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Smoking and cannabis use among childhood cancer survivors: results of the French Childhood Cancer Survivor Study

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ABSTRACT

Background. Unhealthy behaviors among childhood cancer survivors increase the risks for cancer treatment adverse effects. We aimed to assess tobacco and cannabis use prevalence in this population and to identify factors associated with these consumptions.

Methods. This study involved 2,887 5-year survivors from the French childhood cancer survivor study (FCCSS) cohort. Data on health behaviors were compared with those of controls from the general population. Associations of current smoking and cannabis use with clinical features, sociodemographic characteristics and health-related quality of life (QOL) were investigated using multivariable logistic regressions.

Results. Prevalence for tobacco use was lower in survivors (26%) than in controls (41%, $P < 0.001$). Among current smokers, survivors smoked more cigarettes per day and started at a younger age than controls. Women, college graduates, older, married and CNS tumour survivors, as well as those who received chemotherapy and thoracic radiation therapy, were less likely to be smokers and/or cannabis consumers than others. Participants with a poor mental QOL were more likely to smoke.

Conclusions. Preventive interventions and cessation programs must be carried out as early as possible in survivors' life, especially among young males with low educational level and poor mental health.

Impact. This study brings new insights to health behaviors among childhood cancer survivors from a population with high rates of smoking and cannabis use.

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INTRODUCTION

Cancer is the second leading cause of death during childhood.[1] However, pediatric cancer survival has substantially increased over the past decades due to progress in therapy and diagnosis procedures, and five-years survival rates are now about 80% in Western countries.[1] As a result of these improvements, a growing population of childhood cancer survivors (CCS) has emerged.

However, survivors are more likely to experience further health complications than adults without pediatric cancer history because of organ toxicity induced by chemo- and radiotherapy late effects.[2] Thirty years after the diagnosis of cancer, cumulative incidence of second malignant neoplasm and chronic health condition (including endocrine disorders, cardiovascular diseases, renal dysfunctions, musculoskeletal problems) may be over 70% among survivors[2] who constitute a population at greater risk for morbidity and early mortality.[3–6] Unhealthy behaviors, such as smoking, are preventable factors that are potentially prone to further increase the risk of second cancer and chronic health conditions in childhood cancer survivors who already have an excess risk due to their treatment. For instance, Travis et al.[7] showed that smoking itself increased risk of subsequent lung cancer more than 20-fold in Hodgkin's disease survivors, and that smoking appeared to further multiply risks from treatment with alkylating agents and/or radiotherapy. Therefore, CCS are strongly encouraged to adopt healthy lifestyles.

Thus, smoking among survivors of childhood cancer is a major concern; there is a real need for data to assess the magnitude of this public health issue and investigate its determinants to develop targeted interventions and effective policies. Several studies have reported prevalence of smoking among CCS and have compared tobacco use between survivors and control subjects. While most highlighted lower prevalence of smoking among survivors,[8–16] a few reported greater prevalence for smoking among survivors[17,18] or no differences.[19,20] Concerning cannabis consumption, lower prevalence was found among CCS.[11,19,21,22] As the majority of these studies took place in North America[8,9,12,15,17–20] or in the UK,[10,14] their results may not be generalizable to other populations with different distribution of risk behaviors, and need to be supported by other data. No such study has yet been conducted in France, which has a much higher prevalence of tobacco smoking than the UK, the US and Canada according to WHO data.[23] France also has the highest prevalence of cannabis use in Europe despite the fact that it is not legalized (punishable by 1 year in prison or a fine of up to € 3,750 at the time of the present study).[24] It is worthwhile to explore the determinants of smoking/cannabis use among CCS from a population with high rates of tobacco smoking and cannabis use to determine whether these determinants are similar to those reported among CCS from countries with lower rates of tobacco smoking and cannabis use.

In this context, we aimed (a) to compare cigarette smoking and cannabis consumption between survivors of childhood cancer and controls from the general population, and (b) to identify demographic, socioeconomic and clinical risk factors associated to these unhealthy behaviors.

METHODS

Study population

This study is based on data of the FCCSS (French Childhood Cancer Survivor Study) cohort which aims to investigate the overall long-term outcomes of children and adolescents treated for cancer.[25,26] Eligible subjects were five-year cancer survivors treated before reaching age 18 for a solid tumour or a lymphoma in five French centers between 1945 and 2000.

