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## Smoking and cannabis use among childhood cancer survivors: Results of the french childhood cancer survivor study

Nicolas Bougas, Brice C. Fresneau, Sandrine Pinto, Auélie Mayet, Joeffrey Marchi, François Pein, Imène Mansouri, Neige Marie Yvanne Journy, Angela Jackson, Vincent Souchard, et al.

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1                                   **Smoking and cannabis use among childhood cancer survivors:**  
2                                   **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.

## 81 INTRODUCTION

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

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

97 Thus, smoking among survivors of childhood cancer is a major concern; there is a real need for data to assess the  
98 magnitude of this public health issue and investigate its determinants to develop targeted interventions and  
99 effective policies. Several studies have reported prevalence of smoking among CCS and have compared tobacco  
100 use between survivors and control subjects. While most highlighted lower prevalence of smoking among  
101 survivors,<sup>8-16</sup> a few reported greater prevalence for smoking among survivors<sup>17,18</sup> or no differences.<sup>19,20</sup>  
102 Concerning cannabis consumption, lower prevalence was found among CCS.<sup>11,19,21,22</sup> As the majority of these  
103 studies took place in North America<sup>8,9,12,15,17-20</sup> or in the UK,<sup>10,14</sup> their results may not be generalizable to other  
104 populations with different distribution of risk behaviors, and need to be supported by other data. No such study  
105 has yet been conducted in France, which has a much higher prevalence of tobacco smoking than the UK, the US  
106 and Canada according to WHO data.<sup>23</sup> France also has the highest prevalence of cannabis use in Europe despite  
107 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  
108 study).<sup>24</sup> It is worthwhile to explore the determinants of smoking/cannabis use among CCS from a population  
109 with high rates of tobacco smoking and cannabis use to determine whether these determinants are similar to  
110 those reported among CCS from countries with lower rates of tobacco smoking and cannabis use.

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

114

## 115 METHODS

### 116 Study population

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

121 The FCCSS cohort currently includes 7,670 subjects. Data on tumour type and treatment were extracted from  
122 medical records, as well as gender, date of birth and date of diagnosis. Second cancer and cardiovascular  
123 diseases (myocardial infarction, angina, heart failure, valvular diseases, cardiac arrhythmia, conduction disorder,  
124 and pericardial diseases) were ascertained from physician's report or medical records. Epidemiological data,  
125 including health behavior (smoking and cannabis use), health-related quality of life (QOL) and demographic and  
126 socioeconomic characteristics were collected using a self-administered questionnaire derived from the US and  
127 the UK survivors' cohorts.<sup>8,10</sup> Questionnaires were sent in two waves: the first one, from 2005 onwards, involved  
128 survivors treated before 1985, and the second one, from 2010 onwards, involved survivors treated from 1986 to  
129 2000. Three-quarters of the questionnaires (75.5%) were filled between 2005 and 2011. Among the FCCSS  
130 subjects, 802 died before the 1st wave of questionnaires was sent out, 248 died before the 2nd wave of  
131 questionnaires was sent out and 1,697 had unknown current postal address. As a result, 5,023 subjects were  
132 contacted by postal mail to complete this questionnaire; of these, 3,293 (65.6%) answered the questionnaire, and  
133 2,887 (59.7%) answered all the items related to current smoking, current cannabis use, health-related QOL, and  
134 demographic and socioeconomic characteristics (Figure 1).

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

#### 138 **Control population**

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

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

#### 153 **Outcome variables: Smoking status and cannabis use**

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

160 variable (< 14, 14-17, 18-21,  $\geq$  22) or as a continuous variable. Current cannabis use was defined as a binary  
161 variable “smoking regularly cannabis” (yes, no).

### 162 **Correlates under study**

163 Clinical predictors were childhood cancer type (classified according to the International Classification of  
164 Childhood Cancer<sup>29</sup>), decade of childhood cancer diagnosis (divided into four categories: < 1975, 1975–1984,  
165 1985–1994,  $\geq$  1995), age at childhood cancer diagnosis, chemotherapy (no, yes), thoracic radiation therapy (no,  
166 yes), second cancer (no, yes) and cardiovascular disease (no, yes).

