Identifying clusters of health risk behaviors and their predictors in adult survivors of childhood cancer: A report from the French Childhood Cancer Survivor Study

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To cite this article: Pinto, S., B. Fresneau, H. C. Hounsossou, A. Mayet, J. Marchi, F. Pein, N. Journy, I. Mansouri, D. Drubay, V. Letort, S. Lemler, C. Demoor-Goldschmidt, A. Jackson, V. Souchard, G. Vu-Bezin, I. Diallo, C. Rubino, O. Oberlin, N. Haddy, F. de Vathaire, A. Dumas and R. S. Allodji (2020). "Identifying clusters of health risk behaviors and their predictors in adult survivors of childhood cancer: A report from the French Childhood Cancer Survivor Study." Psycho-Oncology 2020. 29(10): 1595-1603. DOI: 10.1002/pon.5470

Short running title: Health behaviors in childhood cancer survivor

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Abbreviations	
FCCSS	French Childhood Cancer Survivor Study cohort
CCSS	Childhood Cancer Survivor Study cohort
SNIIR-AM	French National Medical Insurance and Hospital
CNIL	French Data Protection Authority
INSERM	National Institute of Medical Research and Health
LCA	Latent Class Analysis

Abstract

Objective: Health risk behaviors (HRB) of childhood cancer survivors (CCS) are generally studied separately, despite the evidence suggesting that HRB are not independent. To our knowledge, few studies have examined HRB profiles in the former pediatric cancer patients. In this study, we identified HRB profiles and examined predictors engaging in unhealthy behaviors in CCS.

Methods: We used data from a French cohort of CCS that includes five-year survivors diagnosed between 1945 and 2000 with a solid tumor or a lymphoma and treated before reaching age 18, in five centers in France. A total of 2961 adult CCS answered a self-reported questionnaire pertaining to health behaviors. Latent class analysis was used to identify HRB profiles combining physical activity, smoking, cannabis use, and alcohol drinking. Multinomial logistic analyses examined predictors engaging in unhealthy behaviors.

Results: Three HRB patterns emerged: 'Low risk' (n=1079, 36.5%) included CCS who exhibited the lowest probabilities for the main HRB; 'Moderate risk behaviors' (n=1277, 43.1%), and 'High risk behaviors' (n=605, 20.4%) for CCS who exhibited the highest probabilities for smoking (71.9% with ≤10 cigarettes per day), cannabis use, and alcohol consumption. The multivariable regression revealed that male CCS, less educated or singles were significantly more likely to be in the high risk behaviors group than the low risk group.

Conclusions: As CCS remain a vulnerable population, screening for HBRs should be instituted in long-term follow-up care and multiple targeted health interventions (i.e.,

targeting more than one health behavior simultaneously) among survivors should be established to reduce them.

KEYWORDS: Health behaviors, smoking, alcohol drinking, cannabis use, physical activity, marital status, radiotherapy, childhood cancer survivors, survivorship

BACKGROUND

Improvements in survival rates have resulted in growing concerns about childhood cancer survivors' risks of developing treatment-related conditions.[1-5] Survivors are vulnerable to a broad spectrum of medical and psychosocial 'late effects', often associated with aging.[4,6-8] In addition to these therapy-related late effects, childhood cancer survivors are also vulnerable to other chronic conditions akin to the general population.[9] Engagement in unhealthy behaviors exacerbates these vulnerabilities and places this group at even further risk of experiencing adverse health outcomes later in life.[10,11] Therefore, it is important that survivors minimize preventable risk factors via positive health behaviors and lifestyle choices.

Several studies have investigated health behaviors in adolescents or young adults treated for childhood cancer.[10-14] However, health behaviors of childhood cancer survivors are generally studied separately, despite research indicating they frequently occur together.[9,11,13] Clustering methods allow the study of individuals engaged in multiple risk behaviors,[15,16] and they are highly important because the co-occurrence of multiple health-compromising behaviors may produce more deleterious effects on the health of childhood cancer survivors.

Our study objectives were to identify health behaviors profiles based on data from the French Childhood Cancer Survivors Study (FCCSS) cohort and to identify predictors engaging in unhealthy behaviors.

METHODS

Study population

Participants were members of the FCCSS cohort, which studied the late effects of pediatric cancer and its psychosocial impacts.[17-20] The FCCSS cohort currently includes 7670 five-year childhood cancer survivors diagnosed between 1945 and 2000 with a solid tumor or a lymphoma and treated before reaching age 18, in five centers in France. The FCCSS protocol has been approved by the INSERM national ethics committee and the French National Agency regulating Data Protection (CNIL). Consent was obtained from patients, parents or guardians according to national research ethics requirements. Demographic information, tumor characteristics and cancer treatments were extracted from medical charts record in the centre in which they were treated for childhood cancer. Vital status was obtained from the national registry of death (CépiDC). A self-reported questionnaire was sent in two waves, the first one beginning on September 1, 2005 and the second one finishing in December 31, 2016. Overall, 5023 survivors were still alive before the sending out of the first questionnaire; 3293 answered the questionnaires; 2961 answered all the items of the questionnaire pertaining to health behaviors (Supporting information, Figure S1).

