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Surveillance after childhood cancer: are survivors with an increased risk for cardiomyopathy regularly followed-up?

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BACKGROUND: We aimed to study adherence to cardiac screening in long-term childhood cancer survivors (CCS) at high risk of cardiomyopathy.

METHODS: This study involved 976 5-year CCS at high risk for cardiomyopathy from the French Childhood Cancer Survivor Study. Determinants of adherence to recommended surveillance were studied using multivariable logistic regression models. Association of attendance to a long-term follow-up (LTFU) visit with completion of an echocardiogram was estimated using a Cox regression model.

RESULTS: Among participants, 32% had an echocardiogram within the 5 previous years. Males (adjusted RR [aRR] 0.71, 95% CI 0.58–0.86), survivors aged 36–49 (aRR 0.79, 95% CI 0.64–0.98), Neuroblastoma (aRR 0.53, 95% CI 0.30–0.91) and CNS tumour survivors (aRR 0.43, 95% CI 0.21–0.89) were less likely to adhere to recommended surveillance. Attendance to an LTFU visit was associated with completion of an echocardiogram in patients who were not previously adherent to recommendations (HR 8.20, 95% CI 5.64–11.93).

CONCLUSIONS: The majority of long-term survivors at high risk of cardiomyopathy did not adhere to the recommended surveillance. Attendance to an LTFU visit greatly enhanced the completion of echocardiograms, but further interventions need to be developed to reach more survivors.

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INTRODUCTION

Over the past decades, advances in treatments have substantially improved childhood cancer survival. In Europe, the 5-year survival rate is over 80% [1]. However, childhood cancer survivors (CCS) have to face a large spectrum of health conditions related to the iatrogenic effects of cancer therapies: the prevalence of severe, disabling, life-threatening, or fatal conditions at age 45 years is 80% [2].

Cardiac mortality is higher among CCS than in the general population. A study including survivors from France and the United Kingdom found that CCS were sixfold more likely to die as a result of cardiac diseases [3]. Anthracyclines and radiation therapy to the heart area are well-known causes of cardiotoxicity, following a dose-dependent pattern [4]. CCS exposed to these treatments had an increased risk of cardiomyopathy and congestive heart failure (CHF) [5–7]. For survivors who have received these treatments above a certain dose, several international guidelines [8–11] recommend the completion of lifelong regular echocardiograms to allow earlier

detection of asymptomatic cardiomyopathy, and thus reduce or delay sequelae by treating it. The recommended frequency of echocardiography ranges from every year to every 5 years, depending on the guideline.

Several studies from the Childhood Cancer Survivor Study (CCSS) have documented the adherence to recommended surveillance in North American CCS at high risk of cardiomyopathy [12–14], showing that only 28% of them reported an echocardiogram within the prior 2 years [12]. Another study from North America followed CCS for an average of 8 years and reported that patients were adherent to cardiac screening recommendations for only 9% of their period of follow-up [13], confirming that the majority of high-risk survivors do not adhere to recommendations.

Increasing adherence to recommended cardiac surveillance in the growing and ageing population of CCS is crucial, but there is limited knowledge about how to enhance it [14]. The effectiveness of interventions such as mailed or web-based health-risk information, motivational telephone counselling, Survivorship Care Plan

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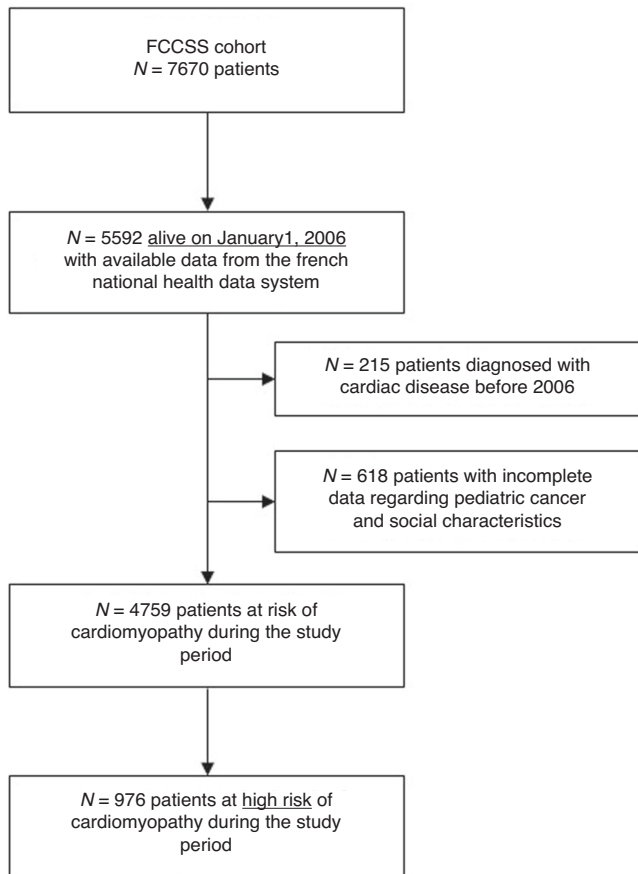


