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Assessment of Selection Bias in Clinic-Based Populations of Childhood Cancer Survivors:

A Report from the Childhood Cancer Survivor Study

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Abstract

Background—It is not known to what extent prevalence estimates of late effects among childhood cancer survivors derived from clinic based samples represent the actual estimates that would be derived if the entire population of childhood cancer survivors was recruited and evaluated for a particular outcome.

Procedure—In a large retrospective cohort study of childhood cancer survivors, the Childhood Cancer Survivor Study (CCSS), the prevalence of chronic health conditions among participants who reported being seen in a cancer center or long-term follow-up clinic was compared to the prevalence of chronic conditions in the entire cohort.

Results—When compared to survivors who had no medical care in the previous two years, survivors accessing medical follow-up were significantly more likely to have chronic health conditions. Relative risks of reporting a chronic health condition were 1.4 (95% CI 1.3 – 1.5) if seen in a cancer center or long-term follow-up clinic and 1.2 (95% CI 1.1-1.3) if seen in a general medical care setting. Estimates derived from only those childhood cancer survivors who were seen in a cancer center or long term follow-up clinic overestimate the prevalence of any chronic disease by 9.3% (95% CI: 7.0-11.6%).

Conclusions—Applying chronic condition prevalence estimates from a clinical population to the general population of childhood cancer survivors must be undertaken with caution. Survivorship research must maintain a high level of scientific rigor to ensure that results reported in the literature are interpreted within the appropriate context.

INTRODUCTION

Improved cure rates have led to an increasing number of investigations designed to enumerate the prevalence of medical late effects among childhood cancer survivors [1,2]. To establish the rate for specific adverse outcomes, and to provide information to guide medical

follow-up of this population, these observational studies have largely relied on patient populations derived from specific clinical settings [3]. Reports that rely on the evaluation of an existing clinical population of childhood cancer survivors to estimate the prevalence of adverse outcomes may be particularly susceptible to bias because of the potential for differential participation of eligible study participants [4,5]. Deriving estimates from a convenient population, for example, those who regularly return to a long term follow-up clinic, limits the generalizability of the results [6]. Moreover, if individuals with a history of a high-risk exposure (e.g., high cumulative dose of anthracycline), exhibiting symptoms, or receiving care for a previously diagnosed late effect of therapy are more likely to visit the clinic, then the potential exists that the prevalence of adverse outcomes may be artificially inflated [7]. Conversely, it is possible that individuals with sub clinical, or undiagnosed disease, may be less likely to be under ongoing clinical surveillance, resulting in an underestimate of the true prevalence of an adverse outcome.

To better understand the potential impact of selection or surveillance bias on the reported prevalence of chronic disease among long-term survivors of pediatric malignancy, we used data from the Childhood Cancer Survivor Study (CCSS) [8], a cohort of over 14,000 five-year survivors of pediatric cancer. The prevalence of chronic disease among long-term childhood cancer survivors who reported receiving care, in the previous two years, in a cancer center or long-term follow-up clinic was compared to the reported prevalence of chronic disease among survivors who had received no medical care or general medical care (i.e., not within a cancer center or survivorship-specific clinic). Absolute differences between the overall population and those seen in a cancer center or long-term follow-up clinic were calculated to estimate potential bias. We hypothesized that those survivors who reported having received care in a cancer center or long-term follow-up clinic during the two years prior to the questionnaire would have higher chronic disease prevalence estimates.

METHODS

Subject Population

This analysis utilized participants in the CCSS, an epidemiologic study designed to evaluate the impact of childhood cancer and its treatment on long-term outcomes relating to physical and mental health, and quality of life. Details of the criteria for cohort inclusion have been reported previously [8]. Briefly, eligible participants were diagnosed and treated for leukemia, lymphoma, central nervous system malignancies, neuroblastoma, kidney cancer, bone or soft-tissue sarcoma at 26 participating institutions. Participants were diagnosed before the age of 21 years during the time period of 1970-1986 and survived at least five years following their original cancer diagnosis. Treatment-related information, including chemotherapy, surgery and radiation therapies was abstracted from the medical records at the treating institution. All participants, or their parent proxy if under the age of 18 years, completed a 289-item baseline questionnaire at study entry (1994-1996). Three subsequent follow-up questionnaires have been completed in 2000, 2003, and 2005. Study questionnaires are available for review and downloading at www.stjude.org/ccss. The current analysis is based upon the 9307 survivors who were alive and who completed both the baseline and the 2003 follow-up survey.