Measurements

The FCCSS self-reported questionnaire was derived from several US and UK childhood cancer survivor studies,[11,17,18,21] and covered the following topics: quality of life, general health, fertility, current medication and health service utilization, psychological distress, socio-economic information and health behaviors. Primary outcome measures included four health behaviors at the time of questionnaire completion: 1) physical activity, 2) smoking, 3) cannabis use, and 4) alcohol consumption. For physical activity,

respondents were categorized into none, occasionally (less than once a month), or usually. Current smoking status was categorized at three levels: never smoked, ≤10 cigarettes per day, or ≥ 11 cigarettes per day. Current cannabis use was considered a binary variable (yes/no). Participants were asked to quantify the number of standard drinks per week. Current alcohol consumption was categorized at three levels: never, ≤ 3 drinks per week, or ≥ 3 drinks per week, which was a threshold used in previous studies.[22,23]

Potential predictors of health behaviours included the type of cancer, age at first cancer diagnosis, and treatment characteristics. Cancer type was classified according to the International Classification of Childhood Cancer, (1st and 2nd edition).[24,25] Age at first cancer diagnosis was categorized into four groups: 0–4 years, 5–8 years, 9–12 years and 12–18 years. The decade of first primary childhood cancer diagnosis was also categorized into four groups: < 1975, 1975–1984, 1985–1994 and or ≥ 1995. Four age groups: < 25 years, 25–29 years, 30–39 years and ≥ 40 years were used to categorize survivor age at the time of self-reported questionnaire completion. Treatments were coded as to whether or not survivors had the following: radiotherapy (yes/no) or chemotherapy (yes/no). Socioeconomic characteristics extracted from the self-reported questionnaire included educational level and marital status. Educational level was divided into three categories: less than high school, high school graduate, and college graduate. Marital status was classified as either single or living with a partner.

Statistical analysis

To characterize the study population, basic descriptive statistics concerning demographic, socioeconomic and clinical characteristics were calculated for all

predictors and covariates used, and the prevalence of health risk behaviors was examined.

Latent class analysis (LCA) was used to identify profiles of health behaviors (clusters). LCA is a statistical tool used to identify homogeneous, mutually exclusive groups (or "classes") existing in a heterogeneous population. Study participants were grouped by their endorsement patterns, allowing for two informative parameters to emerge: (1) the probability of being in a given class for each individual (posterior class probability) and (2) the probability of a response to a certain indicator, given a participant's membership in a latent class (variable-class probabilities).[26] The selection of optimal number of classes was achieved through fit indices, such as Bayesian information criterion (BIC), the adjusted Bayesian information criterion (aBIC), the Bozdogan's consistent AIC (CAIC) and Entropy.[27-29] More optimal models were indicated by lower values for these fit indices.

Finally, multivariable multinomial logistic regression examined associations between latent health behavioral profiles and demographic, socioeconomic and clinical predictor variables.

Analyses were conducted using SAS 9.3 software,[30] mainly using PROC LCA Version 1.3.2 of SAS for all LCA models,[31] and R software 3.3.0.[32] All P-values were two-sided; values < 0.05 were considered statistically significant.

RESULTS

Participants

Table 1 summarizes the characteristics of 2961 survivors who answered questionnaires, including participants' demographic, socioeconomic and clinical characteristics and their engagement in four health risk behaviors (physical activity, smoking, cannabis use, and alcohol consumption). Almost two-thirds of survivors were over 30 years old at the time of questionnaire completion, and 15% were under 25 years old. The majority of survivors had high school graduate or had a college graduate (80%) and approximately 79% of them were single. Half of survivors (51%) were diagnosed before the age of 5 years, and the most common diagnoses were nephroblastoma (19%) and neuroblastoma (14%). Most patients (79%) received chemotherapy and 57% received radiotherapy (Table 1). The median time from childhood cancer to self-reported questionnaires was 26 years.

Almost half of survivors reported usual physically active, about 28% never used alcohol, approximately 74% did not smoke and the vast majority (about 93%) did not use cannabis.

Models were fit with 2 to 6 classes and assessed with fit indices (Supporting information, Tables S1). Thereby, based on the lower CAIC, BIC and aBIC values, the three following clusters were identified: ‘Low risk behaviors’ (n = 1079, 36.4%), ‘Moderate risk behaviors (n = 1277, 43.1%), and ‘High risk behaviors’ (n = 605, 20.4%). The estimated conditional probability and frequency of an individual health risk behavior, according to the three latent classes, are shown (Table 2). Survivors were classified into latent classes corresponding to their highest posterior conditional probability (Table 2). The high risk group exhibited the highest frequencies for smoking (72% for ≥ 11 cigarettes per day), cannabis use (26%), and alcohol consumption (47%

for ≥ 3 drinks per week). The moderate risk behavior group was physically active, but not smoking or using cannabis, and drinking moderate alcohol levels. The low risk behavior group included survivors who exhibited the lowest probabilities for the main risk behaviors.

Demographic, socioeconomic and clinical characteristics according to the latent classes are described in Table 3. Gender, educational level, marital status, age at first cancer, childhood cancer type, decade of diagnosis of first primary childhood cancer and receipt of radiotherapy were statistically different between the three latent classes according to chi-square tests of independence.

Results of multivariable analysis examining predictors of latent class membership, with the low risk behavior group specified as the reference, are shown in Table 4. Subjects who were in the moderate risk group were more likely to have an educational level below high school (OR = 2.5, 95% CI 2.0–3.3) or equivalent to high school graduate (OR = 2.0, 95% CI 1.7–2.5), survivors of CNS tumors as initial childhood cancers (OR = 2.1, 95% CI 1.5–3.1; compared with survivors of nephroblastoma) and survivors treated by radiation therapy (OR = 1.4, 95% CI 1.1–1.7); and males (OR = 0.5, 95% CI 0.4–0.6) were less likely to belong to the moderate risk behavior group.

