Long-term hospitalisations in survivors of paediatric solid tumours in France

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The late effects of treatments for childhood cancers may lead to severe and multiple health conditions requiring hospitalisation. We aimed to estimate the hospitalisation rate among childhood cancer survivors (CCS) in France, to compare them with the general population and to investigate the associated factors. We matched total of 5439 5-year solid CCS diagnosed before the age of 21 between 1945 and 2000 by sex, birth year and region of residence to 386,073 individuals of the French general population. After linkage with the national hospital discharge database, we estimated the relative hospitalisation rate (RHR), the absolute excess risks (AERs) and the relative bed-day ratio (RBDR) during 2006–2018. We used generalised linear models to estimate associations between hospitalisation and survivor characteristics. Overall, the RHR was 2.49 (95% confidence interval [CI] 2.46–2.52) and the RBDR was 3.49 (95% CI 3.46–3.51). We found that neoplasm-related hospitalisations had the highest AER (105.8 per 1000 person-years), followed by genitourinary system diseases (34.4 per 1000 person-years) and cardiovascular diseases (19.2 per 1000 person-years). In adjusted analysis, CCS treated with chemotherapy (risk ratio [RR] 1.62, 95% CI 1.53–1.70), radiotherapy (RR 2.11, 95% CI 1.99–2.24) or both (RR 2.59, 95% CI 2.46–2.73) had a higher risk of hospitalisation than the ones who had not received any of these treatments. CCS treated during the past decades by chemotherapy and/or radiotherapy now had a higher hospitalisation risk for all main categories of diagnosis than the general population. Prevention strategies and medical surveillance programmes may promote a long-term decrease in the hospitalisation rate among CSS.

Advances in cancer treatment, such as improvements in chemotherapy regimens, radiation techniques and surgery, have allowed achieving 5-year survival rates of more than 80% in patients with paediatric cancer. However, late effects from cancer therapies continue to be a challenge. It is estimated that two thirds of childhood cancer survivors (CCS) will experience at least one treatment-related adverse event and 40% will experience at least one severe or life-threatening or disabling event several years after the cancer diagnosis1,2. Potential life-threatening or disabling late effects include second neoplasms, cardiovascular diseases, growth problems

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and mental health issues. This increased morbidity may lead to the development of complex health conditions requiring hospitalisation.

Some researchers have evaluated the long-term risk of hospitalisation among CCS and have reported an overall increased risk in survivors compared with the general population. In addition, their average length of stay in the hospital was up to 35% longer than patients without a history of cancer. A better understanding of the long-term hospitalisation of CCS is thus important to evaluate their health conditions and health care–related costs several years after cure.

In France, there are about 50,000 adult CCS, with a growing number of long-term survivors. However, no studies have analysed and detailed the hospitalisation rate in long-term CCS. The aim of this paper was to estimate the hospitalisation rate among CCS residing in France compared those of the French general population.

We have also described the hospitalisation-related clinical diagnoses and have investigated cancer-related factors associated with an increased probability of hospitalisation.

Materials and methods

Study population. The French Childhood Cancer Survivor Study (FCCSS) is a retrospective cohort of 7670 5-year CCS diagnosed for solid cancer or lymphoma (all malignancies except leukaemia) before the age of 21 years between 1945 and 2000 in five cancer centres in France. Cancer diagnoses were classified according to ICCC-3, with the exception of thyroid cancer, which was included in a separate group due to the specificity of iodine treatment and its consequences. Detailed information on the methods for data collection and patients has been already described in several articles. To study the FCCSS hospitalisation records, we selected survivors who were alive in January 2006, living in metropolitan France and who were linked to the National Health Data System (French acronym: SNDS). Of the 7670 5-years survivors from the FCCSS, 6,818 were still alive on 1 January 2006.

Data sources. The SNDS is the health care claims dataset in France; it covers around 99% of the population. It contains exhaustive data (beginning in 2006) on billing and reimbursement of beneficiaries, including private and public hospital data collected in the national hospital discharge database (French acronym: PMSI).

The PMSI is divided into four categories corresponding to hospitalisation in conventional hospital units (short stays), homecare units, rehabilitation and psychiatry institutions. It includes some demographic characteristics of patients (age, gender, place of residence) as well as clinical information of the hospitalisations such as the number of bed-days spent in hospital, which is the number of days in which the patient stays overnight in a hospital, excluding day hospital visits. We grouped hospitalisations according to the primary diagnosis into the 19 main groups of the ICD-10, excluding the following categories: pregnancy and childbirth, certain injury, poison, and mental health. This increased morbidity may lead to the development of complex health conditions requiring hospitalisation.

