

1 **Adherence to surveillance for second malignant neoplasms and cardiac dysfunction in**
2 **childhood cancer survivors: A Childhood Cancer Survivor Study**

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4 **Authors & Affiliations:**

5 Adam P. Yan MD¹, Yan Chen MSc², Tara O. Henderson MD³, Kevin C. Oeffinger MD⁴, Melissa
6 M. Hudson MD⁵, Todd M. Gibson PhD⁵, Joseph P. Neglia MD⁶, Wendy M. Leisenring ScD⁷,
7 Kirsten K. Ness PhD⁵, Jennifer S. Ford PhD⁸, Leslie L. Robison PhD⁵, Gregory T. Armstrong
8 MD⁵, Yutaka Yasui PhD^{2,5}, Paul C. Nathan MD¹

9
10
11 The Hospital for Sick Children, 555 University Avenue, M5G 2X8, Toronto, ON¹; University of
12 Alberta, 11405 87 Avenue, T6G 1C9, Calgary, AB²; University of Chicago, 5841 Maryland
13 Avenue, 60637, Chicago, IL³; Duke Cancer Institute, 2424 Erwin Drive, 27705, Durham, NC⁴;
14 St. Jude Children's Research Hospital, 262 Danny Thomas Place, 38105, Memphis, TN⁵;
15 University of Minnesota, 2450 Riverside Avenue, 55454, Minneapolis, MN⁶; Fred Hutchinson
16 Cancer Research Center, 1100 Fairview Avenue, 98109, Seattle, WA⁷; Hunter College and the
17 Graduate Center of the City University of New York, 695 Park Avenue, 10065, New York, NY⁸.

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27
28 **Corresponding Author Contact Information:**

29 Dr. Adam Yan
30 Address: The Hospital for Sick Children, 555 University Avenue, Toronto ON, M5G 1X8,
31 Canada
32 Phone Number: 204-807-1685
33 Email Address: adam.yan@sickkids.ca

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47 **ABSTRACT:**

48 **Purpose:** To evaluate childhood cancer survivors' adherence to surveillance protocols for late
49 effects of treatment and to determine the factors impacting adherence.

50

51 **Methods:** Between 2014-2016, 11,337 survivors and 2146 siblings in the Childhood Cancer
52 Survivor Study completed a survey ascertaining adherence to Children's Oncology Group
53 (COG) guidelines for survivors at high-risk of second malignant neoplasms (SMNs) or cardiac
54 dysfunction, and American Cancer Society (ACS) cancer screening guidelines for average risk
55 populations. Adherence rates and factors impacting adherence were analyzed.

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57 **Results:** Median age at diagnosis was seven years (range 0-20.9) and median time from
58 diagnosis was 29 years (range 15-47). Among high-risk survivors, adherence to COG breast,
59 colorectal, skin and cardiac surveillance was 12.6% (95% confidence interval [CI] 10.0-15.3%),
60 37.0% (34.1-39.9%), 22.3% (21.2-23.4%) and 41.4% (40.1-42.7), respectively. Among average-
61 risk survivors, adherence to ACS breast, cervical and colorectal screening was 57.1% (53.2-
62 61.0%), 83.6% (82.7-84.5%) and 68.5% (64.7-72.2%) respectively. 27.0% of survivors and
63 20.0% of primary care providers (PCPs) had a survivor care plan (SCP). For high-risk survivors
64 SCP possession was associated with increased adherence to COG breast (22.3% vs. 8.1%,
65 prevalence ratio (PR) 2.52, CI 1.59-4.01), skin (34.8% vs. 23.0%, PR 1.16, CI 1.01-1.33), and
66 cardiac (67.0% vs. 33.1%, PR 1.73, CI 1.55-1.92) surveillance. For high-risk survivors PCP
67 possession of a SCP was associated only with increased adherence to COG skin cancer
68 surveillance (36.9% vs. 23.2%, PR 1.24, CI 1.08-1.43).

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70 **Conclusion:** Guideline adherence is suboptimal. While survivor SCP possession is associated

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71 with better adherence, few survivors and PCPs have one. New strategies to improve adherence
72 are needed.

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95 **BACKGROUND**

96 Of the 420,000 childhood cancer survivors in the United States,¹ many are at an elevated risk of
97 treatment-related adverse health outcomes such as subsequent malignant neoplasms (SMN) and
98 cardiac dysfunction^{2,3}. Adherence to risk-adapted surveillance for these outcomes can reduce
99 mortality.^{4,5}

100
101 First published in 2003, the *Children's Oncology Group (COG) Long-Term Follow-Up (LTFU)*
102 *Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancer*⁶ recommend SMN
103 and cardiac dysfunction surveillance in survivors at elevated risk for these morbidities. Survivors
104 without an elevated risk are advised to adhere to the American Cancer Society (ACS) guidelines
105 for cancer screening in the general population.⁷ A Childhood Cancer Survivor Study (CCSS)
106 questionnaire⁸ administered between 2002-2003 demonstrated that among 8,347 survivors,
107 46.2%, 11.5%, 26.6% and 28.0% at high risk for breast cancer, colorectal cancer, skin cancer⁵ or
108 cardiac dysfunction (unpublished data Dr. P. Nathan), respectively, received the recommended
109 surveillance. Since then, numerous initiatives have aimed to improve surveillance. In 2006, the
110 Institute of Medicine (IOM) recommended that all childhood cancer survivors receive a
111 survivorship care plan (SCP) that documents cancer treatment-related health risks and the
112 recommended screening and surveillance.⁹ In 2012, the American College of Surgeons
113 Commission on Cancer made SCP provision a requirement for cancer program accreditation.¹⁰ It
114 is now common in pediatric oncology to provide a SCP to patients and their primary care
115 providers (PCPs) at the completion of therapy. While considerable resources have been
116 dedicated to SCP development and distribution, it is unknown if SCPs and other educational
117 efforts have improved guideline adherence. This study's purpose was to assess current adherence
118 to COG and ACS cancer and cardiac surveillance guidelines, and to explore predictors of
119 adherence. We analyzed changes in adherence between 2003 and 2016, and compared survivor

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120 adherence to their siblings, and to general population data from the National Health Interview
121 Survey (NHIS).