Chronic disease status

Chronic disease status was classified using data from the baseline questionnaire, applying the methods previously described by Oeffinger et al. [9] and scored by applying the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 3 [10]. CTCAEv3 was developed to grade the severity of both acute and long-term outcomes for both pediatric and adult cancer patients. Severity of each chronic health condition was

scored into one of five categories: grade 1 - mild; grade 2 - moderate; grade 3 - severe; grade 4 - life-threatening or disabling; and grade 5 - death. For these analysis, chronic disease prevalence was assessed in three groupings: any condition (grade 1-4), severe or life-threatening conditions (grade 3 or 4), and multiple conditions (≥ 2 conditions). In addition, we also examined prevalence proportions for specific chronic conditions, including cardiovascular, endocrine and neurological. Participants were classified as having a cardiovascular, endocrine or neurological condition if they reported ever having been told by a health care professional that they had one of the category specific health outcomes listed in Figure 2.

Medical contact status

Using information provided by participants on the 2003 follow-up survey, cohort members were classified according to their contact with medical professionals in the previous two years. Each participant was assigned to one of the following three groups: (1) Received any care in a cancer center or long-term follow-up clinic, (2) Received general medical care, defined as care delivered by a physician or nurse but not within a cancer center or long-term follow-up clinic for cancer survivors, or (3) No contact with a physician or nurse in the previous to two years.

Data analyses

The prevalence of chronic conditions in each of the three groupings, and in specific categories, was calculated among survivors according to their medical contact status. Prevalence proportions were also stratified by time since the original cancer diagnosis and each cancer type. Age at diagnosis and exposure to radiation or specific treatment modalities were not included in these analyses, both to simplify the presentation of the results, and because, in this large cohort, they are collinear to both cancer type and time since diagnosis. The relative risks of having a chronic condition were calculated for each condition grouping using generalized linear regression models with a binomial distribution and a log link, adjusted for time since diagnosis and cancer type. To evaluate potential over or underestimation of prevalence rates among populations of patients seen at a cancer center or long-term follow-up clinic, we calculated the absolute difference between the prevalence of each chronic disease outcome among those participants who were seen in a cancer center or long term follow-up clinic and the prevalence of each chronic disease outcome for the entire group of survivors. Differences between chronic disease outcome proportions among the survivors who visited a cancer center or long-term follow-up clinic and the total survivor group were compared with a binomial test, and are reported with 95% confidence intervals and exact p-values [11,12]. We derived a modified confidence interval to account for the fact that the clinic visitors are a subgroup of the total population. These were obtained by multiplying the endpoints of the confidence interval for the difference between subjects who did and did not visit the clinics by the proportion of subjects who did not visit a cancer center or long term follow-up clinic (derivation shown in Appendix A).

RESULTS

Characteristics of the 9307 long-term survivors (mean time from diagnosis of 23 years, range 15-35) included in this analysis are provided in Table I. The proportions of survivors with chronic conditions according to medical contact status are provided in Table II. Overall, the prevalence of chronic conditions increases across the levels of medical care, with 69.1% of those seen in a cancer center or long term follow-up clinic reporting any chronic condition, compared to 59.9% of those who received general medical care and 48.7% of those who received no medical care (test for trend $p < 0.001$). This pattern persists for having two or more chronic health conditions, as well as when restricted to the

prevalence of more severe conditions, with 31.3% of those seen in a cancer center or long term follow-up clinic reporting any grade 3-4 chronic condition, compared to 24.3% of those who received general medical care and 18.0% of those who received no medical care (test for trend $p < 0.001$). Time since diagnosis and cancer type did influence the magnitude of the estimated differences. The differences between the prevalence of chronic conditions among those reporting care in a cancer center or long term follow-up clinic during the two years was greatest among those 20 or more years since diagnosis ($p < 0.001$). An initial diagnosis of CNS tumor, soft tissue sarcoma, non-Hodgkin's lymphoma and Wilms tumor were associated with larger percent differences for grade 3-4 chronic and/or two or more chronic conditions (all p -values < 0.001).

