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Decreased Cancer Survival in Individuals Separated at Time of Diagnosis: Critical Period for Cancer Pathophysiology?

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Abstract

Background—It long has been recognized that married patients have improved cancer survival when compared to unmarried patients. This has been postulated as being due to increased support, potentially leading to better compliance with therapy. Conversely, some data exist pointing to a relationship between marital discord and decreased immunity. We examined whether unmarried patients have a different prognosis by whether they are (a) never married; (b) divorced; (c) widowed; or (d) separated at time of diagnosis.

Methods—The public access data of the Surveillance, Epidemiology and End Results (SEER) registry were queried for cancer survival across all 17 registries between 1973 and 2004. Data were last updated by SEER in April, 2007. Records of 3.79 million patients were included in the analysis. We specifically analyzed 5- and 10-year relative survival (5yRS, 10yRS), defined as observed survival divided by observed survival of an age-, race- and gender-matched population without disease, for all cancer patients by marital status, with specific subset analyses as indicated.

Results—Among unmarried patients, those separated at time of diagnosis had the lowest survival, followed by widowed, divorced, and never married patients. 5- and 10-year relative survival of separated patients was 72% and 64% that of married patients, respectively. This relationship persists when data are analyzed by gender.

Conclusions—Separated marital status is associated with a significant decrement in cancer survival, even in comparison with other unmarried groups. While other socioeconomic variables could contribute to this phenomenon, further research into the immunologic correlates of the acutely stressful condition of marital separation should be conducted.

Keywords

cancer survival; marital status

Since George F. Solomon and colleagues published their landmark paper coining the term psychoneuroimmunology¹ and Ader & Cohen² first showed classical conditioning of

immune function, there has been an extraordinary volume of research demonstrating the significant role of psychosocial factors in health. Of the many different psychosocial variables, personal relationships have persistently shown a significant role in physical health, specifically that good relationships are beneficial and poor relationships are deleterious.^{3, 4} Social support and more specifically, marital status have been shown to affect physiological mechanisms including natural killer (NK) cell activity^{5, 6} and other aspects of improved immune function.^{5, 7} In addition, it has been postulated that increased support, potentially available in marriage, leads to better compliance with therapy. Furthermore, disruption of a close relationship⁸⁻¹¹ and abrasive relationships¹¹⁻¹³ have a negative effect on the immune system. Hostile interactions also alter pituitary and adrenal hormones.¹⁴

Cancer prognosis, in particular, has received intensive investigation with one important psychosocial dimension captured by nearly all outcome studies - the positive relationship between married status and survival. ¹⁵⁻¹⁸ Most prior studies, however, have employed a dichotomous characterization of marital status (married versus unmarried). Much less information is available regarding differences in survival among the unmarried population, e.g., analysis of other marital status categories such as separation, divorce, never married, etc. More detailed categorization of the relationship between marital status and cancer survival could yield important clues to the nature of the more global previously established relationship to cancer outcome.

We examined this issue using the Surveillance Epidemiology and End Results (SEER) database. In brief, SEER data are collected by the National Cancer Institute on cancer incidence and survival in the United States from population-based cancer registries covering 26 percent of the US population. Data collection of patient demographics, primary tumor site, tumor morphology, and stage at diagnosis began in 1973 and continues to the present. Public use of surveillance data for research is facilitated by web-based access. (URL: <http://seer.cancer.gov/>)

This study used the SEER data to compare relative survival rates among patients who were married, never married*, divorced, widowed, and separated, in an attempt to delineate potential differences among those patients who are unmarried. We hypothesized that for unmarried cancer patients, the specific subtype of marital status at time of diagnosis (divorced, widowed, separated) would have a differential impact on survival, with separation having the poorest outcome.

MATERIALS AND METHODS

The public-access Surveillance, Epidemiology and End Results (SEER) database was queried using the following parameters in the "Survival" program:

- a. Data: SEER 17 Regs Limited-Use, Nov 2006 Sub (1973–2004 varying)
- b. Statistic: Actuarial Relative Survival
- c. Selection: Actively followed / Malignant behavior / Death certificate, autopsy only excluded / Second and later primaries excluded
- d. Case selection: T = 'All Sites'
- e. Table: 'Marital Status at Diagnosis' and 'Sex'

*SEER data use "single" and "never married" synonymously.

This search mechanism provides data for the population of patients presenting with cancer between 1973 and 2004 in the entire 17 registry SEER database and provides survival rates for patients by marital status and gender. The April 2007 SEER update was used for this query. Specifically analyzed were 5- and 10-year relative survival rates for all cancer patients by marital status, with specific subset analyses as indicated. Records of 3.79 million patients were included in the analysis.

