equation $OR=\exp(\Sigma\beta_{year}W_{year})$. The variance of this statistic, calculated by obtaining the sum of the square of the standard error multiplied by the weight, $\beta=(\Sigma se^2_{year}W_{year})$, was used to estimate the 95% confidence intervals. This procedure controlled for possible confounding effects due to secular changes, such as cancer detection procedures. A test of homogeneity of the logistic coefficients for each set of analyses indicated that the results could be pooled,[35] since P was greater than .1 in each instance.

Individuals with cancer diagnosed before 1970, when the observation began, could not be eliminated from the comparison population; consequently, they were left in the bereaved group. Their inclusion did not create a bias, since diagnosis preceded bereavement. All individuals diagnosed with cancer were removed from the numerator, but they were kept in the denominators of both cohorts until death.

The analyses were conducted for combined malignancies and for tumors hypothesized to be associated with stress[3,4] resulting from the possible mechanisms involved in the bereavement aftermath (e.g., immunodownregulation, humoral changes, and behavioral factors): colon and rectal (*ICD-9* 153–154), respiratory tract (*ICD-9* 140–149, 161–162), breast (*ICD-9* 174, women only), uterus and ovaries (*ICD-9* 179–180, 182–183), lymphatic and hematopoietic tissue (*ICD-9* 200–209), and melanomas (based on morphology; primarily *ICD-9* 172).

Analyses unadjusted for covariates and analyses adjusted for covariates were conducted separately for those bereaved by accident and those bereaved by war; the analyses were also stratified by sex. Sex–bereavement interaction terms were examined. Additional analyses were conducted to ascertain the differential risk of cancer by contrasting both bereaved groups following the removal of individuals with cancer before bereavement. Parents diagnosed with cancer after bereavement were removed from the subsequent years' logistic regression analyses.

Survival Analyses

The data were separated into 2 sets: parents whose cancer was diagnosed before their loss and those whose cancer was diagnosed after their loss. The bereavement date was used as the reference for both members of the matched pair. Survival time was defined as the period (in months) from diagnosis to the parent's death or the conclusion of follow-up. A constant, 0.1, was added to all survival times to avoid computational problems resulting from zero survival time, should diagnosis and death occur in the same month.[36]

Because the control group did not experience this particular form of bereavement and the parents had different bereavement times, we used the Cox model with a time-dependent covariate to analyze the data for those whose cancer was diagnosed before bereavement. The analysis was adjusted for age at diagnosis, sex, region of birth, period of immigration, year of diagnosis, and type of bereavement (war or accident). A time-dependent covariate to bereavement—0 before and 1 following diagnosis—was created; for individuals in the control group, this covariate was always 0. The time-dependent covariate allowed correcting for the time elapsed from diagnosis to the date of bereavement.

For those whose cancer was diagnosed after bereavement, the risk of dying from cancer was compared in cases and controls by means of a Cox proportional hazards model based on the partial likelihood method.[36] The models, for all and specific neoplasms, included age at diagnosis, sex, region of birth, period of immigration, year of diagnosis, and type of bereavement.

Results

Incidence

Table 1 summarizes characteristics of the parents and the comparison population. Sociodemographic differences between each bereaved group and the comparison population for sex, mean age, region of birth, and period of immigration were statistically significant. The sex, mean age, and region of birth of the war-bereaved parents more closely resembled those of the comparison population than those of the accident-bereaved group. These differences between the parents were accounted for by the larger number of individuals of European or American origin among the war-bereaved parents.

Uncontrolled analyses. A significant increased risk for each cancer investigated was found among bereaved fathers, while for mothers, a statistically significant association was found for lymphatic and hematopoietic malignancies in both bereaved groups, uterine and ovarian cancers in the accident-bereaved group, and respiratory malignancies in the war-bereaved group. For all parents, a significant

TABLE 1—Incidence Study: Selected Demographic Characteristics of the Accident-Bereaved, War-Bereaved, and Comparison Populations

