Pathways Linking Treatment Intensity and Psychosocial Outcomes among Adult Survivors of Childhood Leukemia

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Abstract

To determine the pathways between treatment intensity (age at diagnosis, dosage of chemotherapy [intrathecal methotrexate; IT-MTX] and cranial radiation [CRT]) and various psychosocial outcomes, review of medical records and structured interviews were carried out in 510 adult survivors of childhood leukemia. Structural equation modeling revealed that higher treatment intensity during childhood (indicated by treatment with high-dose CRT, low-dose IT-MTX, and adjusted by younger age at diagnosis) predicted more health-compromising behaviors as adults through lower educational achievement. Additionally, higher childhood treatment intensity predicted current negative mood both directly and via changes in perceived limitations. The present study's findings suggest that higher treatment intensity during childhood may serve as a risk factor for adult survivors' health-compromising behaviors through neuropsychological deficits that arise from cancer treatment.

Keywords

childhood leukemia, education, health behaviors, long-term survivors, mood, treatment effects

CANCER IS THE LEADING cause of death by disease in children under the age of 15 years. In the United States, more than 8000 children are diagnosed with cancer each year (American Cancer Society, 1994). Acute lymphoblastic leukemia (ALL) is the most common form of childhood cancer, with approximately 2000 new cases diagnosed each year, and with an approximate increase in incidence rate of 1.6 percent per year (American Cancer Society, 1994; Gurney et al., 1996). Treatments for childhood ALL have vastly improved survival rates in the past few decades. Under current treatment protocols, nearly 90 percent of children with ALL will show remission, and more than 67 percent stay in remission for at least 5 years (Granowetter, 1994; National Cancer Institute, 1994). With survival rates for children with ALL rapidly increasing, attention has turned recently toward the long-term effects of childhood cancer and its treatment on adult survivors. In this report, we focus on the implications of childhood cancer treatment for subsequent adult psychosocial outcomes such as mood and health-related behaviors.

Long-term psychosocial outcomes in childhood cancer survivors

A subset of childhood cancer survivors has been found to experience disturbed mood, behavior problems, and psychological adjustment difficulties (Chang, Nesbit, Youngren, & Robison, 1987; Koocher & O'Malley, 1981; Mulhern, Wasserman, Friedman, & Fairclough, 1989. For reviews, see Dobkin & Morrow, 1985; Kazak, 1994). Survivors of childhood cancer also have reported greater difficulties in school, greater likelihood of repeating a grade, and more unemployment and job discrimination (Chang et al., 1987; Friedman & Mulhern, 1991; Gray et al., 1992; Haupt et al., 1994; Koocher & O'Malley, 1981; Zevon, Neubauer, & Green, 1990). However, a few studies have shown that childhood cancer survivors are well-adjusted and display more positive mood compared with a control group of peers (Gray et al., 1992; Holmes & Holmes, 1975). The reason for these mixed findings is unclear; however, it may be that these psychological difficulties are apparent in only a portion of adult survivors of childhood cancer.

Purpose of the Children's Cancer Group study

The present study resulted from a multi-site Children's Cancer Group (CCG) survey undertaken to assess long-term outcomes among young adult survivors of childhood leukemia. The CCG interview aimed to assess, in the largest sample of leukemia survivors known to date, a global picture of survivors' perceptions of their current functioning in multiple domains, including psychological adjustment, health status, educational achievement, etc. Because the interview probed a wide range of areas, each outcome of interest was limited to several fairly general questions. Additionally, because the goal of this interview was to explore survivors' perceptions of their current functioning, objective testing and clinician ratings of survivors' well-being were not utilized.

Specific questions addressed in the present study

The purpose of the present study is to examine the psychosocial outcomes explored within the CCG interviews: health-compromising behaviors, educational achievement, perceived limitations, and current mood state. Previous studies have examined survivors' adjustment related to many of these outcome measures (see above), but have not to our knowledge examined these psychosocial outcomes simultaneously. The goal of the present study was to develop an overall model depicting the interrelationships between childhood cancer treatment variables and multiple long-term psychosocial outcome variables. Through structural equation modeling, we sought to clarify the pathways through which certain negative psychosocial outcomes could occur; that is, which psychosocial outcomes in leukemia survivors are a direct result of treatment received during childhood, and which are mediated by other factors?

Treatment intensity and health-compromising behaviors

Although somewhat counter-intuitive, evidence suggests that serious illness experiences may not necessarily translate into positive changes in lifestyle behaviors among survivors. Adult sur-

vivors of childhood cancer have been found to report higher incidences of health-compromising behaviors, including higher rates of alcoholism compared with the normal population (Lansky, List, & Ritter-Sterr, 1986), and a lower likelihood of quitting smoking compared with sibling controls (Haupt et al., 1992). These findings parallel research in other areas that found that acutely ill college students were less likely to want information on preventing serious health problems than healthy college students (Kulik & Mahler, 1987), that health status and number of past episodes of illness did not predict health-protective behaviors among college students (Weiss, Larsen, & Baker, 1996), and that accident victims were no more likely to use seat belts after their accidents (Robertson, 1975; Robertson, O'Neill, & Wixom, 1972).