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The FCCSS cohort currently includes 7,670 subjects. Data on tumour type and treatment were extracted from medical records, as well as gender, date of birth and date of diagnosis. Second cancer and cardiovascular diseases (myocardial infarction, angina, heart failure, valvular diseases, cardiac arrhythmia, conduction disorder, and pericardial diseases) were ascertained from physician's report or medical records. Epidemiological data, including health behavior (smoking and cannabis use), health-related quality of life (QOL) and demographic and socioeconomic characteristics were collected using a self-administered questionnaire derived from the US and the UK survivors' cohorts.[8,10] Questionnaires were sent in two waves: the first one, from 2005 onwards, involved survivors treated before 1985, and the second one, from 2010 onwards, involved survivors treated from 1986 to 2000. Three-quarters of the questionnaires (75.5%) were filled between 2005 and 2011. Among the FCCSS subjects, 802 died before the 1st wave of questionnaires was sent out, 248 died before the 2nd wave of questionnaires was sent out and 1,697 had unknown current postal address. As a result, 5,023 subjects were contacted by postal mail to complete this questionnaire; of these, 3,293 (65.6%) answered the questionnaire, and 2,887 (59.7%) answered all the items related to current smoking, current cannabis use, health-related QOL, and demographic and socioeconomic characteristics (Figure 1).

The FCCSS study has been approved by the INSERM national ethics committee and the French National Agency regulating Data Protection (CNIL N°902287). Written informed consent was obtained from patients, parents or guardians according to national recognized ethical guidelines.

Control population

Control population data were extracted from the 2010 Health Barometer, a cross-sectional general population survey conducted in France between October 2009 and July 2010, as described elsewhere.[27] Briefly, a representative random sample of the general population was drawn by randomly generating phone numbers to contact households then selecting one eligible individual aged 15-85 years within each household. Data on health behaviors and sociodemographic background were anonymously collected during a phone interview with a trained interviewer. The sample, which is representative of the French general population, accounted for 27,653 persons. Smoking status was available for the entire sample, whereas information related to cannabis use was available for 22,736 persons (82.2%).

To assure that FCCSS participants ("case group") and general population sample ("control group") were comparable regarding distributions by gender, age group (< 25, 25-29, 30-39, ≥ 40 years), educational level (less than High School, High School graduate, College graduate) and marital status (married, single/divorced/widowed), a frequency matching program[28] using these four variables as matching factors was performed. As we selected a 1:1 case-control ratio, 2,887 persons from the general population survey were defined as "controls" and were included in this study.

Outcome variables: Smoking status and cannabis use

Ever smoking was defined as a binary variable (yes, no) using the question "Have you ever smoked cigarettes regularly?". Current smoking was defined as a binary variable (yes, no) using the question "Do you currently smoke cigarettes regularly?". Subjects who had ever smoked cigarettes regularly but who did not currently smoke were considered as those who quit smoking. Current smokers were asked how many cigarettes they smoke per day, and their age at initiation; number of cigarettes smoked per day was considered as a discrete variable (< 10, 10-20, > 20) or as a continuous variable, and the age in years at smoking initiation as a discrete

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variable (< 14, 14-17, 18-21, ≥ 22) or as a continuous variable. Current cannabis use was defined as a binary variable "smoking regularly cannabis" (yes, no).

Correlates under study

Clinical predictors were childhood cancer type (classified according to the International Classification of Childhood Cancer[29]), decade of childhood cancer diagnosis (divided into four categories: < 1975, 1975–1984, 1985–1994, ≥ 1995), age at childhood cancer diagnosis, chemotherapy (no, yes), thoracic radiation therapy (no, yes), second cancer (no, yes) and cardiovascular disease (no, yes).

Demographic predictors included age (< 30, 30-39, ≥ 40 years) and marital status (being married, being single/divorced/widowed). Socioeconomic predictors included employment status and educational level, which was defined as the highest diploma obtained: below High School, High School graduate, or College graduate (bachelor or higher).

Health-related QOL was assessed using the Medical Outcomes Short Form-36 (SF-36 version 2), for which validity and reliability in CCS has been previously established.[30] Briefly, this questionnaire is made of eight physical and mental health subscales (physical functioning, bodily pain, role limitations caused by physical health problems, role limitations caused by personal or emotional health problems, general mental health, social functioning, vitality and general health perception) which can be summarized with a Physical and a Mental Component Summary score (PCS and MCS, respectively).[31] Scores ranged from 0 to 100, with higher scores representing better levels of health. Based on a similar previous work,[15] we categorized PCS and MCS scores into quartiles.

Statistical analysis

First, demographics, socioeconomics and clinical characteristics of CCS who answered the self-administered questionnaire were compared to those of non-respondents using chi-square tests. We compared health behavior characteristics of participants (smoking prevalence, number of cigarettes smoked per day, age at smoking initiation, and prevalence of current cannabis use) with those of sex-, age-, educational level- and marital status-matched controls from the general population, using chi-square tests and Mann-Whitney U tests.