In this registry, the cause of death is uncertain and therefore, the relative survival (RS) is used in place of the cause-specific survival. Relative survival is defined within SEER as the observed survival for the cohort as compared to an age-race- and gender- matched sample of the general population. The assumption is that survival differences between the index cohort and the comparison matched cohort are due to effects of disease.

Statistical Methods

Statistical analyses included chi-square tests assessing observed survival compared to expected survival at the 5 and 10 year outcome intervals for the entire sample as well as stratified by gender. Chi-square values were computed for all pair-wise comparisons of marital status (never married, married, separated, divorced, widowed and unknown). To adjust for inflation of Type I error due to multiple comparisons the Bonferroni correction was applied. An a priori alpha level was set to 0.01 and divided by 15, the number of independent paired comparisons, yielding an adjusted critical probability value of 0.0006.

Results

Table 1 shows the 5 year and 10 year relative survival for all patients (collapsed across gender and site specific diagnosis) stratified by marital status at time of diagnosis.

Five- and ten-year survival rates (with Standard Error; SE) for married patients were the highest, 63.3 % (0.1%) and 57.5% (0.1%), respectively. Our results replicated prior findings that married individuals have a more favorable outcome than single, separated, widowed, and divorced individuals in terms of 5 and 10 year RS ($p < .0001$). Of note, patients with “unknown” marital status at diagnosis showed the best survival. We included “unknown” in the tables to acknowledge the size of this group, however we chose not to draw any conclusions from what is in essence missing data.

Five- and ten- year survival for separated patients was 45.4% (0.3%) and 36.8% (0.3%) respectively. Thus, the 5- and 10-year relative survival of separated patients is 72% and 64% that of married patients, respectively. Patients who were separated at the time of cancer diagnosis had the poorest survival rate.

Tables 2A and 2B include a matrix of pair-wise group comparisons for 5 year and 10 year relative survival, respectively, for males and females combined. Although all comparisons were statistically significant given the high degree of power (based on the sample size), chi-square values showed marked heterogeneity ranging from 21.72 to 10345.88.

Table 3 presents observed, expected, and relative survival as a function of marital status separately for males and females. The lowest observed survival was the widowed group for both men and women at both time points. This is not unexpected given the fact that the widowed population is older than the separated population. However, relative survival is useful as an analogue for cause-specific survival in the SEER data because, using this metric, the observed survival is corrected for the cohort's expected survival. Not surprisingly, expected survival for widowed patients--as defined as that of an age-, gender-, and race- matched population without disease--was far less than that of the younger,

healthier separated population. This led to the difference in relative survival. Reduced relative survival (RS) in patients separated at time of diagnosis persists as indicated by similar patterns at both 5 and 10 years. The main study hypothesis that specific subtype of marital status at time of diagnosis would have a differential impact on survival was confirmed.

Pair-wise group comparisons of observed versus expected survival are presented separately for men and women in Table 4 A–D. For males, separation status at diagnosis was associated with lower relative survival than all other groups at both 5 and 10 year outcome intervals. Females who were separated at time of diagnosis had lower 5 and 10 year relative survival than all other groups except those who were widowed.

Discussion

The well-described survival benefit of married compared to separated cancer patients may be due to a number of interrelated factors. First, there may be special characteristics of the married population. Married individuals generally have better financial assets and greater social support than the unmarried. As a result, they have better health-related behavior.^{19–21} Second, health status prior to diagnosis is likely to be important. Patients in poor health are less likely to marry and more likely to divorce.²¹ Third, psychological variables have an impact on health. Three that have been studied include perceived loneliness,²² anger,⁵ and substance abuse.²³ Fourth, treatment differences could be a critical variable. More aggressive treatment for married individuals has been shown in several studies including, but likely not limited to, married men with prostate cancer,²⁴ married women, irrespective of race, with breast cancer²⁵ and married patients with lung cancer.²⁶ Lastly, demographics, though more easily statistically “controllable”, also need to be considered. Taken together, these factors predict better survival for married patients across a variety of health problems.

By contrast, there are few data describing differences within the non-married population, and what data there are predominantly discriminate between never-married and divorced/separated populations.²⁷ We report differential reduction of relative survival in cancer patients experiencing marital separation at the time of diagnosis. Our results are generally consistent with data from a longitudinal prospective study of 10,000 marital transitions in the Netherlands that demonstrated that poor health status was associated with transitions from marriage to divorce, in contrast to those who transitioned from marriage to widowhood/widower or from single or divorced to marriage.²⁸ Generally, the acute emotional turmoil of separation is rarely studied separately from the more chronic effect of divorce. It is remarkable, then, that this acute trauma contributes to a significant decrement of 10-year relative survival with respect to every other cadre of patients' marital status.