These findings are somewhat unusual in that one might expect individuals who had experienced serious illnesses or traumatic events to feel more vulnerable and thus to engage in *fewer* health-compromising behaviors. Thus we hypothesized that other factors might be involved which could explain this relationship between illness and higher rates of health-compromising behavior. Several possible mediating factors are discussed below.

Role of mood

One possibility is that survivors' mood might influence the relationship between treatment factors and health-compromising behaviors. Survivors report a higher incidence of treated adult depression compared with the general population (Lansky et al., 1986). Furthermore, intensity of treatment received during childhood has been associated with negative mood. Children treated with cranial radiation therapy (CRT) and chemotherapy may suffer from depressed mood (Madan-Swain & Brown, 1991). Treatment with CRT and intrathecal methotrexate (IT-MTX) chemotherapy has been related to lower scores in happiness, optimism, and activity compared with adult ALL survivors who received only IT-MTX (Zevon et al., 1990). Adult survivors of ALL report more negative mood if they were treated at a young age on high-dose CRT compared with those treated at a young age on low-dose CRT or those treated during adolescence (Zeltzer et al., submitted). However, younger age at diagnosis also has been related to better overall psychological adjustment and lower depression scores (Fritz, Williams, & Amylon, 1988; Koocher, O'Malley, Gogan, & Foster, 1980), although this was not replicated in one study, perhaps due to differences in the measurement of depression (Teta et al., 1986).

Furthermore, individuals in a depressed or anxious mood often engage in risk behaviors such as drinking or drug use, in an attempt to self-medicate their mood (Quitkin, Rifkin, Kaplan, & Klein, 1972; Wurmser, 1979). In addition, feelings of a lack of competence and meaning in life (often associated with depression) are related to increased alcohol and drug use (Harlow & Newcomb, 1990; Newcomb & Harlow, 1986). Thus mood state is one potential mediator, such that individuals who have experienced more intense treatment may be more likely to experience negative moods, which may predispose them to health-compromising behavior.

Role of education

A second possibility is that sociocultural factors, particularly educational achievement, might influence the relationship between treatment and health-compromising behaviors. Previous research has shown that cancer survivors are more likely to have lower educational achievement, including repeating grades, compared with sibling controls and peers (Gray et al., 1992; Haupt et al., 1994), and that almost 50 percent of survivors reported having a documented learning disability (Chang et al., 1987). Furthermore, treatment intensity has been associated with negative neuropsychological outcomes (Bleyer et al., 1990; Mulhern, 1994; for a review, see Madan-Swain & Brown, 1991). Younger children receiving CRT with or without IT-MTX have been found to have lower IQ scores compared with older children and children treated without CRT (e.g. Meadows et al., 1981; Mulhern et al., 1992; Waber et al., 1990). Children treated with a combination of CRT and IT-MTX demonstrated lower IQ scores than those receiving IT-MTX alone (Rowland et al., 1984). It has been suggested that central nervous system (CNS) insults from CRT, and possibly from IT-MTX, may have a greater negative impact on younger children because they are undergoing a period of rapid neural develop-

ment, and other areas of the brain may not be able to assume the functions of the impaired areas (Mulhern, 1994).

Individuals with less education and from a lower socio-economic background are more likely to engage in health-compromising behaviors, such as not obtaining immunizations and not utilizing health care services (Kirscht, 1983), possibly because of being less informed about the consequences of their health-compromising behaviors. Thus we might expect that survivors who received more intense treatment will experience lower educational achievement, and subsequently engage in more health-compromising behaviors.

Treatment intensity versus perceptions of treatment effects

A second question addressed by the modeling analyses of this paper concerned whether negative effects of treatment are related directly to treatment intensity or to survivors' perceptions of treatment impact. Many of the previous findings discussed above examine the relationship between objective measures of treatment intensity to outcomes such as mood and education. However, survivors' perceptions of themselves may also relate strongly to psychological adjustment. For example, among children undergoing treatment for cancer (who often experience hair loss, weight gain, etc.), *perceptions* about their physical appearance related strongly to depression and anxiety (Varni, Katz, Colegrove, & Dolgin, 1995). Thus we included a factor about perceived limitations to test whether the relationship between leukemia treatment and psychological outcomes such as mood was driven by actual intensity of treatment or perceptions of treatment impact.

