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The involvement of primary care physicians in care for childhood cancer survivors

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Abstract

Background

Childhood cancer survivors (CCS) are at risk of developing long-term morbidity, which is likely to be presented to a primary care physician (PCP). Therefore, insight into CCS's PCP-based health care use is needed. We

investigated the volume and underlying health problems of PCP-based health care use and the determinants for PCP-based health care use in CCS.

Procedure

Data from a Dutch cohort of 6018 eligible five-year CCS were linked to the Nivel Primary Care database, which contains detailed data from a representative sample of 10% of all Dutch PCPs. Per CCS, two matched controls were selected. Negative binomial regression was performed to compare the annual number of contacts between CCS and controls, and to identify determinants for PCP-based care use among CCS.

Results

This study included 602 CCS and 1204 controls. CCS were 1.3 times more likely to contact their PCP than controls (95% CI, 1.2–1.5), up to 1.5 times at attained age over 40 years (95% CI, 1.2–1.8). CCS were 4.9 times more likely to contact their PCP for new malignancies, 3.1 for hematological conditions, and 2.8 for endocrine conditions. Female sex, higher attained age, and treatment with radiotherapy were determinants for having more PCP contacts.

Conclusions

PCPs play an important role in care for CCS. CCS use more PCP-based care than matched controls, mainly for severe conditions such as malignancies, hematological, and endocrine conditions. Our results emphasize the importance of disseminating the current knowledge on long-term morbidity in CCS and on their optimal follow-up care among PCPs.

Abbreviations

- CCS
- childhood cancer survivors
- CRR
- contact rate ratio
- DCOG-LATER
- Dutch Childhood Oncology Group–Long-Term Effects After Childhood Cancer
- ICPC
- International Classification of Primary Care
- IQR
- interquartile range
- Nivel
- Netherlands Institute for Health Services Research
- Nivel-PCD
- Nivel Primary Care Database
- PCP
- primary care physician
- Zorg-TTP
- a trusted third party as used in this study

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1 INTRODUCTION

Over the past decades, survival of childhood cancer has improved considerably.[1, 2] However, even many years after the initial cancer treatment, childhood cancer survivors (CCS) are at risk of developing long-term morbidity related to their cancer and treatment, such as organ dysfunction or second malignancies.[3-6]

In many countries, the primary care physician (PCP) plays a crucial role in health care, generally being the first health care provider where (new) symptoms are presented. Few studies have investigated PCP-based health care consumption by long-term CCS.[7, 8] A questionnaire study among U.S. and Canadian PCPs showed that 60% had cared for at least one CCS in the preceding five years.[8] Another questionnaire study showed that 71.0% of the CCS had contacted their PCP in the preceding year.[7] The use of questionnaires in these studies limited detailed investigation of the number of PCP contacts as well as the reasons for PCP contacts. Canadian researchers used data derived from health care registries to study the rate of PCP visits in CCS during the first five years after diagnosis and thereafter.[9, 10] They showed that CCS visit their PCP more often as compared with controls.[9, 10] The reason for contacting the PCP was investigated only during the first five years after diagnosis.[9] No tumor- or treatment-related risk factors for a high PCP-based health care use have been established in long-term CCS.[7, 10] Consequently, guidelines for PCP-based care for long-term CCS are lacking. Recognizing these limitations, a study on long-term CCS's PCP-based health care use is needed. This study aims to compare the number of PCP contacts and the type of health conditions presented in five-year CCS to age- and sex-matched controls. We linked data from a large cohort of CCS with a primary care database containing detailed information on all PCP visits from a representative sample of all PCPs in the Netherlands. Furthermore, we investigated tumor- and treatment-related determinants among CCS.

2 METHODS

2.1 Patient population: The DCOG-LATER cohort

The baseline population consisted of 6165 five-year CCS treated for pediatric malignancies in one of the seven pediatric oncology centers in the Netherlands between 1963 and 2002 (Dutch Childhood Oncology Group–Long-Term Effects After Childhood Cancer (DCOG-LATER) cohort). For all cohort members, details on cancer diagnosis and treatment schedules were retrospectively obtained from medical records using a standardized protocol. Methods of patient identification and data collection have been previously described elsewhere.[11]

2.2 The Nivel primary care database

In the Netherlands, all citizens are obliged to be registered at a PCP practice, because the PCP acts as a gatekeeper for secondary care. The Netherlands Institute for Health Services Research (Nivel) collects longitudinal data that are routinely recorded by PCPs, and processes these data into the Nivel Primary Care Database (Nivel-PCD). Because PCPs also use these data for reimbursement with medical insurance companies, they are likely to be complete.[12]

The Nivel-PCD contains data on the number and type of contacts with primary care providers and health conditions that are presented.[12] Health conditions are coded using the International Classification of Primary Care (ICPC).[13, 14]

Currently, data are collected from 498 PCP practices[12] (9.9% of all PCP practices in the Netherlands[15]) covering 2008 to 2016. The patients from the participating Nivel primary care practices are a representative sample of the Dutch population.[12]

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2.3 Linkage procedure

CCS from the DCOG-LATER cohort were linked to the Nivel-PCD using a deterministic linkage method, based on a unique identifier (Supporting Information Figure S1). If no unique identifier was available (*n* = 937, 16.6% of all CCS eligible for linkage), CCS were linked based on a combination of birth date, sex, and postal code.