122

123 **METHODS**

124 **Participants**

125 The CCSS is a retrospective cohort study with longitudinal follow-up of five-year cancer
126 survivors diagnosed before age 21 between 1970-1999 from 25 North American centers.¹¹ Each
127 site's Institutional Review Board approved the study, and participants provided consent.
128 Eligibility for this analysis was limited to participants (n=11,337) who completed a questionnaire
129 between 2014-2016. The CCSS has completed three trials aimed at increasing cardiac
130 (ECHOS¹²), breast (EMPOWER¹³) and skin (ASK¹⁴) surveillance; participants were excluded
131 from the analysis for the outcome evaluated in that study. Participants who developed a SMN or
132 grade 3-4 (severe to life-threatening) heart failure based on the Common Terminology Criteria
133 for Adverse Events (CTCAE) Version 4.03¹⁵ prior to questionnaire completion were excluded
134 from the analysis for the outcome that they developed.

135

136 **Cancer and cardiac surveillance in high-risk survivors**

137 For survivors at high risk of cardiac dysfunction or breast (females only), colorectal or skin
138 cancer, we assessed adherence to COG's LTFU Guidelines, Version 4.0
139 (www-survivorshipguidelines.org)⁶ published in 2013 (eTables 1 and 2). For cardiac screening,
140 survivors were asked, "When was the last time you had an echocardiogram (ultrasound of the
141 heart to look at the heart muscles and heart valves) or a MUGA scan?". For breast cancer,
142 survivors were asked, "When was the last time you had a mammogram?" and "When was the
143 last time you had a breast MRI?". Both mammogram and breast MRI were recommended, while
144 only mammogram was recommended in the previous guidelines (Version 3.0, 2008). For

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145 colorectal cancer, survivors were asked, “When was the last time you had a sigmoidoscopy, or
146 colonoscopy to view the colon for signs of cancer or other problems?”. For skin cancer survivors
147 were asked “When was the last time you had a skin exam for signs of cancer by a healthcare
148 provider?”. For each investigation, participants selected “never”, “less than 1 year ago”, “1-2
149 years ago”, “more than 2 but less than 5 years ago”, “5 or more years ago”, “I had one but I don’t
150 recall when”, or “I don’t know if I ever had one”. For each guideline, survivors were classified as
151 “adherent” if they completed the test within the period recommended in eTables 1 and 2.

152

153 **Cancer screening in average-risk survivors**

154 Survivors not at high-risk risk for breast or colorectal cancer are advised to adhere to ACS
155 screening recommendations (eTable 3) for the general (average risk) population.⁷ We assessed
156 ACS guideline adherence among survivors at average risk of developing colorectal, breast
157 (females only) and cervical (females only) cancer. Adherence was compared to a sex-, race- and
158 age-adjusted cohort of siblings, and to age and race matched aggregate population data from the
159 2015 NHIS,¹⁶ a cross-sectional survey of American health status and healthcare utilization.

160

161 **Predictors of screening and surveillance**

162 Sociodemographic data and surveillance practices were captured in the questionnaire while
163 cancer and treatment data was extracted from medical records. SCP receipt by the survivor and
164 PCP was reported by the survivor. Survivors were defined as not having a SCP if they answered
165 “no” when asked, “Do you currently have a cancer survivorship care plan and/or a summary of
166 treatment for your cancer?”. PCPs were defined as not having a SCP if the survivor answered
167 “no” or “I don’t have a primary care doctor” when asked, “Does your local or primary care
168 doctor have a copy of your cancer survivorship care plan and/or a summary of your treatment for
169 your cancer?”. Chronic health conditions were classified using the CTCAE Version 4.03.¹⁵

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170 Adverse health status was determined using six previously defined domains (general health,
171 mental health, cancer-related pain, cancer-related anxiety, functional status, and activity
172 limitations).¹⁷⁻¹⁹ Cigarette and alcohol use were also analyzed.^{20,21} Siblings were asked the same
173 questions except for those addressing cancer-related pain and anxiety.

174

175 **Change in adherence to breast, colorectal and cardiac surveillance over time**

176 To assess changes in adherence to COG guidelines between questionnaires from 2002-2003,
177 2007-2009 and 2014-2016, survivors at high-risk of a given outcome (eTable 1 and 2) were
178 identified at each time point. Using the COG guidelines current at the time of each
179 questionnaire, survivors were classified as adherent to breast, colorectal and cardiac surveillance
180 if they completed the recommended surveillance for that outcome within the recommended time.
181 Changes in skin surveillance adherence were not assessed as prior questionnaires did not assess
182 this outcome.

183

184 **Statistical analysis**

185 Descriptive statistics were calculated for risk group assignment, demographic, disease, and
186 health status variables. Adherence was reported as percentages. Adherence was compared
187 between survivors and the general population using the Wald-test. Survivors' adherence between
188 questionnaires and to siblings was compared using a log binomial regression model. The
189 Generalized Estimating Equation was used to account for potential within-family correlation of
190 survivors and siblings and correlation of multiple measurements within same survivor. The
191 prevalence ratio (PR) for adherence was estimated for each demographic and health status
192 variable and compared in multivariable regression models. Variables with a p-value <0.2 in the
193 univariate analysis were included in the multivariable analysis. Due to the small sample size in
194 the high-risk breast analysis, covariates from the univariate analysis were further selected

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195 through backward-elimination. Multivariable analysis results were used to determine predictors
196 of adherence. Independent variable collinearity was evaluated by examining variance inflation
197 factors and tolerance. Sampling weights were used to account for under-sampling of acute
198 lymphoblastic leukemia survivors. Variables that were highly correlated were not included in the
199 same model. Analysis was completed with SAS Version 9.4.