Overall model

The evidence indicating that certain patterns of treatment may lead to neuropsychological deficits suggests that there is a common, underlying treatment intensity factor (reflecting the physical impact of treatment on the survivor, based on dosage of treatment protocols and the age at which these were received) that influences psychological and behavioral outcomes. We expected that survivors with a high-intensity treatment profile (high-dose CRT, low-dose IT-MTX, younger age at diagnosis: see p. 28 for an explanation of this profile) would engage in higher rates of health-compromising behaviors and that these effects would in many cases be mediated by alterations in mood and educational achievement. Additionally, we hypothesized that there would be both direct and indirect paths between treatment intensity and mood.

Method

Participants

Eligibility criteria for study entry as a survivor included: diagnosis of ALL between 1970 and 1986, treatment on a CCG protocol before age 20 years, age at least 18 years by 15 October 1990, survival for at least 2 years after diagnosis, in remission, and not receiving anti-leukemia treatment at study entry.

Twenty-three of the 33 CCG institutions agreed to participate in the study and were able to obtain Human Subjects Committee approval, providing a total of 731 eligible survivors enrolled at these institutions. Only 6.3 percent of this group declined participation, while 9.3 percent could not be traced, 1.5 percent were deceased, and 1.8 percent were unable to be interviewed (9 with Downs syndrome, 2 drug-dependent, 1 non-English speaking, and 1 brain damaged), resulting in a total of 593 survivors who agreed to participate. Eighty-three participants did not complete all measures included in this study, and thus were excluded from study analyses. Excluded participants did not differ from included participants in any demographic variables, including gender, race, employment, education, marital status, or age at interview. Thus the excluded participants did not appear to represent a biased subset of the total participants. The number of participants from each site ranged from 1 to 90. A multivariate analysis of variance (MANOVA) was conducted to examine differences on the dependent variables by site. Because of the small numbers of participants at some sites, the three sites that had fewer than 10 participants were combined for purposes of analyses. The MANOVA was not significant ($F < 1$), and none of the univariate tests for each dependent variable was significant (all $ps > .10$), indicating that there were no differences by site for the dependent measures in this study. Further

details on study participants and non-participants can be found in Haupt et al. (1994).

Participants ranged in age from 18 to 33 years old, with a mean age of 23 (SD = 3.21) years. Fifty-one percent were male, and 49 percent were female. The majority of participants were White (87.9 percent); 4.4 percent were Hispanic, 3.5 percent were African-American, 1.7 percent were Asian-American, and 0.3 percent were American-Indian.

Measures

Mood To assess mood in young adulthood, the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1971), a 65-item self-report questionnaire designed to measure six identifiable mood states (tension/anxiety, depression, anger, confusion, vigor, fatigue) was used. This questionnaire has demonstrated reliability (coefficient alphas for all subscales ≥.90) and validity (see McNair et al., 1971). Participants were asked to rate the extent to which the adjectives described the way they had been feeling during the past week on a scale ranging from 0 ('not at all') to 4 ('extremely'). In the present study, only the tension/anxiety, depression, and anger subscales were used because they represent the affective portions of the POMS. Higher scores indicate greater mood disturbance. Coefficient alpha for the POMS measure in the present study was .94 for the total of the three subscales.

Health-compromising behaviors Target areas for health-compromising behaviors were determined based on domains investigated by previous researchers among injured or chronically ill patients (Mulhern et al., 1995; Weinstein, 1989). Research seeking to identify factors that predict health behaviors typically includes both health-compromising (e.g. smoking, alcohol use) and health-protective (e.g. safety-related, exercise) behaviors. We sampled from both of these domains. Participants were asked about the amount they had engaged in four types of risk behaviors: (1) the average number of cigarettes they smoked in a day during the entire period in which they smoked; (2) the average number of drinks they had per week during the entire period in which they drank; (3) the average number of times per week they used marijuana, cocaine, heroin, LSD, amphetamines, or barbiturates over the past 6 months; and (4) how often they used seat belts when driving, assessed on a scale ranging from 1 ('always') to 4 ('never'). Higher scores on this factor indicate greater engagement in risk behaviors.

Perceived limitations School and work limitations were assessed with two yes/no questions. Participants were asked whether cancer 'has limited your ability to work or do what you would like to do' and whether cancer 'has interfered with your schooling'. Responses were scored as 'no' = 1 and 'yes' = 2; thus higher scores indicate greater limitations.

Educational achievement Educational achievement was assessed through three measures (see Haupt et al., 1994 for more information on the derivation of these variables): (1) highest educational level attained; (2) average grade in school ('A' = 6, 'F' = 1); and (3) whether the participant repeated a grade in school ('yes' = 1, 'no' = 2). Higher scores on this factor indicate higher educational achievement.