The comparison of the proportion of survivors with endocrine, cardiac or neurological chronic health conditions according to medical contact status yielded similar results. Again, those who received care at a cancer center or long term follow-up clinic were more likely to have a prevalent endocrine, cardiac or neurological chronic condition than those who received general medical care or no medical care. Endocrine conditions were reported in 9.6% of those who received care at a cancer center or long term follow-up clinic, 6.4% of those who received general medical care and 2.6% of those who received no medical care in the two years prior to questionnaire completion. Corresponding proportions for cardiac chronic conditions were 3.1%, 2.8%, and 2.0%. For neurological chronic conditions the proportions were 4.3%, 3.1%, and 2.1%.

The prevalence percentages and relative risks of having any chronic condition, a grade 3-4 chronic condition or more than two chronic conditions, adjusted for time since diagnosis and cancer type are shown in Figure 1, comparing those who received care in a cancer center or long-term follow-up clinic and those who received general medical care to those who received no medical care. Cancer survivors who received general medical care were 1.2 (95% CI: 1.1-1.3) times more likely to have any chronic condition, 1.2 (95% CI: 1.1-1.4) times more likely to have a grade 3 or 4 chronic condition and 1.4 (95% CI: 1.2-1.5) times more likely to have multiple chronic conditions than those who reported no medical care. Those seen in a cancer center or long term follow-up clinic were 1.4 (95% CI: 1.3-1.5) more likely to report any chronic condition, 1.6 (95% CI: 1.4-1.8) times more likely to report a grade 3-4 chronic condition and 1.8 (95% CI: 1.6-2.0) times more likely to report multiple chronic conditions than those who received no medical care.

Table III shows the absolute differences between the prevalence of each chronic condition outcome in the entire CCSS survivor group and the group of survivors who were seen in a cancer center or long term follow-up clinic during the previous two years. The absolute differences between the prevalence of any chronic condition, any grade 3-4 chronic condition, and two or more chronic conditions between the entire group of survivors and those who received care in a cancer center or long term follow-up clinic were 9.3% (95% CI: 7.0-11.6%), 6.8% (95% CI: 4.5-9.1%) and 10.3% (95% CI 7.8-12.8%), respectively.

DISCUSSION

This evaluation clearly demonstrates that the prevalence of chronic conditions among long-term childhood cancer survivors may be over estimated by as much as 10% if a study includes only participants seen in the setting of a cancer center or long term follow-up clinic for cancer survivors. This overestimation was seen for overall and category specific (endocrine, cardiac and neurological) chronic conditions. In addition, the observed difference in prevalence increases as time from diagnosis increases, and can vary substantially by cancer type. While there has been general agreement that clinically-based populations in the setting of childhood cancer survivors can not automatically be considered

representative of the larger population of cancer survivors, this is the first study to directly assess the frequency and magnitude of the selection that is present for overall chronic health conditions in very long-term survivors of childhood cancer.

There are examples of how clinically-based convenience samples may differ with regard to disease prevalence estimates among the general populations. Eustache et al. [13] evaluated selection bias in a study of reproductive health among three groups of male partners of pregnant women. They reported that those who agreed to give a semen sample were more likely than those who only filled out a questionnaire to have taken longer than twelve months to conceive (9.7% vs. 5.0%), and that the two groups who participated at any level were more likely than the general population to have a history of urogenital disease (8.8% versus 1-2%). In another study, Uter et al. [14] compared the prevalence of contact allergies between a clinic population and the general population and found a higher prevalence of contact allergies among the clinic population (48% versus 28%). Both of these investigations, like ours, reported that bias resulted in an inflated estimate of disease prevalence.

There are also examples of how disease co-morbidities and disease severities differ among clinic populations when compared to community populations with the same underlying diagnoses. Wilfley et al.[15] compared a clinic sample to a community sample of individuals with binge eating disorders and found that members of the clinic sample were more likely to have social adjustment problems than the community sample, and that their primary eating disorders were more severe than the eating disorders of the community sample. Similarly, Bak et al.[16] demonstrated that hospitalized people with schizophrenia were shown to have different patterns of co-morbid psychopathology from those who were assessed outside the hospital, potentially leading to an overestimation of the more florid features of psychosis in the overall population of individuals with schizophrenia. The survivors in our study who reported receiving either general medical care, or care in a cancer center or long term follow-up clinic, in the two years prior to questionnaire completion, were more likely to have chronic conditions (comorbidities) in general, of greater severity, and in combination when compared to those who reported no medical care, even when the survivors had similar underlying cancer diagnoses.

