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Long-term auditory complications after childhood cancer: A report from the Swiss Childhood Cancer Survivor Study

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Keywords: cancer registry, childhood cancer survivors, cranial radiation, Europe, ototoxicity, platinum compounds

Abbreviations: BMT, bone marrow transplantation; CI, confidence interval; CNS, central nervous system; CSF-shunt, cerebrospinal fluid shunt; Gy, gray; HR, hazard ratio; ICCC-3, International Classification of Childhood Cancer, Third edition; IQR, interquartile range; OR, odds ratio; SCCR, Swiss Childhood Cancer Registry; SCCSS, Swiss Childhood Cancer Survivor Study

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ABSTRACT

Background: Auditory complications are an adverse event of childhood cancer treatment, especially common in children treated with platinum chemotherapy or cranial radiation. Variation between diagnostic childhood cancer groups has rarely been studied, and we do not know if the burden of auditory complications has changed over the last decades.

Procedure: Within the Swiss Childhood Cancer Survivor Study, we sent a questionnaire to all survivors who were diagnosed at age 16 years or less between 1976 and 2005.We compared prevalence of self-reported hearing loss and tinnitus between all diagnostic childhood cancer groups and siblings, used multivariable logistic regression to analyze the effect of treatment-related factors on hearing loss, and compared the cumulative incidence of hearing loss between different periods of cancer diagnosis.

Results: Prevalence of self-reported hearing loss was higher in survivors (10%) than in siblings (3%, $P < 0.001$), and highest in survivors of central nervous system tumors (25%). Significant risk factors were treatment with platinum compounds (carboplatin: odds ratio [OR] 2.4; cisplatin: OR 9.4), cranial radiation (>29 Gy: OR >1.7), or brain surgery (OR 2.2). Children diagnosed in 1986–1995, when platinum compounds came into widespread use, had a significantly higher cumulative incidence of hearing loss than those diagnosed in 1976–1985. In the most recent period, 1996–2005, the risk decreased again, both for patients treated with platinum compounds and with cranial radiation.

Conclusions: Our data show that the burden of hearing loss has stabilized in recently treated survivors, suggesting that survivors have benefited from new treatment regimens that use less ototoxic radiation and more carefully dosed platinum compounds.

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INTRODUCTION

Ototoxicity, leading to auditory complications like hearing loss or tinnitus, is an adverse event of childhood cancer treatment, especially common in children treated with platinum chemotherapy or cranial radiation.[1,2] Since its introduction in the 1980s, platinum chemotherapy has been widely used to treat many kinds of childhood cancer. Platinum compounds can damage the hair cells, the spiral ganglion neurons, and the stria vascularis in the cochlear duct of the inner ear, and may cause sensorineural hearing loss or tinnitus in both ears.[3–5] Radiation can damage any of the auditory structures, causing sensorineural, conductive or mixed hearing loss or tinnitus.[6,7] The treatment can affect one or both ears, depending on the area radiated. Auditory complications cause functional limitations, affect speech development, and impair neurocognitive functioning, educational performance, and quality of life.[8–1]

A large U.S. study found an increased risk of auditory complications in a diverse cohort of survivors, but included only survivors from early diagnosis years (1970–1986).[12] Since 1986 ototoxicity from platinum chemotherapy may have increased as cisplatin came into common use. Later, cisplatin has been increasingly replaced by the less ototoxic carboplatin, and radiation techniques have improved and deliver lower radiation doses to the cochlea.[13,14] It remains unclear if and how more current treatment regimens have shifted the burden of long-term auditory complications in survivors of all diagnostic groups.

Recent estimates of prevalence and incidence of auditory complications vary widely,[1] and studies are hard to compare. Studies on long-term outcomes have tended to focus on selected diagnostic groups, including brain tumor,[15,16] neuroblastoma,[8] hepatoblastoma,[17] or nasopharyngeal carcinoma,[18] or included a selected treatment group.[19] The overall burden of auditory complications and variations between diagnostic groups have not been well described. We addressed these open questions by investigating the prevalence of self-reported hearing loss and tinnitus in survivors of all diagnostic childhood cancer groups, among survivors diagnosed between 1976 and 2005, and compared those

results to that of siblings. We also assessed the effects of cancer treatment on hearing loss, and if the incidence of hearing loss has changed over time.