Medical variables Data regarding medical variables were obtained from the survivors' clinical records at the CCG Operations Office. Standard doses of CRT were determined according to CCG protocols as either 18 or 24 Gy. However, because some participants (5.7 percent) received doses that deviated from protocol (dosage of CRT ranged from 2 to 40 Gy), dose of CRT was created as a continuous variable. Survivors received IT-MTX in cumulative doses (determined independent of body weight) which was rated as a continuous variable (range 2–339 mg, median total dose = 83 mg). Age at diagnosis also was obtained and coded as a continuous variable. Because dosages for CRT and IT-MTX according to CCG protocols could be categorized as none, low (18 Gy, <83 mg), or high (24 Gy, >83 mg), modeling analyses were repeated with CRT and IT-MTX as categorical variables. Results were the same as those presented below.

Procedures

Each participant was mailed a consent form approved by each institution's Human Subjects Protection Committee. When signed consents

were received at the principal investigator's site, telephone interviews were arranged with each participant and were carried out by trained interviewers. The interview followed a structured format and included questions about education, marital status, employment history, fertility, offspring, health, and health-compromising behaviors. At the end of the interview, the POMS was administered. Only the data regarding mood, health-compromising behaviors, current limitations, and education are considered in this paper.

Analysis

Structural equation modeling was conducted using the EQS software (Bentler, 1995). Structural equation modeling allows for the testing of the goodness-of-fit of observed data and predicted models, and reduces the biasing effects of measurement error in parameters through the specification of paths among theoretically error-free latent factors. The latent factors capture correlations among measured variables. Because the data in this study did not meet assumptions of multivariate normality (normalized Mardia's coefficient of kurtosis = 432), the robust maximum likelihood (ML) method was used to depict more accurately chi-squares and standard errors. Both the Satorra-Bentler chi-square and the ML chi-square statistics are presented for each model. Bentler and Dudgeon (1996) and Curran, West, and Finch (1996) provide a detailed rationale for the use of these statistics. Goodness-of-fit of our proposed model was measured by the nonnormed fit index (NNFI), and the robust comparative fit index (CFI). These indices have a range from 0 to 1, with 1.0 indicating that the model is a perfect description of the data. We also presented the root mean square error of approximation (RMSEA) to estimate the fit of the models below, with values of < .05 indicating 'close' fits (Browne & Cudeck, 1993). Significance of parameter estimates was determined by robust standard errors, i.e., corrected for nonnormality (Bentler & Dudgeon, 1996). Measured variables are represented by rectangles, and latent factors by circles.

We formed a treatment intensity latent variable to indicate the impact of treatment on a survivor. This factor was formed based on previous research that showed that younger age at diagnosis and high dose of CRT places survivors at risk for negative outcomes (Mulhern, 1994). Since the CCG treatment protocols during the study period typically combined high doses of CRT with low doses of IT-MTX , it was expected that the high intensity group would be indicated by high-dose CRT but low-dose IT-MTX, in addition to younger at age of diagnosis. Age at diagnosis was included to give more meaning to the treatment intensity variable, since previous research has suggested that high-dose CRT at a younger age places survivors at greatest risk for negative psychological outcomes.[1]

Summary of latent factors and hypotheses

Our first latent factor was treatment intensity, indicated by the measured variables CRT, IT-MTX, and age at diagnosis. The primary psychosocial outcome latent factor of interest was health-compromising behaviors, indicated by the measured variables alcohol use, substance use, cigarette use, and seat belt use. The potential psychosocial mediators tested included: mood, indicated by the measured variables depression, anxiety, and anger; education, indicated by the measured variables highest educational level attained, average grade in school, and repeating any grades in school; and perceived limitations, indicated by the measured variables work limitations and school limitations.

We hypothesized that higher treatment intensity would lead to lower educational achievement, and subsequent engagement in more health-compromising behaviors. We also hypothesized that higher treatment intensity would lead to more negative mood, which would be associated with more health-compromising behaviors. Finally, we hypothesized both a direct and an indirect (via perceived limitations) relationship between treatment intensity and negative mood.

Results

Descriptive statistics and factor analysis

Tables 1 and 2 present means, standard deviations, and correlations among the measured variables.