Statistical analysis. The hospitalisation and bed-day rates were calculated for both the FCCSS and reference populations as the total number of hospitalisations or bed-days divided by the number of person-years
childhood cancer treatment and 2006 was 19.9 years (SD: 9.9, interquartile range 12–26). The in-patient bed-day risk was higher among survivors of CNS tumours, gonadal tumours and retinoblastoma (Table 3). The in-patient bed-day rate for the first relapses of childhood cancer and secondary neoplasms, these numbers were, respectively, RHR = 2.12 (95% CI 3.46–3.51, p < 0.001). When excluding hospitalisation for neoplasms, which could be linked to long-term factors, they had more than three times as many in-patient bed-days as the reference population (RBDR 3.49, 95% CI 3.33–3.38).

Hospitalisations and bed-days. The following results are presented in Table 2. We identified 27,598 hospitalisations in FCCSS survivors, which accounted for 74,814 in-patient bed-days. For the FCCSS survivors, the hospitalisation rate was 401.2 per 1000 PY while the bed-day rate was 1084.4 per 1000 PY. In the matched reference population, the hospitalisation rate was 161.3 per 1000 PY and the bed-day rate was 311.1 per 1000 PY. Hence, the AER of hospitalisation was 239.9 per 1000 PY and the AER of in-patient bed-days was 773.2 per 1000 PY for FCCSS survivors. The RHR was 2.49 (95% CI 2.46–2.52, p < 0.001), meaning that FCCSS survivors were hospitalised more than twice as often as the matched reference population. Additionally, they had more than three times as many in-patient bed-days as the reference population (RBDR 3.49, 95% CI 3.46–3.51, p < 0.001). When excluding hospitalisation for neoplasms, which could be linked to long-term relapses of childhood cancer and secondary neoplasms, these numbers were, respectively, RHR = 2.12 (95% CI 2.08–2.15) and RBDR = 3.36 (95% CI 3.33–3.38).

Hospitalisations and bed-days and the survivors’ characteristics. Figure 2 shows that the hospitalisation rate was significantly higher in all types of primary cancer compared with the reference population, except in survivors of thyroid tumours (RHR 0.81, 95% CI 0.69–0.95) (Table 1). Central nervous system (CNS) tumour survivors had the highest RHR (3.56, 95% CI 3.45–3.67) and the highest RBDR (6.29, 95% CI 6.20–6.39) (Table 1). In detail, CNS tumour survivors were most likely to be hospitalised for congenital malformations (RHR 14.34, 95% CI 11.22–18.06), diseases of the nervous system (RHR 10.45, 95% CI 9.29–11.7), with a very high in-patient bed-day rate for the first group of pathologies (RBDR 33.88, 95% CI 30.27–37.81 and RBDR 32.19, 95% CI 31.02–33.39, respectively), but not for hospitalisation for endocrine diseases (Supplementary Table 1). In a multivariate analysis, compared with neuroblastoma, thyroid tumour survivors were at lower risk of both hospitalisation and in-patient bed-days (RR 0.66, 95% CI 0.56–0.78 and RR 0.73, 95% CI 0.66–0.80, respectively), while CNS tumour survivors (RR 1.29, 95% CI 1.22–1.36), kidney tumour survivors (RR 1.09, 95% CI 1.04–1.14) and other primary cancer survivors (RR 1.39, 95% CI 1.30–1.48) were at higher risk (Table 3). The in-patient bed-day risk was higher among survivors of CNS tumours, gonadal tumours and retinoblastoma (Table 3).
| Age at January 2006 (Start date) | N° Hospitalizations | AER per 1,000 FY | RHR (95% CI) | N° Bed-days in FCCS (per 1,000 FY) | Bed-days rate in EGB (per 1,000 FY) | AER per 1,000 FY | RRDR (95% CI) |
|---------------------------------|---------------------|------------------|--------------|----------------------------------|---------------------------------|-----------------|-------------|
| <20                             | 1535 (28.2)         | 4012             | 116.1        | 2.35 (2.28–2.43)                 | 7755                            | 136.3           | 253.7       |
| 20–30                           | 2066 (38)           | 407.1            | 295.7        | 3.66 (3.59–3.73)                 | 27,159                          | 182.7           | 851.0       |
| 31–40                           | 1311 (24.1)         | 496.0            | 330.2        | 2.99 (2.93–3.06)                 | 23,168                          | 304.5           | 1104.4      |
| >=41                            | 527 (9.7)           | 756.5            | 469.5        | 2.64 (2.56–2.71)                 | 16,732                          | 630.7           | 1989.6      |

| Status at December 2018 (Ending date) | N° Hospitalizations | AER per 1,000 FY | RHR (95% CI) | N° Bed-days in FCCS (per 1,000 FY) | Bed-days rate in EGB (per 1,000 FY) | AER per 1,000 FY | RRDR (95% CI) |
|----------------------------------------|---------------------|------------------|--------------|----------------------------------|---------------------------------|-----------------|-------------|
| Alive                                  | 5056 (93)           | 298.9            | 135.2        | 1.83 (1.8–1.85)                  | 44,789                          | 310.8           | 370.7       |
| Death                                  | 383 (7)             | 2509.9           | 2370.5       | 18 (17.61–18.4)                  | 30,025                          | 314.3           | 8877.8      |