Because multiple individuals in the Nivel-PCD could have identical birth date, sex, and postal code, a linked person was assumed to be the CCS only if a record of the primary cancer diagnosis was found in the Nivel-PCD (*n* = 24).

2.4 Ethical statement

Dutch law allows the use of Electronic Health Records for research purposes under certain conditions. According to this legislation, it is not necessary to obtain informed consent from patients or approval from a medical ethics committee for this type of observational study that contains no directly identifiable data (Dutch Civil Law, Article 7: 458). No waiver of ethical approval was therefore obtained by an Institutional Review Board or ethics committee. The linkage was performed via a trusted third party (Zorg-TTP) which removed all directly identifiable data before making the data sets available for the researchers.

This linkage research was conducted according to the DCOG-LATER Privacy Regulations as well as the Nivel Privacy Regulations.

2.5 Follow-up

The start of follow-up was defined as the date of five-year survival after the diagnosis of childhood cancer, registration date at the PCP practice, or January 1, 2008, whichever was the latest. End of follow-up was defined as date of death, date of leaving the PCP practice or December 31, 2016, whichever was the earliest. Subjects had to be registered at the PCP practice for at least three months and the PCP practice had to meet the Nivel quality criteria for adequate registration.

2.6 Control group

For each CCS, two controls were selected from the same PCP practice as where the CCS was registered, matched for year of birth, sex, and follow-up period. If no control with a fully overlapping follow-up period was available, the two reference persons with the most overlap were selected as controls, and follow-up time was counted only for the period where the CCS and those controls had full overlap.

2.7 Outcome definition

Primary outcome was the number of PCP contacts per year of follow-up. Contacts could be with the PCP or psychological wellbeing practitioner and included consultations at the PCP practice, phone consultations, e-mail consultations, or home visits.

Secondary outcome was the reason for contact, defined as health condition(s), which were registered as ICPC codes13, 14 up to a maximum of three health conditions per individual contact. According to the ICPC, all health conditions were categorized into 17 chapters based on organ system. Because the ICPC does not contain a separate chapter for (subsequent) malignancies, all malignancies were recategorized in two additional chapters: “CCS childhood cancer,” which referred to the CCS's primary diagnosis of childhood cancer and “subsequent malignancy,” which referred to any new primary malignancy.

2.8 Statistical analysis

To gain insight into the representativeness of the linked cohort, baseline characteristics were calculated for the total DCOG-LATER cohort, the CCS study population, and controls. Because the CCS

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study population was not traceable in the total DCOG-LATER cohort, owing to privacy protection regulations, differences between these groups were not tested statistically.

The mean contact rate was calculated as the mean number of PCP contacts per year of follow-up. Negative binomial regression was performed to calculate crude contact rate ratios (CRR) comparing CCS and matched controls in terms of total annual number of contacts, annual number of contacts per contact type, and annual number of contacts per type of health condition.16 Within CCS, two multivariable negative binomial regression models were developed to identify tumor- and treatment-related risk factors for having more PCP contacts. Statistical significance was assumed when *P* values were below 0.05. For all analyses, Stata-SE version 15 was used.

In the Netherlands, the care for four health problems (asthma, COPD, diabetes mellitus, and cardiovascular risk management) is partly organized as guideline-based care conducted by a somatic practice nurse or PCP. This type of care is not present in the Nivel-PCD. Therefore, to gain insight into possible underestimation, we performed a sensitivity analysis in which we added the annual number of protocolled contacts for those diseases (3 for diabetes, 1.5 for asthma/COPD, and 1 for cardiovascular risk management).

3 RESULTS

3.1 Results of linkage/baseline characteristics

Of the 6018 CCS eligible for linkage, 602 CCS were linked to the Nivel-PCD, that is, they registered at a PCP that was affiliated with Nivel and identifiable in the Nivel-PCD (Supporting Information Figure S1). The characteristics of the included CCS suggest that this sample is representative for the total DCOG-LATER cohort (Table 1).

[table 1]

More than half of the linked CCS were male (55.2%), the median age at diagnosis was 5.32 years (interquartile range [IQR], 2.74–10.48). Most CCS were survivors of hematological malignancies (50.2%; Table 1). Median age at end of follow-up was 32 years in both CCS and controls.

3.2 Number of PCP visits

In both CCS and controls, the median follow-up time during which data on PCP visits were available was 4.32 years (IQR 1.00–7.00). Among CCS, 93.2% contacted their PCP, as compared with 89.1% among controls ($P < 0.001$). CCS had a 1.3 times higher contact rate than controls (3.93 median annual contacts in CCS vs 2.96 in controls; CRR = 1.33, 95% confidence interval (CI), 1.20–1.46, $P < 0.001$) (Table 2).