Subjects significantly more likely to be in the high risk group were males (OR = 1.3, 95% CI 1.0–1.6), survivors with an educational level below high school (OR = 3.8, 95% CI 2.8–5.1) or equivalent to high school graduate (OR = 2.5, 95% CI 2.0–3.1), singles (OR = 1.3, 95% CI 1.0–1.7), and survivors treated before 1975 (OR = 1.4, 95% CI 1.1–1.8). When compared with those having nephroblastoma, survivors of CNS tumor (OR = 0.2,

95% CI 0.2–0.4) were less likely to belong to the high risk group, when compared to the low risk behavior group.

DISCUSSION

Main findings and comparisons with other studies

The current study was designed to explore the latent classes of adolescent HRBs in a large cohort of childhood cancer survivors. Although several studies have focused on risk behaviors in childhood cancer survivors,[9,11,13,14,33-36] few studies have examined the clustering of healthy behaviors.[11,13] We identified three classes characterized by unique behavior patterns: a high risk group (20.4%), a moderate risk behavior group (43.1%), and a low risk behavior group (36.4%). This three-class model fit was consistent with the previous study by Lown et *al.*, in the US Childhood Cancer Survivor Study (CCSS).[11] However, in our study approximately 36% of survivors were in the low risk behavior group which was low when compared to the 46% of survivors in the low risk cluster in the US CCSS study.[11] This difference may be explained by two reasons: 1) the definitions used for health risk behaviors were not completely equivalent. Lown et *al.,* did not include other additional health risk behaviors such as cannabis use in their study;[11] 2) the research subjects in both studies were different, so the health risk behaviors are distributed differently between US and French populations. For instance, the prevalence of smoking in our study was about 26%, which was high when compared to the 17% in US survivors.[11]

Demographic, social, health, and treatment-related risk factors for inclusion in the high or moderate risk behavior clusters were identified in our study. We found that male

survivors were significantly more likely to be in the high risk group. An earlier study conducted in the Swiss childhood cancer cohort also reported that male childhood cancer survivors were more likely to be risk takers.[13] Our findings support this conclusion, where males exhibited greater levels of engagement in most risk behaviors, when compared to females. Another study among childhood cancer survivors reported low educational attainment as a risk factor for inclusion in the high risk group.[11] We found that when compared to childhood cancer survivors with a college graduate those with a low educational attainment (high school graduate or below), were significantly more likely to be in the high risk group. Marital status was associated with high risk behaviors in French cohort, which is consistent with the finding reported for US cohort.[11] Similar to the US cohort,[11] we also found that survivors treated by radiation therapy were significantly more likely to be in the moderate behavior group.

Study strengths and limitations

These findings provide important information to guide future research and clinical practice in the screening, preventing, and reducing health risk behaviors in childhood cancer survivors. Multiple behavior interventions (i.e., targeting more than one health behavior simultaneously) has the potential to have a much greater public health impact when compared to single behavior interventions. On the other hand, this study suffers from several limitations. Data were self-reported and may not be completely accurate. This study was a multicentre study that did not fully represent adult cancer survivors in France. Equally, 34% of 5023 patients did not answer the questionnaires. There were significant differences between responders and non-responders have been showed in demographic and treatment characteristics (gender, childhood cancer type, age at first

cancer, decade of diagnosis of first cancer, radiotherapy, and chemotherapy) (Supporting information, Tables S2 & S3). Our findings may have been subject to selection bias and it may be assumed that the prevalence of health risk behaviors and their patterns may have been different than what the data shown. All childhood cancer survivors' health risk behaviors were self-reported and thus subject to reporting bias. 'Wish bias' that is, the tendency to underreport health compromising, or over report socially desirable behaviors,[37] may have differentially affected survivor's replies. LCA is a type of person-centered approach; thus, different results may be obtained from different samples. Lastly, the health risk behaviors were self-reported at a single point in time, the lack of longitudinal assessment may also have influenced our estimates of cluster membership. However, despite these limitations, this study is one of a few to focus on determinants of health risk behavior patterns in childhood cancers survivors.

In conclusion, demographic, social, health, and treatment-related risk factors in childhood cancer survivors' appear to influence health risk behaviors. As childhood cancer survivors remain a vulnerable population, the characterization of survivor groups according to health risk behaviors and the identification of the potential predictors of these health risk behavior profils are important for risk stratification of childhood cancer survivors.[38,39] Consequently, screening for health risk behaviors should be instituted in long-term follow-up care and multiple targeted health interventions among survivors should be established to reduce them.

ACKNOWLEDGEMENTS

We thank the patients and all the clinicians and research staff who participated in the study. We are grateful to Françoise Terrier, Isao Kobayashi and Martine Labbé for their crucial contributions to this work.

This study was partially supported by the INCa/ARC foundation with the CHART project, the French Agence Nationale Pour la Recherche Scientifique (Hope-Epi project), the ARC foundation with the Pop-HaRC project, Ligue Nationale Contre le Cancer, and Programme Hospitalier de Recherche Clinique. These funding agencies had no role in the design and conduct of the study, in the collection, management, analysis and interpretation of the data, or in the preparation, review, and approval of the manuscript.

The authors declare no conflict of interest.

REFERENCES

1. Oeffinger KC, Mertens AC, Sklar CA, Kawashima T, Hudson MM, Meadows AT, *et al*. Chronic health conditions in adult survivors ofchildhood cancer. *N Engl J Med.* 2006; 355: 1572-1582.

2. Robison LL, Hudson MM. Survivors of childhood and adolescent cancer: life-long risks and responsibilities. *Nat Rev Cancer* 2014; 14: 61-70.