Why would separation at time of diagnosis result in reduced survival relative to those who are divorced, widowed or never married? Differences in stage of cancer at time of diagnosis could be a factor. To evaluate this possibility, we reviewed two subsets of SEER data which represented two of the most common diagnoses (breast cancer and prostate cancer). Stage distribution (Local, Regional, Distant) for the separated group was not significantly different except for the widowed group. All marital status groups showed a predominance of local disease (i.e., earliest stage) at time of diagnosis. By comparison all marital status groups had the lowest number of patients with distant disease (i.e., most advanced stage) at time of diagnosis. (For prostate cancer, 80–83% of all marital groups had a local stage of disease at time of diagnosis; 4–10 % of all marital groups had advanced disease; for breast cancer, 57–65% of all marital groups had local stage and 3–7% were advanced.)

In view of these findings, we hypothesize that separation is unique as a marital status. It requires an abrupt change in one's way of life. Separated status carries a degree of uncertainty (change in home, finances) as well as the likelihood of less social support than is traditionally available for widowed patients. Divorced patients have likely established more equilibrium (social and cultural supports) than those separated. Regardless of who initiated the separation, the act of separating involves intense and complicated feelings of pain, disappointment, and, most importantly anger. These feelings are usually most intense at the time of separation. Being widowed can also be an abrupt change in the way of life, however the feelings of the survivor are usually less complicated and with less intense anger. Anger has been shown to significantly affect the immune system^{5, 13, 14, 29, 30} which may, in part, explain both the short term and long term effects of separation on morbidity and mortality.

Of the different plausible mechanisms (differential financial assets, social support, health-related behavior, prior health status, psychological variability, etc.) which may contribute to reduced survival, we chose to focus on the stress-immunity hypothesis since there is more evidence available to support it. The impact of stress on health has been noted since Holmes and Rahe.³¹ Differences in the broad construct of "health" have been described in patients after marital dissolution. Marital dissolution has been shown to affect the immune system in both men and women.^{10, 11} Furthermore, stress has been shown to affect the immune system in both animals and humans.³² Stress, defined by a perception that the demands of the environment are greater than one's adaptive capacity, has been shown to lead to certain behaviors in humans, including increased smoking, decreased exercise and physical activity, decreased sleep, and less compliance with medical regimens.³³ In animal models of stress, the initiation, growth, and metastases of certain tumors have been shown to worsen. In humans, stress can potentially affect antiviral defenses, DNA repair, and cellular aging as well as influence progression and recurrence of certain tumors.³⁴

Recently, stress has been shown to cause an increase in pro-inflammatory cytokines, adhesion molecules, and acute phase reactants, leading to CNS changes with sequelae including depression, fatigue, impaired sleep, and cognitive dysfunction.³⁵ In a study looking at the particular stress of breast biopsy in women, natural killer cell activity (NKCA) and interferon (IFN) gamma production were both decreased before biopsy and up to a month after biopsy was done.³⁶ Furthermore, NKCA have been shown to be suppressed in breast cancer patients who have poor social supports.³⁷

In a study looking at Ovarian Cancer, stress led to impaired NKCA with a decrease in NK cell response to interferon gamma, decreased T-cell proliferation and decreased NKCA in tumor infiltrating lymphocytes (TIL).³⁸ In this study, satisfaction with social relationships had a positive correlation with increased NK cell cytotoxicity and an increase in NKCA in TIL in ovarian cancer. However, a study by Von Ah et al.³⁹ showed that optimism and satisfaction with social support have minimal effect on NKCA or IFN gamma except by decreasing the harmful effects of stress on the immune system. It is unclear, then, if separation from a spouse affects morbidity and mortality simply as a stressful life event or if the lack of social support has an additive effect on the immune system. This topic could be investigated in future studies.

There are notable deficiencies in the degree of granularity in the data we report from the SEER registry. We were unable to determine the duration of separation--only that it was coded as being present at time of cancer diagnosis. Similarly, we were unable to determine whether or not the cancer patient initiated the separation. In some studies,²⁷ this has been shown to impact health; i.e., parties initiating the separation had health more similar to that of divorced patients.

The role of stress and cancer is likely bi-directional. Those under stress have compromised immune systems, and the diagnosis of cancer and separation are both major stressors.