Fig. 1 Flow-chart of the patients from the FCCSS cohort included in the present study. FCCSS French Childhood Cancer Survivor Study.

(SCP), or long-term follow-up clinic attendance is unclear and poorly documented [15], although these interventions are likely to increase adherence to recommended surveillance [16].

In this context, the aim of this work was (1) to describe adherence to recommended surveillance in CCS at high risk of cardiomyopathy, (2) to identify the sociodemographic and clinical predictors of adherence, and (3) to assess whether attending a long-term follow-up visit influences the subsequent completion of an echocardiogram in survivors who were not previously adherent to recommendations.

METHODS

Study design and data source

The FCCSS (French Childhood Cancer Survivor Study) cohort includes 7670 5-year CCS treated before age 18 for a solid malignant tumour or lymphoma in five French centers between 1945 and 2000 [17]. The FCCSS aims to explore the long-term outcomes of children/adolescents treated for solid tumours or lymphoma (for more information, see <https://fccss.fr/?lang=en>).

Data on childhood cancer were extracted from patients' medical records. Data on echocardiograms were obtained through data on outpatient claims and hospital discharge summaries extracted from the French National health data system (SNDS) [18]. These data were available from January 1, 2006, to December 31, 2018. Vital status was obtained from the national registry of causes of death (CépiDC). Second cancers and cardiac diseases (including myocardial infarction, angina, heart failure, valvular diseases, cardiac arrhythmia, conduction disorder, and pericardial disease) were identified using medical records, long-term follow-up visit reports, and data from the SNDS and CépiDC databases. Cardiac disease cases were confirmed by the medical doctors and/or the cardiologists following patients [7].

The FCCSS study was approved by the INSERM Institutional review board (CEEI n°12-077) and the French National Agency regulating Data Protection

(CNIL N°902287). Patients, parents, or guardians' consent was obtained according to national research ethics requirements.

Study population

As of January 1, 2006, 5592 of the 7670 subjects from the FCCSS cohort (72.9%) were still alive and had available data on echocardiograms from the French National Health data system (Fig. 1). Subjects who have been diagnosed with cardiac disease before 2006 ($n = 215$) and those with incomplete data regarding childhood cancer and sociodemographic characteristics ($n = 618$) were excluded. Of the 4759 remaining subjects, the 976 (20.5%) survivors at high risk of cardiomyopathy were included in the present study. Survivors were considered at high risk of cardiomyopathy because of:

- cumulative anthracycline dose >250 mg/m², according to the International Guideline Harmonization Group [8],
- radiation dose ≥ 30 Gy to more than 10% of the left ventricular volume, according to previous findings from the FCCSS cohort [7],
- or cumulative anthracycline dose >100 mg/m² and radiation ≥ 30 Gy to any volume of the left ventricular (Supplementary Fig. S1).

Outcome measure: adherence to recommended surveillance

Recommended surveillance for patients at high risk of cardiomyopathy was at least one echocardiogram every 5 years [8]. Data on echocardiograms were collected from January 1, 2006, to the date of the diagnosis of cardiac disease ($n = 92$), the date of death ($n = 37$), or December 31, 2018 ($n = 847$). Being adherent to recommended surveillance was defined as having an echocardiogram over the last 5 years of the data collection period (Fig. 2), which required that patients had a data collection period of at least 5 years ($n = 930$). Being long-term adherent was defined as receiving an echocardiogram over the last 5 years and another one between 5 and 10 years before the end of the data collection period (Fig. 2), which required that patients had a data collection period of at least 10 years ($n = 873$).