[table 2]

In CCS aged below 20 years, the contact rate was 2.68, and in CCS aged over 40 years, the contact rate was 4.84. As compared with controls, CCS aged 20 and older had a significantly higher health care consumption, and the CRR for having any contact at the PCP was the highest in CCS aged over 40 (CRR = 1.49; 95% CI, 1.22–1.84; Table 2 and Figure 1).

[Figure 1]

Crude contact rate ratio for the number of primary care physician contacts in childhood cancer survivors as compared with controls by attained age

This figure displays the crude contact rate ratios in CCS as compared with controls, for the number of primary care physician contacts by attained age, which was calculated by negative binomial regression. Exact values of the contact rate ratio and *P* values are displayed in Table 2. The squares represent the

point estimates of the contact rate ratio, and the vertical lines represent the 95% confidence interval. The horizontal line represents the value 1 (no difference between CCS and controls).

Supporting Information Table S1 and Supporting Information Figure S2 show that the most common types of contacts were PCP consultations and phone or e-mail PCP consultations. Psychological wellbeing practitioners were consulted by a minority of both CCS and controls (9.1% and 8.8%, respectively).

Supporting Information Table S2a shows that a low number of patients received protocolled medical checks performed by the somatic practice nurse. A sensitivity analysis, calculating the maximum effect of possible underestimation of the total contact rate in both CCS and controls who received this protocolled care, has led to comparable results (Supporting Information Tables S2b–c).

3.3 Type of health conditions

The most prevalent health conditions for which CCS contacted the PCP were conditions of the skin (62.1%), musculoskeletal conditions (56.2%), and conditions of the respiratory tract (49.0%) (Table 3). Conditions of the skin and respiratory conditions occurred more often in CCS as compared with controls (Figure 2). The most prevalent skin conditions leading to a PCP visit in CCS were contact dermatitis or other eczema, dermatophytosis, and warts (Supporting Information Table S3). The most prevalent respiratory conditions in CCS were upper respiratory tract infections, cough, and hay fever/allergic rhinitis (Supporting Information Table S3).

[Table 3][Figure 2]

Incidence rate ratio for the number of primary care physician contacts per ICPC chapter in childhood cancer survivors as compared with controls

This figure displays the crude contact rate ratios in CCS as compared with controls, for the number of primary care physician contacts by attained age, which was calculated by negative binomial regression. Exact values of the contact rate ratio and *P* values are displayed in Table 3. The squares represent the point estimates of the contact rate ratio, and the vertical lines represent the 95% confidence interval. The horizontal line represents the value 1 (no difference between CCS and controls).

Table 3, Figure 2, and Supporting Information Table S3 show that, as compared with controls, CCS were 4.9 times as likely to contact their PCP for subsequent malignancies (mainly musculoskeletal tumors, leukemia, and tumors of the nervous system), 3.1 times as likely to contact their PCP for hematological conditions (mainly purpura and anemia), and 2.8 times as likely to contact their PCP for endocrine conditions (mainly vitamin deficiencies, diabetes mellitus, and other endocrine deficiencies). Supporting Information Table S3 provides insight into the top five most prevalent specific conditions per type of health condition, for CCS and controls separately.

3.4 Determinants for health care use in CCS

Two multivariable regression models were built to identify tumor- and treatment-related determinants for the number of PCP contacts in CCS. Both models were adjusted for follow-up time, sex, and attained age. The first model showed that female CCS and CCS with a higher attained age had a significantly higher number of PCP contacts, but no tumor-related determinants were found (Table 4, model 1). The second model including crude treatment indicators confirmed female sex and attained age as determinants for more PCP-based health care use. Moreover, this model showed that CCS treated with surgery only and with radiotherapy only are at significantly increased risk of having more PCP contacts during follow-up compared with those treated with chemotherapy only (CRR = 1.23; 95% CI, 1.00–1.51 and IRR = 1.49; 95% CI, 1.15–1.93, respectively; Table 4, model 2).

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[table 4]

4 DISCUSSION

This study showed that CCS have a higher PCP-based health care use than controls, up to 1.5-fold more at attained age over 40 years. CCS used more care for nearly all types of health conditions, especially for subsequent malignancies, hematological conditions, and endocrine conditions. Female sex, higher attained age, and treatment with radiotherapy only were determinants for having more PCP contacts.