Based on the factors identified in the seminal review of the relationship between marital relationships and health problems³ and voluminous subsequent evidence⁴ it would be beneficial to identify the specific stress factors in separation. Furthermore, it will be important to determine how these factors induce physiologic responses and how the acute physiological responses continue to influence health over time.

Why is there an impact of separation at diagnosis at 5 and 10 year survival? Is the stress of separation associated with greater biological vulnerability during the early cascade of oncogenic events? What are the characteristics of host factors that are particularly hospitable to cancer progression? If there is a “critical period”, what is the biological substrate causing the long term impact of separation on survival? We believe prospective studies are needed to address these questions. Recent work identifying specific profiles of gene expression in immune cells in individuals who experience chronically high levels of loneliness may help to provide a mechanistic understanding of these complex relationships.²²

Other possible factors reducing survival in those who are separated may include the previously noted psychological and behavioral consequences of stress, e.g., reduced compliance with cancer treatment, reduced maintenance of healthy behaviors (good diet, exercise, sleep, etc.), and possible depression at time of diagnosis perhaps extending into the future. Clearly other mechanisms (e.g., differential financial assets, social support, prior health status, etc.) may also be involved.

Although we identify a need for further research to increase our understanding of the causative factors affecting survival, it is important to note that there are interventions that can assist patients at present. Studies have demonstrated that psychological interventions can impact the immune system and survival. Davidson et. al. showed positive effects from brief mindfulness training on the brain and immune function.⁴⁰ Even more compelling is Andersen’s work showing that brief group psychological interventions have correlated with improved survival and enhanced immunity up to 13 years post-diagnosis.⁴¹

Given what is already known about stress and the immune system, early identification of psychological vulnerabilities in patients appears warranted. For example, determining the newly diagnosed patient’s emotional adjustment (conflict and support systems, etc.), essentially monitoring Miller’s 6th vital sign³⁵ prior to cancer treatment could lead to recommendations for additional psychosocial supports.

Survival may be facilitated further if patients’ psychological functioning is not only assessed and treated at time of diagnosis, but followed more closely and over longer terms post cancer treatment. This might also involve monitoring marital changes, educating patients about the importance of social supports and offering recommendations for seeking greater support when needed.

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TABLE 1

5 and 10 Year Relative Survival for All Patients Stratified by Marital Status at Time of Diagnosis

Status	n	5yRS (SE)	10yRS (SE)
Married	2,184,055	63.3% (0.00)	57.5% (0.00)
Never Married	467,031	57.3% (0.1)	51.7% (0.1)
Divorced	271,446	52.4% (0.1)	45.6% (0.2)
Widowed	628,215	47.2% (0.1)	40.9% (0.1)
Separated	51,857	45.4% (0.3)	36.8% (0.3)
Unknown	187,052	70.9% (0.2)	65.2% (0.2)

TABLE 2

Table 2 A Chi Square & P Values for Pair-wise Group Comparisons 5 Year Survival for Males and Females

	Never Married	Married	Separated	Divorced	Widowed
Married	1211.49 <.0001				
Separated	680.17 <.0001	1458.03 <.0001			
Divorced	456.81 <.0001	2700.25 <.0001	237.31 <.0001		
Widowed	2805.13 <.0001	10345.88 <.0001	21.72 <.0001	550.21 <.0001	
Unknown	1998.36 <.0001	741.63 <.0001	2197.65 <.0001	3316.88 <.0001	7318.45 <.0001

Table 2 B Chi Square & P Values for Pair-wise Group Comparisons 10 Year Survival for Males and Females

	Never Married	Married	Separated	Divorced	Widowed
Married	1171.68 <.0001				
Separated	1030.29 <.0001	1863.22 <.0001			
Divorced	726.86 <.0001	3278.77 <.0001	380.69 <.0001		
Widowed	2935.06 <.0001	9067.65 <.0001	101.48 <.0001	435.42 <.0001	
Unknown	1885.73 <.0001	696.25 <.0001	2592.29 <.0001	3658.89 <.0001	6975.6 <.0001