Long-term follow-up (LTFU) visit

Since 2012, FCCSS survivors were contacted to have an LTFU visit. The visit included a medical check-up and a review of the patient's medical history with a specialized clinician, who then informed the patient of the long-term health risks related to treatments received during childhood/adolescence and recommended a cardiac follow-up if necessary. Data on LTFU visits were only available for the patients treated at Gustave Roussy, one of the five cancer centers from which patients were enrolled. Among the 654 patients at high risk of cardiomyopathy from this center that were contacted for LTFU visit; 153 had at least one LTFU visit between 2012 and 2018.

Predictors of adherence to recommended surveillance

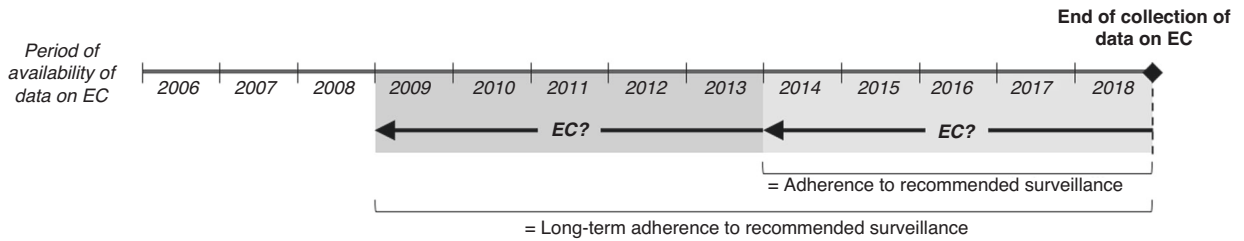
Sociodemographic predictors were sex, age at the end of the data collection period, and level of deprivation estimated using the French deprivation index (FDep). Briefly, FDep was calculated using median household income, percentage of graduates in the population, percentage of blue-collar workers and unemployment rate within the area of the home address [19].

Clinical predictors included childhood cancer type (classified according to the International Classification of Childhood Cancer and divided into 8 categories: Wilms Tumour, neuroblastoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, soft tissue sarcoma, bone sarcoma, CNS tumour, or other solid cancers), age at diagnosis, cumulative anthracycline dose >250 mg/m², Cardiac radiation ≥ 30 Gy to $\geq 10\%$ of the LV volume, and diagnosis of second cancer.

Statistical analysis

First, sociodemographic and childhood cancer characteristics of patients at high risk for cardiomyopathy were described, as well as those of all the patients of the FCCSS. Treatment exposures of patients at high risk for cardiomyopathy were described according to childhood cancer type. The proportion of patients at high risk for cardiomyopathy who were adherent to recommended surveillance, i.e., who had an echocardiogram over the last 5 years of their data collection period, and the proportion of patients at high risk for cardiomyopathy who were long-term adherent to recommended surveillance, i.e., who had two echocardiograms over the last 10 years of their data collection period, were calculated.

- Survivors at high risk of cardiomyopathy who did not die and were not diagnosed with cardiac disease during the period of availability of data ($n = 847$):



- Survivors at high risk of cardiomyopathy who died or were diagnosed with cardiac disease during the period of availability of data ($n = 129$):

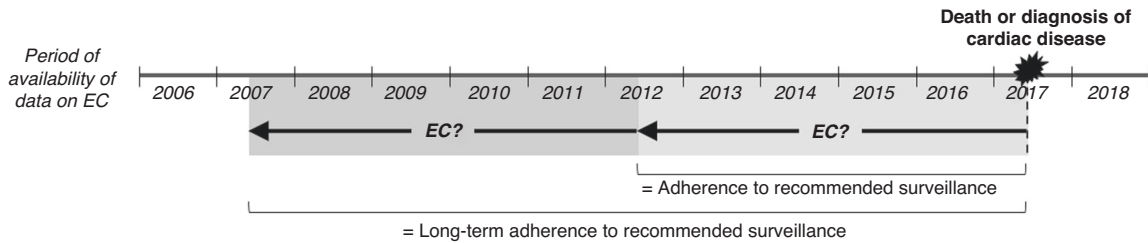


Fig. 2 Definition of adherence and long-term adherence to recommended cardiac surveillance for survivors at high risk of cardiomyopathy. EC echocardiogram.