3. Kero AE, Järvelä LS, Arola M, Malila N, Madanat-Harjuoja LM, Matomäki J, *et al*. Late mortality among 5-year survivors of early onset cancer: a population-based register study. *Int J Cancer* 2015; 136: 1655-1664.

4. Signorelli C, Wakefield CE, Fardell JE, Wallace WHB, Robertson EG, McLoone JK, *et al*. The impact of long-term follow-up care for childhood cancer survivors: A systematic review. *Crit Rev Oncol Hematol* 2017; 114: 131-138.

5. Allodji RS, Haddy N, Vu-Bezin G, Dumas A, Fresneau B, Mansouri I, *et al*. Risk of subsequent colorectal cancers after a solid tumor in childhood: Effects of radiation therapy and chemotherapy. *Pediatr Blood Cancer* 2019; 66:e27495.

6. Geenen MM, Cardous-Ubbink MC, Kremer LC, van den Bos C, van der Pal HJ, Heinen RC, *et al*. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA* 2007; 297: 2705-2715.

7. Mertens AC, Liu Qi, Neglia JP, Wasilewski K, Leisenring W, Armstrong GT, *et al*. Cause-specific late mortality among 5 year survivors of childhood cancer: The Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2008; 100: 1368-1379.

8. Gudmundsdottir T, Winther JF, de Fine Licht S, Bonnesen TG, Asdahl PH, Tryggvadottir L, *et al*. Cardiovascular disease in Adult Life after Childhood Cancer in Scandinavia: A population-based cohort study of 32,308 one-year survivors. *Int J Cancer* 2015; 137: 1176–1186.

9. Lown EA, Goldsby R, Mertens AC, Greenfield T, Bond J, Whitton J, *et al*. Alcohol consumption patterns and risk factors among childhood cancer survivors compared to siblings and general population peers. *Addiction* 2008; 103: 1139–48.

10. Ford JS, Barnett M, Werk R. Health Behaviors of Childhood Cancer Survivors. *Children (Basel)* 2014; 1: 355–373.

11. Klosky JL, Howell CR, Li Z, Foster RH, Mertens AC, Robison LL, *et al*. Risky health behavior among adolescents in the childhood cancer survivor study cohort. *J Pediatr Psychol* 2012; 37: 634–646.

12. Lown EA, Hijiya N, Zhang N, Srivastava DK, Leisenring WM, Nathan PC, *et al*. Patterns and predictors of clustered risky health behaviors among adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Cancer* 2016; 122: 2747–2756.

13. Emmons K. Smoking among childhood cancer survivors: We can do better. *J Natl Cancer Inst.* 2008; 100: 1048–1049.

14. Rebholz CE, Rueegg CS, Michel G, Ammann RA, von der Weid NX, Kuehni CE, *et al*. Clustering of health behaviours in adult survivors of childhood cancer and the general population. *Br J Cancer* 2012; 107: 234-242.

15. Milam J, Slaughter R, Tobin JL, Unger JB, Ritt-Olson A, Freyer DR, *et al*. Childhood Cancer Survivorship and Substance Use Behaviors: A Matched Case-Control Study Among Hispanic Adolescents and Young Adults. *J Adolesc Health* 2018; 63: 115-117.

16. Busch V, Van Stel HF, Schrijvers AJ, de Leeuw JR. Clustering of health-related behaviors, health outcomes and demographics in Dutch adolescents: a cross-sectional study. *BMC Public Health* 2013; 13: 1118.

17. Alzahrani SG, Watt RG, Sheiham A, Aresu M, Tsakos G. Patterns of clustering

of six health-compromising behaviours in Saudi adolescents. *BMC Public Health* 2014; 14: 1215.

18. De Vathaire F, Hawkins M, Campbell S, Oberlin O, Raquin MA, Schlienger JY, *et al*. Second malignant neoplasms after a first cancer in childhood: temporal pattern of risk according to type of treatment. *Br J Cancer* 1999; 79: 1884-1893.

19. Allodji RS, Diallo I, El-Fayech C, Kahlouche A, Dumas A, Schwartz, *et al*. Association of radiation dose to the eyes with the risk for cataract after nonretinoblastoma solid cancers in childhood. *JAMA Ophthalmol* 2016; 134: 390–397.

20. Mansouri I, Allodji RS, Hill C, El-Fayech C, Pein F, Diallo S, *et al*. The role of irradiated heart and left ventricular volumes in heart failure occurrence after childhood cancer. *Eur J Heart Fail*. 2019; 21: 509-518.

21. Dumas A, Berger C, Auquier P, Michel G, Fresneau B, Sètchéou Allodji R, *et al*. Educational and occupational outcomes of childhood cancer survivors 30 years after diagnosis: a French cohort study. Br J *Cancer* 2016; 114: 1060-1068.

22. Hawkins MM. Long term survival and cure after childhood cancer. *Arch. Dis. Child* 1989; 64: 798-807.

23. Kabat GC, Kim M, Shikany JM, Rodgers AK, Wactawski-Wende J, Lane D, *et al*. Alcohol consumption and risk of ductal carcinoma in situ of the breast in a cohort of postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 2010; 19: 2066-2072.

24. Holahan JC, Brennan LP, Schutte KK, Holahan CK, Hixon JG, Moos RH. Drinking Level versus Drinking Pattern and Cigarette Smoking Among Older Adults. *Alcohol Clin Exp Res* 2018 ; 42: 795–802.