Studies designed to evaluate the prevalence of chronic conditions among childhood cancer survivors should include an appropriate sample of the target population. In order to document the most unbiased disease estimates, it is important that investigators first recognize the potential for introduction of bias, and then use rigorous and diligent recruitment strategies when enumerating the prevalence of medical late effects in clinical populations of childhood cancer survivors. In real practice, not every eligible case will be successfully recruited and studied. [17] Thus, regardless of the participation rate, it is essential to conduct analyses to characterize and estimate the potential degree of bias that may be introduced [18]. At a minimum, direct comparison of known characteristics of participants and non-participants on those measures likely to be associated with either the exposure or the outcome of interest should be carried out. This requires that the initial study design should take into consideration the need to characterize participants and non-participants, which will often require collection of additional data on the eligible population.

The literature contains numerous reports of long-term outcomes among survivors of childhood cancer derived from clinical series utilizing data that are either prospectively collected or retrospectively abstracted from existing medical records. Because both of these approaches are subject to selection bias, it is essential that interpretation of the rates of conditions resulting from these research studies be carefully considered. The multitude of quantifiable and non-quantifiable factors that determine where, when and why a given

patient is seen make each clinical series unique. Our results suggest that caution must be used when extrapolating the results to any broader population.

The data utilized in the current report were derived from the CCSS cohort. It is important to recognize and acknowledge that the CCSS cohort is also subject to potential selection bias. The underlying assumptions of our analyses are that the CCSS study participants who reported having a cancer clinic visit in the previous two years are a valid representation of the larger survivorship clinic population, and that those who reported no such cancer clinic visit are a proportionately valid representation of the larger survivorship non-clinic population. With approximately 30% of the eligible CCSS population not participating in the study due to lost to follow-up or declining the invitation to participate, it is possible, if not likely, that the study participants reflected a selected group. While extensive efforts have been made to characterize participants and non-participants with regard to demographic factors, cancer-related characteristics including treatment exposures [8,17], one might anticipate that observed rates of chronic health conditions do not reflect the true rates within the broader survivor population. If one assumes that CCSS participants may be biased toward those with a higher rate of chronic health conditions (i.e., those not experiencing late effects of therapy are less likely to participate in research and be under active medical care within a cancer center or long-term follow-up program than those who are not experiencing adverse late effects), then our observed estimate of approximately 10% would reflect a conservative figure.

The proportion of visits to long-term follow-up clinics among non-participants in the CCSS cohort is not known. However, among those who were alive and completed the baseline survey, but who did not participate in the 2003 follow-up questionnaire (non-responders), chronic condition status is available, because this was measured at baseline. Table IV shows a series of two by two tables that demonstrate the effect of extremes of differential participation bias on our unadjusted observed estimate (that survivors seen in long term follow-up clinics are 1.7 times more likely than those who do not seek medical care to have chronic condition). For simplicity, only participants who were seen in long term follow-up clinic or who received no medical care were included in this example (N=2425). If all non-responders with grade 3-4 chronic disease were seen in long-term follow-up clinics and all non-responders without grade 3-4 chronic disease in this cohort received no medical care, the risk ratio we observed would greatly underestimate the prevalence of grade 3-4 chronic conditions (RR: 10.3 vs. 1.7). Conversely, at the other extreme, if all of the non-responders with grade 3-4 chronic disease received no medical care, and all of the non-responders without grade 3-4 chronic disease were seen in long-term follow-up clinics, the risk ratio we observed (1.7) would greatly overestimate the prevalence of grade 3-4 chronic conditions.

These extremes are unlikely. Three other scenarios are more likely. The first, shown in the fourth panel of Table IV demonstrates that non-differential participation (in terms of long-term follow-up clinic visits) would have biased the risk ratio toward the null. The second, shown in the fifth panel of Table IV, demonstrates that if CCSS participants with chronic conditions were more likely to have been seen in long-term follow-up clinic than non-responders (that is, if the twice yearly newsletter from the study encouraged them to seek medical attention), our estimate of the association between grade 3-4 chronic conditions and visits to the long-term follow-up clinic would be higher than the true estimate among all childhood cancer survivors. Finally, as shown in the sixth panel of Table IV, if non-responders with grade 3-4 chronic conditions visit the long term follow-up clinic at a higher rate than the CCSS participants (i.e., if the really sick survivors dropped out of the cohort because participation was a burden), our estimate of the association between grade 3-4 chronic conditions would underestimate the association between grade 3-4 chronic conditions and visits to the long term-follow-up clinic.