An initial confirmatory factor analysis was

Table 1. Descriptive statistics for measured variables

Variable	*M*	SD
Age at diagnosis (years)	10.46	4.71
Dose of IT-MTX (mg)	97.10	74.56
Dose of CRT (Gy)	1866	691
Alcohol use	5.50	15.02
No seat belt use	1.90	1.08
Drug use	0.24	2.04
Cigarettes smoked	2.37	6.31
Perceived work limitations	1.16	.37
Perceived school limitations	1.42	.50
Anger	9.74	8.04
Depression	8.97	9.30
Tension/anxiety	7.21	6.07
Not repeat grade	1.82	.38
Education level	13.70	2.06
Average grade	4.80	0.78

$N = 510$. IT-MTX: intrathecal methotrexate. CRT: cranial radiation. Alcohol use: number of drinks per week. No seat belt use has a range of 1 to 4 (with 4 indicating no seat belt use). Drug use: number of times participant used marijuana, cocaine, heroin, LSD, amphetamines, or barbiturates per week. Amount smoked: number of cigarettes per day. Perceived work and school limitations have a range of 1 to 2 (with 1 indicating 'no', and 2 indicating 'yes'). Depression has a range of 0 to 48; anger has a range of 0 to 44; and tension/anxiety has a range of −4 to 28. Higher scores on these scales indicate greater anger, depression, or tension. Our sibling-control sample from this study reported average POMS scores as follows: anger $M = 8.09$, SD = 7.06; depression $M = 6.97$, SD = 7.19; tension/anxiety $M = 6.09$, SD = 5.76. Not repeat grade has a range of 1 to 2 (with 1 indicating 'yes', and 2 indicating 'no'). Average grade ranges from 1 ('F') to 6 ('A')

performed to test the adequacy of the factor structure and the measurement model. Latent variables were allowed to intercorrelate, without any evaluation of hypothesized causality among them. The fit indexes for the initial confirmatory factor analysis indicated that the model was an adequate fit [χ^2 (80, $N = 510$) = 138.8 (ML χ^2 = 151), $p < .05$, NNFI = .93, CFI = .94, RMSEA < .05, CI of RMSEA .026–.05]; additionally, all measured variables loaded significantly onto their respective latent constructs, indicating that the latent constructs were estimated successfully. Correlations among latent variables can be found in Table 3. The goal of the modeling analyses is to create a model that reproduces the observed correlations in Table 3.

Structural model

In the next model, we replaced the correlations among latent factors with hypothesized paths. We tested our hypothesized model that mood and educational achievement mediate the relationship between treatment intensity and health-compromising behaviors. One path proved to be nonsignificant (that from mood to health-compromising behaviors) and was deleted; an additional path from education to perceived limitations was suggested by the Lagrange multiplier test. Goodness of fit statistics for the final model indicate that the model is a close representation of the data [χ^2 (84, $N = 510$) = 154.6 (ML χ^2 = 171.9), $p < .05$, NNFI = .92, CFI = .93, RMSEA < .05]. The final model is presented in Figure 1, together with standardized loadings of measured variables on latent variables. Significant paths in the model are discussed below. [2]

Pathways related to mood Mood did not mediate the relationship between treatment intensity and subsequent health-compromising behaviors, as indicated in Figure 1. Although the direct path from higher childhood treatment intensity to greater current negative mood was significant, the path from mood to health-compromising behaviors was not. It bears noting that the indirect effect of treatment intensity on negative mood through perceived limitations

Table 2. Correlations among measured variables

Variable	*V1*	*V2*	*V3*	*V4*	*V5*	*V6*	*V7*	*V8*	*V9*	*V10*	*V11*	*V12*	*V13*	*V14*	*V15*
V1: Age at diagnosis	—	.496**	−.236**	.028	−.034	−.031	.043	.157**	.195**	−.157**	−.126**	−.083	.080	.302*	.258**
V2: Dose of IT-MTX		—	−.282**	−.023	.023	−.040	.006	.023	.091*	−.089*	−.069	−.009	.001	.051	.097*
V3: Dose of CRT			—	.014	−.076	.033	−.026	−.058	−.124**	.027	.016	.033	−.044	−.053	−.092*
V4: Alcohol use				—	.101*	.044	.289**	−.042	.018	.105*	.092*	.058	.009	−.075	.116**
V5: No seat belt use					—	.028	.235**	.003	.058	.092*	.024	−.018	−.065	−.256**	.220**
V6: Drug use						—	.218**	−.038	.013	.025	.057	−.031	−.125**	−.092*	−.088*
V7: Cigarettes smoked							—	−.025	.097*	.112*	.054	.025	−.085	−.225**	.190**
V8: Perceived work limit								—	.338**	.107*	.179**	.180**	−.035	−.025	.026
V9: Perceived school limit									—	.033	.099*	.103*	−.134**	−.039	−.102*
V10: Anger										—	.722**	.612**	−.040	−.160**	.117**
V11: Depression											—	.635**	.012	−.114*	−.089*
V12: Tension/anxiety												—	.018	−.089*	−.018
V13: Not repeat grade													—	.283**	.256**
V14: Education level														—	.415**
V15: Average grade															—

$N = 510$. IT-MTX: intrathecal methotrexate. CRT: cranial radiation. * $p < .05$; ** $p < .01$