200

201 **RESULTS:**

202 **Cohort characteristics**

203 Of the 18,043 survivors in the CCSS cohort, 11,337 (62.8%; 5916 female) completed the
204 questionnaire, along with 2146 (1245 female) siblings. Table 1 displays demographic, disease,
205 and treatment data and eTable 4 displays health status data. Median age at primary cancer
206 diagnosis was seven years (range 0-20.9) and time from primary diagnosis to questionnaire
207 completion was 29 years (range 15-47). SCP possession was reported by 27% of survivors, and
208 20% reported PCP possession of their SCP. No differences existed in SCP possession by sex.
209 Compared to survivors treated between 1970-1979, survivors treated between 1980-1989 (PR
210 1.11, 95% confidence interval [CI] 1.00-1.23, $p=0.043$), and 1990-1999 (PR 1.32, CI 1.16-1.49,
211 $p<0.001$) were more likely to have a SCP. ECHOS¹² (n=398), ASK¹⁴ (n=728) and EMPOWER¹³
212 (n=162) participants were excluded from the cardiac, skin, and breast analyses respectively.
213 Non-responders were more likely to be male, younger at diagnosis and have had leukemia
214 (eTable 5).

215

216 **Cancer and cardiac surveillance in high-risk survivors**

217 There were 625, 1070, 5125 and 4220 survivors at high risk for developing breast cancer,
218 colorectal cancer, skin cancer or cardiac dysfunction respectively (Table 2). Adherence to breast,
219 colorectal, skin and cardiac surveillance was 12.64% (CI 10.0-15.3%), 37.0% (CI 34.1-39.9%),

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220 22.3% (CI 21.2-23.4%) and 41.4% (CI 40.1-42.7) respectively (eFigure 2). In multivariable
221 analyses, survivor-reported SCP possession was associated with increased adherence to breast
222 (22.3% vs. 8.1%, PR 2.52, CI 1.59-4.01), skin (34.8% vs. 23.0%, PR 1.16, CI 1.01-1.33), and
223 cardiac (67.0% vs. 33.1%, PR 1.73, CI 1.55-1.92) surveillance. PCP SCP possession was
224 associated with increased adherence to skin surveillance (39.6% vs. 23.2%, PR 1.24, CI 1.08-
225 1.43). Having a check-up related to past cancer in the past two years (regardless of location or
226 provider) increased breast (PR 7.94 CI 1.99-31.74), skin (PR 1.50, CI 1.28-1.76) and cardiac (PR
227 1.58, CI 1.39-1.80) surveillance. Visiting a doctor more than five times in the past two years
228 increased skin (PR 1.47, CI 1.28-1.69) and cardiac (PR 1.06, CI 0.99-1.14) surveillance. Visiting
229 a special cancer survivorship clinic in the past 2 years increased cardiac surveillance (PR 1.16,
230 CI 1.04-1.30) but visiting a cancer specialist did not increase adherence to any of the guidelines.
231 There were no differences in adherence by sex. Table 3 and eTable 6 show the relationship
232 between other factors and adherence.

233

234 **Change in adherence to breast, colorectal and cardiac surveillance over time**

235 Among high-risk survivors adherence increased from 14.3% to 41.0% ($p < 0.001$) for colorectal
236 and from 22.4% to 38.5% ($p < 0.001$) for cardiac surveillance and decreased from 37.9% to 13.1%
237 ($p < 0.001$) for breast surveillance between 2007 and 2016 (Figure 1).

238

239 **Cancer screening in average-risk survivors**

240 There were 627, 5630 and 596 survivors at average risk for developing breast, cervical or
241 colorectal cancer was respectively (Table 2). Adherence to ACS breast, cervical and colorectal
242 screening was 57.1% (CI 53.2-61.0%), 83.6% (CI 82.7-84.5%) and 68.5% (CI 64.7-72.2%)
243 respectively. In multivariable analyses, survivor SCP possession was not associated with
244 increased adherence to breast, cervical or colorectal screening. PCP SCP possession was

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245 associated with increased adherence to breast (PR 1.28, CI 1.13-1.45) and colorectal (PR 1.12,
246 CI 1.04-1.21) screening. Table 4 and eTable 7 show the relationship between other factors and
247 adherence. Compared to NHIS general population estimates, survivors were more adherent to
248 ACS cervical (PR 1.08, CI 1.07-1.10, $p < 0.001$), and colorectal (PR 1.15, CI 1.09-1.22, $p < 0.001$)
249 screening. Compared to siblings, survivors were less adherent to ACS cervical screening (PR
250 0.95, CI 0.93-0.97, $p < 0.001$) (eFigure 3).

251

252 **DISCUSSION**

253 We evaluated the surveillance and screening practices of 11,337 childhood cancer survivors. In
254 other groups at high risk of malignancy, surveillance decreases mortality^{22,23}, and this is
255 assumed to also be true for at-risk childhood cancer survivors. We demonstrated that less than
256 half of high-risk survivors receive the recommended SMN and cardiac surveillance, which likely
257 exposes them to preventable morbidity/mortality. SCPs are intended to improve adherence by
258 providing follow-up information, and by facilitating the transition from cancer treatment to
259 survivorship and from pediatric to adult care. Despite the IOM's recommendation⁹ and the
260 Commission on Cancer's mandate¹⁰, few survivors and PCPs have a SCP. Survivors treated after
261 1990 were more likely to have a SCP suggesting that dissemination is increasing, potentially due
262 to these recommendations. In 2017 the Commission on Cancer lowered their standard regarding
263 the percentage of survivors that must receive a SCP from 75% to 50%¹⁰ to reflect the reality that
264 many centers lack the resources to comply. A recent systematic review evaluating SCPs
265 concluded that "existing research provides little evidence that SCPs improve health".²⁴ In
266 contrast, SCP possession by high-risk survivors in our analysis was associated with increased
267 breast, skin, and cardiac surveillance. It is uncertain whether SCP possession leads to adherence,
268 or whether SCP possession is a marker of a survivor who is focused on their health and thus
269 likely to adhere to preventative health practices including surveillance.