25. International Classification of Diseases for Oncology (ICD-O), first edition.

Geneva, World Health Organization. 1976

26. Percy C, Van Holten V, Muir CS, editors. International Classification of Diseases for Oncology, 2nd edition. Geneva, Switzerland: World Health Organization. 1992

27. Ji Y, Xu H, Zhang Y, Liu Q. Heterogeneity of adolescent health risk behaviors in rural western China: A latent class analysis. *PLoS One* 2018; 13: e0199286.

28. Sclove SL. Application of model-selection criteria to some problems in multivariate analysis. *Psychometrika.* 1987; 52: 333–343.

29. Bozdogan H. Model selection and Akaike's information criterion (AIC): The general theory and its analytical extensions. *Psychometrika* 1987; 52: 345–370.

30. McLachlan GJ. On bootstrapping the likelihood ratio test statistic for the number of components in a normal mixture model. *Applied Statistics* 1987; 36: 318–324.

31. SAS Institute Inc. Base SAS® 9.3 Procedures Guide: Statistical Procedures. Cary, NC: SAS Institute Inc. 2011

32. Lanza ST, Collins LM, Lemmon DR, Schafer JL. PROC LCA: A SAS procedure for latent class analysis. *Struct Equ Modeling* 2007; 14: 671–694.

33. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/. 2016

34. Carretier J, Boyle H, Duval S, , *et al*. A Review of Health Behaviors in Childhood and Adolescent Cancer Survivors: Toward Prevention of Second Primary Cancer. *J Adolesc Young Adult Oncol* 2016; 5: 78-90.

35. Balcerek M, Schuster T, Korte E, Philip T, Laurence V, Stark DP, *et al*. Health-Related Behaviour Among Children of Childhood Cancer Survivors in Germany. *Klin*

Padiatr 2017; 229: 118-125.

36. Kappa SS, Lewis RW, Mertens AC, Walsh SM, Wasilewski-Masker K, Meacham LR. A brief survey of health habits among childhood cancer survivors. *Pediatr Blood Cancer* 2018; 65: e27345.

37. Brinkman TM, Lown EA, Li C, Tonning Olsson I, Marchak JG, Stuber ML, , *et al*. Alcohol consumption behaviors and neurocognitive dysfunction and emotional distress in adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *Addiction* 2019; 114: 226-235.

38. Wynder EL, Higgins IT, Harris RE. The wish bias. *J Clin Epidemiol* 1990; 43: 619–621.

39. Sadak KT. Associates of Engagement in Adult-Oriented Follow-Up Care for Childhood Cancer Survivors. *J Adolesc Health*. 2017; 60: 127-128.

40. Szalda D, Piece L, Brumley L, Li Y, Schapira MM, Wasik M, *et al*. Associates of Engagement in Adult-Oriented Follow-Up Care for Childhood Cancer Survivors. *J Adolesc Health*. 2017; 60: 147-153.

Table 1: Demographic, socioeconomic, clinical and health behavioral characteristics of the study population from the FCCSS Cohort (N =2961).

Characteristics	N (%)	Characteristics	N (%)
Sex		**Decade of diagnosis of first cancer**	
Males	1480 (50.0)	< 1975	603 (20.4)
Females	1481 (50.0)	1975 – 1984	1195 (40.4)
Age at self-questionnaire, years		1985 – 1994	774 (26.1)
< 25	458 (15.5)	≥ 1995	389 (13.1)
25 – 29	614 (20.7)	**Radiotherapy**	
30 – 34	662 (22.4)	No	1267 (42.8)
35 – 39	567 (19.1)	Yes	1694 (57.2)
> 40	660 (22.3)	**Chemotherapy**	
Educational level		No	621 (21.0)
Less than high school	579 (19.6)	Yes	2340 (79.0)
High school graduate	1160 (39.2)	**Time to self-questionnaire[b]**	
College graduate	1222 (41.3)	Median (range), years	26.0 (9.4-57.9)
Marital status		**Physical activity**	
Single	2335 (78.9)	None	821 (27.7)
Living with a partner	626 (21.1)	Occasionally	751 (25.4)
Childhood cancer type		Usually	1389 (46.9)
Nephroblastoma	561 (18.9)	**Smoking**	
Neuroblastoma	421 (14.2)	None	2178 (73.6)
Hodgkin's lymphoma	196 (6.6)	≤10 cigarettes per day	318 (10.7)
Non-Hodgkin's lymphoma	356 (12.0)	≥ 11 cigarettes per day	465 (15.7)
Soft tissue sarcoma	345 (11.7)	**Cannabis use**	
Bone sarcoma	279 (9.4)	No	2766 (93.4)
CNS tumour	311 (10.5)	Yes	195 (6.6)
Retinoblastoma	135 (4.6)	**Alcohol consumption**	
Other solid cancers[a]	357 (12.1)	None	821 (27.7)
Age at first cancer, years		≤ 3 drinks per week	1278 (43.2)
0 – 4	1523 (51.4)	> 3 drinks per week	862 (29.1)
5 – 8	541 (18.3)		
9 – 12	449 (15.2)		
12 – 18	448 (15.1)		

CNS=central nervous system; [a]gonadal tumour, thyroid tumour and other types of carcinoma; [b]Interval time from childhood cancer to the self-reported questionnaire.