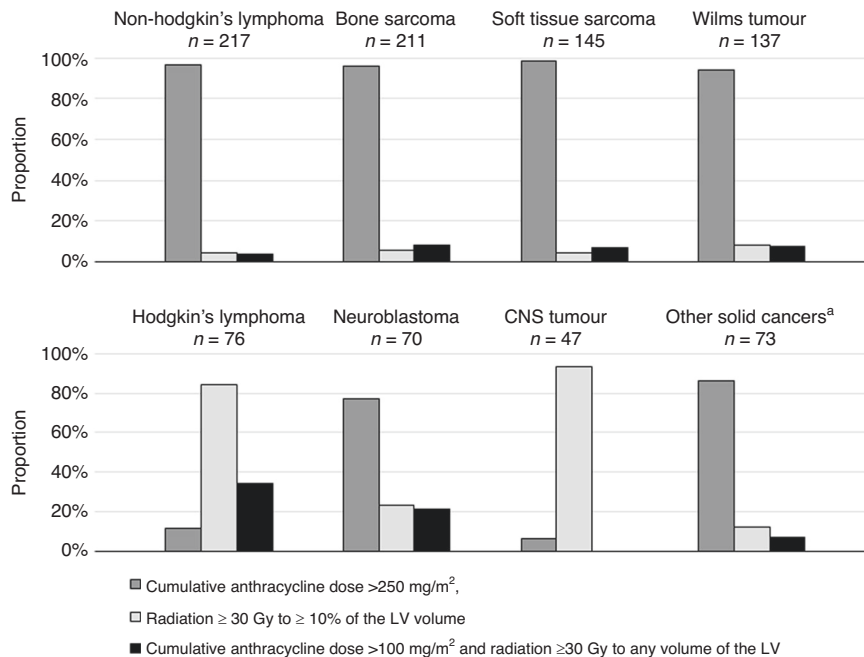


Fig. 3 Description of treatment exposures according to the childhood cancer diagnosed in patients at high risk for cardiomyopathy. CNS central nervous system, LV left ventricular. ^a Gonadal tumour, thyroid tumour, retinoblastoma and other types of carcinoma.

Then, the etiological part of the statistical analysis consisted of two separate analyses:

- Associations between sociodemographic/clinical factors and adherence/long-term adherence to recommended surveillance among patients at high risk for cardiomyopathy were studied using multivariable modified Poisson regression models with robust errors. Using odds ratio estimates from logistic regression would have exaggerated the relative risk (RR) estimates as the prevalence of adherence to recommended surveillance (>30%) was relatively high [20, 21]. Treatment exposures were not included in the multivariable models due to overlap with childhood

cancer diagnosis (Fig. 3). Results were reported as crude and adjusted RRs with their 95% confidence intervals (CI).

- To assess whether attending a long-term follow-up visit influenced the subsequent completion of an echocardiogram in survivors who were not adherent to recommended surveillance at the time of the LTFU program implementation, we isolated the subgroup of survivors at high risk of cardiomyopathy who had not had any echocardiograms during the 5 years preceding the date of the LTFU program implementation, i.e., from January 1, 2007, to January 1, 2012 (Fig. 4). In this subgroup ($n = 512$), the association between attendance to an LTFU visit and the completion of an echocardiogram from 2012 until the end of the study period was