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271 Despite the current suboptimal adherence to COG guidelines, adherence improved between 2003
272 and 2016. This was most evident for colorectal (14.3% to 41.0%) and cardiac surveillance
273 (22.4% to 38.5%). Reasons for these increases are likely multifactorial. In 2012, only 12% of
274 general internists²⁵ and 9% of family doctors²⁶ felt at least “somewhat familiar” with care
275 guidelines for childhood cancer survivors. Physician awareness of COG guidelines may be
276 increasing as the time from initial publication grows. As the number of patients with SCs
277 increases, PCPs may be becoming more comfortable with SCs. Survivors can receive cancer
278 related care from PCPs or survivorship clinics. Survivorship clinics may be more familiar with
279 guidelines and may provide additional education. In the 2 years preceding the questionnaire,
280 16.1% of survivors attended a survivorship clinic, but attendance only increased cardiac
281 surveillance. Given that survivorship clinics utilize increased resource compared to PCP
282 clinics²⁷, we must reevaluate survivorship care to create cost effective programs that meaningfully
283 impact survivors’ health.

284

285 Our study did not assess barriers to obtaining surveillance tests. ECHOS¹² participants reported
286 not obtaining echocardiograms due to a lack of time, forgetting, a perception that screening is not
287 important, concerns about insurance and cost, and because physicians did not recommend
288 testing. Many survivors report difficulty transitioning from pediatric to adult care.²⁸ Within the
289 two years preceding the survey, 54.7% of survivors had a routine check-up related to their past
290 cancer, and 92.5% had a physician visit, suggesting that survivors receive care, but that
291 surveillance does not consistently occur at these visits. Previously identified psychosocial
292 barriers include poor mental health, lower socioeconomic status, and lower educational level;²⁸
293 we identified variable effects of these factors on adherence. Skin examination adherence was
294 particularly poor (22.3%). Belief in self-capacity to screen, fear of body shaming, fear of facing a

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295 SMN diagnosis, and rejection of the benefit of examination may contribute to the poor uptake of
296 skin examinations. However, given the ease of completing a skin examination, poor uptake
297 suggests a lack of awareness of the need for surveillance, rather than concerns regarding the
298 invasiveness, scheduling or time commitment of the investigation. Patients and PCPs may also
299 find the recommendations overly burdensome given the high frequency of investigations
300 required.

301
302 The CCSS has conducted three trials aimed at increasing surveillance. ECHOS showed that
303 telephone-counseling addressing barriers to surveillance increased echocardiogram adherence.¹²
304 EMPOWER showed that mailed information coupled with motivational telephone interviewing
305 increased mammography but not MRI adherence.¹³ ASK¹⁴ is aimed at increasing skin cancer
306 surveillance and is ongoing. Web-based interventions have successfully altered survivor's
307 physical activity levels and health-related quality of life, and similar platforms exist to enhance
308 late effect awareness and surveillance.²⁹ Further studies utilizing these approaches such as
309 EMPOWER II (ClinicalTrials.gov Identifier: NCT03435380) are underway. These strategies
310 may improve surveillance and the health of survivors; however, scaling them to the larger
311 community of survivors, many of whom are not engaged with survivorship programs, may be
312 difficult.

313
314 There was better adherence to ACS than to COG recommendations with 57.1%, 83.6% and
315 68.5% adherent to ACS breast, cervical and colorectal screening respectively. There may be
316 greater awareness of ACS guidelines as they are population-based guidelines that PCPs utilize
317 more regularly. We found that survivors were less adherent to breast screening than the general
318 population, and less adherent to cervical screening than siblings. This is possibly because
319 survivors avoid testing to escape worrying about the potential of a SMN³⁰.

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321 Our study has several limitations. First, we used self-reported data regarding completion of
322 surveillance and receipt of SCPs. There are no studies assessing the validity of childhood cancer
323 survivors' self-reported screening practices. In other populations, self-reported history of cancer
324 screening has been validated,³¹ suggesting that the same is true for childhood cancer survivors.
325 Many oncologists send SCPs directly to PCPs, which may result in survivors underreporting
326 PCP's SCP possession. Second, when breast surveillance was assessed in 2003, only
327 mammogram was recommended, whereas now both mammogram and breast MRI are
328 recommended, making comparison of change over time difficult. Having to obtain MRIs may
329 explain why adherence dropped by 24.9% between 2003 and 2016. Many females (35.7%) had a
330 MRI or mammogram within the recommended period, but were classified as non-adherent. In a
331 model of adolescent Hodgkin lymphoma survivors, breast cancer mortality at age 75 was 16.3%
332 with mammography, and 15.4% with mammography and MRI, suggesting that having both tests
333 may be unnecessary.⁴ Physicians may not recommend both tests if they feel that completing just
334 one is adequate. It may also be difficult to obtain MRIs. Third, the CCSS regularly corresponds
335 with participants, and this may increase late effect awareness and surveillance compared to the
336 general population of survivors leading to an overestimation of adherence. Adherence may also
337 differ between responders and non-responders (eTable 5). Fourth, survivors who participated in
338 ASK, EMPOWER, or ECHOS were not included in the analysis for the outcome targeted in the
339 study they participated in, but were included in the other analyses. It is possible that a "halo"
340 effect exists, and participating in a study may increase adherence to guidelines not targeted in
341 that study. In addition, adherence may be underestimated due to the use of strict adherence
342 definitions. A survivor who had a test just beyond the recommended time would be classified as
343 non-adherent, yet a short delay in testing is unlikely to adversely affect health outcomes. Finally,

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344 CCSS survivors were treated in the 1970s-1990s and their health habits and adherence may not
345 be representative of survivors treated more recently.