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

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

### 179 **Statistical analysis**

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

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

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

199 years at first cancer, decade of diagnosis at first cancer, radiation therapy) were incorporated into this propensity  
200 score through a logit model to calculate the probability of response of each participant.<sup>26,33</sup>

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

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

207

## 208 **RESULTS**

### 209 **Characteristics of participants**

210 Overall, response to the questionnaire was significantly associated with gender, cancer type, age at cancer,  
211 decade of diagnosis and radiation therapy (Table 1). About half of the responders (48.0%) were diagnosed under  
212 5 years of age. Most responders were diagnosed before 1995 (86.3%) whereas 52.8% of the non-responders were  
213 diagnosed from 1995 onwards. The most prevalent diagnoses were Wilms tumour (18.4%) and Neuroblastoma  
214 (14.3%). Retinoblastoma was the less common diagnosis among responders (4.5%), but the most frequent  
215 among non-responders (20.2%). About half of non-responders (48.4%) received radiation therapy, against 57.0%  
216 among the responders (Table 1). Mean age at study was 33.4 years. Overall, 20.2% of participants had an  
217 educational level below High School and 79.9% were not married.

### 218 **Smoking status and cannabis use: comparison between childhood cancer survivors and controls from the** 219 **general population**

220 Smoking status and cannabis use in FCCSS participants and sex-, age-, education level- and marital status-  
221 matched controls from the general population are described in Table 2. Prevalence of current smoking was lower  
222 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%,  $P$   
223  $< 0.001$ ). Age at smoking initiation was lower in survivors (17.5 vs 18.5 years,  $P < 0.001$ ). Among CCS, 677 of  
224 those who have ever smoked have quit smoking (47.5%). When smoking, participants smoked slightly more  
225 cigarettes per day than controls from general population (11.6 vs 11.0,  $P=0.016$ ). Prevalence of current cannabis  
226 use was similar among survivors (6.6%) and controls (6.8%,  $P=0.676$ ). Using a chi-square test, current smoking  
227 and current cannabis use among survivors were strongly associated ( $p<0.001$ , Supplementary Table S1).

228 Survivors of each type of cancer were significantly less likely to smoke than the general population (Table 3).  
229 Survivors of CNS tumour had the lowest risk of smoking compared to the general population (RR 0.31, 95% CI  
230 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).  
231 Regarding cannabis use, only the CNS tumour survivors were significantly less likely to consume cannabis than  
232 the general population (RR 0.35, 95% CI 0.17 to 0.71), while survivors of soft tissue sarcoma had the highest  
233 odds (RR 1.36, 95% CI 0.94 to 1.99) (Table 3).

### 234 **Factors associated with smoking among childhood cancer survivors**

235 Results of multivariable analysis examining associations between current smoking and clinical, demographic,  
236 socioeconomic and QOL predictors among survivors are presented in Table 4. Survivors of CNS tumour had a  
237 significantly lower risk of being current smokers compared to survivors of Wilms Tumour (RR 0.43, 95% CI  
238 0.31 to 0.59). Survivors who had received chemotherapy (RR 0.85, 95% CI 0.73 to 0.99), those who had

239 received thoracic radiation therapy (RR 0.80, 95% CI 0.64 to 0.99), those who had a second cancer (RR 0.65,  
240 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  
241 likely to be current smokers. No differences were found between smokers and non-smokers regarding age at first  
242 cancer. Current smokers were more likely to be males (RR 1.40, 95% CI 1.23 to 1.59) and less likely to be  
243 married (RR 0.82, 95% CI 0.69 to 0.97). Older survivors ( $\geq 40$  years) were less likely to smoke than younger  
244 ones ( $< 30$  years) (RR 0.78, 95% CI 0.62 to 0.99). Survivors who graduated from College were less likely to be  
245 current smokers than those who dropped out before High School (RR 0.59, 95% CI 0.50 to 0.70). Participants  
246 with a poor score for physical QOL ( $< 1^{\text{st}}$  quartile) were less likely to be current smokers compared to others  
247 (RR 0.84, 95% CI 0.71 to 0.98). Conversely, survivors with a poor score for mental QOL ( $< 1^{\text{st}}$  quartile) were  
248 more likely to smoke compared to those with a high score for mental QOL ( $> 3^{\text{rd}}$  quartile) (RR 1.60, 95% CI  
249 1.34 to 1.91). We did not find any effect modification by CNS tumour or thoracic radiation therapy. Males were  
250 less likely to quit smoking (RR 0.82, 95% CI 0.73 to 0.92), whereas survivors who were married (RR 1.23, 95%  
251 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  
252 cancer (RR 1.27, 95% CI 1.04 to 1.55) were more likely to quit.