| Year of diagnosis | N° Hospitalizations | AER per 1,000 FY | RHR (95% CI) | N° Bed-days in FCCS (per 1,000 FY) | Bed-days rate in EGB (per 1,000 FY) | AER per 1,000 FY | RRDR (95% CI) |
|-------------------|---------------------|------------------|--------------|----------------------------------|---------------------------------|-----------------|-------------|
| <1970             | 351 (6.5)           | 688.3            | 387.4        | 2.29 (2.21–2.37)                 | 10,688                          | 677.7           | 1820.3      |
| 1970–1979         | 980 (18)            | 611.4            | 414.3        | 3.1 (3.03–3.17)                  | 19,820                          | 375.3           | 1257.9      |
| 1980–1989         | 1809 (33.3)         | 433.3            | 303.8        | 3.34 (3.28–3.41)                 | 29,690                          | 227.8           | 1066.3      |
| >=1990            | 2299 (42.3)         | 249.4            | 156.4        | 2.68 (2.62–2.74)                 | 14,616                          | 150.3           | 342.9       |

| Age at first cancer | N° Hospitalizations | AER per 1,000 FY | RHR (95% CI) | N° Bed-days in FCCS (per 1,000 FY) | Bed-days rate in EGB (per 1,000 FY) | AER per 1,000 FY | RRDR (95% CI) |
|---------------------|---------------------|------------------|--------------|----------------------------------|---------------------------------|-----------------|-------------|
| 0–1                 | 1288 (23.7)         | 5687             | 345.1        | 219.0                            | 12,031                          | 227.3           | 501.4       |
| 2–4                 | 1276 (23.5)         | 5646             | 362.9        | 216.3                            | 18,753                          | 268.3           | 888.4       |
| 5–9                 | 1207 (22.2)         | 6617             | 437.5        | 273.0                            | 19,619                          | 326.9           | 965.6       |
| 10–14               | 1108 (20.4)         | 6839             | 492.1        | 298.4                            | 18,031                          | 397.4           | 895.5       |
| >=15                | 560 (10.3)          | 2591             | 363.5        | 164.2                            | 6380                            | 384.3           | 508.7       |

| First primary cancer type | N° Hospitalizations | AER per 1,000 FY | RHR (95% CI) | N° Bed-days in FCCS (per 1,000 FY) | Bed-days rate in EGB (per 1,000 FY) | AER per 1,000 FY | RRDR (95% CI) |
|---------------------------|---------------------|------------------|--------------|----------------------------------|---------------------------------|-----------------|-------------|
| Other solid cancer        | 312 (5.7)           | 152.8            | 261.3        | 2.71 (2.58–2.84)                 | 3645                            | 285.9           | 642.3       |
| Kidney tumors             | 825 (15.2)          | 172.1            | 281.0        | 2.63 (2.56–2.71)                 | 12,249                          | 335.7           | 838.3       |
| Neuroblastoma             | 746 (13.7)          | 126.7            | 200.4        | 2.58 (2.49–2.67)                 | 6727                            | 219.9           | 483.2       |

Continued
| Treatment received | Total Patients (%) | Patients Hospitalized (%) | N° Hospitalizations | Hospitalization rate in FCCSS (per 1000 PY) | Hospitalization rate in EGB (per 1,000 PY) | AER per 1,000 PY | RHR (95% CI) | N° Bed-days | Bed-days rate in FCCSS (per 1000 PY) | Bed-days rate in EGB (per 1,000 PY) | AER per 1000 PY | RBDR (95% CI) |
|-------------------|---------------------|---------------------------|--------------------|----------------------------------|----------------------------------------|----------------|--------------|----------|-----------------------------------|----------------------------------|----------------|-------------|
| No radiotherapy or chemotherapy | 720 (13.2) | 394 (10.5) | 1789 | 192.6 | 152.0 | 40.6 | 1.27 (1.21–1.33) | 3105 | 333.9 | 280.8 | 53.1 | 1.19 (1.15–1.23) |
| Radiotherapy | 696 (12.8) | 549 (14.6) | 4670 | 549.3 | 233.6 | 315.7 | 2.35 (2.28–2.42) | 15,418 | 1804.4 | 500.9 | 1303.5 | 3.60 (3.55–3.66) |
| Chemo-therapy | 1990 (36.6) | 1236 (32.9) | 7273 | 284.5 | 125.8 | 158.7 | 2.26 (2.21–2.31) | 19,361 | 755.6 | 226.9 | 528.7 | 3.33 (3.28–3.38) |
| Radiotherapy and Chemotherapy | 2033 (37.4) | 1577 (42) | 13,864 | 545.3 | 158.3 | 387.0 | 3.45 (3.39–3.5) | 36,930 | 1446.8 | 297.7 | 1149.1 | 4.86 (4.81–4.91) |

Table 1. Survivor characteristics and hospitalisation and bed-day rates. FCCSS, French Childhood Cancer Survivor Study; EGB, general sample of beneficiaries; AER, absolute access risk; PY, person-year; RHR, relative hospitalization ratio; RBDR, relative bed-days ratios.