Our analyses also assume that there is no misclassification in the reporting of the type of medical care sought during the previous two years. Some respondents who reported grade 3 or 4 chronic conditions between 1994-1996 reported receiving no medical care from 2001-2003 which may seem suspect. However, the largest proportions of survivors in this category (Table II) were bone and brain tumor survivors, where an amputation is classified with a grade 3 severity, and severe cognitive loss with a grade 4 severity. Long term survivors with a disability that can not be re-mediated may not seek frequent medical intervention.

We undertook these analyses to document that selection bias does exist when relying upon survivors who are active within clinically-based follow-up. Survivorship research must maintain a high level of scientific rigor to ensure that results reported in the literature are interpreted within the appropriate context. The ultimate objective of this research is to provide an accurate evidence-base on which to make recommendations for follow-up and screening of those successfully treated for their cancer [19,20], and form the basis for the design and testing of intervention-based research. If clinically-based series are heavily influenced by selection-bias, then recommendations derived from these investigations will not provide accurate information for risk based monitoring.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Prevalence of chronic conditions by contact in the medical system in the 2 years prior to survey completion and relative risks of having a chronic condition comparing those who received either general medical care or care in a cancer center or long term follow-up clinic to those who did not receive care.

*Relative risks adjusted for time since diagnosis and cancer type

Table I

Specific chronic conditions

Grade	Cardiovascular Condition	Neurological Condition	Endocrine Condition
1	<ul style="list-style-type: none"> Cardiovascular Dysrhythmia, not on medication Hypertension, not on medication Lipid disorder, unspecified Valvular disease, unspecified Heart disease, unspecified Other disorders of circulatory system Cardiomyopathy, not on medication Dysrhythmia, on medication 	<ul style="list-style-type: none"> Seizure disorder, not on medication Problems with balance/vertigo Disturbance in coordination Tremors Weakness in legs, mild limitation Weakness in arms, mild limitations Facial nerve palsy Decreased or prolonged sense of touch or feeling in hands, fingers, arms or back Other disturbance of skin sensation Phantom limb pain Other conditions of brain Other nervous system disorders 	<ul style="list-style-type: none"> Hypothyroidism, not on medication Diabetes, not on medication Disorder of the pituitary, unspecified Ovarian hypofunction, not on medication Testicular hypofunction, not on medication Unspecified endocrine disorder
2	<ul style="list-style-type: none"> Hypertension, on medication Aortic valve disorder Mitral valve disorder Raynaud's syndrome Lymphedema, other 	<ul style="list-style-type: none"> Seizure disorder, on medication Weakness in legs, moderate limitation Monoplegia, unspecified Obstructive hydrocephalus Other disorders of central nervous system 	<ul style="list-style-type: none"> Hypothyroidism, on medication Thyroid nodules, not requiring surgery Diabetes, on oral medication Growth hormone deficiency Osteoporosis
3	<ul style="list-style-type: none"> Coronary artery disease, on medication Congestive heart failure, on medication Atrial fibrillation or flutter Supraventricular dysrhythmia Hypotension 	<ul style="list-style-type: none"> Facial/cranial nerve paralysis Paralysis of vocal cords Neurogenic bowel 	<ul style="list-style-type: none"> Hyperthyroidism Thyroid nodules, requiring thyroidectomy Diabetes, on insulin Ovarian failure, on estrogen replacement Testicular failure, on testosterone replacement Panhypopituitarism Diabetes insipidus Corticoadrenal insufficiency
4	<ul style="list-style-type: none"> Myocardial infarction Heart transplant for cardiomyopathy Cerebrovascular accident Endocarditis Cardiac arrest 	<ul style="list-style-type: none"> Cognitive deficit, severe Intracranial abscess Symptomatic torsion dystonia Monoplegia of lower limb Diplegia of upper limbs 	

Grade	Cardiovascular Condition	Neurological Condition	Endocrine Condition
	<ul style="list-style-type: none">Arterial embolism	<ul style="list-style-type: none">HemiplegiaParaplegiaQuadriplegiaOther specified paralytic syndromesParalysis, unspecified	