Table 3. Correlations among latent variables

Variable	*F1*	*F2*	*F3*	*F4*	*F5*
F1: Treatment intensity	—				
F2: Perceived limitations	−.31**	—			
F3: Mood	.15**	.24**	—		
F4: Educational achievement	−.41**	−.12	−.18**	—	
F5: Health-compromising behavior	−.04	.08	.14	−.49**	—

** $p < .01$

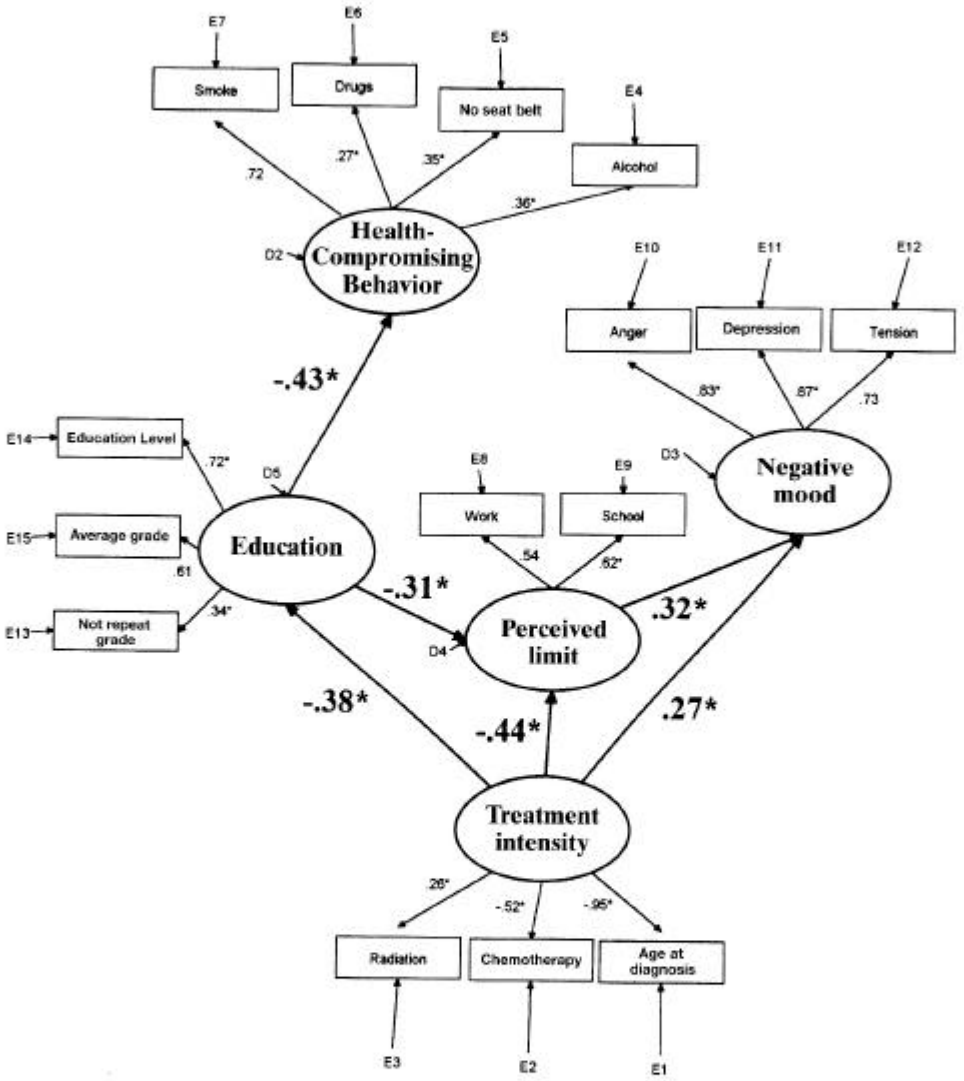

Figure 1. Predicting long-term psychological outcomes of mood, perceived limitations, educational achievement, and health-compromising behaviors from treatment intensity variables. Standardized regression coefficients are presented. * $p \leq .05$.

was significant ($p < .05$), indicating that higher treatment intensity was associated with fewer perceived limitations, which then was associated with less negative mood.

Pathways related to education Education proved to be a significant mediator of the relationship between treatment intensity and health-compromising behaviors. The indirect effect of treatment intensity on health-compromising behaviors via education was significant ($p < .05$). That is, higher treatment intensity was directly related to lower educational achievement, which then was associated with more health-compromising behaviors. Additionally, educational achievement negatively affected perceived limitations. However, the indirect effect of treatment intensity on perceived limitations via educational achievement was not significant ($p > .05$).

Finally, the model revealed a relationship between educational achievement and negative mood that was mediated by perceived limitations ($p < .05$). Lower educational achievement was associated with higher perceived cancer-related limitations, which then was associated with more current negative mood.