We compared the prevalence of current smoking/cannabis use between each type of childhood cancer group using a chi-square test of independence. We used modified Poisson regression models with robust errors to estimate relative risks (RRs) and 95% confidence intervals (CI) for current smoking and cannabis use in survivors of each childhood cancer type *versus* controls from the general population, with adjustment for demographic and socioeconomic variables (sex, age, educational level and marital status). We used modified Poisson regression rather than logistic regression because current smoking was common.[32]

Then, factors associated with current smoking, smoking cessation and cannabis use among childhood cancer survivors were investigated using multivariate modified Poisson regression models with robust errors. Socioeconomic characteristics (gender, age, marital status, educational level, employment status), health-related QOL (MCS and PCS scores) and clinical features (childhood cancer type, age at diagnosis, cancer treatments, second cancer, cardiovascular disease) were all included as predictive variables to explore their associations with current smoking and cannabis use. To take into account the possible non-response bias, the models were also adjusted for a propensity score that estimated the propensity of response to the questionnaire within the FCCSS cohort: characteristics that differed between responders and non-responders (sex, childhood cancer type, age in

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years at first cancer, decade of diagnosis at first cancer, radiation therapy) were incorporated into this propensity score through a logit model to calculate the probability of response of each participant.[26,33]

In addition, possible effect modification by CNS (central nervous system) tumour and thoracic radiation therapy was tested using multiplicative interaction terms to explore whether CNS tumour survivors and survivors treated with thoracic radiation therapy had different risk factors for smoking and cannabis use compared to their counterparts, as they are known to adopt healthier behaviors than other survivors.[8,10]

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 as statistically significant.

RESULTS

Characteristics of participants

Overall, response to the questionnaire was significantly associated with gender, cancer type, age at cancer, decade of diagnosis and radiation therapy (Table 1). About half of the responders (48.0%) were diagnosed under 5 years of age. Most responders were diagnosed before 1995 (86.3%) whereas 52.8% of the non-responders were diagnosed from 1995 onwards. The most prevalent diagnoses were Wilms tumour (18.4%) and Neuroblastoma (14.3%). Retinoblastoma was the less common diagnosis among responders (4.5%), but the most frequent among non-responders (20.2%). About half of non-responders (48.4%) received radiation therapy, against 57.0% among the responders (Table 1). Mean age at study was 33.4 years. Overall, 20.2% of participants had an educational level below High School and 79.9% were not married.

Smoking status and cannabis use: comparison between childhood cancer survivors and controls from the general population

Smoking status and cannabis use in FCCSS participants and sex-, age-, education level- and marital status-matched controls from the general population are described in Table 2. Prevalence of current smoking was lower in CSS than in controls (25.9% vs 40.7%, P < 0.001), as well as prevalence of ever smoking (49.4% vs 56.6%, P < 0.001). Age at smoking initiation was lower in survivors (17.5 vs 18.5 years, P < 0.001). Among CCS, 677 of those who have ever smoked have quit smoking (47.5%). When smoking, participants smoked slightly more cigarettes per day than controls from general population (11.6 vs 11.0, P=0.016). Prevalence of current cannabis use was similar among survivors (6.6%) and controls (6.8%, P=0.676). Using a chi-square test, current smoking and current cannabis use among survivors were strongly associated (p<0.001, Supplementary Table S1).

Survivors of each type of cancer were significantly less likely to smoke than the general population (Table 3). Survivors of CNS tumour had the lowest risk of smoking compared to the general population (RR 0.31, 95% CI 0.24 to 0.42), whereas survivors of soft tissue sarcoma had the highest risk (RR 0.76, 95% CI 0.64 to 0.90). Regarding cannabis use, only the CNS tumour survivors were significantly less likely to consume cannabis than the general population (RR 0.35, 95% CI 0.17 to 0.71), while survivors of soft tissue sarcoma had the highest odds (RR 1.36, 95% CI 0.94 to 1.99) (Table 3).

Factors associated with smoking among childhood cancer survivors

Results of multivariable analysis examining associations between current smoking and clinical, demographic, socioeconomic and QOL predictors among survivors are presented in Table 4. Survivors of CNS tumour had a significantly lower risk of being current smokers compared to survivors of Wilms Tumour (RR 0.43, 95% CI 0.31 to 0.59). Survivors who had received chemotherapy (RR 0.85, 95% CI 0.73 to 0.99), those who had

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received thoracic radiation therapy (RR 0.80, 95% CI 0.64 to 0.99), those who had a second cancer (RR 0.65, 95% CI 0.44 to 0.96) and those who had a cardiovascular disease (RR 0.72, 95% CI 0.52 to 0.99) were less likely to be current smokers. No differences were found between smokers and non-smokers regarding age at first cancer. Current smokers were more likely to be males (RR 1.40, 95% CI 1.23 to 1.59) and less likely to be married (RR 0.82, 95% CI 0.69 to 0.97). Older survivors (≥ 40 years) were less likely to smoke than younger ones (< 30 years) (RR 0.78, 95% CI 0.62 to 0.99). Survivors who graduated from College were less likely to be current smokers than those who dropped out before High School (RR 0.59, 95% CI 0.50 to 0.70). Participants with a poor score for physical QOL (< 1st quartile) were less likely to be current smokers compared to others (RR 0.84, 95% CI 0.71 to 0.98). Conversely, survivors with a poor score for mental QOL (< 1st quartile) were more likely to smoke compared to those with a high score for mental QOL (> 3rd quartile) (RR 1.60, 95% CI 1.34 to 1.91). We did not find any effect modification by CNS tumour or thoracic radiation therapy. Males where less likely to quit smoking (RR 0.82, 95% CI 0.73 to 0.92), whereas survivors who were married (RR 1.23, 95% CI 1.09 to 1.38), those with a high educational level (RR 1.45, 95% CI 1.24 to 1.70) and those who had a second cancer (RR 1.27, 95% CI 1.04 to 1.55) were more likely to quit.