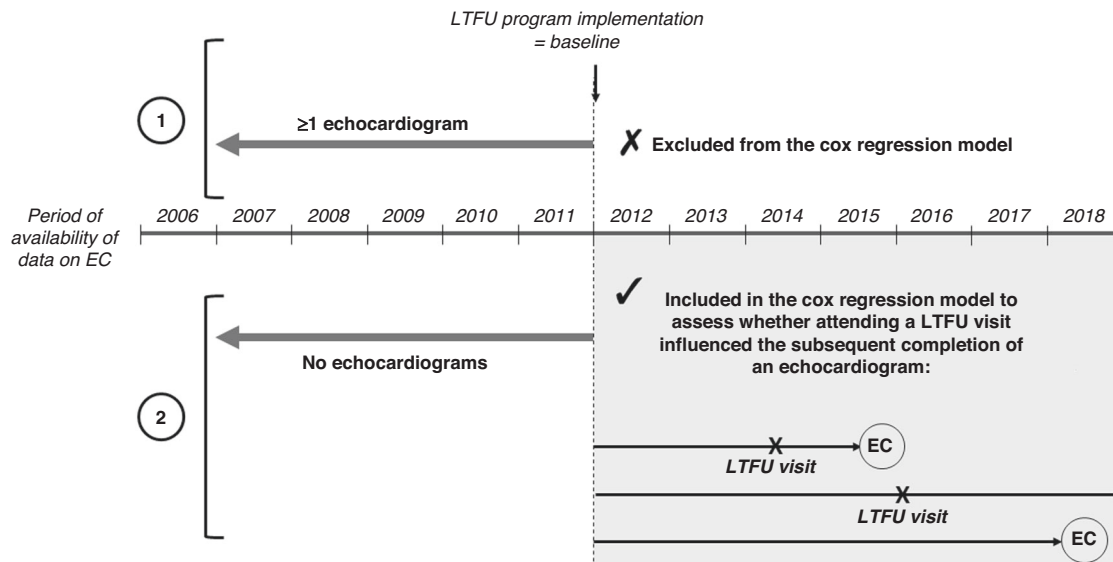


Fig. 4 Survivors at high risk of cardiomyopathy included in the Cox regression model to assess whether attending a long-term follow-up visit influenced the subsequent completion of an echocardiogram. Subjects who were not adherent to recommended surveillance at the time of the LTFU program implementation (2) were included ($n=512$), whereas subjects who were not adherent to recommended surveillance at the time of the LTFU program implementation (1) were excluded. EC echocardiogram, LTFU long-term follow-up.

studied using a Cox regression model. We used time-on-study time scale, with time 0 (baseline) corresponding to the date of the implementation of the LTFU visits program (January 1, 2012). Having an LTFU visit was modelled as a time-dependent variable. Survival was censored at the date of echocardiography or at the end of their data collection period. The model was adjusted for sociodemographic and clinical factors, except for treatment exposures due to overlap with pediatric cancer diagnosis (Fig. 3). Results were expressed as hazard ratios (HRs) with their 95% confidence intervals (CI). To better estimate the causal effect of LTFU visit on completion of echocardiograms, the Cox regression model was weighted by inverse probability of treatment weighting (IPTW) to minimize the effects of confounding due to the differences in baseline characteristics between patients who had an LTFU visit and those who did not [20]. IPTW uses the propensity score which was calculated by running a logit model including having an LTFU visit as the outcome and a set of baseline characteristics (sex, age, level of deprivation, childhood cancer type, age at diagnosis, and second cancer) as covariates.

All analyses were conducted using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). All P values were two-sided; P values < 0.05 were considered statistically significant.

RESULTS

Sociodemographic and childhood cancer characteristics of CSS at high risk of cardiomyopathy

Among the 976 CSS at high risk of cardiomyopathy, 421 (43.1%) were females and the mean age was 39.2 years (range: 18–72). The most prevalent diagnoses were non-Hodgkin's lymphoma (22.2%), bone sarcoma (21.6%), soft tissue sarcoma (14.9%) and Wilms tumour (14.0%) (Table 1). More than 80% of the high-risk survivors of CNS tumour and Hodgkin's lymphoma were exposed to radiation ≥ 30 Gy to more than 10% of the left ventricular volume, whereas high-risk survivors of other cancers were mainly exposed to cumulative anthracycline dose > 250 mg/m² (Fig. 3).

Adherence to recommended surveillance

Overall, 31.6% of the patients at high risk of cardiomyopathy were adherent (i.e., they had performed an echocardiogram over the last 5 years of their data collection period), and 15.2% were long-term adherent (i.e., they had performed two echocardiograms over the last 10 years). Among those who had an LTFU visit ($n = 153$), these proportions were 52.8% and 32.9%, respectively.

Predictors of adherence to recommended surveillance

Males and patients aged 36–49 (vs. patients aged < 36) were less likely to have an echocardiogram over the last 5 years (adjusted RR [aRR] 0.71, 95% CI 0.58–0.86, and aRR 0.79, 95% CI 0.64–0.98, respectively) (Table 2). Neuroblastoma and CNS tumour survivors (vs. Wilms tumour survivors) were also less adherent to recommended surveillance (aRR 0.53, 95% CI 0.30–0.91, and aRR 0.43, 95% CI 0.21–0.89, respectively). CCS diagnosed after 5 years of age and those who had a second cancer were more likely to be adherent (aRR 1.27, 95% CI 1.01–1.62 and aRR 1.43, 95% CI 1.13–1.82, respectively).

Similar trends were reported when studying factors associated with long-term adherence to recommended surveillance, but only associations with sex and age at cancer diagnosis remained significant (Supplementary Table S1).