### 253 **Factors associated with current cannabis use among childhood cancer survivors**

254 Survivors of CNS tumour had a significantly lower risk of being current cannabis users compared to survivors of  
255 Wilms Tumour (RR 0.35, 95% CI 0.16 to 0.80) (Table 4). No differences were found regarding thorax radiation  
256 therapy, chemotherapy, age at first cancer, second cancer and cardiovascular diseases. Cannabis users were more  
257 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  
258 use decreased with age: CCS aged 30-39 years and those aged 40 years or older were less likely to be current  
259 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  
260 0.57, respectively). Compared to survivors who dropped out before High School, those who graduated from  
261 College were less likely to be current cannabis users (RR 0.62, 95% CI 0.41 to 0.93). Participants with a poor  
262 score for mental health ( $< 1^{\text{st}}$  quartile) were more likely to be current cannabis users compared to those with a  
263 high score for mental QOL ( $> 3^{\text{rd}}$  quartile) (RR 1.95, 95% CI 1.20 to 2.92). We did not find any effect  
264 modification by CNS tumour or thoracic radiation therapy.

265

## 266 **DISCUSSION**

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

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



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

285 Early onset of smoking is of particular concern since it increases the risk for developing related morbidities  
286 (such as cardiovascular diseases and lung cancer) and affects all-cause mortality.<sup>34</sup> In our study, age of smoking  
287 initiation among childhood cancer survivors was 17.5 years. Similar age of initiation (17.4 years) was reported in  
288 the British cohort.<sup>10</sup> Alarmingly, we found that survivors initiated smoking at a younger age than controls from  
289 the general population, which differ from results of British and Swiss studies.<sup>10,16</sup> It is well-known that an early  
290 age of smoking initiation is associated with a heavier smoking in adulthood;<sup>35</sup> thus, it is not surprising that we  
291 also reported that FCCSS survivors smoked more cigarettes per day than controls (11.3 vs 9.3). However,  
292 survivors from the British cohort smoked less cigarettes than controls from the general population (11.8 vs  
293 14.3).<sup>10</sup>

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

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

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

318 associated with later smoking, while some others supported the alternative hypothesis that smoking at baseline  
319 increases susceptibility to poor mental health condition.<sup>39</sup>

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

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

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

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

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

358 behaviors in our analyses using the SF-36, a validated measure of QOL, which was the case in only one other  
359 study.<sup>15</sup>

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

371

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516 TABLES  
 517

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

		Responders	Non-responders	<i>p</i> -value <sup>a</sup>
		n (%)	n (%)	
<b>Clinical characteristics</b>				
Childhood cancer type	Wilms Tumour	607 (18.4%)	173 (10.0%)	< <b>0.001</b>
	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 <sup>b</sup>	399 (12.1%)	214 (12.4%)	
Age in years at first cancer	< 5	1,580 (48.0%)	957 (55.3%)	< <b>0.001</b>
	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%)	< <b>0.001</b>
	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%)	< <b>0.001</b>
	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%)	-	
<b>Demographic and socioeconomic characteristics</b>				
Sex	Males	1,655 (50.3%)	963 (55.7%)	< <b>0.001</b>
	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.

<sup>a</sup> Chi-square test.

<sup>b</sup> 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	<i>p</i> -value
Ever smoking, n (%)			< <b>0.001</b> <sup>a</sup>
No	1,459 (50.6%)	1,253 (43.4%)	
Yes	1,424 (49.4%)	1,633 (56.6%)	
Current smoking, n (%)			< <b>0.001</b> <sup>a</sup>
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	< <b>0.001</b> <sup>b</sup>
- Age in years at smoking initiation, n (%)			< <b>0.001</b> <sup>a</sup>
< 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	<b>0.016</b> <sup>b</sup>
- Number of cigarettes smoked per day, n (%)			<b>0.028</b> <sup>a</sup>
<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 <sup>a</sup>
No	2,698 (93.5%)	2,539 (93.2%)	
Yes	189 (6.6%)	186 (6.8%)	

SD, standard deviation.

<sup>a</sup> Chi-square test.