346

347 In summary, we demonstrated that survivors at increased risk of SMNs or cardiac dysfunction
348 report sub-optimal adherence to recommended surveillance for these outcomes. Survivor SCP
349 possession was shown to be generally effective at increasing adherence, however few survivors
350 have a SCP. Greater SCP awareness may improve their value. Few survivors attended
351 specialized survivorship clinics, and attendance did not improve adherence. This data
352 underscores the importance of improving survivorship care including increased SCP
353 dissemination and developing and testing new interventions. Further research assessing barriers
354 to adherence is also needed to assist in developing programs for increasing adherence.

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369 **Table 1^a: Demographic, diagnostic and treatment data of survivors and siblings**

Characteristic:	Survivors (n=11,337)		Siblings (n=2146)	
Sex^b	n	%	n	%
Male	5421	47.8	900	42.0
Female	5916	52.2	1245	58.0
Age at diagnosis				
0-4 years	4300	40.4	N/A	
5-9 years	2530	23.7	N/A	
10-14 years	2541	20.5	N/A	
15-20.9 years	1966	15.4	N/A	
Cancer Diagnosis				
Acute lymphoblastic leukemia	2805	34.0	N/A	
Other leukemia	579	4.5	N/A	
CNS tumor	2000	15.4	N/A	
Hodgkin lymphoma	1380	10.7	N/A	
Non-Hodgkin lymphoma	935	7.2	N/A	
Kidney tumor	1070	8.3	N/A	
Neuroblastoma	844	6.5	N/A	
Soft tissue sarcoma	773	6.0	N/A	
Bone sarcoma	951	7.3	N/A	
Race/ethnicity				
White, Non-Hispanic	9732	85.3	1914	89.2
Black, Non-Hispanic	485	4.4	29	1.4
Hispanic/Latin	525	4.6	61	2.8
Other	595	5.6	142	6.6
Age at questionnaire				
<18 years	65	0.5	5	0.2
18-24 years	848	9.7	51	2.4
25-34 years	3430	34.7	374	17.4
35-39 years	2264	18.3	363	16.9
40-44 years	1796	14.0	357	16.6
≥45 years	2934	22.7	996	46.4
Education^b				
<College	4875	44.1	654	30.5
College graduate	6436	55.9	1492	69.5
Marital Status^b				
Married	5920	51.7	1568	73.9
Single	4070	39.6	340	16.0
Divorced or separated	1040	8.8	213	10.0

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Table 1: Demographic, diagnostic and treatment data of survivor and siblings (continued)

Characteristic:	Survivors (n=11,337)		Siblings (n=2146)	
	n	%	n	%
Household income (\$) ^b				
<20,000	1328	12.9	91	4.5
20,000-59,999	3091	30.2	428	21.2
60,000-99,999	2722	26.6	552	27.4
≥100,000	3090	30.2	945	46.9
Insurance Coverage ^b				
Yes or Canadian	10477	92.6	2045	95.7
No	787	7.4	91	4.3
Employment ^b				
Employed or caring for home	9222	83.6	2027	95.4
Looking for work or unable to work	1880	16.4	97	4.6
Survivor has survivorship care plan				
Yes	2883	27.0	N/A	
No	6627	56.5	N/A	
Missing	1827	16.5	N/A	
Primary care doctor has survivorship care plan or records ^c				
Yes	2255	20.0	N/A	
No	6072	53.5	N/A	
Missing	3010	26.6	N/A	

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Table 2^{a,b}: Risk group assignment of childhood cancer survivors and siblings

Characteristic:	Survivors (n=11,337)		Siblings (n=2146)	
	N	%	N	%
Breast Cancer Risk Group^c:				
COG high risk	625	9.5	N/A	
ACS average risk	627	9.5	469	37.7
Not at risk	3921	71.9	766	61.5
Missing ^d	327	5.1	0	0
Developed breast cancer prior to survey	264	4.1	10	0.8
Colon Cancer Risk Group:				
COG high risk	1070	8.3	N/A	
ACS average risk	596	4.6	491	22.9
Not at risk	9119	82.8	1654	77.1
Missing ^e	500	3.9	0	0
Developed colon cancer prior to survey	52	0.4	1	0.05
Skin Cancer Risk Group:				
COG high risk	5125	45.2	N/A	
Not at risk	4891	49.7	2142	99.8
Missing ^e	525	4.5	0	0
Developed skin cancer prior to survey	68	0.6	4	0.2
Cervical Cancer Risk Group^f:				
ACS average risk	5630	94.1	1216	97.7
Not at Risk	270	5.7	23	1.8
Developed cervical cancer	16	0.3	6	0.5
Cardiac Dysfunction Risk Group:				
COG high risk	4220	43.7	N/A	
1 yearly echo	1359	11.7	N/A	
2 yearly echo	1356	12.1	N/A	
5 yearly echo	1505	19.9	N/A	
Not at risk	5314	44.5	2137	99.6
Missing ^d	1048	8.9	0	0
Had a cardiac event prior to survey	357	2.8	9	0.4

Surveillance adherence in childhood cancer survivors

Table 3^{a,b}: Multivariable analyses of predictors of adherence to COG-recommended surveillance for high-risk survivors