Impact of the LTFU visit on completion of echocardiograms

Of the survivors at high risk of cardiomyopathy, 512 were not adherent to recommended surveillance at the time of the LTFU program implementation, i.e., had not had any echocardiograms during the 5 years preceding January 1, 2012. Of them, 79 attended an LTFU visit; 46 (58.2%) subsequently performed an echocardiogram. In this subgroup of non-adherent survivors at the time of the LTFU program implementation, attendance to an LTFU visit was positively associated with the completion of an echocardiogram from 2012 until the end of the study period; the adjusted HR was 8.20 (95% CI 5.64–11.93) in the Cox regression model weighted by IPTW.

DISCUSSION

Using data from a national health administrative database, we reported that the majority of survivors at high risk for cardiomyopathy were not adherent to recommended surveillance. This finding was consistent with those previously reported in North American studies, in which echocardiograms were self-reported [12, 15, 22, 23]. Nathan et al. [12] reported that only 28% of CCS at high risk of cardiomyopathy were adherent to recommended surveillance in the CCSS, while this proportion was 32% in the present study. These proportions were similar, but it should be noted that recommendations were different between the US and France [9]. Thus, the definitions of adherence were different:

Table 1. Sociodemographic and childhood cancer characteristics of all FCCSS patients and of FCCSS patients at high risk for cardiomyopathy.

	All patients	Patients at high risk of cardiomyopathy
	N = 4759	N = 976
<i>Sociodemographic characteristics</i>		
Sex, n (%)		
Females	2143 (45.0)	421 (43.1)
Males	2616 (55.0)	555 (56.9)
Age, n (%)		
<36 years	1869 (39.3)	295 (30.2)
36–49 years	2280 (47.1)	580 (59.4)
≥50 years	610 (12.8)	101 (10.4)
Deprivation score, mean ± s.d.	−0.4 ± 1.8	−0.5 ± 1.8
<i>Childhood cancer characteristics</i>		
Childhood cancer, n (%)		
Wilms tumour	756 (15.9)	137 (14.0)
Neuroblastoma	674 (14.2)	70 (7.2)
CNS tumour	646 (13.6)	47 (4.8)
Non-Hodgkin's lymphoma	534 (11.2)	217 (22.2)
Soft tissue sarcoma	510 (10.7)	145 (14.9)
Bone sarcoma	412 (8.7)	211 (21.6)
Hodgkin's lymphoma	271 (5.7)	76 (7.8)
Other solid cancers ^a	956 (20.1)	73 (7.5)
Age at diagnosis, n (%)		
<5 years	2367 (49.7)	310 (31.8)
≥5 years	2392 (50.6)	666 (68.2)
Anthracycline dose >250 mg/m ² , n (%)		
No	3945 (82.9)	162 (16.6)
Yes	814 (17.1)	814 (83.4)
Cardiac radiation ≥30 Gy to ≥10% of the LV volume, n (%)		
No	4588 (96.4)	805 (82.5)
Yes	171 (3.6)	171 (17.5)
Second cancer, n (%)		
No	4412 (92.7)	881 (90.3)
Yes	347 (33.0)	95 (9.7)

CNS central nervous system, LV left ventricular, s.d. standard deviation.

^aGonadal tumour, thyroid tumour, retinoblastoma and other types of carcinoma.

an echocardiogram within the last year in CCSS [12], and an echocardiogram within the last 5 years in the present study.

We identified several predictors of non-adherence to recommended cardiac surveillance among patients at high risk for cardiomyopathy. Males were less likely to adhere than females, supporting that gender is a well-known predictor of healthcare utilization [13, 24]. This may be due to stereotypical health-related beliefs, with men not seeing themselves vulnerable to disease or considering that asking for help is less acceptable for men [25]. Subjects aged 36–49 were less likely to be adherent than those aged <36, but no differences were found between those aged ≥50 and those aged <36. This result suggested a temporary drop in adherence during adulthood, at age 36–49 years. Such a pattern has not been documented in other studies, in which age was

generally entered as a continuous variable in models [12, 23]. Patients in this age group may not have discussed their childhood cancer with a care provider for a long time, and they may not feel concerned about cardiac outcomes, as they are still young individuals.