TABLE 3

Marital Status at Diagnosis and Five and Ten Year Survival Outcomes

Marital Status	Sex	Outcome Interval	Sample Size	Observed Survival	Expected Survival	Observed Survival	Expected Survival	Observed Percent	Expected Percent	Relative Survival
Never Married	Male	5 year	247948	111577	219434	45.00	88.50	50.85	50.85	50.85
Married	Male	5 year	1303265	638600	1064768	49.00	81.70	59.98	59.98	59.98
Separated	Male	5 year	20302	6172	15876	30.40	78.20	38.87	38.87	38.87
Divorced	Male	5 year	120044	45497	103358	37.90	86.10	44.02	44.02	44.02
Widowed	Male	5 year	158952	44030	103478	27.70	65.10	42.55	42.55	42.55
Unknown	Male	5 year	108492	63793	87553	58.80	80.70	72.86	72.86	72.86
Never Married	Male	10 year	247948	85790	191664	34.60	77.30	44.76	44.76	44.76
Married	Male	10 year	1303265	443110	831483	34.00	63.80	53.29	53.29	53.29
Separated	Male	10 year	20302	3451	12202	17.00	60.10	28.29	28.29	28.29
Divorced	Male	10 year	120044	30251	85711	25.20	71.40	35.29	35.29	35.29
Widowed	Male	10 year	158952	20505	63104	12.90	39.70	32.49	32.49	32.49
Unknown	Male	10 year	108492	45350	68241	41.80	62.90	66.45	66.45	66.45
Never Married	Female	5 year	219083	128602	199146	58.70	90.90	64.58	64.58	64.58
Married	Female	5 year	880790	546971	808565	62.10	91.80	67.65	67.65	67.65
Separated	Female	5 year	31555	12906	26254	40.90	83.20	49.16	49.16	49.16
Divorced	Female	5 year	151402	81000	138381	53.50	91.40	58.53	58.53	58.53
Widowed	Female	5 year	469263	168935	347255	36.00	74.00	48.65	48.65	48.65
Unknown	Female	5 year	78560	46115	67719	58.70	86.20	68.10	68.10	68.10
Never Married	Female	10 year	219083	105598	178991	48.20	81.70	59.00	59.00	59.00
Married	Female	10 year	880790	448322	720486	50.90	81.80	62.22	62.22	62.22
Separated	Female	10 year	31555	8741	21300	27.70	67.50	41.04	41.04	41.04
Divorced	Female	10 year	151402	64346	122938	42.50	81.20	52.34	52.34	52.34
Widowed	Female	10 year	469263	102769	239793	21.90	51.10	42.86	42.86	42.86
Unknown	Female	10 year	78560	36138	57113	46.00	72.70	63.27	63.27	63.27

Table 4

Table 4 A Chi Square & P Values for Group Comparisons 5 Year Males

	Never Married	Married	Separated	Divorced	Widowed
Married	1703.49 <.0001				
Separated	303.68 <.0001	838.79 <.0001			
Divorced	460.76 <.0001	2819.01 <.0001	60.19 <.0001		
Widowed	692.36 <.0001	3404.91 <.0001	31.69 <.0001	17.99 <.0001	
Unknown	3199.25 <.0001	1282.85 <.0001	1602.48 <.0001	4350.98 <.0001	4901.46 <.0001

Table 4 B Chi Square & P Values for Group Comparisons 10 Year Males

	Never Married	Married	Separated	Divorced	Widowed
Married	1499.02 <.0001				
Separated	550.93 <.0001	1105.13 <.0001			
Divorced	918.74 <.0001	3564.87 <.0001	118.17 <.0001		
Widowed	1265.11 <.0001	3659.36 <.0001	44.22 <.0001	62.51 <.0001	
Unknown	2931.12 <.0001	1217.24 <.0001	1870.8 <.0001	4974.05 <.0001	5134.41 <.0001

Table 4 C Chi Square & P Values for Group Comparisons 5 Year Females

	Never Married	Married	Separated	Divorced	Widowed
Married	136.04 <.0001				
Separated	582.45 <.0001	865.93 <.0001			
Divorced	298.27 <.0001	925.97 <.0001	225.86 <.0001		
Widowed	3722.84 <.0001	9198.95 <.0001	0.87 0.3502	1207.57 <.0001	

Table 4 C Chi Square & P Values for Group Comparisons 5 Year Females

	Never Married	Married	Separated	Divorced	Widowed
Unknown	57.23 <.0001	1.11 0.2911	701.6 <.0001	409.06 <.0001	2513.18 <.0001

Table 4 D Chi Square & P Values for Group Comparisons 10 Year Females

	Never Married	Married	Separated	Divorced	Widowed
Married	152.04 <.0001				
Separated	753.33 <.0001	1064.68 <.0001			
Divorced	370.14 <.0001	1098.29 <.0001	320.97 <.0001		
Widowed	3537.35 <.0001	7986.23 <.0001	10.74 0.0010	1064.71 <.0001	
Unknown	81.38 <.0001	5.73 0.0166	915.2 <.0001	523.32 <.0001	2586.42 <.0001