Factors associated with current cannabis use among childhood cancer survivors

Survivors of CNS tumour had a significantly lower risk of being current cannabis users compared to survivors of Wilms Tumour (RR 0.35, 95% CI 0.16 to 0.80) (Table 4). No differences were found regarding thorax radiation therapy, chemotherapy, age at first cancer, second cancer and cardiovascular diseases. Cannabis users were more likely to be males (RR 2.81, 95% CI 2.06 to 3.82) and unemployed (RR 1.58, 95% CI 1.08 to 2.30). Cannabis use decreased with age: CCS aged 30-39 years and those aged 40 years or older were less likely to be current cannabis users than those under 30 years of age (RR 0.60, 95% CI 0.42 to 0.87, and RR 0.31, 95% CI 0.17 to 0.57, respectively). Compared to survivors who dropped out before High School, those who graduated from College were less likely to be current cannabis users (RR 0.62, 95% CI 0.41 to 0.93). Participants with a poor score for mental health (< 1st quartile) were more likely to be current cannabis users compared to those with a high score for mental QOL (> 3rd quartile) (RR 1.95, 95% CI 1.20 to 2.92). We did not find any effect modification by CNS tumour or thoracic radiation therapy.

DISCUSSION

In this multicenter cohort study including a large number of long-term childhood cancer survivors, we found that the prevalence of current smoking in survivors (26%) was lower than in sex-, age-and educational level-matched controls from the general population (41%). However, survivors who smoked were prone to start at a younger age and to smoke more cigarettes per day than smokers from the general population. Prevalence of current cannabis use was similar in survivors and controls. We also identified several risk factors associated with current smoking and cannabis use.

About half of survivors (49%) in the FCCSS study had ever smoked and 25% were current smokers, which is higher than the prevalence found in other cohorts of survivors. Indeed, prevalence of ever and current smoking were lower in the North American cohort (27% and 17%, respectively)[8] and in the British cohort (30% and 20%, respectively).[10] These differences may reflect substantial discrepancies in smoking habits between countries, as suggested by WHO data showing that age-standardized prevalence of tobacco smoking is much higher in France than in the U.K., the U.S. or Canada.[23] Nevertheless, in our study, survivors smoked less than controls, which is

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in line with what have been found in the North American and the British cohorts,[8,10] and in most of the previous studies.[11,12,14,16] Conversely, two other U.S. studies[17,18] reported that survivors were more likely to be current smokers than controls and had especially high smoking rates (35-37%). It should be noted that, in these studies, the current smoking group included both regular and occasional smokers. Overall, differences in survivors' characteristics (e.g., nationality, age, socioeconomic status) and in smoking status definition could contribute to conflicting results between studies regarding smoking rates.

Early onset of smoking is of particular concern since it increases the risk for developing related morbidities (such as cardiovascular diseases and lung cancer) and affects all-cause mortality.[34] In our study, age of smoking initiation among childhood cancer survivors was 17.5 years. Similar age of initiation (17.4 years) was reported in the British cohort.[10] Alarmingly, we found that survivors initiated smoking at a younger age than controls from the general population, which differ from results of British and Swiss studies.[10,16] It is well-known that an early age of smoking initiation is associated with a heavier smoking in adulthood;[35] thus, it is not surprising that we also reported that FCCSS survivors smoked more cigarettes per day than controls (11.3 vs 9.3). However, survivors from the British cohort smoked less cigarettes than controls from the general population (11.8 vs 14.3).[10]

Overall, determinants of tobacco smoking among French survivors from our study were also reported in other studies from other countries with different rates of smoking, suggesting that risk factors for smoking in CCS may be similar across countries, regardless of the country's smoking pattern. We found that the survivors of childhood CNS tumors had a lower risk of being current smokers, as previously suggested in other cohort studies.[8,10] Since survivors of CNS malignancies are prone to suffer from permanent neurocognitive impairment,[36] partly because of their treatment, it has been hypothesized that these survivors must be very dependent on others, which should prevent them from having the opportunity to initiate smoking.[8,10]