FCCSS women were slightly more frequently hospitalised and accumulating more bed-days than men (Table 1). In an adjusted analysis, compared with the reference population, FCCSS women had a lower relative hospitalisation risk (RR 0.97, 95% CI 0.95–0.99) than FCCSS men; however, they had a higher in-patient relative bed-day risk (RR 1.29, 95% CI 1.27–1.31) (Table 3).

In a univariate analysis, there was no clear variation in the RHR according to the calendar period and the age at childhood cancer diagnosis, nor with the age at the start of the SNDS follow-up (2006) (Table 1). Compared with the reference population, the hospitalisation rate in the FCCSS survivors increased with age. This phenomenon was denoted by the higher AER with increasing age at the start of the SNDS follow-up. There were similar results for in-patient bed-days (Table 1). In a multivariate analysis, the variations in the adjusted RHR according to age at childhood cancer diagnosis were very low, and the variations in adjusted RBDR were low, whereas the RHR and RBDR significantly decreased as the age at the start of the SNDS follow-up increased. These changes were greater in patients treated between 1970 and 1990 than in the ones treated before that time (Table 3).

When investigating the role of age in each hospitalisation category for the RHR (Supplementary Table 2) and the RBDR (Supplementary Table 3) in a multivariate analysis, there were no clear variations, except for an increase with age at childhood cancer for hospitalisation for auditory diseases and a decrease for hospitalisation for genitourinary diseases.

**Role of treatments.** Survivors who had been treated with surgery or who had not received treatment had a small increase in the hospitalisation rate (RR 1.27, 95% CI 1.21–1.33) (Table 1). However, the hospitalisation and bed-day risks increased in survivors who had been treated with chemotherapy (RR 1.62, 95% CI 1.53–1.70 and RR 2.63, 95% CI 2.53–2.74, respectively), radiotherapy (RR 2.11, 95% CI 1.98–2.22 and RR 2.72, 95% CI 2.61–2.83, respectively) or both (RR 2.60, 95% CI 2.46–2.73 and RR 3.72, 95% CI 3.58–3.86, respectively) compared with survivors who had not received these treatments (Table 3). Chemotherapy was also associated with a significant increase in hospitalisation related to neoplasms, endocrine disorders and cardiovascular diseases; this increase was enhanced by radiotherapy (Supplementary Table 3). Chemotherapy was the most important.
Table 2. Hospitalisations and bed-days in the French Childhood Cancer Survivor Study (FCCSS) survivors and the reference sample according to the 10th revision of the International Classification of Diseases. FCCSS, French Childhood Cancer Survivor Study; EGB, general sample of beneficiaries; AER, absolute access risk; PY, person-year; RHR, relative hospitalization ratio; RBDR, relative bed-days ratios.