To our knowledge, this study is the first to gain insight into the types of health conditions for which five-year CCS require more PCP-based care as compared with the general population. We found that CCS required more PCP care for nearly all types of health conditions, especially for subsequent malignancies, hematological conditions, and endocrine conditions. Previously, we investigated the hospitalization rates in long-term CCS. Subsequent neoplasms and endocrine disorders were also among the most important causes for hospitalization.17 Hematological conditions did not lead to elevated hospitalization rates in CCS.17 However, in this study, CCS were over three times more likely to require health care for hematological conditions than controls. Most frequent hematological conditions in CCS were purpura/coagulation defects and pernicious-/iron deficiency anemia. Hematological conditions in long-term CCS are not well described in the literature. It is important to further investigate long-term hematological conditions in CCS and to determine whether screening could be beneficial. We, moreover, found that most CCS contacted their PCP for benign conditions of the skin and that for skin conditions, CCS contacted their PCP 1.2 times as often as controls. The literature on benign skin conditions in long-term CCS is scarce, and skin conditions were not known to elevate hospitalization rates in CCS.17 Our results suggest the importance of investigating the course of disease of different benign skin conditions as compared with the general population, and to determine whether different treatment might be beneficial for CCS. PCPs need to be aware that older CCS and female CCS have increased health care use. These determinants were previously described in five-year CCS.10 Also in the general population, female sex and higher age are determinants for PCP-based care use.18, 19 The increase of the contact rate with attained age was more prominent in CCS than in controls in our study. This may be because that CSS are likely to develop long-term morbidity as they age, but may also be due to differences in attained age groups. CCS with higher attained ages were diagnosed in earlier decades than CCS with lower attained ages and more often received radiotherapy (Supporting Information Table S4). Either way, PCPs need to be aware that older CCS are likely to require more care than both the general population and younger CCS.

Concerning treatment-related determinants for high PCP-based health care use in CCS, we found that CCS treated with radiotherapy only were nearly 1.5 times more likely to contact their PCP as compared with CCS treated with chemotherapy only. CCS treated with surgery only were 1.2 times more likely. In the Netherlands, the follow-up care of survivors is well organized by Late-Effect Outpatient Clinics, which are present in hospital-based pediatric oncology centers. In these outpatient clinics, CCS are routinely followed-up and screening for late effects is undertaken according to the evidence-based follow-up guideline as developed by the Dutch Childhood Oncology Group.20 According to this guideline, CCS treated with surgery only often do not require hospital-based follow-up. Therefore, CCS treated with surgery only might be more likely to consult their PCP in case of symptoms.

Our study has some methodological strengths and limitations. First, by using data on PCP visits derived from a national registry, we excluded recall bias, which is a concern when using patient-reported data. A second strength is that the detailed information in the Nivel-PCD enabled us to investigate the number of PCP contacts, as well as the reason for PCP consultation, which generates unique insight into the types of health problems that PCPs are likely to encounter in CCS. Last, by combining these data with clinical information from the DCOG-LATER cohort, we were able to identify subgroups of CCS

that require more care from the PCP. However, we did not have information available on the late-effect outpatient clinic follow-up attendance in CCS, so we could not correlate the PCP contact rate to outpatient clinic follow-up attendance. Although most long-term CCS in the Netherlands receive follow-up care in specialized late-effect clinics, we still observed an increased rate of PCP-based health care. Therefore, we assume that PCP-based health care use may be even higher in countries without local or national specialized CCS care. A second limitation of this study is that we could only include CCS that were registered with PCPs affiliated with the Nivel–PCD (about 10%).[12, 15] Because in the Netherlands everyone is obliged to be registered at a PCP and PCPs affiliated with the Nivel-PCD were representative for the Dutch population, we assumed no selection bias.[12] Besides, the characteristics of the included CCS were very similar to those of the entire CCS cohort. In a previous questionnaire study in the United States and Canada, PCPs reported discomfort regarding care for CCS.[8] Different models of follow-up care for CCS have been developed and also shared care models involving the PCP have been suggested.[21] A Dutch study showed that PCPs were willing to participate in such a shared care model, if adequate guidelines and medical information were provided.[22] Shared care between pediatric oncologists and PCPs in long-term follow-up for CCS seemed feasible in a pilot study in the Netherlands, leading to high rates of both CCS and PCP satisfaction.[23] A web-based survivor care plan, developed by the pediatric oncologist, in which both CCS and their PCP are provided with a personalized plan for follow-up according to the current evidence-based survivorship guidelines, could be an effective asset to provide adequate shared care.[24] Evidence-based guidelines for follow-up care for CCS have been developed[20] and are currently being harmonized globally.[25] Until now PCPs are not involved in this effort and they report unfamiliarity with CCS surveillance guidelines.[8]

In conclusion, CCS have a high health care use in the PCP practice, especially women, those who are older and those who have received radiotherapy. PCPs should be aware that these patients use more care and that they are more likely to present with subsequent malignancies, hematological conditions, and endocrine conditions. Because the number of CCS will increase, PCPs will be more involved in their complex care. This will have consequences for the organization of care for CCS at the PCP practice. Therefore, it is important to disseminate knowledge on long-term morbidity in CCS and on the evidence-based guidelines of care for CCS among PCPs, in shared care programs and in PCP training programs.