The risks of second cancer and chronic health conditions are known to be increased by radiation therapy and chemotherapy[2] and must be further multiplied by health behaviors, including current smoking.[7] Therefore, it is reassuring that FCCSS survivors who underwent thoracic radiation therapy and chemotherapy were less likely to be current smokers, consistently with findings reported by Frobisher et al.[10] It is possible that the "cancer experience" of these survivors was more intense, and thus they may be more engaged with cancer survivorship and its emphasis of healthier lifestyles. Our results regarding demographic and socioeconomic factors associated with smoking among childhood cancer survivors indicated that women, college graduates, older (≥ 40 years old), and married participants were less likely to be current smokers. Similar relationships were reported in several other studies,[15,17] including the North American[8] and the UK[10] cohorts. Sociodemographic predictors of current smoking reported in survivors also corresponded to those found in the French population,[37] and it has been recognized that survivors are no different from their peers in regard to sociodemographic factors associated with being a smoker.[8,10,15,16]

To our knowledge, only one study investigated the association between QOL and smoking in survivors, and this study found no significant associations.[15] We showed that poorer mental health was related to smoking, which echoes what has been found in the general population.[37,38] Nevertheless, the direction of the relationship is difficult to determine because we only had SF-36 measures at the time of the questionnaire, and not at the time of smoking initiation. In general population, several studies reported that baseline depression or anxiety was

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associated with later smoking, while some others supported the alternative hypothesis that smoking at baseline increases susceptibility to poor mental health condition.[39]

More surprisingly, FCCSS survivors with a poor physical score (PCS score < 1st quartile) were less likely to being current smokers than survivors with greater physical health. This finding may be the consequence of serious and disabling sequelae of cancers such as bone sarcomas or CNS tumors which may keep them from having unhealthy behaviors (e.g., amputation or psychomotor disorders). Furthermore, we found that survivors with comorbidities such as second cancer and cardiovascular were less likely to be current smokers, which supports the hypothesis that poor health condition may prevent current smoking.

Compared to tobacco use, cannabis use is poorly documented among childhood cancer survivors. Few authors reported that survivors were less likely to consume cannabis but these studies were conducted only in adolescents/young adults[11,22] or among a very small number of participants.[19,22] We did not find any difference between FCCSS participants and controls from general population concerning current cannabis use. Predictors related to cannabis use in our study were very similar to those related to current smoking. Poor mental health condition was strongly associated with being current cannabis users, in line with findings from Milam et al.[22] showing that higher depressive symptoms were related to marijuana use in survivors.

The present study had a few limitations. The FCCSS did not include survivors of leukemia; survivors of solid tumors or lymphoma were recruited in five French centers, therefore proportion of each type of cancer in our sample may not fully represent the proportion of each type of cancer in the whole French population. Despite the fact that about one third of the eligible survivors in FCCSS did not answer the questionnaire, almost 3,000 participants have been involved in the present study. Several differences were found between responders and non-responders regarding gender and clinical characteristics which could slightly distort the prevalence of smoking and cannabis use reported in this study. Nevertheless, this potential non-response bias was taken into account in our etiological analyses since the models investigating risk factors of current smoking/cannabis use and smoking cessation were adjusted for a propensity score that estimated the propensity of response to the questionnaire within the FCCSS cohort.[26,33]

Smoking status and cannabis use were self-reported using a questionnaire and thus were subject to reporting bias. As a result, prevalence of smoking and number of cigarettes smoked per day may have been somewhat underestimated due to a known tendency to underreport unhealthy behaviors (or over report healthy behaviors) in health surveys.[40] However, studies conducted elsewhere also relied on responses to questionnaire rather than on biomarkers measurements, which allows comparison across studies. Smoking and cannabis prevalence data in FCCSS was collected from 2005 to the mid-2010s, whereas health behaviors data in general population was from a large nationally representative survey conducted during the year 2010. Fortunately, prevalence of smoking and cannabis use over the period of data collection remained relatively stable in France.[41,42]

One strength of this work was that controls from the general population were sex-, age-, educational level- and marital status-matched with FCCSS participants. Matching by gender and/or by age was common in other similar studies, unlike matching on educational level and marital status, although these two sociodemographic predictors are highly correlated to tobacco or cannabis use, in the general population[43,44] as well as in childhood cancer survivors.[10] Our study is one of the few to compare simultaneously smoking prevalence, age at initiation and number of cigarettes smoked per day between survivors and controls from the general population. Another strength was that physical and mental health-related QOL were considered as potential predictors of health

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behaviors in our analyses using the SF-36, a validated measure of QOL, which was the case in only one other study.[15]

In conclusion, this large study brings important information about smoking and cannabis use among childhood cancer survivors. Overall, survivors of childhood cancer had lower smoking rates than the general population, whereas cannabis use prevalence was similar among survivors and the general population. Especially, survivors who received chemotherapy and/or thoracic radiation therapy, and therefore had an increased risk of second cancer and chronic health conditions, were less likely to be smokers. Nevertheless, smokers among survivors started smoking at a younger age and smoked more cigarettes per day than smokers from the general population. Thus, it is crucial to identify them at early age and to implement strategies to help them quit smoking, as well as to carry out preventive interventions as early as possible in survivors' life. The identification of factors associated with these health behaviors gives clinicians few keys to adapt their recommendations to the profile of their patients: young survivors, males, those with low socioeconomic status and those with poor mental health condition must be especially targeted by multiple interventions to reduce smoking and cannabis use.