| Hospitalisations | No. Hospitalizations in FCCSS (per 1000 PY) | Hospitalisation rate in FCCSS (per 1000 PY) | No. Hospitalizations in EGB (per 1000 PY) | Hospitalisation rate in EGB (per 1000 PY) | AER per 1000 PY | (95% CI) | RHR | (95% CI) | N° Bed-Days in FCCSS | Bed-Days rate in FCCS (per 1000 PY) | No. Bed-Days in EGB (per 1000 PY) | Bed-Days rate in EGB (per 1000 PY) | AER per 1000 PY | RBDR | (95% CI) |
|------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------------------------------------|---------------|--------|------|--------|----------------------|----------------------------------------|-------------------------------------|----------------------------------------|---------------|-------|--------|
| Total            | 27,598                                      | 401.2                                       | 805,758                                    | 161.3                                       | 240.0         | 2.49   |      |        | 74,814               | 1084.4                                | 1,555,993                          | 311.1                     | 773.3 | 3.49   |
| Infec- tions     | 245                                          | 3.6                                          | 7585                                        | 1.5                                         | 2.0           | 2.35   | (2.06-2.66) | 1512                 | 21.9                                | 35,350                             | 7.1                        | 14.8  | 3.10   |
| Neo- prasms      | 10,100                                      | 146.8                                        | 205,097                                    | 41.0                                        | 105.8         | 3.58   | (3.51-3.65) | 16,156               | 234.2                               | 289,619                            | 57.9                      | 176.3 | 4.04   |
| Haematological   | 237                                          | 3.4                                          | 5233                                        | 1.0                                         | 2.4           | 3.29   | (2.88-3.74) | 858                  | 12.4                                | 19,169                             | 3.8                        | 8.6   | 3.24   |
| Endo- crine      | 830                                          | 12.1                                         | 17,153                                     | 3.4                                         | 8.6           | 3.51   | (3.28-3.76) | 2185                 | 31.7                                | 67,426                             | 13.5                      | 18.2  | 2.35   |
| Mental           | 300                                          | 4.4                                          | 18,899                                     | 3.8                                         | 0.6           | 1.15   | (1.03-1.29) | 782                  | 11.3                                | 48,923                             | 9.8                        | 1.6   | 1.16   |
| Neuro- logical   | 803                                          | 11.7                                         | 23,414                                     | 4.7                                         | 7.0           | 2.49   | (2.32-2.67) | 4433                 | 64.3                                | 55,985                             | 11.2                      | 53.1  | 5.74   |
| Ocular           | 326                                          | 4.7                                          | 13,992                                     | 2.8                                         | 1.9           | 1.69   | (1.51-1.89) | 453                  | 6.6                                 | 8277                               | 1.7                        | 4.9   | 3.97   |
| Auditory         | 109                                          | 1.6                                          | 4311                                        | 0.9                                         | 0.7           | 1.84   | (1.51-2.22) | 236                  | 3.4                                 | 6865                               | 1.4                        | 2.0   | 2.49   |
| Cardio- vascular | 1900                                         | 27.6                                         | 42,035                                     | 8.4                                         | 19.2          | 3.28   | (3.14-3.43) | 9065                 | 131.4                               | 139,661                            | 27.9                      | 103.5 | 4.70   |
| Pulmo- nary       | 601                                          | 8.7                                          | 20,994                                     | 4.2                                         | 4.5           | 2.08   | (1.92-2.25) | 4155                 | 60.2                                | 84,894                             | 17.0                      | 43.2  | 3.55   |
| Gastro- intestinal| 2113                                         | 30.7                                         | 116,056                                    | 23.2                                        | 7.5           | 1.32   | (1.27-1.38) | 5901                 | 85.5                                | 171,616                            | 34.3                      | 51.2  | 2.49   |
| Skin             | 393                                          | 5.7                                          | 14,316                                     | 2.9                                         | 2.8           | 1.99   | (1.82-2.2)  | 872                  | 12.6                                | 25,460                             | 5.1                        | 7.5   | 2.48   |
| Musculo- skeletal | 881                                          | 12.8                                         | 54,634                                     | 10.9                                        | 1.9           | 1.17   | (1.1-1.25)   | 3317                 | 48.1                                | 137,421                            | 27.5                      | 20.6  | 1.75   |
| Genitou-inary    | 3462                                         | 50.3                                         | 79,401                                     | 15.9                                        | 34.4          | 3.17   | (3.06-3.27) | 11,259               | 163.2                               | 148,360                            | 29.7                      | 113.5 | 5.50   |
| Congenital Malfor- mations | 153 | 2.2 | 3514 | 0.7 | 1.5 | 3.16 | (2.68-3.71) | 498 | 7.2 | 7390 | 1.5 | 5.7 | 4.88 | (4.47-5.33) |
| Symptoms Unclassi- fied | 1160 | 16.9 | 42,017 | 8.4 | 8.5 | 2.01 | (1.89-2.12) | 3108 | 45.0 | 60,888 | 12.2 | 32.9 | 3.70 | (3.57-3.83) |
| Injury— Poisoning | 1003 | 14.6 | 53,385 | 10.7 | 3.9 | 1.36 | (1.28-1.45) | 4344 | 63.0 | 136,490 | 27.3 | 35.7 | 2.31 | (2.24-2.38) |
| Other Factors     | 2982                                         | 43.4                                         | 83,722                                     | 16.8                                        | 26.6          | 2.59   | (2.25-2.68) | 5680                 | 82.3                                | 112,199                            | 22.4                      | 59.9  | 3.67   |
| Total Exclud- ing Neoplasms | 17,498 | 254.4 | 600,661 | 120.2 | 134.2 | 2.12 | (2.08-2.15) | 58,658 | 850.2 | 1,266,374 | 253.2 | 597.0 | 3.36 | (3.33-3.38) |

Discussion

In a cohort of 5439 5-year solid CCS, we found that individuals treated for childhood cancer in 1940–2000 in France were recently hospitalised more than twice as often as the general population during a 13-year follow-up (2006–2018). This increase in the hospitalisation rate occurred among cancer survivors who had been treated...
with chemotherapy and/or radiotherapy. The hospitalisation rate was elevated for all ICD-10 groups of hospitalisation-related pathologies, although the RHR was the highest for hospitalisation related to neoplasms, endocrine conditions and circulatory system diseases.

Our results are consistent with similar studies performed in the USA, Canada, the Nordic countries and the Netherlands in which CCS experienced a higher hospitalisation rate compared with the general population of their countries4–9. In Europe, the RHR was generally higher: about two times higher in the Netherlands6 and the Nordic countries9, with a bed-day ratio of 5 in the Nordic countries, and an RHR of about 2.8 and a bed-day ratio of 3.7 in Scotland17, findings similar to our results. On the other hand, there was a lower hospitalisation rate in a small Utah cohort and in the large US Childhood Cancer Survivor Study (CCSS)4,5, probably because most of the children in those studies had been treated before the end of the 1970s. That time corresponds to the beginning of generalised use of combined chemotherapy18, which was more toxic than the previous single-agent chemotherapy.