In sum, educational achievement was the only significant mediator of the relationship between treatment intensity and health-compromising behaviors. Treatment intensity related to negative mood both directly and indirectly.[3]

Discussion

Treatment intensity and health-compromising behaviors

We explored in this study explanations for why cancer survivors (who might be expected to perceive greater vulnerability to future health threats due to their previous illness) have been found to report increased likelihood of engaging in health-compromising behaviors (Lansky et al., 1986). Higher intensity treatment in this study was indicated by high-dose CRT and low-dose IT-MTX, in addition to younger age at diagnosis.[4] We found that the most plausible path linking treatment intensity to health-compromising behavior involved educational achievement. Higher treatment intensity predicted more health-compromising behaviors by lowering educational achievement. The finding of higher treatment intensity predicting lower educational achievement is consistent with previous research demonstrating that survivors treated with high-dose CRT performed three grades below their age levels (Peckham, Meadows, Bartel, & Marrero, 1988), were more likely than sibling controls to be enrolled in special education programs, and less likely to attend college (Haupt et al., 1994).

These findings suggest that high-intensity treatment regimens may place childhood cancer survivors at heightened risk for health-compromising behavior by influencing their neuropsychological ability and subsequent educational achievement. Children who receive high intensity treatment may suffer neuropsychological deficits (Meadows et al., 1981; Mulhern, 1994; Waber et al., 1990) that hinder their educational achievement and also result in their being placed in an environment at school where certain health-compromising behaviors (e.g. drug use, smoking) are more strongly encouraged by peers, or where information about the risks of these behaviors may be less readily available.

Treatment intensity and mood

A second major finding of the study was that treatment intensity related to negative mood through two opposite pathways. First, more intense treatment was related directly to more negative mood. CRT may dysregulate neurotransmitter systems (e.g. serotonin, norepinephrine) that have been implicated in the onset of depression (Davison & Neale, 1990). Alternatively, the distress resulting from cancer treatment procedures may contribute to post-traumatic stress disorder (PTSD) in some children. Studies have demonstrated PTSD symptoms in children with cancer (age 3–6) undergoing bone marrow transplantation (Stuber, Nader, Yasuda, Pynoos, & Cohen, 1991). Chronic PTSD in these young children may have gone unrecognized and untreated, resulting in anxiety, depression, and/or anger that persisted into adulthood. Finally, both PTSD and chemotherapy have been associated with sleep disturbances in children (Kaufman, Tarnowski, & Olson, 1989; Susman et al., 1981). Chronic sleep deprivation then may worsen affective symptoms.

An additional indirect effect was found in the opposite direction between treatment intensity

and mood through perceived limitations. That is, higher treatment intensity predicted fewer perceived limitations, which then was associated with less negative mood. This finding demonstrates that survivors' perceptions of vulnerability are related to negative mood. The relation between higher treatment intensity and fewer perceived cancer-related limitations suggests that survivors' perceptions about treatment are not the same as actual treatment protocol intensity. Some survivors (e.g. those diagnosed during adolescence) may have been more aware of the impact of their cancer experience on their lives. For example, among adult survivors of childhood cancer who were mostly teenagers at the time of diagnosis, 40 percent reported being teased about their physical appearance or being treated as outcasts (Wasserman, Thompson, Wilimas, & Fairclough, 1987), and over half reported concerns about their body (Fritz & Williams, 1988). These survivors may have experienced greater disruption in schoolwork or have been more sensitive about their physical appearance: factors that may have increased their perceptions of cancer-related limitations. Some survivors may then have generalized these perceived limitations to global and stable perceptions of a lack of control in life, which can lead to learned helplessness and depression in children and adolescents (Kaslow, Tannenbaum, & Abramson, 1983).

We believe that these opposite findings with treatment intensity and negative mood are both equally valid pathways (significant to the same extent in the model) and can be explained primarily by the age at which a child was diagnosed and treated. Children treated at a younger age may suffer traumatic reactions to the treatment itself, which could have long-lasting effects on mood (thus the positive direct relation between treatment intensity and negative mood). On the other hand, those treated at an older age (adolescence) may rely more heavily on their peers' evaluations of them. Thus adolescents may be more vulnerable to being teased at school, which might lead them to perceive themselves as having more limitations, and subsequently to experience negative mood (thus the negative relation between treatment intensity and perceived limitations, and the positive relation between perceived limitations and negative mood).

Education and mood

Perceived limitations were found to mediate the relationship between educational achievement and negative mood. Lower educational achievement was associated with greater perception of cancer-related limitations, which then was associated with more negative mood. This finding is important in that it does not support suggestions by other researchers (Madan-Swain & Brown, 1991) that depression may be directly associated with limitations in cognitive functioning.