	Bereaved Groups		Comparison Population (1974) (n = 1 019 255)
	Accident (n = 1815)	War (n = 4469)	
Male, %	47.0	47.7	48.5
Mean age in 1974, y (SD)	54.4 (9.0)	55.0 (8.3)	55.3 (8.3)
Region of birth, %			
Israel	6.8	8.4	10.9
Europe/America/Oceania	39.3	55.4	54.1
Asia	26.3	19.8	19.0
Africa	27.5	16.4	16.0
Unknown	0.0	0.1	0.0
Period of immigration, %			
Before 1948	22.4	36.2	24.9
1948–1954	45.1	36.9	39.6
1955–1960	11.2	9.8	10.1
1961–1964	9.2	5.6	8.6
1965–1971	3.3	2.3	5.9
1972–1989	2.0	0.7	0.0
Born in Israel	6.8	8.4	10.9
Unknown	0.1	0.2	0.0

TABLE 2—Incidence Study: Summary of the Uncontrolled Logistic Regression Analyses for Risk of Cancer Among Accident-Bereaved and War-Bereaved Parents

Cancer Site	Comparison Population (N)	Accident-Bereaved			War-Bereaved		
		n	OR (95% CI)	*P*	n	OR (95% CI)	*P*
Both sexes							
All	131 493	214	1.04 (0.91, 1.19)	NS	554	1.05 (0.97, 1.15)	NS
Colon/rectal	22 034	31	1.01 (0.71, 1.44)	NS	93	1.07 (0.87, 1.31)	NS
Lymphatic/hematopoietic	11 564	20	1.96 (1.27, 3.02)	<.003	56	1.59 (1.22, 2.06)	<.0007
Melanoma[a]	3 518	5	3.28 (1.39, 7.74)	<.007	17	1.77 (1.10, 2.83)	<.02
Respiratory	17 511	34	1.53 (1.09, 2.14)	<.02	73	1.20 (0.95, 1.51)	NS
Fathers							
All	65 615	122	1.30 (1.09, 1.56)	<.004	300	1.22 (1.09, 1.36)	<.001
Colon/rectal	11 602	22	1.59 (1.05, 2.42)	<.03	54	1.32 (1.01, 1.73)	<.05
Lymphatic/hematopoietic	6 300	8	2.58 (1.30, 5.09)	<.007	28	1.77 (1.22, 2.56)	<.003
Respiratory	12 935	30	2.08 (1.45, 2.97)	<.0001	54	1.36 (1.04, 1.78)	<.03
Mothers							
All	65 878	92	0.92 (0.75, 1.13)	NS	254	0.94 (0.83, 1.06)	NS
Breast	18 255	23	1.12 (0.75, 1.69)	NS	73	1.17 (0.93, 1.47)	NS
Uterine/ovarian	8 186	15	2.01 (1.21, 3.32)	<.007	34	1.31 (0.94, 1.84)	NS
Colon/rectal	10 432	31	1.17 (0.62, 2.20)	NS	93	1.09 (0.80, 1.49)	NS
Lymphatic/hematopoietic	5 264	20	2.57 (1.46, 4.50)	<.002	56	1.78 (1.23, 2.58)	<.002
Respiratory	4 576	34	2.04 (0.79, 5.23)	NS	73	1.72 (1.10, 2.69)	<.02

Note. OR = odds ratio; CI = confidence interval; NS = not significant (*P* > .05).
[a]Melanoma was not stratified by sex owing to insufficient sample size.

risk for lymphatic and hematopoietic tumors and melanomas was found in both bereaved groups, and a significant risk for respiratory tumors was found in the accident-bereaved group (Table 2).

Controlled analyses. A statistically significant association was found for lymphatic and hematopoietic malignancies and melanomas among all bereaved parents and for respiratory tumors among the accident-bereaved group. Similarly, among fathers, the risk for lymphatic and hematopoietic malignancies in both groups, and the risk for respiratory cancer in the accident-bereaved group, were statistically significant (Table 3). Among mothers, the risk for lymphatic and hematopoietic malignancies and respiratory tumors in both groups, and the risk for uterine and ovarian cancers in the accident-bereaved group, were statistically significant. There were no significant sex–bereavement interaction terms. The comparison between the 2 bereaved groups yielded no significant differences in their respective risks.