Previous studies have shown that survivors are more at risk of hospitalisation due to neoplasms, recurrences and/or subsequent4,7,9,17,19. These results are similar to our findings in which both the AER and RHR were the highest in CCS. In two studies from North America, survivors were hospitalised more often because of blood disorders4,19. However, our results indicate that although blood disorders had a higher RHR, this category had a very low hospitalisation rate and AER. This outcome could be partially explained by the fact that our cohort did not include leukaemia survivors. One study from the UK reported that CCS had a four-fold risk of being

**Figure 1.** The relative hospitalisation ratio and the relative bed-day ratio according to the 10th revision of the International Classification of Diseases.

**Figure 2.** The relative hospitalisation ratio and the relative bed-day ratio by the type of primary cancer.
hospitalised for cardiovascular disease compared to that expected from people of same age, sex and calendar year stratum. Another study from the Netherlands showed a higher RHR but the lowest AER for endocrine conditions. These results are consistent with our findings but inconsistent with findings from the Nordic countries, where there was excessive hospitalisation mainly due to nervous system diseases.

Researchers have reported a significantly higher hospitalisation rate in survivors of Hodgkin’s lymphoma, CNS tumours and bone tumours compared with other primary cancer types. However, our results showed few variations in the RHR according to the primary cancer type, except for thyroid and CNS tumours. A high hospitalisation rate for nervous system diseases and congenital malformations have been also reported in CNS tumour survivors, but the reclassification of neurofibromatosis from a tumour of uncertain behaviour in ICD-9 to congenital malformation in ICD-10 partially explains this excessive hospitalisation. On the contrary, in one study renal tumour survivors were not at additional risk of hospitalisation, and in another one they had among the lowest hospitalisation rate, which disagrees with our findings. However, this could be explained by the fact that we accounted for day hospital admissions, which include dialysis. In fact, our results show that their excessive hospitalisation comes from genitourinary system diseases.

Among FCCSS survivors, women experienced slightly higher hospitalisation and bed-day rates than men (respectively, 446.6 versus 363.5 per 1000 PY and 1242.3 versus 952.9 per 1000 PY, respectively). Compared with the reference population, women and men had a similar RHR and a higher AER for hospitalisation and bed-days, and women had a higher RBDR. These results are similar to a population-based cohort performed in Utah, but not to another population-based cohort study performed in another US state, in which both the RHR and AER were higher for women. Our findings are also different from the U.S. CCSS, in which women had a much lower RHR and AER than men. In the Netherlands, two studies evidenced a higher hospitalisation rate but a lower RHR in women than in men, whereas in the Scotland the standardised bed days ratio was almost the same in women and men.

Our findings are consistent with those of earlier studies in the Netherlands in which survivors initially treated with radiotherapy had a particularly increased hospitalisation rate for neoplasms, endocrine diseases and circulatory system diseases. Another study in British Columbia, Canada, reported that hospital-related morbidity was elevated for all combinations of primary treatment and was highest for those who had received radiation, chemotherapy and surgery. Our findings identified chemotherapy as a factor associated with hospitalisation especially for genitourinary system diseases, where cisplatin or ifosfamide have been established as treatment-related causes of chronic renal damage in CCS22.

| Number of hospitalizations | Number of bed-days |
|---------------------------|-------------------|
| RR (95% CI)               | RR (95% CI)      |
| Intercept                 | 1.79 (1.66–1.93)*** | 0.93 (0.89–0.98)*** |
| Women (Ref = Men)         | 0.97 (0.95–0.99)*** | 1.29 (1.27–1.31)*** |
| Age in 2006               | 0.99 (0.99–0.99)*** | 0.99 (0.98–0.99)*** |
| Age at first cancer (Ref = 0–1) |                   |                   |
| 2–4                      | 0.89 (0.86–0.93)*** | 1.38 (1.35–1.41)*** |
| 5–9                      | 0.99 (0.94–1.03)   | 1.33 (1.29–1.37)*** |
| 10–14                    | 1.04 (0.99–1.11)   | 1.23 (1.19–1.28)*** |
| ≥ 15                     | 0.83 (0.77–0.9)*** | 1 (0.96–1.05)      |
| Year of diagnosis (Ref = > 1990) |               |                   |
| < 1970                   | 1.05 (0.93–1.19)   | 1.86 (1.73–2)***   |
| 1970–1979                | 1.32 (1.22–1.43)***| 1.82 (1.74–1.9)*** |
| 1980–1989                | 1.34 (1.27–1.41)***| 2.07 (2.01–2.13)***|
| First primary cancer type (Ref = Neuroblastoma) |                   |                   |
| Other solid cancer        | 1.39 (1.3–1.48)*** | 1.4 (1.34–1.47)*** |
| Kidney tumors             | 1.09 (1.04–1.14)***| 0.98 (0.95–1.01)   |
| Lymphoma                  | 0.99 (0.94–1.04)   | 0.98 (0.95–1.01)   |
| Soft tissue sarcomas      | 0.97 (0.92–1.03)   | 0.95 (0.91–0.98)***|
| Bone sarcomas             | 1.01 (0.95–1.08)   | 1.03 (0.99–1.07)   |
| Central nervous system tumor | 1.29 (1.22–1.36)***| 1.97 (1.9–2.03)*** |
| Gonadal/Germ cell tumours | 1.02 (0.96–1.1)    | 1.39 (1.34–1.45)***|
| Thyroid tumor             | 0.66 (0.56–0.78)***| 0.73 (0.66–0.8)*** |
| Retinoblastoma            | 0.98 (0.92–1.04)   | 1.59 (1.54–1.65)***|
| Treatment (Ref = No radiotherapy or chemotherapy) |               |                   |
| Chemotherapy              | 1.62 (1.53–1.70)***| 2.63 (2.53–2.74)***|
| Radiotherapy              | 2.10 (1.98–2.22)***| 2.72 (2.61–2.83)***|
| Radiotherapy and Chemotherapy | 2.60 (2.46–2.73)***| 3.72 (3.58–3.86)***|