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TABLES

Table 1. Demographic, socioeconomic and clinical characteristics of responders (N=3,293) and non-responders (N=1,730) in the FCCSS cohort.

		Responders n (%)	Non-responders n (%)	*p-value*[a]
Clinical characteristics				
Childhood cancer type	Wilms Tumour	607 (18.4%)	173 (10.0%)	< ***0.001***
	Neuroblastoma	470 (14.3%)	212 (12.3%)	
	Hodgkin's lymphoma	213 (6.5%)	99 (5.7%)	
	Non-Hodgkin's lymphoma	388 (11.8%)	137 (7.9%)	
	Soft tissue sarcoma	376 (11.4%)	151 (8.7%)	
	Bone sarcoma	315 (9.6%)	157 (9.1%)	
	CNS tumour	377 (11.4%)	237 (13.7%)	
	Retinoblastoma	148 (4.5%)	350 (20.2%)	
	Other solid cancers[b]	399 (12.1%)	214 (12.4%)	
Age in years at first cancer	< 5	1,580 (48.0%)	957 (55.3%)	< ***0.001***
	5-9	731 (22.2%)	320 (18.5%)	
	10-14	710 (21.6%)	306 (17.7%)	
	≥ 15	272 (8.3%)	147 (8.5%)	
Decade of diagnosis of first cancer	< 1975	670 (20.3%)	57 (3.3%)	< ***0.001***
	1975 - 1984	1,293 (39.3%)	104 (6.0%)	
	1985 - 1994	880 (26.7%)	656 (37.9%)	
	≥ 1995	450 (13.7%)	913 (52.8%)	
Chemotherapy	No	704 (21.4%)	400 (23.1%)	*0.156*
	Yes	2,589 (78.6%)	1,330 (76.9%)	
Thoracic radiation therapy	No	1,785 (84.6%)	1,569 (90.7%)	< ***0.001***
	Yes	508 (15.4%)	161 (9.3%)	
Second cancer	No	2,732 (94.6%)	-	
	Yes	155 (5.4%)	-	
Cardiovascular disease	No	2,711 (93.9%)	-	
	Yes	176 (6.1%)	-	
Demographic and socioeconomic characteristics				
Sex	Males	1,655 (50.3%)	963 (55.7%)	< ***0.001***
	Females	1,638 (49.7%)	767 (44.3%)	
Age in years at the questionnaire	< 25	516 (15.7%)	-	
	25-29	669 (20.3%)	-	
	30-39	1,356 (41.2%)	-	
	≥ 40	752 (22.8%)	-	
Educational level	Less than High School	655 (20.2%)	-	
	High School graduate	1,257 (38.8%)	-	
	College graduate	1,327 (41.0%)	-	
Unemployed and seeking work	No	2,659 (92.1%)	-	
	Yes	228 (7.9%)	-	
Marital status	Single, divorced or widowed	2,632 (79.9%)	-	
	Married	661 (20.1%)	-	

CNS, central nervous system.
[a] Chi-square test.
[b] Gonadal tumour, thyroid tumour and other types of carcinoma.

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Table 2. Smoking status and cannabis use in childhood cancer survivors from the FCCSS cohort (N=2,887) compared with sex-, age-, education level- and marital status-matched controls from the general population.

	Survivors	**Controls**	*p-value*
Ever smoking, n (%)			< ***0.001***[a]
No	1,459 (50.6%)	1,253 (43.4%)	
Yes	1,424 (49.4%)	1,633 (56.6%)	
Current smoking, n (%)			< ***0.001***[a]
No	2,140 (74.1%)	1,711 (59.3%)	
Yes	747 (25.9%)	1,176 (40.7%)	
- Age in years at smoking initiation, mean ± SD	17.5 ± 3.6	18.5 ± 4.0	< ***0.001***[b]
- Age in years at smoking initiation, n (%)			< ***0.001***[a]
< 14	35 (4.9%)	32 (3.4%)	
14-17	406 (56.3%)	378 (40.1%)	
18-21	213 (29.5%)	403 (42.7%)	
≥ 22	67 (9.3%)	130 (13.8%)	
- Number of cigarettes smoked per day, mean ± SD	11.6 ± 7.8	11.0 ± 8.9	***0.016***[b]
- Number of cigarettes smoked per day, n (%)			***0.028***[a]
<10	284 (39.1%)	503 (43.0%)	
10-20	391 (53.9%)	561 (47.9%)	
>20	51 (7.0%)	107 (9.1%)	
Current cannabis use, n (%)			*0.676*[a]
No	2,698 (93.5%)	2,539 (93.2%)	
Yes	189 (6.6%)	186 (6.8%)	

SD, standard deviation.
[a] Chi-square test.
[b] Mann-Whitney U Test.