Characteristic:	Breast Cancer^c (n=625 women; adherent 79)		Colon Cancer (n=1070 men and women; adherent 396)		Skin Cancer (n=5125 men and women; adherent 1162)		Cardiac Dysfunction (n=4220 men and women; adherent 1643)	
	PR	CI	PR	CI	PR	CI	PR	CI
Education								
<College school (ref)								
College graduate			0.98	0.83-1.15	1.18 ^d	1.04-1.34 ^d		
Employment								
Employed or caring for home (ref)								
Looking for work or unable to work							0.99	0.88-1.10
Household income (\$)								
60,000-99,999 (ref)								
<20,000					0.75 ^d	0.60-0.94 ^d	1.05	0.96-1.15
20,000-59,999					0.77 ^d	0.66-0.90 ^d	1.00	0.92-1.09
100,000+					1.06	0.93-1.20	1.04	0.97-1.12
Cancer diagnosis								
Leukemia (ref)								
CNS			0.81	0.35-1.90	0.87	0.73-1.04	0.44	0.14-1.37
HD			0.91	0.42-1.98	0.93	0.79-1.09	1.04	0.95-1.14
NHL			1.05	0.47-2.36	0.91	0.73-1.13	0.97	0.87-1.08
Kidney (Wilms)			1.19	0.53-2.66	0.81	0.64-1.02	0.95	0.84-1.06
Neuroblastoma			1.09	0.42-2.85	0.84	0.65-1.09	1.01	0.92-1.11
Soft tissue sarcoma			0.89	0.39-2.02	0.78 ^c	0.62-0.98 ^d	0.76 ^d	0.61-0.94 ^d
Bone cancer			1.11	0.49-2.50	0.59 ^c	0.43-0.81 ^d	0.86 ^d	0.76-0.97 ^d
Insurance coverage								
Yes (ref)								
No			0.74	0.41-1.33	0.57 ^d	0.37-0.87 ^d	0.95	0.81-1.12
Marital Status								
Married (ref)								
Single					1.08	0.94-1.25	1.08	0.98-1.19
Divorced or separated					0.98	0.81-1.19	1.07	0.91-1.25
Age at diagnosis								
0-4 years (ref)								
5-9			1.66 ^d	1.11-2.49 ^d	0.88	0.74-1.04	1.03	0.97-1.11
10-14			2.03 ^d	1.33-3.09 ^d	0.87	0.73-1.04	0.99	0.88-1.11
15-21			2.34 ^d	1.52-3.61 ^d	1.00	0.83-1.20	0.96	0.85-1.10
Era of diagnosis								
1970-1979 (ref)								
1980-1989			0.71 ^d	0.59-0.86 ^d			1.05	0.91-1.20
1990-1999			0.47 ^d	0.28-0.79 ^d			1.09	0.90-1.32

Surveillance adherence in childhood cancer survivors

Table 3^{a,b}: Multivariable analyses of predictors of adherence to COG-recommended surveillance for high-risk survivors (continued)

Characteristic:	Breast Cancer ^c (n=625 women; adherent 79)		Colon Cancer (n=1070 men and women; adherent 396)		Skin Cancer (n=5125 men and women; adherent 1162)		Cardiac Dysfunction (n=4220 men and women; adherent 1643)	
	PR	CI	PR	CI	PR	CI	PR	CI
Highest grade chronic health condition								
No (ref)								
Grade 1,2			1.23	0.86-1.77	1.27 ^d	1.05-1.54 ^d	1.01	0.94-1.08
Grade 3,4			1.43	0.99-2.05	1.35 ^d	1.11-1.64 ^d	1.02	0.94-1.10
Admitted to hospital in the past 12 months								
No (ref)								
Yes					0.96	0.83-1.11	1.06 ^d	1.00-1.12 ^d
Number of physician visits in the past 2 years								
0-4 (ref)								
5-10			1.10	0.91-1.32	1.47 ^d	1.28-1.69 ^d	1.06 ^d	0.99-1.14 ^d
11-20			1.17	0.94-1.46	1.54 ^d	1.30-1.82 ^d	1.11 ^d	1.02-1.19 ^d
More than 20			1.11	0.88-1.40	1.59 ^d	1.28-2.00 ^d	1.12 ^d	1.02-1.23 ^d
Most recent routine check-up related to past cancer								
More than 2 year ago (ref)								
Less than 2 years ago	7.94 ^d	1.99-31.74 ^d	1.14	0.93-1.40	1.50 ^c	1.28-1.76 ^c	1.58 ^d	1.39-1.80 ^d
Last visit with a cancer specialist								
More than 2 year ago (ref)								
Less than 2 years ago								
Last visit to a special clinic for cancer survivors								
More than 2 year ago (ref)								
Less than 2 years ago					1.05	0.93-1.19	1.16 ^d	1.04-1.30 ^d
Survivor has survivorship care plan								
No (ref)								
Yes	2.52 ^d	1.59-4.01 ^d	1.06	0.86-1.30	1.16 ^d	1.006-1.33 ^d	1.73 ^d	1.55-1.92 ^d
Unknown	1.20	0.57-2.51	1.03	0.80-1.32	1.00	0.83-1.21	1.47 ^d	1.29-1.68 ^d
Primary care doctor has survivorship care plan^c								
No (ref)								
Yes			1.08	0.87-1.34	1.24 ^d	1.08-1.43 ^d	1.04	0.97-1.11
Unknown			0.97	0.80-1.18	1.03	0.89-1.18	1.06	0.97-1.15

Surveillance adherence in childhood cancer survivors

Table 4^{a,b}: Multivariable analysis of predictors of adherence to ACS recommended screening for average-risk survivors