Limitations of the study

Due to the retrospective, self-report nature of the study, the direction of some of the proposed pathways is not entirely clear. For example, because negative mood and perceived cancer-related limitations were assessed at the same time, it is possible that increased negative mood could lead to increased perceived cancer-related limitations.[5] In addition, the fact that the perceived limitations questions included past limitations, whereas the mood questions probed current mood state, suggests at least some temporal precedence for perceived limitations over negative mood.

Second, the role of neuropsychological deficits remains speculative because only survivors' self-report of educational achievement was measured in this study. This study represents a first step toward understanding the pathways to health-compromising behaviors in adult survivors, and future studies that included neuropsychological testing would help to test the validity of this explanation.

Another limitation of this study involved the broadness of questions in the interview. Because of the wide range of areas probed in this survey, we were unable to obtain detailed information on any particular area of adjustment. For example, the perceived limitations factor could have been greatly strengthened through additional questions that probed the extent and duration of these limitations. Future studies could build on the present study by incorporating such information, as well as utilizing multi-informant measures.

Summary and implications

This large-sample study of young adult survivors of ALL provides an overall model of the

interrelationships between childhood treatment intensity and long-term psychological and behavioral outcomes including treatment behaviors and mood in early adulthood. The results corroborate previous analyses suggesting a positive relationship between the intensity of childhood treatment and health-compromising behaviors as an adult. However, present results differ from previous research in suggesting that the association between these two variables is not direct, but rather is mediated primarily by lower educational achievement. Results also suggest that childhood treatment intensity is related to negative mood during adulthood through two opposite pathways: a direct relation between higher treatment intensity and more negative mood; and an indirect relation between higher treatment intensity and less negative mood through lower perceived limitations.

These findings indicate the importance of targeting health-compromising behaviors and negative mood among survivors of childhood ALL. The consequences of engaging in unhealthy habits may be more negative for long-term survivors compared with the general population (Mulhern et al., 1995), and therefore the need for developing programs to change these behaviors among survivors is imperative. The results of this modeling analysis indicate that while survivors who receive more intense treatment may be more at risk for negative psychosocial outcomes, it may be only the subset of these survivors who experience lower educational achievement who are then at risk for engaging in health-compromising behaviors. Thus, survivors with lower educational achievement may need to be exposed to additional information about the likelihood and severity of potential negative outcomes of their health-compromising behaviors. Survivors receiving more intense treatment could be targeted for educational programs that might not only increase educational achievement, but also provide an environment that would lower the risk of these survivors engaging in health-compromising behaviors.

Notes

1. Two other important age-related variables, date of treatment and age at interview, were initially considered for inclusion in our structural model. However, because they correlate so highly with age at diagnosis (r with date of treatment = −.75; r with age at interview = .47), these variables together with age at diagnosis would have overridden the weight of the other treatment variables (CRT and IT-MTX) in our treatment intensity latent variable. Second, including these other age-related variables would have diminished the theoretical significance of the treatment intensity latent variable. High treatment risk is typically represented by young age at diagnosis and high-dose CRT; date of treatment and age at interview do not represent risk factors for long-term psychosocial outcomes. Because of the high correlation of these two variables with age at diagnosis, readers interested in assessing the relationships between these variables and the other outcomes could substitute either of these variables for age at diagnosis in the final model.
2. We also tested the final structural model with both of the perceived limitations variables labeled as categorical. The combination of goodness-of-fit measures indicated that the model remained a marginally adequate fit [χ^2 (84, N = 510) = 654, $p < .001$, NNFI = .97, CFI = .98, RMSEA = .12].
3. We also conducted a multiple group analysis to test whether path weights were equal for male and female leukemia survivors. With all paths among factors and from factors to measured variables constrained to be equal, the multiple group model revealed an adequate fit [χ^2 (184, N = 251, 259) = 304, $p < .05$, NNFI = .91, CFI = .92, RMSEA < .05]. The Lagrange multiplier test revealed that all constraints of equality between factors were appropriate, but that freeing equality constraints between certain factor to variable paths (mood to depression, and from health-compromising behaviors to alcohol, drug, and cigarette use) would improve the model fit. These results indicate that the pathways among the latent variables do not differ for male and female cancer survivors.
4. Treatment-related variables in this study reflect the fact that CCG protocols changed over time; earlier protocols called for higher doses of CRT, whereas the protocols during the latter years of the study called for more IT-MTX and less CRT. Additionally, the constraints on criteria for study entry (survivors diagnosed between the years of 1970 and 1986, and survivors at least 18 years of age by 1990) forced children diagnosed at less than 6 years of age also to be those diagnosed in earlier years of the study period.
5. The fit of the model using this proposed reversed pathway remained about the same; however, this final model does not reproduce the observed correlations among the latent variables as well.

Appendix

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