Table 2: The frequencies and estimated conditional probabilities of reporting each health risk behavior according to the latent classes in childhood cancer survivors (FCCSS Cohort, N =2961)

Health risk behaviors	Low risk behaviors – Cluster 1		Moderate risk behaviors – Cluster 2		High risk behaviors – Cluster 3	
	N(%)	Pr*	N(%)	Pr*	N(%)	Pr*
Overall prevalence	**1079 (36.4%)**	**0.25**	**1277 (43.1%)**	**0.54**	**605 (20.4%)**	**0.21**
Physical activity						
None	-	0.01	544 (42.6)	0.35	277 (45.8)	0.40
Occasionally	175 (16.2)	0.29	407 (31.9)	0.23	169 (27.9)	0.26
Usually	904 (83.8)	0.69	326 (25.5)	0.42	159 (26.3)	0.33
Smoking						
None	933 (86.5)	0.84	1233 (96.6)	0.92	12 (2.0)	0.14
≤10 cigarettes per day	146 (13.5)	0.14	14 (1.1)	0.02	158 (26.1)	0.28
≥ 11 cigarettes per day	-	0.02	30 (2.4)	0.06	435 (71.9)	0.58
Cannabis use						
No	1040 (96.4)	0.95	1277 (100.0)	1.00	449 (74.2)	0.75
Yes	39 (3.6)	0.05	-	0.00	156 (25.8)	0.25
Alcohol consumption						
None	-	0.00	714 (55.9)	0.45	107 (17.7)	0.16
≤ 3 drinks per week	598 (55.4)	0.59	457 (35.8)	0.38	223 (36.9)	0.37
≥ 3 drinks per week	481 (44.6)	0.40	106 (8.3)	0.17	275 (45.5)	0.47

Pr = Estimated conditional probabilities of reporting each health risk behavior form the from Latent Class Analysis (LCA); Cluster 1 = Physically active, not smoking or not using cannabis, but drinking at least moderate; Cluster 2 = Relatively inactive, but not smoking, not using cannabis and not drinking much; and Cluster 3 = Inactive, smoking, using cannabis and drinking at least moderate.

Table 3: Demographic, socioeconomic and clinical characteristics according to the latent classes in childhood cancer survivors (FCCSS Cohort)

Demographic, socioeconomic, clinical risk factors	Low risk behaviors – Cluster 1	Moderate risk behaviors – Cluster 2	High risk behaviors – Cluster 3	P-values
	N (%)	N (%)	N (%)	
Sex				
Males	603 (55.9)	512 (40.1)	365 (60.3)	<.0001
Females	476 (44.1)	765 (59.9)	240 (39.7)	
Age at self-questionnaire, years				
< 25	170 (15.8)	199 (15.6)	89 (14.7)	0.1526
25 – 29	213 (19.7)	251 (19.7)	150 (24.8)	
30 – 34	245 (22.7)	298 (23.3)	119 (19.7)	
35 – 39	206 (19.1)	235 (18.4)	126 (20.8)	
> 40	245 (22.7)	294 (23.0)	121 (20.0)	
Educational level				
Less than high school	134 (12.4)	297 (23.3)	148 (24.5)	<.0001
High school graduate	349 (32.3)	540 (42.3)	271 (44.8)	
College graduate	596 (55.2)	440 (34.5)	186 (30.7)	
Marital status				0.0094
Single	827 (76.6)	1006 (78.8)	502 (83.0)	
Living with a partner	252 (23.4)	271 (21.2)	103 (17.0)	
Childhood cancer type				<.0001
Nephroblastoma	207 (19.2)	227 (17.8)	127 (21.0)	
Neuroblastoma	156 (14.5)	165 (12.9)	100 (16.5)	
Hodgkin's lymphoma	71 (6.6)	95 (7.4)	30 (5.0)	
Non-Hodgkin's lymphoma	151 (14.0)	125 (9.8)	80 (13.2)	
Soft tissue sarcoma	131 (12.1)	125 (9.8)	89 (14.7)	
Bone sarcoma	100 (9.3)	123 (9.6)	56 (9.3)	
CNS tumour	69 (6.4)	210 (16.4)	32 (5.3)	
Retinoblastoma	58 (5.4)	53 (4.2)	24 (4.0)	
Other solid cancers[a]	136 (12.6)	154 (12.1)	67 (11.1)	
Age at first cancer, years				0.0113
0 – 4	566 (52.5)	618 (48.4)	339 (56.0)	
5 – 8	182 (16.9)	252 (19.7)	107 (17.7)	
9 – 12	152 (14.1)	218 (17.1)	79 (13.1)	
12 – 18	179 (16.6)	189 (14.8)	80 (13.2)	
Decade of diagnosis of first cancer				0.0368
< 1975	215 (19.9)	269 (21.1)	119 (19.7)	
1975 – 1984	425 (39.4)	491 (38.4)	279 (46.1)	
1985 – 1994	300 (27.8)	343 (26.9)	131 (21.7)	
≥ 1995	139 (12.9)	174 (13.6)	76 (12.6)	
Radiotherapy				<.0001
No	517 (47.9)	461 (36.1)	289 (47.8)	
Yes	562 (52.1)	816 (63.9)	316 (52.2)	
Chemotherapy				0.6040
No	229 (21.2)	274 (21.5)	118 (19.5)	
Yes	850 (78.8)	1003 (78.5)	487 (80.5)	