TABLE 3—Incidence Study: Summary of the Controlled Logistic Regression Analyses for Risk of Cancer Among Accident-Bereaved and War-Bereaved Parents[a]

Cancer Site	Accident Bereaved		War Bereaved	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Both sexes				
All	1.03 (0.90, 1.18)	NS	0.95 (0.88, 1.04)	NS
Colon/rectal	1.00 (0.70, 1.44)	NS	0.97 (0.79, 1.19)	NS
Lymphatic/hematopoietic	2.01 (1.30, 3.11)	<.002	1.47 (1.13, 1.92)	<.005
Melanoma[b]	4.62 (1.93, 11.06)	<.0007	1.71 (1.06, 2.76)	<.03
Respiratory	1.50 (1.07, 2.11)	<.02	1.06 (0.84, 1.34)	NS
Fathers				
All	1.09 (0.91, 1.31)	NS	0.95 (0.85, 1.07)	NS
Colon/rectal	1.39 (0.90, 2.16)	NS	1.06 (0.81, 1.38)	NS
Lymphatic/hematopoietic	1.48 (1.02, 2.16)	<.05	2.38 (1.19, 4.73)	<.02
Respiratory	1.84 (1.28, 2.65)	<.002	1.11 (0.85, 1.46)	NS
Mothers				
All	1.03 (0.84, 1.27)	NS	0.95 (0.84, 1.08)	NS
Breast	1.32 (0.86, 2.02)	NS	1.16 (0.92, 1.46)	NS
Uterine/ovarian	2.19 (1.32, 3.63)	<.003	1.16 (0.82, 1.64)	NS
Colon/rectal	1.62 (0.85, 3.09)	NS	1.12 (0.82, 1.54)	NS
Lymphatic/hematopoietic	2.95 (1.67, 5.19)	<.0002	1.90 (1.31, 2.75)	<.001
Respiratory	2.78 (1.06, 7.29)	<.05	1.86 (1.19, 2.92)	<.007

Note. OR = odds ratio; CI = confidence interval; NS = not significant (*P* > .05).
[a]Controlled for sex, year of birth, region of origin, and period of immigration.
[b]Melanoma was not stratified by sex owing to insufficient sample size.

To further examine these significant findings, we conducted analyses controlling for the same confounders on subgroups that were large enough to warrant separate consideration: cancer of the trachea, bronchus, and lung (*ICD-9* 162) and lymphatic and hematopoietic malignancies, divided into non-Hodgkin's lymphomas (*ICD-9* 200 and 202) and leukemias (*ICD-9* 204–208). Most of the significant associations observed in the broader groups remained (Table 4). Both bereaved groups had a significantly increased risk for non-Hodgkin's lymphomas and leukemias, but lung cancer was associated only with bereavement through accidents.

Survival

The first data set contained 54 matched pairs of parents whose cancer was diagnosed before the bereavement date; 80% of them were bereaved by war. None of the covariates examined, other than year of diagnosis (paired $t_{106} = -4.79$, $P < .0001$), differed significantly between cases and controls (Table 5). Period of immigration, year of diagnosis, age at diagnosis, region of origin, sex, and type of bereavement (war or accident) were controlled for in the Cox regression analyses. The cancer sites were as follows: breast, 16 pairs; colon and rectal, 4 pairs; lymphatic and hematopoietic, 2 pairs; respiratory, 6 pairs; uterine and ovarian, 4 pairs; other sites, 22 pairs.

TABLE 4—Incidence Study: Summary of the Controlled Logistic Regression Analyses for Risk of Lung Cancer, Non-Hodgkin's Lymphoma, and Leukemia Among Accident-Bereaved and War-Bereaved Parents[a]

	Accident Bereaved			War Bereaved		
Cancer Site, Both Sexes	n	OR (95% CI)	*P*	n	OR (95% CI)	*P*
Lung[b]	24	1.54 (1.02, 2.31)	<.05	55	1.14 (0.87, 1.48)	NS
Non-Hodgkin's Lymphoma	9	2.38 (1.24, 4.57)	<.01	21	1.79 (1.16, 2.74)	<.01
Leukemia	7	4.04 (1.92, 8.47)	<.0001	21	1.97 (1.28, 3.04)	<.05

Note. OR = odds ratio; CI = confidence interval; NS = not significant (*P* > .05).
[a]Controlled for sex, year of birth, region of origin, and period of immigration.
[b]Lung cancer includes cancer of trachea, bronchus, and lung.