Table II

Study population

	Contact with the medical system in the 2 years prior to survey completion			
	Total N=9307 N (%)	No medical care N=1124 N (%)	General medical care N=6872 N (%)	Care at cancer center/ LTFU clinic N=1311 N (%)
Time since diagnosis				
15-19 years	2588 (27.8)	328 (29.2)	1792 (26.1)	468 (35.7)
20-24 years	3294 (35.4)	385 (34.2)	2471 (36.0)	438 (33.4)
25 + years	3425 (37.8)	411 (36.5)	2609 (37.9)	405 (30.9)
Cancer type				
Leukemia	3166 (34.0)	450 (40.0)	2284 (33.2)	432 (32.9)
CNS Malignancy	1176 (12.6)	136 (12.1)	909 (13.2)	131 (9.9)
Hodgkin Lymphoma	1187 (12.8)	90 (8.0)	834 (12.1)	263 (20.1)
Non-Hodgkin Lymphoma	701 (8.5)	85 (7.6)	533 (7.8)	83 (6.3)
Wilms Tumor	869 (9.3)	103 (9.2)	660 (9.6)	106 (8.1)
Neuroblastoma	628 (6.7)	89 (7.9)	459 (6.7)	80 (6.1)
Soft Tissue Sarcoma	819 (8.8)	96 (8.5)	607 (8.8)	116 (8.8)
Bone Malignancy	761 (8.2)	75 (6.7)	586 (7.0)	100 (7.6)

Table III

Percentages of chronic conditions among childhood cancer survivor overall, by time since diagnosis and by cancer type

	Any grade 1 through 4 chronic condition			Any grade 3 or 4 chronic condition			Two or more chronic conditions		
	No medical care %	General medical care %	Care at cancer center/LTFU clinic %	No medical care %	General medical care %	Care at cancer center/LTFU clinic %	No medical care %	General medical care %	Care at cancer center/LTFU clinic %
All survivors	48.7	59.9	69.1	18.0	24.3	31.3	24.3	34.7	45.2
Time since diagnosis									
15-19 years	45.7	56.1	63.9	17.7	20.5	23.3	23.2	31.1	42.7
20-24 years	48.8	56.8	69.4	17.1	22.2	33.6	25.7	32.9	42.0
25 + years	50.9	65.4	74.8	19.0	28.9	38.3	23.8	39.1	51.6
Cancer type									
Leukemia	42.0	47.7	56.9	10.9	13.6	16.7	17.8	24.7	33.8
CNS Malignancy	62.5	79.8	88.6	28.7	34.3	48.9	42.7	59.9	80.2
Hodgkin Lymphoma	53.3	71.5	79.5	24.4	29.6	37.3	37.8	42.6	50.2
Non-Hodgkin Lymphoma	40.0	55.7	67.5	9.4	21.8	25.3	15.3	27.0	39.8
Wilms Tumor	35.0	44.1	56.6	9.7	13.8	22.6	14.7	21.1	28.3
Neuroblastoma	56.2	55.6	62.5	14.6	16.6	28.8	23.6	30.0	38.8
Soft Tissue Sarcoma	56.2	62.9	75.9	24.0	28.0	40.5	32.3	36.6	51.7
Bone Malignancy	68.0	81.6	81.0	50.7	59.7	62.0	28.0	49.0	56.0

Percent differences between chronic condition prevalence among childhood cancer survivors seen in a long term follow-up clinic or cancer center and the overall prevalence of chronic conditions in the childhood cancer survivor cohort