Characteristic:	Breast Cancer (n=627 women; adherent 358)		Colon Cancer (n=596 men and women; adherent 408)		Cervical Cancer (n=5630 women; adherent 4714)	
	PR	CI	PR	CI	PR	CI
Education						
<College (ref)						
College graduate	1.04	0.97-1.12	1.06 ^b	1.00-1.13 ^b	1.05 ^c	1.03-1.08 ^c
Employment						
Employed or caring for home (ref)						
Looking for work or unable to work					0.95	0.91-1.00
Household income						
60,000-99,999 (ref)						
<20,000	1.21	0.92-1.60	0.88	0.69-1.11	1.00	0.96-1.04
20,000-59,999	0.93	0.84-1.04	0.96	0.87-1.06	1.00	0.99-1.01
100,000+	0.98	0.91-1.06	0.98	0.93-1.03	1.00	0.99-1.01
Cancer diagnosis						
Leukemia (ref)						
CNS			0.93 ^c	0.87-0.99 ^c	0.97	0.95-1.003
HD			0.90	0.79-1.04	0.99	0.98-1.004
NHL			0.88 ^c	0.78-0.99 ^c	1.00	0.99-1.01
Kidney (Wilms)			1.12 ^c	1.04-1.21 ^c	1.00	0.99-1.01
Neuroblastoma			0.60	0.10-3.55	0.98	0.95-1.01
Soft tissue sarcoma			1.00	0.97-1.03	0.95 ^c	0.90-0.99 ^c
Bone cancer			0.91	0.82-1.01	1.00	0.98-1.01
Insurance coverage						
Yes (ref)						
No	0.58 ^c	0.35-0.97 ^c	0.75	0.48-1.17	0.83 ^c	0.75-0.92 ^c
Marital Status						
Married (ref)						
Single	0.76 ^c	0.62-0.95 ^c	0.94	0.81-1.09	0.98 ^c	0.96-0.99 ^c
Divorced or separated	0.63 ^c	0.50-0.79 ^c	0.98	0.90-1.06	1.00	0.99-1.01
Age at diagnosis						
0-4 years (ref)						
5-9	0.95	0.80-1.11	1.03-1.06	1.00		
10-14	0.93	0.83-1.05	1.10	0.85-1.44	1.00	0.99-1.01
15-21	1.13	0.98-1.30	1.21	0.93-1.58	1.00	0.98-1.01
Era of diagnosis						
1970-1979 (ref)						
1980-1989	0.77 ^b	0.67-0.90 ^b			1.01	0.99-1.03
1990-1999	^e	^e	^e	^e	1.02 ^c	1.00-1.04 ^c

Surveillance adherence in childhood cancer survivors

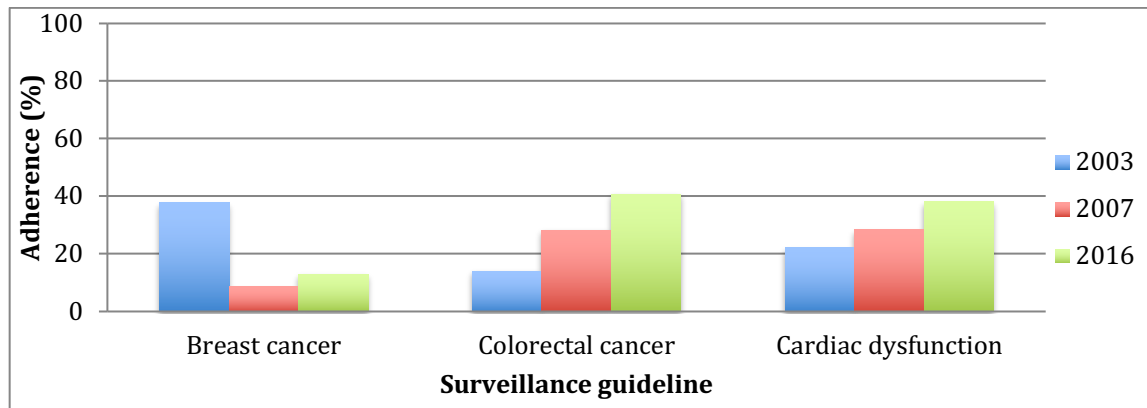
Table 4^{a,b}: Multivariable analysis of predictors of adherence to ACS recommended screening for average-risk survivors (continued)

Characteristic:	Breast Cancer (n=627 women; adherent 358)		Colon Cancer (n=596 men and women; adherent 408)		Cervical Cancer (n=5630 women; adherent 4714)	
	PR	CI	PR	CI	PR	CI
Highest grade chronic health condition						
None (ref)						
Grade 1,2						
Grade 3,4	1.03	0.84-1.26	1.23 ^b	1.05-1.43 ^b	1.00	0.99-1.01
Admitted to hospital in the past 12 months						
No (ref)						
Yes					0.99	0.99-1.00
Number of physician visits in the past 2 years						
0-4 (ref)						
5-10	1.15 ^c	1.03-1.29 ^c	1.22 ^c	1.11-1.35 ^c	1.04 ^c	1.02-1.05 ^c
11-20	1.23 ^c	1.10-1.39 ^c	1.20 ^c	1.08-1.33 ^c	1.03 ^c	1.02-1.05 ^c
More than 20	1.07	0.85-1.35	1.17 ^c	1.05-1.31 ^c	1.04 ^c	1.03-1.06 ^c
Most recent routine check-up related to past cancer						
More than 2 year ago (ref)						
Less than 2 years ago	1.16 ^c	1.07-1.26 ^c			1.01	0.99-1.02
Last visit with a cancer specialist						
More than 2 year ago (ref)						
Less than 2 years ago					0.99	0.99-1.00
Last visit to a special clinic for cancer survivors						
More than 2 year ago (ref)						
Less than 2 years ago			0.93 ^c	0.89-0.98 ^c	1.00	0.99-1.00
Survivor has survivorship care plan						
No (ref)						
Yes	0.94	0.85-1.04	0.92 ^c	0.87-0.98 ^c	1.01	0.99-1.01
Unknown	1.03	0.92-1.15	0.81 ^c	0.68-0.98 ^c	1.00	0.99-1.02
Primary care doctor has survivorship care plan^f						
No (ref)						
Yes	1.28 ^c	1.13-1.45 ^c	1.12 ^c	1.04-1.21 ^c		
Unknown	1.04	0.92-1.17	1.05	0.99-1.11		

Surveillance adherence in childhood cancer survivors

FIGURES

Figure 1: Changes in adherence to the Children’s Oncology Group’s high-risk screening guidelines 2003, 2007 and 2016.