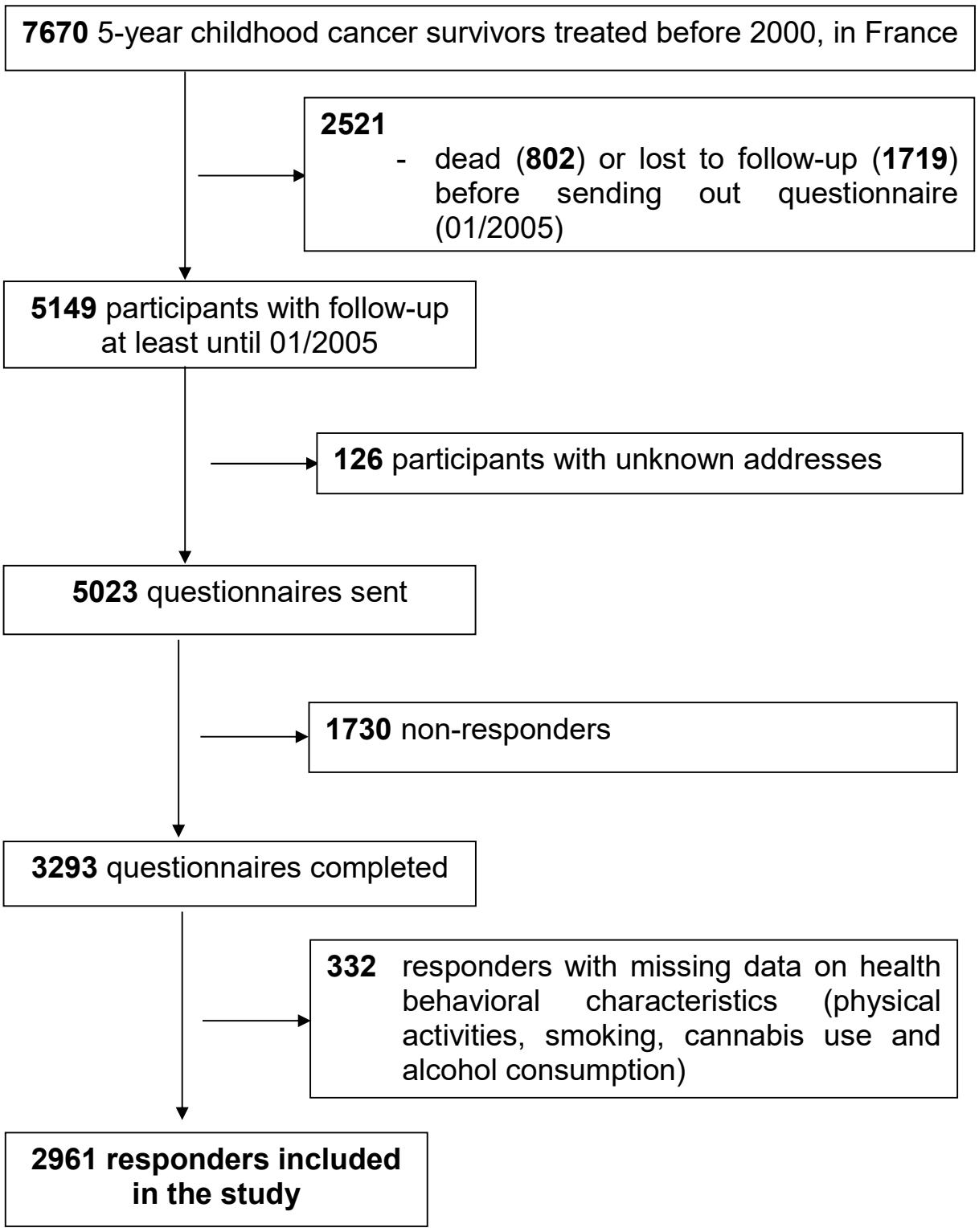
P-values from Chi-square test; Cluster 1 = Physically active, not smoking or not using cannabis, but drinking at least moderate; Cluster 2 = Relatively inactive, but not smoking, not using cannabis and not drinking much; and Cluster 3 = Inactive, smoking, using cannabis and drinking at least moderate.

Table 4: Odds ratios for determinants of health behavior patterns in childhood cancer survivors (FCCSS Cohort): results of multinomial regression analyses examining predictors of latent class membership with "Low-risk behaviors - Cluster 1" (N=1079) specified as the reference.

Demographic, socioeconomic, clinical risk factors	Moderate risk behaviors – Cluster 2 N=1079 OR [95% CI]	High risk behaviors – Cluster 3 N=605 OR [95% CI]	P-values
Sex			<.0001
Males	0.5 [0.4-0.6]**	1.3 [1.0-1.6]*	
Females	**Ref (OR=1)**	**Ref (OR=1)**	
Educational level			<.0001
Less than high school	2.5 [2.0-3.3]**	3.8 [2.8-5.1]**	
High school graduate	2.0 [1.7-2.5]**	2.5 [2.0-3.1]**	
College graduate	**Ref (OR=1)**	**Ref (OR=1)**	
Marital status			0.0034
Single	0.8 [0.7-1.0]	1.3 [1.0-1.7]*	
Living with a partner	**Ref (OR=1)**	**Ref (OR=1)**	
Childhood cancer type			<.0001
Nephroblastoma	**Ref (OR=1)**	**Ref (OR=1)**	
Neuroblastoma	1.0 [0.7-1.4]	1.0 [0.7-1.5]	
Hodgkin's lymphoma	1.1 [0.8-1.7]	0.7 [0.4-1.2]	
Non-Hodgkin's lymphoma	0.9 [0.6-1.3]	0.8 [0.6-1.3]	
Soft tissue sarcoma	0.9 [0.7-1.3]	1.2 [0.8-1.7]	
Bone sarcoma	1.3 [0.9-1.8]	1.1 [0.7-1.7]	
CNS tumour	2.1 [1.5-3.1]*	0.5 [0.3-0.9]**	
Retinoblastoma	0.9 [0.6-1.3]	0.6 [0.4-1.1]	
Other solid cancers[a]	1.1 [0.8-1.5]	0.9 [0.6-1.4]	
Age at first cancer, years			0.5711
0 – 4	**Ref (OR=1)**	**Ref (OR=1)**	
5 – 8	1.1 [0.9-1.4]	1.0 [0.7-1.3]	
9 – 12	1.2 [0.9-1.6]	0.9 [0.7-1.3]	
12 – 18	0.9 [0.7-1.2]	0.9 [0.6-1.3]	
Decade of diagnosis of first cancer			0.1270
< 1975	**Ref (OR=1)**	**Ref (OR=1)**	
1975 – 1984	1.1 [0.8-1.4]	1.4 [1.0-1.8]*	
1985 – 1994	1.1 [0.8-1.4]	1.0 [0.7-1.3]	
≥ 1995	1.1 [0.8-1.5]	1.2 [0.8-1.7]	
Radiotherapy			0.001
No	**Ref (OR=1)**	**Ref (OR=1)**	
Yes	1.4 [1.1-1.7]**	1.0 [0.8-1.2]	