Table 3. Multivariate analysis of the total number of hospitalizations and bed-days. RR, risk ratio; CI, confidence interval. ***p < 0.01, **p < 0.05.
Unexpectedly, we did not observe a variation in the RHR and RBDR according to the age at childhood cancer onset\(^1\). Our results about the variations in RHR and RBDR according to year of childhood cancer diagnosis and the age at the start of SNDS follow-up have to be interpreted with caution because these two variables are linked—that is, survivors treated in later years are likely to be older at the start of the follow-up. As a general matter, the differences in results among studies are hardly explained by variations in demographic and clinical characteristics. A more thorough investigation would require performing a meta-analysis. Our results should be interpreted with caution because the SNDS data are only available for 2006–2018, a period of time after the FCCSS recruitment period (1945–2000). Thus, a selection bias could occur in older patients at the time of the SNDS follow-up. For example, patients treated before 1970 who survived until 2006 are not representative of all patients treated before 1970 and correspond to a different distribution of the treatment types.

To our knowledge, this is the first detailed study of the hospitalisation of long-term CCS compared with the general population in France. We used a national administrative database, which provided comprehensive information on hospitalisations over 13 years in both CCS and their reference population. An advantage of our study is that we have accounted for hospitalisation in day hospital units. Admissions to day hospital units are mainly for chemotherapy, radiotherapy and extracorporeal dialysis. By considering in-patient bed-days, we could focus on more severe hospitalisation that required more medical care.

Our study is subject to some limitations. First, we were not able to identify hospitalisations related to relapse or metastasis of childhood cancer to the ones related to secondary neoplasms. Second, we considered only hospitalisation in conventional hospital units because information regarding rehabilitation and psychiatric institution hospitalisation was not available in the EGB sample, which constitutes our reference. Thus, we have underestimated the hospitalisation rate, especially mental-related hospitalisation. Nevertheless, the conventional hospital units treat more than 90% of all patients hospitalised in France\(^2\). Moreover, given that the EGB includes a population that does not receive health care and the data are stored for a period of 20 years\(^3\), the EGB allows researchers to carry out longitudinal studies of hospitalisations\(^4\). Third, we could not address the association between specific types of hospitalisations with specific modalities of therapy (e.g. chemotherapy and radiation doses) because this requires special considerations. We will perform these investigations in separate publications. Lastly, the FCCSS included only patients from five non-profit private cancer treatment centres in France, which are not representative of all French childhood cancer treatment centres. Nevertheless, we have found that this did not impact the long-term survivor’s medical expenditure\(^5\).

In summary, we have shown that the hospitalisation and in-patient bed-day rates among CCS in France were more than twice higher than in the general population. The association of cancer treatment with the different types of hospitalisations suggests special attention should be paid to prevent long-term complications in all organ systems, especially among CCS treated with combined therapies.

**Data availability**

The datasets generated and/or analysed during the current study are not publicly available because they contain potentially identifying patient information. However, the datasets are available from the corresponding author upon reasonable request.