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DATA SHARING STATEMENT

Data supporting the results reported in this article are stored at Nivel. Owing to privacy protection regulations of both Nivel and DCOG-later, data are not publicly available.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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Tables and Figures

Table 1. Baseline characteristics of the total cohort, the study population linked to Nivel Primary Care Database, and selected controls

	Total cohort (*n* = 6165)	**Study population (*n* = 602)**	**Controls (*n* = 1204)**
Sex, *n* (%)			
Male	3434 (55.7%)	332 (55.2%)	664 (55.2%)
Female	2731 (44.3%)	270 (44.9%)	540 (44.9%)
Age at diagnosis, *n* (%)			
<5 years	2727 (45.3%)[a] [a] Missing in 146 CCS who declined to be included in the DCOG-LATER registry.	282 (46.8%)	NA
5–9 years	1632 (27.1%)[a] [a] Missing in 146 CCS who declined to be included in the DCOG-LATER registry.	157 (26.1%)	NA
10–14 years	1283 (21.3%)[a] [a] Missing in 146 CCS who declined to be included in the DCOG-LATER registry.	126 (20.9%)	NA
>15 years	377 (6.3%)[a] [a] Missing in 146 CCS who declined to be included in the DCOG-LATER registry.	37 (6.2%)	NA
Decade of diagnosis, *n* (%)			
<1984	1012 (32.6%)	175 (29.1%)	NA

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	Total cohort (*n* = 6165)	**Study population (*n* = 602)**	**Controls (*n* = 1204)**
1985–1994	2179 (35.3%)	228 (37.9%)	NA
1995–2001	1974 (32.0%)	199 (33.1%)	NA
Diagnosis, *n* (%)			
Hematological tumors	3155 (51.2%)	302 (50.2%)	NA
Solid tumors	2165 (35.1%)	216 (35.9%)	NA
CNS tumors	843 (13.7%)	84 (14.0%)	NA
Treatment modality, *n* (%)			
Surgery only	579 (9.8%)[b] [b] Missing in 236 CCS, of whom 146 declined to be included in the DCOG-LATER registry and another 90 had missing treatment details.	72 (12.1%)[d] [d] Missing in 6 CCS for whom treatment details were missing.	NA
Chemotherapy ± surgery	2909 (47.2%)[b] [b] Missing in 236 CCS, of whom 146 declined to be included in the DCOG-LATER registry and another 90 had missing treatment details.	300 (50.3%)[d] [d] Missing in 6 CCS for whom treatment details were missing.	NA
Radiotherapy ± surgery	464 (7.5%)[b] [b] Missing in 236 CCS, of whom 146 declined to be included in the DCOG-LATER registry and another 90 had missing treatment details.	49 (8.2%)[d] [d] Missing in 6 CCS for whom treatment details were missing.	NA
Chemotherapy + radiotherapy ±surgery	1976 (32.1%)[b] [b] Missing in 236 CCS, of whom 146 declined to be included in the DCOG-LATER registry and another 90 had missing treatment details.	175 (29.4%)[d] [d] Missing in 6 CCS for whom treatment details were missing.	NA
Stem cell transplantation, (%)	227 (3.8%)[c] [c] Missing in 148 CCS, of whom 146 declined to be part of the DCOG-LATER registry and 2 had missing treatment details.	21 (3.5%)	NA
Follow-up, median (IQR)			
Median age at start of follow-up, years	NA	27.1 (20.4–34.5)	27.19 (20.4–34.5)
Median time since diagnosis to end of follow-up, years	NA	24.9 (20.1–33.0)	NA

Abbreviations: CCS, childhood cancer survivor; Nivel, Netherlands Institute for Health Services primary care registration; IQR, interquartile range; FUP, follow-up; CT, chemotherapy; RT, radiotherapy.
a Missing in 146 CCS who declined to be included in the DCOG-LATER registry.

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b Missing in 236 CCS, of whom 146 declined to be included in the DCOG-LATER registry and another 90 had missing treatment details.

c Missing in 148 CCS, of whom 146 declined to be part of the DCOG-LATER registry and 2 had missing treatment details.

d Missing in 6 CCS for whom treatment details were missing.

FIGURE 1 Crude contact rate ratio for the number of primary care physician contacts in childhood cancer survivors as compared with controls by attained age This figure displays the crude contact rate ratios in CCS as compared with controls, for the number of primary care physician contacts by attained age, which was calculated by negative binomial regression. Exact values of the contact rate ratio and P values are displayed in Table 2. The squares represent the point estimates of the contact rate ratio, and the vertical lines represent the 95% confidence interval. The horizontal line represents the value 1 (no difference between CCS and controls).