Abbreviations: OR = odds ratio; CI = 95% confidence interval; Cluster 1 = Physically active, not smoking or not using cannabis, but drinking at least moderate; Cluster 2 = Relatively inactive, but not smoking, not using cannabis and not drinking much; and Cluster 3 = Inactive, smoking, using cannabis and drinking at least moderate; *P-values < 0.05, **P-values < 0.005.

Supplementary material Figure S1 - Study flow diagram



Supplementary material Table S1: Model fit statistics and selection criteria for Latent Class Analysis (LCA) of health behavioral in childhood cancer survivors with 2-6 latent classes

Number of classes	*BIC*	*CAIC*	*aBIC*	*Entropy (R^2)*
2	287.93	302.93	240.27	0.58
3[a]	**262.96**	**285.96**	**189.88**	**0.52**
4	292.88	323.88	194.38	0.53
5	331.87	370.87	207.95	0.64
6	385.05	432.05	235.71	0.54

Abbreviations: BIC = Bayesian information criterion; CAIC=consistent AIC; aBIC = sample-size-adjusted BIC; Entropy (R^2). A smaller fit statistics indicate a better model fit. [a]Selected as final model.

Supplementary material Table S2: Comparison responders and non-responders to self-reported questionnaire in key demographic and treatment characteristics in childhood cancer survivors (FCCSS Cohort)

Demographic, socioeconomic, clinical risk factors	Responders N = 3293 (65.6%)	Non-responders N = 1730 (34.4%)	P-values
Sex			
Males	1655 (50.3)	963 (55.7)	0.0003
Females	1638 (49.7)	767 (44.3)	
Childhood cancer type			<.0001
Nephroblastoma	607 (18.4)	173 (10.0)	
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[a]	399 (12.1)	214 (12.4)	
Age at first cancer, years			<.0001
0 – 4	1707 (51.8)	1011 (58.4)	
5 – 8	596 (18.1)	265 (15.3)	
9 – 12	503 (15.3)	205 (11.8)	
12 – 18	487 (14.8)	249 (14.4)	
Decade of diagnosis of first cancer			<.0001
< 1975	670 (20.3)	57 (3.3)	
1975 – 1984	1293 (39.3)	104 (6.0)	
1985 – 1994	880 (26.7)	656 (37.9)	
≥ 1995	450 (13.7)	913 (52.8)	
Radiotherapy			<.0001
No	1415 (43.0)	892 (51.6)	
Yes	1878 (57.0)	838 (48.4)	
Chemotherapy			0.1564
No	704 (21.4)	400 (23.1)	
Yes	2589 (78.6)	1330 (76.9)	

P-values from Chi-square test.

Supplementary material Table S3: Comparison completed answers and incompleteness answers and non-responders in key demographic and treatment characteristics in childhood cancer survivors (FCCSS Cohort)

Demographic, socioeconomic, clinical risk factors	Completed answers	Incompleteness answers and non-responder	P-values
	N = 2961 (59.0%)	N = 2062 (41.0%)	
Sex			
Males	1480 (50.0)	1138 (55.2)	0.0003
Females	1481 (50.0)	924 (44.8)	
Childhood cancer type			<.0001
Nephroblastoma	561 (18.9)	219 (10.6)	
Neuroblastoma	421 (14.2)	261 (12.7)	
Hodgkin's lymphoma	196 (6.6)	116 (5.6)	
Non-Hodgkin's lymphoma	356 (12.0)	169 (8.2)	
Soft tissue sarcoma	345 (11.7)	182 (8.8)	
Bone sarcoma	279 (9.4)	193 (9.4)	
CNS tumour	311 (10.5)	303 (14.7)	
Retinoblastoma	135 (4.6)	363 (17.6)	
Other solid cancers[a]	357 (12.1)	256 (12.4)	
Age at first cancer, years			<.0001
0 – 4	1523 (51.4)	1195 (58.0)	
5 – 8	541 (18.3)	320 (15.5)	
9 – 12	449 (15.2)	259 (12.6)	
12 – 18	448 (15.1)	288 (14.0)	
Decade of diagnosis of first cancer			<.0001
< 1975	603 (20.4)	124 (6.0)	
1975 – 1984	1195 (40.4)	202 (9.8)	
1985 – 1994	774 (26.1)	762 (37.0)	
≥ 1995	389 (13.1)	974 (47.2)	
Radiotherapy			<.0001
No	1267 (42.8)	1040 (50.4)	
Yes	1694 (57.2)	1022 (49.6)	
Chemotherapy			0.0390
No	621 (21.0)	483 (23.4)	
Yes	2340 (79.0)	1579 (76.6)	

P-values from Chi-square test.