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**References**

1. Geuten, M. M. et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA* **297**, 2705 (2007).
2. Oeffinger, K. C. et al. Chronic health conditions in adult survivors of childhood cancer. *N. Engl. J. Med.* **355**, 1572–1582 (2006).
3. Freyer, D. R. Transition of care for young adult survivors of childhood and adolescent cancer: Rationale and approaches. *J. Clin. Oncol.* https://doi.org/10.1200/JCO.2009.23.4278 (2010).
4. Kirchhoff, A. C. et al. Risk of hospitalization for survivors of childhood and adolescent cancer. *Cancer Epidemiol. Biomark. Prev. Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol.* **23**, 1280–1289 (2014).
5. Kurt, B. A. et al. Hospitalization rates among survivors of childhood cancer in the childhood cancer survivor study cohort. *Pediatr. Blood Cancer* **59**, 126–132 (2012).
6. Sieswerda, E. et al. High hospitalization rates in survivors of childhood cancer: A longitudinal follow-up study using medical record linkage. *PLoS ONE* **11**, e0159518 (2016).
7. Streefkerk, N. et al. A detailed insight in the high risks of hospitalizations in long-term A childhood cancer survivors—a Dutch LATER linkage study. *PLoS ONE* **15**, e0232708 (2020).
8. Mueller, B. A., Doodly, D. R., Weiss, N. S. & Chow, E. J. Hospitalization and mortality among pediatric cancer survivors: A population-based study. *Cancer Causes Control* **29**, 1047–1057 (2018).
9. de Fine Licht, S. et al. Long-term inpatient disease burden in the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study: A cohort study of 1,297 childhood cancer survivors. *PLoS Med.* **14**, e1002296 (2017).
10. Nathan, P. C., Henderson, T. O., Kirchhoff, A. C., Park, E. R. & Yabroff, K. R. Financial hardship and the economic effect of childhood cancer survivorship. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **36**, 2198–2205 (2018).
11. Berger, C. et al. Objectifs et organisation de la surveillance à long terme après un cancer dans l’enfance. *Bull. Cancer (Paris)* **102**, 579–585 (2015).
12. de Vathaire, F. et al. Solid malignant neoplasms after childhood irradiation: Decrease of the relative risk with time after irradiation. *C. R. Acad. Sci. III* **318**(3), 483–490 (1995).
13. Haddy, N. et al. Cardiac diseases following childhood cancer treatment: Cohort study. *Circulation* **133**, 31–38 (2016).
14. Scaliteur, L.-M. et al. French administrative health care database (SNDS): The value of its enrichment. *Therapies* **74**, 215–223 (2019).
15. Tuppin, P. et al. Value of a national administrative database to guide public decisions: From the système national d’information interrégimes de l’Assurance Maladie (SNIIRM) to the système national des données de santé (SNDS) in France. *Rev. DÉpidémiol. Santé Publ.* **65**, S149–S167 (2017).
16. Bezin, J. et al. The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. *Pharmacoepidemiol. Drug Saf.* **26**, 954–962 (2017).

17. Brewster, D. H. et al. Subsequent hospitalisation experience of 5-year survivors of childhood, adolescent, and young adult cancer in Scotland: A population based, retrospective cohort study. *Br. J. Cancer* **110**, 1342–1350 (2014).

18. DeVita, V. T. & Chu, E. A history of cancer chemotherapy. *Cancer Res.* **68**, 8643–8653 (2008).

19. Lorenzi, M. F. et al. Hospital-related morbidity among childhood cancer survivors in British Columbia, Canada: Report of the childhood, adolescent, young adult cancer survivors (CAYACS) program. *Int. J. Cancer* **128**, 1624–1631 (2011).

20. Reulen, R. C. et al. Risk of cerebrovascular disease among 13 457 five-year survivors of childhood cancer: A population-based cohort study. *Int. J. Cancer* **148**, 572–583 (2021).

21. Font-Gonzalez, A. et al. Risk and associated risk factors of hospitalization for specific health problems over time in childhood cancer survivors: A medical record linkage study. *Cancer Med.* **6**, 1123–1134 (2017).

22. Skinner, R. Late renal toxicity of treatment for childhood malignancy: Risk factors, long-term outcomes, and surveillance. *Pediatr. Nephrol. Berl. Ger.* **33**, 215–225 (2018).

23. Agence technique de l’information sur l’hospitalisation & (ATIH). In *Synthèse Analyse de l’activité Hospitalière 2018* https://www.atih.sante.fr/sites/default/files/public/content/3675/synthese_aah_2018_v2.pdf (2017).

24. De Roquefeuil, L., Studer, A., Neumann, A. & Merlière, Y. L’échantillon généraliste de bénéficiaires: Représentativité, portée et limites. *Prot. Organ. Soins* **40**, 213 (2009).

25. Bejarano-Quisoboni, D. et al. Health care expenditures among long-term survivors of pediatric solid tumors: Results from the French Childhood Cancer Survivor Study (FCCSS) and the French network of cancer registries (FRANCIM). *PLoS ONE* **17**, e0267317 (2022).

**Author contributions**

F.D.V. and N.P.F. conceived and designed the study. F.D.V. had full access to all the data in the study and take responsibility for its integrity. D.B.Q. carried out the data preparation. D.B.Q. and F.D.V. carried out the statistical analyses. D.B.Q. drafted the manuscript. All authors analyzed and interpreted the data, and contributed to drafting of the manuscript by providing input and guidance over numerous manuscript drafts.

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**Competing interests**

The authors declare no competing interests.

**Additional information**

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