Regarding clinical predictors, we found that CNS tumour and neuroblastoma survivors were less likely to adhere to cardiac surveillance. As the most prevalent long-term outcomes in these survivors are endocrine, neurological, cognitive, sensory, psychiatric, or musculoskeletal disorders [26, 27], cardiac screening may have been somewhat overlooked among them. High-risk patients diagnosed during infancy or early childhood (<5 years) were less adherent than others. Marr et al. [13] reported a similar trend, but associations were not significant, and Nathan et al. [12] did not find any association between adherence and age at diagnosis. Finally, the diagnosis of a second cancer was associated with better adherence to recommended surveillance, as reported in the CCSS [12, 23]. Recurrence of cancer may be the occasion for an oncologist to review the patient's treatment history and eventually to encourage the patient to undergo an echocardiogram.

Beyond demographic and clinical predictors, there are probably psychological barriers to adherence [28]. Some survivors may avoid medical care in an attempt to forget their childhood cancer; they may feel that the long-term follow-up they have to undergo is a source of anxiety and prevents them from living a normal life [29]. However, psychological barriers remain poorly documented [15] since patients who avoid healthcare professionals are not likely to involve themselves in qualitative studies that investigate how CSS manage their long-term medical follow-up. Another reason for poor adherence could be a lack of survivor knowledge of their treatment exposures and associated surveillance recommendations [15]. Several studies have shown that having frequent clinic visits increased adherence to recommendations in high-risk patients [15] and thus may address this unawareness. Among patients who were not adherent to recommendations, we reported that attendance to the LTFU visit strongly increased the probability of performing an echocardiogram afterwards (HR = 8.2). This result, in line with findings from previous studies [13, 30], demonstrates the effectiveness of LTFU visits in referring non-adherent survivors to the screening process. Nevertheless, LTFU visits are not sufficient to reach full adherence. In our study, less than one quarter of high-risk patients had an LTFU visit, and 42% of those who attended did not have an echocardiogram afterwards. Marr et al. reported that among survivors at high risk for cardiomyopathy with at least one clinic attendance, 45% did not have an echocardiogram afterwards [13]. Furthermore, there is evidence that attendance at LTFU clinics is poor [15, 31]. Further interventions, including implementation of survivorship care plans (SCP), phone counselling, and mailed/web-based information regarding treatment, risks, and screening instructions, have the potential to either increase attendance at LTFU clinics [15, 32, 33] or complement LTFU visits [15, 16, 34, 35]. Moreover, primary care physicians' knowledge of long-term risks and surveillance recommendations for patients treated for childhood cancer is often lacking, which needs to be addressed [36–39]. Giving CCS as much opportunity as possible to receive recommendations is crucial to increase adherence.

This study has several strengths. It is the first study on adherence to recommended surveillance in CCS at high risk for cardiomyopathy to deal with data from a country outside of North America, and it includes almost 1,000 high-risk survivors. Unlike some other studies [12, 22, 23], data on echocardiograms were not self-reported by patients, but extracted from a health administrative database. The studies with self-reported data included survivors who had agreed to respond to a survey and who were probably more concerned about their long-term follow-up, which may have overestimated the proportions of adherence. In our study, 32% of survivors at high-risk for cardiomyopathy adhered to

Table 2. Factors associated with adherence to recommended surveillance (i.e., completion of an echocardiogram over the last 5 years) among survivors at high risk for cardiomyopathy ($n = 930$).