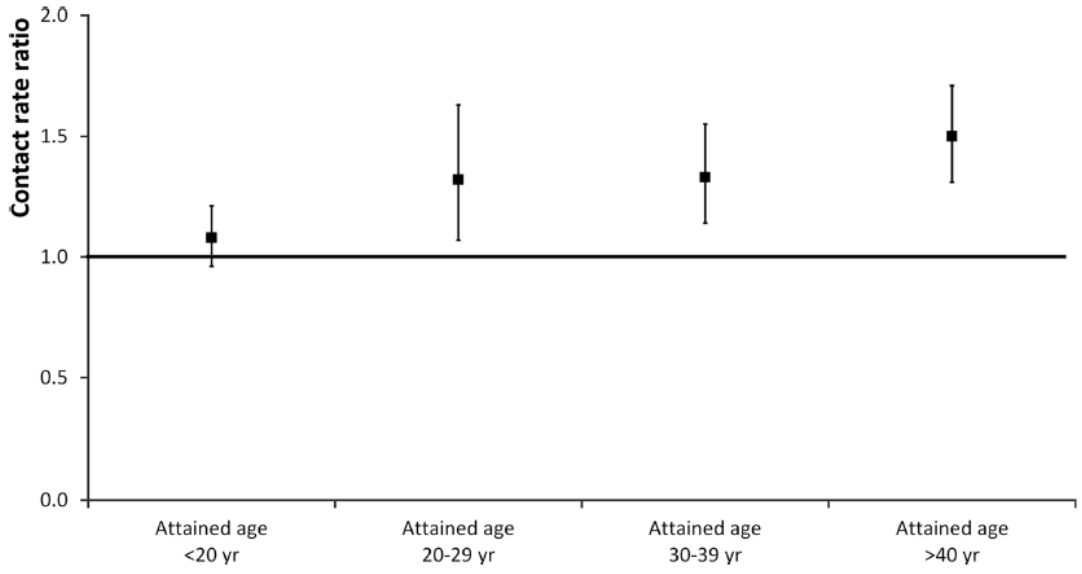

Table 2. Mean follow-up and mean annual number of contacts with the primary care physician per attained age for childhood cancer survivors and controls

	CCS (*n* = 602)				Controls (*n* = 1204)					
	No. CCS	Mean FUP (p10–90)	No. CCS ≥1 contact (%)	Contact rate[a] [a] Contact rate was calculated as the mean number contacts per person per follow-up time within the different age groups in years. (p10–p90)	No. controls	Mean FUP (p10–90)	No. controls ≥1 contact (%)	Contact rate[a] [a] Contact rate was calculated as the mean number contacts per person per follow-up time within the different age groups in years. (p10–p90)	Contact rate ratio[b] [b] Contact rate ratio, confidence intervals, and *P* values were calculated by negative binomial regression adjusting for multiple contacts. (95% CI)	*P*
Any age	602	4.32 (1.00–7.00)	561 (93.2%)	3.93 (0.33–8.75)	1204	4.32 (1.00–7.00)	1073 (89.1%)	2.96 (0.00–6.50)	1.33 (1.20–1.46)	<0.001
Attained age <20 years	110	3.10 (0.52–6.26)	90 (81.8%)	2.68 (0.00–7.04)	221	3.03 (0.37–6.12)	174 (78.7%)	2.49 (0.00–6.31)	1.08 (0.83–1.39)	0.576
Attained age 20–29 years	315	2.93 (0.50–6.00)	275 (87.3%)	3.59 (0.00–8.32)	630	2.93 (0.50–6.00)	502 (79.7%)	2.71 (0.00–6.53)	1.32 (1.14–1.54)	<0.001
Attained age 30–39 years	272	3.10 (0.54–6.00)	241 (88.6%)	4.28 (0.00–9.00)	543	3.11 (0.63–6.00)	465 (85.6%)	3.24 (0.00–7.41)	1.32 (1.14–1.54)	<0.001
Attained age ≥40 years	145	3.41 (0.75–7.00)	126 (86.9%)	4.84 (0.00–11.00)	292	3.43 (0.75–7.00)	251 (86.0%)	3.24 (0.00–7.94)	1.49 (1.22–1.84)	<0.001

Notes: Attained-age groups were not mutually exclusive; depending on their total follow-up time, included subjects could have had PCP contacts during one or more attained-age periods.

The available follow-up time in years during all separate attained age categories was calculated for each included subject. For every separate PCP contact, the age at PCP contact was calculated and all PCP contacts were categorized into attained-age categories for each included subject. Then the number of contacts per follow-up year was calculated for each attained-age category.

Abbreviations: 95% CI, 95% confidence interval; CCS, childhood cancer survivors; FUP, follow-up time in years; PCP, primary care physician.

[a] Contact rate was calculated as the mean number contacts per person per follow-up time within the different age groups in years.

[b] Contact rate ratio, confidence intervals, and *P* values were calculated by negative binomial regression adjusting for multiple contacts.

Table 3. Annual number of contacts with the primary care physician per ICPC chapter for childhood cancer survivors and controls