Surveillance adherence in childhood cancer survivors

Table and Figure Captions:

Table 1: Demographic, diagnostic and treatment data of survivor and siblings

^a Sampling weights were used to account for under-sampling of survivors of acute lymphoblastic leukemia.

^b Percentages for individual characteristics calculated on total number of participants providing information for those characteristics

^c Survivor reports that his or her primary care doctor has their survivorship care plan or records

Table 2^a: Risk group assignment of childhood cancer survivors and siblings

^a Sampling weights were used to account for under-sampling of survivors of acute lymphoblastic leukemia.

^b ECHOS participants removed from cardiac dysfunction group, EMPOWER participants removed from breast cancer group, and ASK participants removed from skin cancer group. COG and ACS group assignment are mutually exclusive. Patients in the COG risk group for an outcome were not eligible for inclusion in the ACS risk group for that outcome.

^c Among female survivors only n=5916

^d Unknown risk group as treatment data is missing

COG: Children's Oncology Group, ACS: American Cancer Society

Table 3: Multivariable analysis of predictors of adherence to COG-recommended surveillance for high-risk survivors

^a Variables with a p-value <0.2 in the univariate analysis were included in the multivariable analysis. For the breast cancer high-risk group analysis, due to its small number of breast cancer cases, the selected covariates by the univariate analysis were further selected by a backward-elimination variable selection in the multivariable analysis. All variables with a p-value <0.20 in the univariate analysis were included in the multivariable analysis. Independent variable collinearity was evaluated by examining variance inflation factors and tolerance. Variables that were highly correlated were not included in the same models. The multivariable analysis of colorectal cancer, skin cancer and cardiac dysfunction is adjusted for sex, race, and age at questionnaire and age at diagnosis. The multivariable analysis of breast cancer surveillance is adjusted for race, age at questionnaire and age at diagnosis.

^b Sampling weights were used to account for under-sampling of survivors of acute lymphoblastic leukemia.

^c Breast cancer adherence defined as completing both mammography and breast MRI within the recommended period. In the general population, breast cancer screening was optional for women aged 40-44 so these women were excluded from this analysis.

^d Denotes statistical significance

^e Survivor reports that his or her primary care doctor has their survivorship care plan or records

Ref: Reference, MRI: Magnetic Resonance Imaging, CNS: Central Nervous System, HL: Hodgkin Lymphoma,

NHL: Non-Hodgkin Lymphoma

Surveillance adherence in childhood cancer survivors

Table 4: Multivariable analysis of predictors of adherence to ACS recommended screening for average-risk survivors

^a Sampling weights were used to account for under-sampling of survivors of acute lymphoblastic leukemia.

^b All variables with a p-value <0.20 in the univariate analysis were included in the multivariable analysis.

Independent variable collinearity was evaluated by examining variance inflation factors and tolerance. Variables that were highly correlated were not included in the same models. The multivariable analysis of colorectal cancer, skin cancer and cardiac dysfunction is adjusted for sex, race, age at questionnaire and age at diagnosis. The multivariable analysis of breast cancer surveillance adjusted for race, age at questionnaire and age at diagnosis.

^c Denotes statistical significance

^d No eligible survivors age 0-4 screened for colon cancer so 5-9 used as reference age.

^e No eligible survivors

^f Survivor reports that his or her primary care doctor has their survivorship care plan or records

Ref: Reference, CNS: Central Nervous System, HL: Hodgkin Lymphoma, NHL: Non-Hodgkin Lymphoma

Figure 1: Changes in adherence to the Children's Oncology Group's high-risk screening guidelines 2003, 2007 and 2016.

^a When breast cancer screening was assessed in 2003, 2007 and 2016 there were n=311, n=339, and n=382 eligible survivors at each time point respectively. In 2003, 2007 and 2016, n=118, n=29 and n=50 survivors were adherent to breast cancer screening. Between 2003 and 2016 adherence statistically decreased p<0.001.

^b When colorectal cancer screening was assessed in 2003, 2007 and 2016 there were n=468, n=663, and n=886 eligible survivors at each time point respectively. In 2003, 2007 and 2016, n=67, n=189 and n=363 survivors were adherent to colorectal cancer screening. Between 2003 and 2016 adherence statistically increased p<0.001.

^c When cardiac dysfunction screening was assessed in 2003, 2007 and 2016 there were n=1386, n=1478, and n=1545 eligible survivors at each time point respectively. In 2003, 2007 and 2016, n=310, n=423 and n=594 survivors were adherent to cardiac dysfunction screening. Between 2003 and 2016 adherence statistically increased p<0.001.

Author Contributions:

Adam P. Yan contributed to the conception and design of the study, contributed to the analysis and interpretation of data, and drafted the manuscript. Yan Chen and Yutaka Yasui provided statistical support and critically reviewed the manuscript. Tara O. Henderson, Kevin C. Oeffinger, Melissa M. Hudson, Todd M. Gibson, Joseph P. Neglia, Wendy M. Leisenring, Kirsten K. Ness, Jennifer S. Ford, Leslie L. Robison and Gregory T. Armstrong contributed to the conception and design of the study and critically reviewed the manuscript. Paul C. Nathan was the senior author who contributed to the conception and design of the study, contributed to data interpretation, and critically reviewed the manuscript.

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