	Total number	Adherence, n (%)	Crude RR (95% CI)	Adjusted RR ^a (95% CI)
Sex				
Females (ref)	406	161 (39.7)	1	1
Males	524	133 (25.4)	0.64 (0.53–0.77)***	0.71 (0.58–0.86)***
Age (years)				
<36	275	98 (35.6)	1	1
36–49	555	153 (27.6)	0.77 (0.63–0.95)*	0.79 (0.64–0.98)*
≥50	100	43 (43.0)	1.21 (0.92–1.59)	1.09 (0.82–1.46)
Deprivation score				
Quintiles 1 and 2 (ref)	364	131 (36.0)	1	1
Quintiles 3	216	70 (32.4)	0.90 (0.71–1.14)	0.96 (0.76–1.21)
Quintile 4	187	51 (27.3)	0.76 (0.58–0.99)*	0.84 (0.64–1.10)
Quintile 5 (most deprived)	163	42 (25.8)	0.72 (0.53–0.96)*	0.79 (0.59–1.05)
Childhood cancer				
Wilms tumour (ref)	133	51 (38.4)	1	1
Neuroblastoma	66	12 (18.2)	0.47 (0.27–0.83)**	0.53 (0.30–0.91)*
Hodgkin's lymphoma	64	20 (31.3)	0.82 (0.53–1.24)	0.72 (0.47–1.11)
Non-Hodgkin's lymphoma	212	56 (22.8)	0.69 (0.50–0.94)*	0.72 (0.52–1.00)
Soft tissue sarcoma	139	40 (28.8)	0.75 (0.53–1.05)	0.75 (0.53–1.05)
Bone sarcoma	204	82 (40.2)	1.05 (0.80–1.38)	1.01 (0.75–1.35)
CNS tumour	45	7 (15.6)	0.41 (0.20–0.83)*	0.43 (0.21–0.89)**
Other solid cancers ^b	67	26 (38.8)	1.00 (0.70–1.47)	0.99 (0.69–1.44)
Age at diagnosis				
<5 years (ref)	298	80 (26.9)	1	1
≥5 years	632	214 (33.9)	1.26 (1.02–1.57)*	1.27 (1.01–1.62)*
Anthracycline dose >250 mg/m ²				
No (ref)	144	41 (28.5)	1	–
Yes	786	253 (32.2)	1.13 (0.86–1.49)	–
Cardiac radiation ≥30 Gy to ≥10% of the LV volume				
No (ref)	778	246 (31.6)	1	–
Yes	152	48 (31.6)	1.00 (0.79–1.29)	–
Second cancer				
No (ref)	844	252 (29.9)	1	1
Yes	86	42 (48.8)	1.65 (1.29–2.09)***	1.43 (1.13–1.82)**

CI confidence interval, CNS central nervous system, FDep French deprivation index, NA non-available, RR relative risk, SD standard deviation.

^aAdjusted for all other variables in the multivariable modified Poisson regression model.

^bGonadal tumour, thyroid tumour, retinoblastoma and other types of carcinoma.

* P value < 0.05; ** P value < 0.01; *** P value < 0.001.

the recommended surveillance. When limited to those who had responded to a questionnaire for other studies conducted in the FCCSS, this proportion was 36%. Cardiac diseases were also identified using a health administrative database and validated with medical reports; survivors with cardiac diseases were followed-up until the year of the cardiac disease diagnosis to avoid including echocardiograms undergone for reasons other than surveillance (e.g., symptoms or monitoring).

This study has some limitations. None of the high-risk patients were leukemia survivors since the FCCSS only includes patients treated for a solid malignant tumour or lymphoma. We estimated the effect of having an LTFU visit on the completion of an echocardiogram with observational data, whereas an interventional study such as a randomized controlled trial would have been more appropriate for this purpose. Therefore, our model was weighted using the inverse probability of treatment weighting (IPTW) method to simulate a random allocation of the LTFU visit to

survivors [40]. Finally, data on LTFU visits were only available for the patients from Gustave Roussy, one of the five cancer centers included in this study. Nevertheless, the majority (67%) of the survivors at high risk for cardiomyopathy were followed-up in this center.

Most CCS at high risk of cardiomyopathy did not adhere to the recommended surveillance despite their risk of treatment-related cardiac outcomes. Thus, there is an absolute need to improve opportunities for high-risk patients to receive surveillance. LTFU visits greatly enhanced the completion of echocardiography, but only a limited number of survivors access such visits. Further interventions based on innovative tools that can reach a large number of patients, such as web-based platforms and communication technologies, should be developed to increase awareness of late effects in survivors and inform them that tertiary prevention strategies can be set up to reduce the risk of cardiomyopathy. Better information and coordination between the actors involved in the

patient's follow-up is crucial—for instance, explicit information about the dose of treatment received and the recommended follow-up should be systematically given in a Survivorship Care Plan. The identification of social, clinical, and psychological predictors of non-adherence to recommended surveillance should help to tailor interventions targeting survivors at high risk for cardiomyopathy, to better design interventions, and to reach full adherence to recommended surveillance.

DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

AD, RSA, BF, NH, NB and FDV designed the study. All authors participated to the collection and assembly of data. NB performed the statistical analysis and drafted the manuscript with the help of AD, BF, RSA and FDV. All authors revised the work, approved its final version and agreed to be accountable for all its aspects.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The FCCSS study was approved by the INSERM Institutional review board (CEEI N°12-077) and the French National Agency regulating Data Protection (CNIL N°902287). Patients, parents, or guardians' consent was obtained according

to national research ethics requirements. The study was performed in accordance with the Declaration of Helsinki.

CONSENT FOR PUBLICATION

Not applicable.

ADDITIONAL INFORMATION

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