	CCS (*n* = 602)		**Controls (*n* = 1204)**			
	No. CCS ≥1 contact (%)	**Contact ratea** **[a] Contact rate was calculated as the mean number contacts per person per follow-up time within the different age groups in years.** **(p10–p90)**	**No. controls ≥1 contact (%)**	**Contact ratea** **[a] Contact rate was calculated as the mean number contacts per person per follow-up time within the different age groups in years.** **(p10-p90)**	**Contact rate ratiob** **[b] Contact rate ratio, confidence intervals, and *P* values were calculated by negative binomial regression adjusting for multiple contacts.** **(95% CI)**	***P***
Subsequent malignancies	33 (5.48%)	0.03 (0.00–0.00)	15 (1.25%)	0.01 (0.00-0.00)	4.89 (2.08–11.45)	**<0.001**
Hematological conditions	62 (10.30%)	0.09 (0.00–0.11)	62 (5.15%)	0.03 (0.00–0.00)	3.12 (1.98–4.91)	**<0.001**
Endocrine conditions	121 (20.10%)	0.23 (0.00–0.50)	123 (10.22%)	0.08 (0.00–0.13)	2.75 (2.02–3.75)	**<0.001**
Urinary tract conditions	114 (18.94%)	0.20 (0.00–0.50)	172 (14.29%)	0.10 (0.00–0.25)	1.98 (1.48–2.64)	**<0.001**
Neurological conditions	143 (23.75%)	0.18 (0.00–0.50)	223 (18.52%)	0.09 (0.00–0.29)	1.97 (1.50–2.58)	**<0.001**
Conditions of the circulatory tract	111 (18.44%)	0.17 (0.00–0.40)	173 (14.37%)	0.10 (0.00–0.20)	1.78 (1.32–2.39)	**<0.001**

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	CCS (*n* = 602)		**Controls (*n* = 1204)**			
	No. CCS ≥1 contact (%)	**Contact ratea** **[a] Contact rate was calculated as the mean number contacts per person per follow-up time within the different age groups in years.** **(p10–p90)**	**No. controls ≥1 contact (%)**	**Contact ratea** **[a] Contact rate was calculated as the mean number contacts per person per follow-up time within the different age groups in years.** **(p10-p90)**	**Contact rate ratiob** **[b] Contact rate ratio, confidence intervals, and *P* values were calculated by negative binomial regression adjusting for multiple contacts.** **(95% CI)**	***P***
Eye conditions	124 (20.6%)	0.10 (0.00–0.33)	204 (16.94%)	0.07 (0.00–0.25)	1.49 (1.07–2.07)	**0.017**
Conditions of the digestive tract	238 (39.53%)	0.34 (0.00–1.00)	370 (30.73%)	0.23 (0.00–0.67)	1.45 (1.18–1.77)	**<0.001**
Conditions of the respiratory tract	295 (49.00%)	0.40 (0.00–1.20)	515 (42.52%)	0.30 (0.00–1.00)	1.34 (1.13–1.59)	**0.001**
Social circumstances	72 (11.96%)	0.09 (0.00–0.14)	111 (9.22%)	0.07 (0.00–0.00)	1.31 (0.90–1.91)	0.158
General health conditions	247 (41.03%)	0.30 (0.00–0.96)	417 (34.63%)	0.23 (0.00–0.67)	1.29 (1.05–1.57)	**0.013**
Ear conditions	136 (22.59%)	0.16 (0.00–0.50)	288 (23.92%)	0.12 (0.00–0.38)	1.29 (0.99–1.68)	0.063
Psychological/psychiatric conditions	179 (29.7%)	0.34 (0.00–1.00)	326 (27.08%)	0.27 (0.00–0.78)	1.23 (0.98–1.54)	0.075
Conditions of the female gonads	133 (22.09%)	0.18 (0.00–0.60)	221 (18.36%)	0.15 (0.00–0.50)	1.21 (0.93–1.57)	0.159
Conditions of the skin	374 (62.13%)	0.53 (0.00–1.33)	677 (56.23%)	0.44 (0.00–1.25)	1.20 (1.04–1.39)	**0.012**
Musculoskeletal	338	0.48 (0.00–1.33)	642	0.44 (0.00–1.20)	1.09 (0.93–1.27)	0.308

	CCS (*n* = 602)		**Controls (*n* = 1204)**			
	No. CCS ≥1 contact (%)	**Contact ratea** [a] **Contact rate was calculated as the mean number contacts per person per follow-up time within the different age groups in years. (p10–p90)**	**No. controls ≥1 contact (%)**	**Contact ratea** [a] **Contact rate was calculated as the mean number contacts per person per follow-up time within the different age groups in years. (p10-p90)**	**Contact rate ratiob** [b] **Contact rate ratio, confidence intervals, and *P* values were calculated by negative binomial regression adjusting for multiple contacts. (95% CI)**	***P***
conditions	(56.15%)		(53.32%)			
Pregnancy	115 (19.10%)	0.17 (0.00–0.50)	270 (22.43%)	0.21 (0.00–0.67)	0.79 (0.61–1.02)	0.074
Conditions of the male gonads	56 (9.30%)	0.05 (0.00–0.00)	152 (12.62%)	0.06 (0.00–0.17)	0.72 (0.46–1.11)	0.132
Pediatric malignancy	125 (20.76%)	0.12 (0.00–0.33)	NA	NA	NA	NA

- Abbreviations: 95% CI, 95% confidence interval; CCS, childhood cancer survivor; FUP, follow-up time in years; ICPC, International Classification of Primary Care (=coding system for diseases and symptoms/complaints); NA, not applicable.
- The values in bold are statistically significant values (p<0.05).
- [a] Contact rate was calculated as the mean number contacts per person per follow-up time within the different age groups in years.
- [b] Contact rate ratio, confidence intervals, and *P* values were calculated by negative binomial regression adjusting for multiple contacts.