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

CNS, central nervous system; FCCSS, French childhood cancer survivor study; RR, relative risk.  
<sup>a</sup>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 <sup>a</sup> [95% CI]	RR <sup>a</sup> [95% CI]	RR <sup>a</sup> [95% CI]
<b>Clinical characteristics</b>				
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	<b>0.43 [0.31-0.59]</b>	1.05 [0.80-1.37]	<b>0.35 [0.16-0.80]</b>
	Retinoblastoma	0.73 [0.51-1.04]	1.25 [0.91-1.72]	0.94 [0.43-2.06]
	Other solid cancers <sup>b</sup>	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	<b>0.85 [0.73-0.99]</b>	0.98 [0.86-1.13]	1.08 [0.73-1.60]
Thoracic radiation therapy	No	1	1	1
	Yes	<b>0.80 [0.64-0.99]</b>	1.09 [0.94-1.28]	0.89 [0.54-1.47]
Second cancer	No	1	1	1
	Yes	<b>0.65 [0.44-0.96]</b>	<b>1.27 [1.04-1.55]</b>	1.12 [0.55-2.25]
Cardiovascular disease	No	1	1	1
	Yes	<b>0.72 [0.52-0.99]</b>	1.17 [0.95-1.43]	0.82 [0.42-1.58]
<b>Demographic and socioeconomic characteristics</b>				
Sex	Females	1	1	1
	Males	<b>1.40 [1.23-1.59]</b>	<b>0.82 [0.73-0.92]</b>	<b>2.81 [2.06-3.82]</b>
Age in years at the questionnaire	< 30	1	1	1
	30-39	0.98 [0.82-1.16]	1.09 [0.92-1.28]	<b>0.60 [0.42-0.87]</b>
	≥ 40	<b>0.78 [0.62-0.99]</b>	1.19 [0.97-1.46]	<b>0.31 [0.17-0.57]</b>
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	<b>0.59 [0.50-0.70]</b>	<b>1.45 [1.24-1.70]</b>	<b>0.62 [0.41-0.93]</b>
Unemployed and seeking work	No	1	1	1
	Yes	1.20 [0.99-1.45]	1.07 [0.89-1.28]	<b>1.58 [1.08-2.30]</b>
Marital status	Single, divorced or widowed	1	1	1
	Married	<b>0.82 [0.69-0.97]</b>	<b>1.23 [1.09-1.38]</b>	0.72 [0.48-1.08]
<b>Health-related quality of life</b>				
SF-36 MCS score	< Q1 (38.7)	<b>1.60 [1.34-1.91]</b>	0.86 [0.74-1.00]	<b>1.95 [1.30-2.92]</b>
	Q1 (38.7) – median (46.8)	<b>1.26 [1.05-1.51]</b>	0.93 [0.80-1.08]	<b>1.54 [1.03-2.29]</b>
	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)	<b>0.84 [0.71-0.98]</b>	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, 1<sup>st</sup> quartile; Q3, 3<sup>rd</sup> quartile; RR, relative risk.

<sup>a</sup> Relative risks were adjusted for all the covariates presented in the table and for the propensity of response to the questionnaire.

<sup>b</sup> gonadal tumour, thyroid tumour and other types of carcinoma.

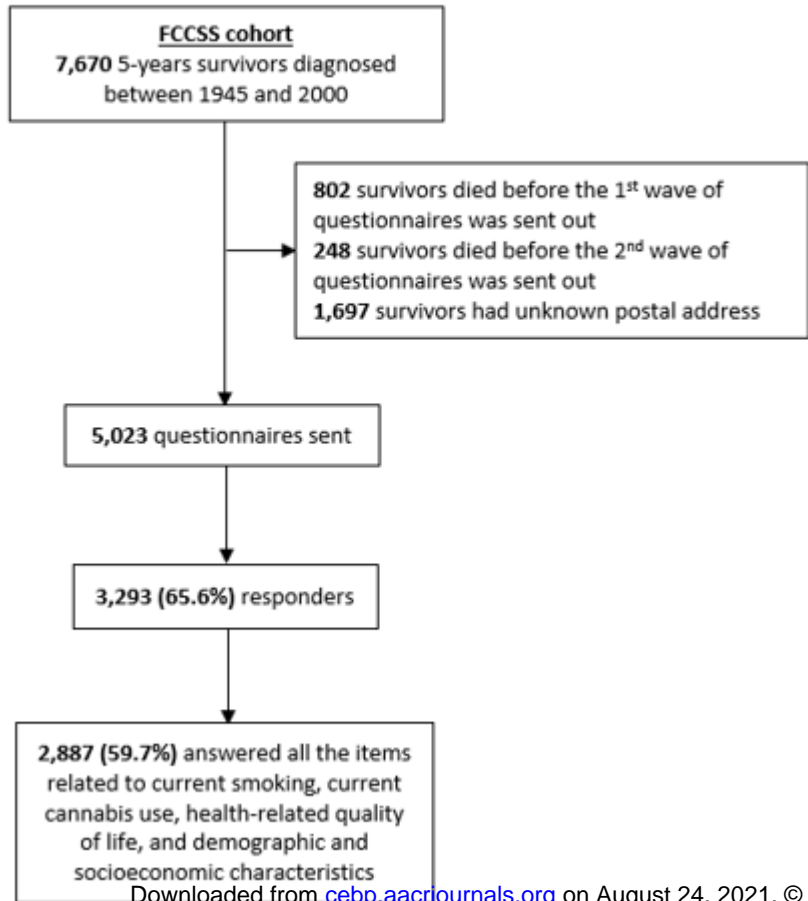
565

566 **FIGURES**

567

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

**Figure 1.**



# Cancer Epidemiology, Biomarkers & Prevention

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for Cancer Research

## 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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