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Table 3. Prevalence and odds ratios for being current smoker and current cannabis user among childhood cancer survivors (overall and by cancer type) from the FCCSS cohort (N=2,887) compared to the general population.

	Current smokers		**Current cannabis users**	
	%	RR[a] [95% CI]	%	RR[a] [95% CI]
FCCSS overall	25.9%	**0.64 [0.59-0.68]**	6.6%	1.00 [0.82-1.21]
Wilms Tumour	27.8%	**0.70 [0.60-0.80]**	5.9%	0.93 [0.65-1.33]
Neuroblastoma	28.8%	**0.68 [0.58-0.80]**	8.0%	1.04 [0.74-1.48]
Hodgkin's lymphoma	21.7%	**0.55 [0.42-0.73]**	5.7%	1.02 [0.57-1.84]
Non-Hodgkin's lymphoma	28.6%	**0.70 [0.59-0.83]**	7.6%	1.11 [0.76-1.64]
Soft tissue sarcoma	29.9%	**0.76 [0.64-0.90]**	8.1%	1.36 [0.94-1.99]
Bone sarcoma	25.2%	**0.66 [0.54-0.81]**	5.8%	1.10 [0.68-1.79]
CNS tumour	14.3%	**0.31 [0.24-0.42]**	2.8%	**0.35 [0.17-0.71]**
Retinoblastoma	22.7%	**0.51 [0.37-0.70]**	7.0%	0.80 [0.42-1.54]
Other solid cancers	26.4%	**0.69 [0.58-0.82]**	7.4%	1.32 [0.90-1.95]
Chi-square test of independence	*p<0.001*		*p=0.159*	

CNS, central nervous system; FCCSS, French childhood cancer survivor study; RR, relative risk.
[a] Relative risks ratios were adjusted for sex, age, educational level and marital status.

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Table 4. Demographic, socioeconomic, health-related quality of life, and clinical factors related to current smoking, smoking cessation and current cannabis use in childhood cancer survivors from the FCCSS cohort.

		Current smoking N=2,887	**Smoking cessation** N=1,424	**Current cannabis use** N=2,887
		RR[a] [95% CI]	RR[a] [95% CI]	RR[a] [95% CI]
Clinical characteristics				
Childhood cancer type	Wilms Tumour	1	1	1
	Neuroblastoma	1.00 [0.81-1.22]	0.90 [0.75-1.09]	1.22 [0.77-2.95]
	Hodgkin's lymphoma	1.03 [0.72-1.45]	0.91 [0.70-1.19]	1.07 [0.49-2.31]
	Non-Hodgkin's lymphoma	1.02 [0.81-1.28]	0.85 [0.68-1.07]	1.09 [0.66-1.80]
	Soft tissue sarcoma	1.13 [0.91-1.40]	0.86 [0.71-1.06]	1.46 [0.90-2.37]
	Bone sarcoma	1.08 [0.82-1.42]	0.99 [0.79-1.24]	1.19 [0.62-2.30]
	CNS tumour	**0.43 [0.31-0.59]**	1.05 [0.80-1.37]	**0.35 [0.16-0.80]**
	Retinoblastoma	0.73 [0.51-1.04]	1.25 [0.91-1.72]	0.94 [0.43-2.06]
	Other solid cancers[b]	0.96 [0.75-1.23]	0.95 [0.77-1.18]	1.39 [0.82-2.37]
Age in years at first cancer	< 5	1	1	1
	5-9	0.88 [0.73-1.05]	1.08 [0.92-1.27]	1.06 [0.72-1.56]
	≥ 10	0.96 [0.79-1.17]	1.13 [0.94-1.35]	1.09 [0.70-1.70]
Chemotherapy	No	1	1	1
	Yes	**0.85 [0.73-0.99]**	0.98 [0.86-1.13]	1.08 [0.73-1.60]
Thoracic radiation therapy	No	1	1	1
	Yes	**0.80 [0.64-0.99]**	1.09 [0.94-1.28]	0.89 [0.54-1.47]
Second cancer	No	1	1	1
	Yes	**0.65 [0.44-0.96]**	**1.27 [1.04-1.55]**	1.12 [0.55-2.25]
Cardiovascular disease	No	1	1	1
	Yes	**0.72 [0.52-0.99]**	1.17 [0.95-1.43]	0.82 [0.42-1.58]
Demographic and socioeconomic characteristics				
Sex	Females	1	1	1
	Males	**1.40 [1.23-1.59]**	**0.82 [0.73-0.92]**	**2.81 [2.06-3.82]**
Age in years at the questionnaire	< 30	1	1	1
	30-39	0.98 [0.82-1.16]	1.09 [0.92-1.28]	**0.60 [0.42-0.87]**
	≥ 40	**0.78 [0.62-0.99]**	1.19 [0.97-1.46]	**0.31 [0.17-0.57]**
Educational level	Less than High School	1	1	1
	High School graduate	0.88 [0.75-1.03]	1.09 [0.92-1.29]	0.94 [0.65-1.37]
	College graduate	**0.59 [0.50-0.70]**	**1.45 [1.24-1.70]**	**0.62 [0.41-0.93]**
Unemployed and seeking work	No	1	1	1
	Yes	1.20 [0.99-1.45]	1.07 [0.89-1.28]	**1.58 [1.08-2.30]**
Marital status	Single, divorced or widowed	1	1	1
	Married	**0.82 [0.69-0.97]**	**1.23 [1.09-1.38]**	0.72 [0.48-1.08]
Health-related quality of life				
SF-36 MCS score	< Q1 (38.7)	**1.60 [1.34-1.91]**	0.86 [0.74-1.00]	**1.95 [1.30-2.92]**
	Q1 (38.7) – median (46.8)	**1.26 [1.05-1.51]**	0.93 [0.80-1.08]	**1.54 [1.03-2.29]**
	Median (46.8) – Q3 (53.0)	1.13 [0.94-1.37]	0.98 [0.85-1.15]	1.21 [0.79-1.85]
	> Q3 (53.0)	1	1	1
SF-36 PCS score	< Q1 (46.4)	**0.84 [0.71-0.98]**	1.12 [0.99-1.27]	0.86 [0.60-1.24]
	> Q1 (46.4)	1	1	1