TABLE 5—Survival Study: Selected Demographic Characteristics of the Bereaved Parents and Matched Control Subjects

	Cancer Diagnosed Before Bereavement		Cancer Diagnosed After Bereavement	
	Cases (n = 54)	Controls (n = 54)	Cases (n = 677)	Controls (n = 677)
Male, %	42.6	42.6	55.7	55.7
Mean age in 1974, y (SD)	58.6 (8.4)	56.6 (8.9)	58.8 (8.2)	58.6 (8.4)
Mean year at diagnosis[a] (SD)	1970.8 (2.6)	1973.1 (2.3)	1984.3 (5.3)	1984.0 (5.2)
Region of birth, %				
Israel	5.6	5.6	7.5	7.5
Europe[b]	70.4	70.4	65.9	65.9
Asia	9.3	9.3	13.6	13.6
Africa	14.8	14.8	13.0	13.0
Period of immigration, %				
Before 1948	55.6	25.9	41.4	27.6
1948–1954	24.1	48.1	35.3	38.7
1955–1960	11.1	9.3	7.5	10.6
1961–1964	3.7	3.7	5.5	7.4
1965–1971	0.0	7.4	1.9	6.4
1972–1989	0.0	0.0	0.9	1.8
Born in Israel	5.6	5.6	7.5	7.5

[a]Expressed in fractions of years.
[b]Includes America and Oceania.

After confounders were adjusted for, parents whose cancer was diagnosed before the bereavement date had a significantly higher risk of dying afterward than did controls (relative risk [RR] = 2.12; 95% confidence interval [CI] = 1.14, 3.95; $P < .02$). This elevation was statistically significant among fathers (RR = 3.52; 95% CI = 1.33, 9.30; $P < .02$) but not among mothers (RR = 1.61; 95% CI = 0.68, 3.79; $P = .28$). This risk was apparent among war-bereaved parents (RR = 2.24; 95% CI = 1.11, 4.51; $P < .03$) but not among accident-bereaved parents (RR = 1.80; 95% CI = 0.65, 5.02; $P = .57$). The association among the mothers remained nonsignificant (RR = 0.67; 95% CI = 0.13, 3.42; $P = .63$) when the analysis excluded breast, uterine, and ovarian tumors so that the cancer sites would be comparable across sexes; only 11 out of 31 female pairs remained. Neither sex interaction terms nor accident-bereaved/war-bereaved interaction terms were significant when added to the model.

We identified 677 pairs consisting of parents with cancer diagnosed after bereavement and their respective controls; 72.4% of the parents were war bereaved. No significant differences were found between cases and controls by age, age at diagnosis, or year of diagnosis; however, the cases had immigrated earlier (extended McNemar $\chi^2_{21} = 66.20$, $P < .0001$) (Table 5). Period of immigration, age at diagnosis, region of origin, sex, and type of bereavement were controlled for in the regression analysis. The cancer sites were as follows: breast, 81 pairs; colon and rectal, 109 pairs; lymphatic and hematopoietic, 66 pairs; respiratory, 96 pairs; uterine and ovarian, 44 pairs; other sites, 281 pairs.

After covariates based on the partial likelihood method were adjusted for, there were no significant differences in the risk of dying between these parents and their controls, either for combined or for specific tumor sites. These negative findings remained when the data were stratified by sex and bereavement type. To investigate the possibility that bereavement's impact on survival might vary with the time elapsed between onset of bereavement and diagnosis of cancer, we divided the group into quartiles based on the time from the child's death to the parent's diagnosis (year range in quartiles: 0–6.4, 6.4–11.2, 11.2–15.4, 15.4–22.0). The control was tagged to the quartile of the respective case. These analyses did not show a trend or an increased death risk among the bereaved. Additionally, when a covariate accounting for time between diagnosis and bereavement was added to the model, it was nonsignificant.

Discussion

Reviews of studies on the role of psychosocial factors in cancer incidence and progression have been critical of the methods the studies used.[2,6,7] We relied on a design that was relatively free of these problems. First, we used a population-based cohort in which the single stressful event was independent of the subject's recall. Fox[6] noted that cancer patients recall more stressful events than controls. Second, extended follow-up allowed for a sufficient incubation period.[7,37] Third, the registers enabled linking the deceased children to their parents and searching for cancer cases. The ICR also enabled us to extract adequate controls. Fourth, universal access to reputable medical care reduced the likelihood that subjects left for treatment abroad. Fifth, our comparison population was large. Finally, our inquiry was not narrowed to the effect of stress on overall cancer rates. Other authors[22] have argued that in cancer progression, psychological or behavioral factors interacting with the immune system would be expected to differ across sites; analogous arguments may be applied to onset.