FIGURE 2 Incidence rate ratio for the number of primary care physician contacts per ICPC chapter in childhood cancer survivors as compared with controls This figure displays the crude contact rate ratios in CCS as compared with controls, for the number of primary care physician contacts by attained age, which was calculated by negative binomial regression. Exact values of the contact rate ratio and P values are displayed in Table 3. The squares represent the point estimates of the contact rate ratio, and the vertical lines represent the 95% confidence interval. The horizontal line represents the value 1 (no difference between CCS and controls).

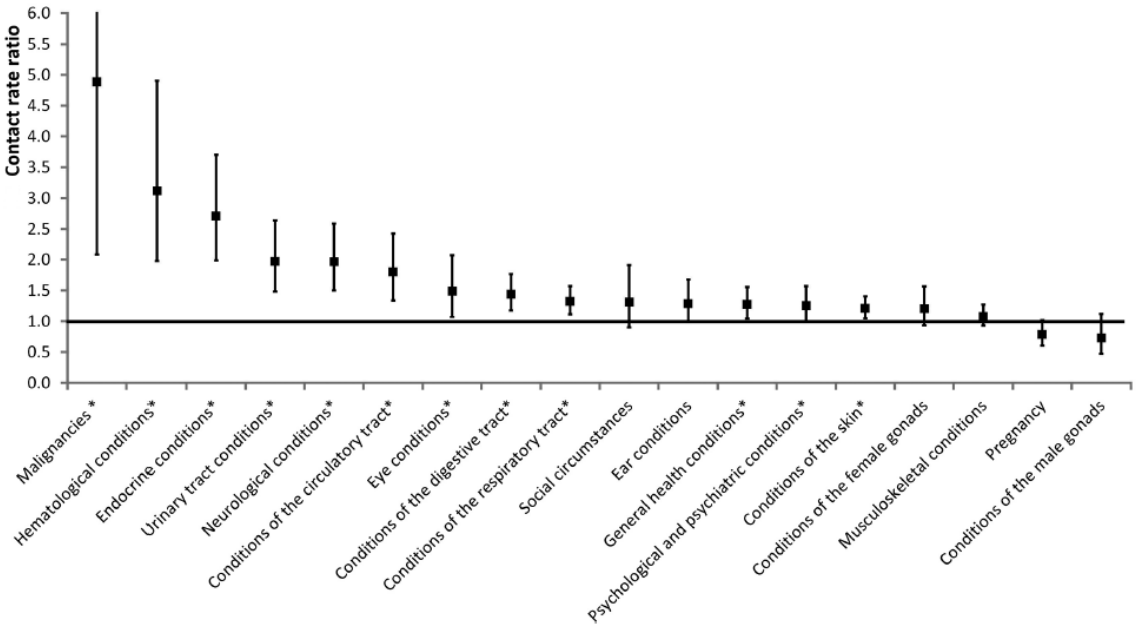

Table 4. Multivariable risk factor analyses for the number of contacts with the primary care physician among childhood cancer survivors

	Model 1 including tumor type		**Model 2 including therapy**	
	Adjusted CRR (95% CI)	***P***	**Adjusted CRR (95% CI)**	***P***
Sex				
Male	Ref		Ref	
Female	1.94 (1.70–2.21)	**<0.001**	1.96 (1.72–2.23)	**<0.001**
Attained age				
<20 years	Ref	Ref		
20–29 years	1.26 (1.02–1.56)	**0.029**	1.23 (1.00–1.53)	**0.048**
30–39 years	1.61 (1.31–1.99)	**<0.001**	1.53 (1.23–1.90)	**<0.001**
≥40 years	1.81 (1.43–2.28)	**<0.001**	1.58 (1.23–2.04)	**<0.001**
Diagnosis				
Hematological tumors	Ref	-		
Solid tumors	0.95 (0.82–1.09)	0.456	-	
Central nervous system tumors	1.21 (0.99–1.49)	0.065	-	
Therapy				

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	Model 1 including tumor type		**Model 2 including therapy**	
	Adjusted CRR (95% CI)	***P***	**Adjusted CRR (95% CI)**	***P***
Surgery only	-		1.23 (1.00–1.51)	**0.047**
Chemotherapy ± surgery	-		Ref	
Radiotherapy ± surgery	-		1.49 (1.15–1.93)	**0.002**
Chemotherapy + radiotherapy ± surgery	-		1.16 (0.98–1.36)	0.082

- Note: Two negative binomial regression models for the mean total number of contacts, expressed as CRR, adjusted for follow-up time.
- In multivariable model 1, the CRR for any contact with the PCP was calculated additionally adjusted for sex, attained age, and childhood cancer diagnosis. In multivariable model 2, the CRR for any contact with the PCP was calculated additionally adjusted for sex, attained age, and therapy.
- Abbreviations: 95% CI, 95% confidence interval; CRR, contact rate ratio; PCP, primary care physician.
- The values in bold are statistically significant values ($p<0.05$).