CI, confidence interval; CNS, central nervous system; MCS, Mental Component Summary; PCS, Physical Component Summary; Q1, 1st quartile; Q3, 3rd quartile; RR, relative risk.
[a] Relative risks were adjusted for all the covariates presented in the table and for the propensity of response to the questionnaire.
[b] gonadal tumour, thyroid tumour and other types of carcinoma.

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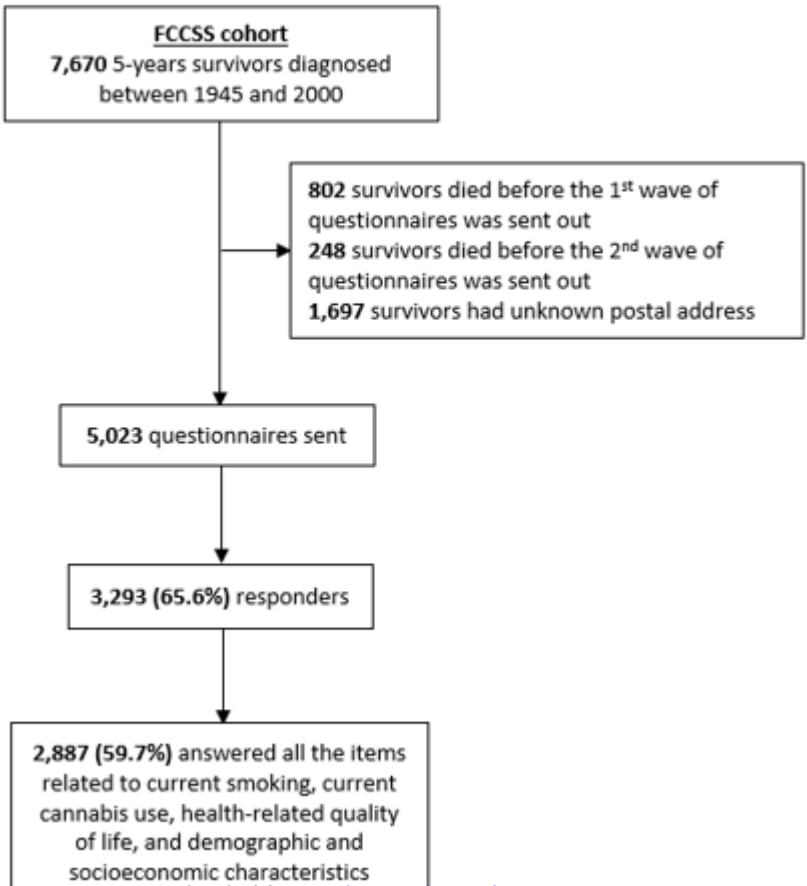
566 **FIGURES**

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568 **Figure 1.** Flow-chart of the FCCSS cohort subjects participating in the present study.

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Figure 1.



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Smoking and cannabis use among childhood cancer survivors: results of the French Childhood Cancer Survivor Study

Nicolas Bougas, Brice Fresneau, Sandrine Pinto, et al.

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