Incidence

As found in previous studies,[10,14,27] we found that bereavement had no significant effect on overall cancer incidence. (One study[13] reported a moderate effect for conjugal loss in

men under the age of 74, but follow-up was too brief to ascertain incidence.) However, we found significantly higher risk for specific sites. As others have done,[23] we posited that psychological factors might play a role in some malignancies, but not all.

The most intriguing and novel of these findings, and also the most theoretically cogent,[3] was the risk for hematopoietic and lymphatic tumors. In vitro studies have shown an interplay of neural, endocrine, and cellular components (e.g., natural killer cell activity) in the immune system.[38] Bereavement and depression, a likely outcome of unresolved grief[39] in these parents, modify the immune system.[22,23,40] In the case of bereavement, researchers[41–43] have shown that there is a modification in the proliferative response to mitogens and lower natural killer cell activity. These in vitro measures of cellular immunity were deemed controversial,[44] but their clinical significance is congruent with in vivo observations conducted among renal transplant patients receiving immunosuppressive agents.[3,45] The role of bereavement in the onset of hematopoietic and lymphatic neoplasms may be imputed to the biological mechanisms cited above. Interestingly, the occupational stress of firefighters has been suggested as a cause of hematopoietic and lymphatic tumors in this population,[46] but these individuals are also exposed to toxins. As for melanomas, the role of immunocompromise has been noted recently.[47]

Case–control studies have shown that stress has positive effects on several cancer sites[15,17,18,48]; however, the validity of these studies has been challenged.[6] In our cohort-based study, we found elevated risk in 2 additional sites with an adequate number of cases for analyses: (1) in the respiratory tract, among accident-bereaved fathers and mothers as well as war-bereaved mothers, and (2) in uterine and ovarian tumors, among accident-bereaved mothers. Conceivably, the elevated incidence of respiratory malignancies among accident-bereaved parents may be related to a greater prevalence of premorbid risk-taking behavior in this group compared with controls. This behavior, we hypothesized, may be differentially distributed among families; there may be a higher prevalence of smoking among parents whose offspring have accidents. The risk for cancer may subsequently be reinforced by the interaction between heavy smoking and depression—the latter a possible consequence of bereavement.[49] While we are not ruling out this hypothesis, bereavement and depression by themselves could lead to increased smoking[1]; this may be reflected in the higher risk found in 3 of the 4 groups of bereaved parents. As in most studies, humoral-dependent tumors (e.g., breast cancer[9]) did not show an increased risk, whereas for the second site investigated (uterine–ovarian), the results remain inconclusive.

Survival

An increased risk of death was found among parents whose cancer was diagnosed before bereavement. Although the increase was higher for both sexes, it was significant only among fathers.

As mentioned earlier, the link between psychological factors and cancer survival has generated contradictory results.[50] While 3 studies[51–53] on breast cancer suggested a greater risk, a fourth[54] showed no association. We found that fathers who had cancer at the time of bereavement were at higher risk for a more rapid demise. The risk in mothers was not statistically significant. Should our finding be confirmed, the risk may arise from behavioral factors,[19,49] the lowering of immunologic defenses, or both.[55,56] A recent study[57] demonstrating the independent, adverse effects of stress and depressive symptoms on the course of illness in HIV-infected men, as measured by the impact on lymphocyte subsets, provides further evidence of the role of immunodownregulation.

Conclusions

The uncontrolled analyses showed a slightly higher incidence of cancer after bereavement, consistent with the lay belief that stress leads to cancer. After confounders were controlled for, however, the increased risk was confined to certain neoplasms. The study also showed that experiencing a devastating loss accelerated demise in cancer patients. These findings may suggest that bereaved patients with cancer who face renewed stressors need special attention. In contrast, patients whose diagnosis follows major stressors are not at similar risk; some adaptation may have occurred. The association between stress and cancer onset and progression[58] is undoubtedly complex but certainly worth pursuing.[4] □

Contributors

I. Levav planned the study, analyzed the data, and wrote the paper. R. Kohn assisted in planning the study, developing the statistics, analyzing the data, and writing the paper. J. Iscovich assisted in planning the study, developing the linkage procedures, supervising the data collection, and writing the paper. J. H. Abramson assisted in analyzing the data and writing the paper. W. Y. Tsai designed the data analysis procedures, analyzed the survival data, and developed the specific statistics used for the study. D. Vigdorovich designed the procedures for data management and data linkage and supervised the data collection. All authors reviewed the final manuscript.

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