Table IV

	Any grade 1-4 chronic condition			Any grade 3-4 chronic condition			2 or more chronic conditions		
	% D	95% CI	p	% D	95% CI	p	% D	95% CI	p
All Survivors	9.3	(7.0-11.6)	<0.001	6.8	(4.5-9.1)	<0.001	10.3	(7.8-12.8)	<0.001
Time since diagnosis									
15-19 years	7.7	(3.7-11.6)	<0.001	2.6	(-0.8-6.1)	0.12	10.6	(6.5-14.6)	<0.001
20-24 years	11.9	(7.8-15.9)	<0.001	10.4	(6.4-14.5)	<0.001	8.8	(4.5-13.0)	<0.001
25+ years	10.1	(6.1-14.1)	<0.001	9.4	(5.0-13.8)	<0.001	12.9	(8.3-17.4)	<0.001
Cancer type									
Leukemia	8.8	(4.4-13.1)	<0.001	3.0	(-0.2-6.3)	0.05	8.9	(4.8-13.0)	<0.001
CNS Tumors	9.8	(4.5-15.2)	0.003	13.6	(5.6-21.6)	0.001	20.0	(13.4-26.7)	<0.001
Hodgkin Lymphoma	7.6	(3.2-12.1)	0.002	6.3	(1.3-11.4)	0.01	6.3	(0.9-11.6)	0.02
Non-Hodgkin Lymphoma	12.3	(2.7-21.8)	0.02	4.6	(-4.1-13.3)	0.27	12.7	(2.9-22.4)	0.006
Wilms tumor	12.1	(3.2-20.9)	0.008	8.3	(1.0-15.6)	0.01	7.0	(-0.9-15.0)	0.06
Neuroblastoma	6.0	(-4.0-15.9)	0.25	11.0	(1.9-20.0)	0.006	9.3	(-0.6-19.2)	0.06
Soft Tissue Sarcoma	11.9	(4.5-19.2)	0.004	11.2	(3.0-19.4)	0.004	13.5	(5.1-21.9)	0.001
Bone Malignancy	0.8	(-6.3-8.0)	0.82	3.0	(-5.9-11.9)	0.51	8.2	(-0.9-17.2)	0.08

p = p-value; %D = percent difference; CI = confidence interval

Table V

Potential bias in results due to non-participation

1) Observed association: *between visit to a long-term follow-up clinic and grade 3-4 chronic condition*

		Grade 3-4 Chronic Condition		Risk Ratio = $\frac{411 / (900 + 411)}{202 / (202 + 922)} = 1.7$
		Yes	No	
Long-term follow-up clinic	Yes	411	900	
	No	202	922	
		613	1822	
Non-participants		+695	+2636	
Marginals for bias estimates		1308	4458	

2) Extreme one: *All non-responders with chronic condition (N=695) visited long-term follow-up clinic, all those without chronic condition (N=2636) did not visit long term follow-up clinic*

		Grade 3-4 Chronic Condition		Risk Ratio = $\frac{1106 / (1106 + 900)}{202 / (202 + 3558)} = 10.3$
		Yes	No	
Long-term follow-up clinic	Yes	1106	900	
	No	202	3558	
		1308	4458	

3) Extreme two: *No non-responders with chronic conditions (N=695) visited long-term follow-up clinic, all without chronic condition (N=2636) visited long term follow-up clinic*

		Grade 3-4 Chronic Condition		Risk Ratio = $\frac{411 / (411 + 3536)}{897 / (897 + 922)} = 0.2$
		Yes	No	
Long-term follow-up clinic	Yes	411	3536	
	No	897	922	
		1308	4458	

4) Non-differential participation bias: *50% of non-responders with chronic conditions (N=348/695) visited long term follow-up clinic, 50% of those without chronic condition (N=1318/2636) visited long term follow-up clinic*

		Grade 3-4 Chronic Condition		Risk Ratio = $\frac{759 / (759 + 2218)}{549 / (549 + 2240)} = 1.3$
		Yes	No	
Long-term follow-up clinic	Yes	759	2218	
	No	549	2240	
		1308	4458	

5) Differential participation bias: *non-responders with chronic conditions do not visit long term follow-up clinic as frequently as CCSS participants (because our newsletter alerted our participants to attend), the rate among those without chronic condition as observed: 60% of the non-responders with chronic conditions (N=417/695) visited long term follow-up clinic, 49% of those without chronic condition (N=1292/2636) visited long term follow-up clinic*

		Grade 3-4 Chronic Condition		Risk Ratio = $\frac{828 / (828 + 2192)}{480 / (480 + 2266)} = 1.6$
		Yes	No	
Long-term follow-up clinic	Yes	828	2192	
	No	480	2266	
		1308	4458	

6) Differential participation bias: *non-responders with chronic conditions visit long term follow-up clinic more frequently as CCSS participants (sicker participants dropped out of the cohort because it was a burden), the rate among those without chronic condition as observed: 80% of the non-participants with chronic conditions (N=556/695) visited long term follow-up clinic, 49% of those without chronic condition (N=1292/2636) visited long term follow-up clinic*

		Grade 3-4 Chronic Condition		Risk Ratio = $\frac{967 / (967 + 2192)}{311 / (311 + 2266)} = 2.6$
		Yes	No	
Long-term follow-up clinic	Yes	967	2192	
	No	311	2266	
		1308	4458	