METHODS

The Swiss Childhood Cancer Survivor Study

The Swiss Childhood Cancer Survivor Study (SCCSS) is a population based, long-term follow-up study of all patients registered in the Swiss Childhood Cancer Registry (SCCR), who were diagnosed 1976–2005 at age 16 years or less, and who have survived 5 years or more after initial diagnosis of cancer.[20] The SCCR is a population-based registry and includes all children and adolescents in Switzerland who were diagnosed with leukemia, lymphoma, central nervous system (CNS) tumors, malignant solid tumors, or Langerhans cell histiocytosis before they turned [21.21]

From 2007 to 2013, we traced addresses and sent a questionnaire to all survivors.Nonresponderswere mailed a second copy of the questionnaire [4–6] weeks after the first. If they again did not respond, we contacted them by phone. We asked survivors for consent to contact their siblings, who made up the comparison group. If survivors agreed, we sent the same questionnaire to siblings, minus the cancer related questions. Siblings who did not respond to the first questionnaire received a second copy [4–6] weeks later, but we did not contact them by phone. Details of the study design have been published elsewhere.[20]

The Ethics Committee of Canton Bern granted ethical approval to the SCCR and SCCSS.

Explanatory variables and outcomes

Explanatory variables

We obtained sociodemographic, cancer-, and treatment-related information from the SCCR, which includes detailed medical information on the tumor and therapy. Missing treatment information was complemented by data extracted from hospital records. We extracted the following variables from the SCCR: sex, cancer diagnosis, year and age of cancer diagnosis, age at survey, chemotherapy

(yes/no), clinical study participation (yes/no), treatment protocol, radiotherapy (yes/no, area, dose), surgery (yes/no, area, type), and bone marrow transplant (BMT) (yes/no). Cancer diagnosis was classified according to the International Classification of Childhood Cancer, third edition (ICCC-3).[22] We determined whether patients were treated with cisplatin and carboplatin (yes/no) from SCCR data on clinical study participation and treatment protocols. We summarized radiation doses to the head and categorized cranial radiation into four categories: no cranial radiation, 1–29 Gy, 30–49 Gy, and 50 Gy or higher. We also collected information on brain surgery (yes/no) and cerebrospinal fluid-shunt implant (CSF-shunt) (yes/no). To analyze cumulative incidence of hearing loss, we classified the survivors into four treatment group categories: platinum compounds only, cranial radiation only, cranial radiation and platinum compounds, and neither of the two treatments. We divided cancer diagnoses into the following periods: 1976–1985, 1986–1995, and 1996–2005.We divided age at survey into four categories: 5–15 years, 16–20 years, 21–40 years, and 41–60 years.

Auditory outcomes

The SCCSSquestionnaire asked survivors and siblings about their auditory health. Participants were asked if a doctor had told them they had auditory complications (Supplementary Fig. S3) and then asked to describe the severity and laterality (unilateral/bilateral) of the auditory complication. We created a binary variable (yes/no) for hearing loss and tinnitus; missing information on auditory complications was coded as no (hearing loss, 3% in survivors and siblings; tinnitus, 2% in survivors and 1% in siblings).We categorized severity of hearing loss as mild hearing loss, moderate hearing loss, or deafness.We asked responders who had auditory complications and were older than 15 years at the time of survey (n = 1,606) for the year of first occurrence of hearing loss. Survivors less than or 15 years old were not included in our analysis of cumulative incidence of hearing loss.

Statistical analysis

First, we used chi-square tests to compare prevalence of self-reported hearing loss and tinnitus in survivors and siblings, and described laterality and severity of hearing loss. We stratified survivors by diagnostic group and compared prevalence of hearing loss in survivors and siblings.

Second, we performed uni- and multivariable logistic regressions only on survivor data to identify the effect of cancer-related treatment (use of platinum compounds, cranial radiation, brain surgery, CSF-shunt, and BMT) on hearing loss after cancer diagnosis. We included all treatment-related variables and adjusted for sex and age at cancer diagnosis in the multivariable regression model according to the literature.[9,23] We computed likelihood ratio tests to calculate global P values.

Third, we used the Kaplan–Meier method to estimate cumulative incidence curves and calculated cumulative incidence for hearing loss 15 years after cancer diagnosis, stratified by treatment group. We assessed time trends in cumulative incidence of hearing loss after cancer diagnosis, based on the period in which the survivor was diagnosed. We estimated incidence curves and hazard ratios (HRs) for survivors overall and separately for each treatment group and stratified by period of cancer diagnosis. We used inverse probability weights to adjust the incidence curves for diagnostic groups[24] and log-rank tests to test for equivalence of incidence curves.

To increase comparability of survivors and siblings with respect to sex and age at survey, we standardized the siblings to the survivors by the above-mentioned characteristics (our method is described in previous publications).[25] We imputed age at time of occurrence of hearing loss if a survivor reported hearing loss but not the year of first occurrence (n = 43).We used observed values (sex, age at cancer diagnosis, cancer diagnosis, cranial radiotherapy, platinum chemotherapy) in the imputation model to generate the missing age.[26]

We used the software package Stata (Version 13, Stata Corporation, Austin, Texas) for all analyses, and the missforest package for R 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria) for multiple imputation.

RESULTS

Characteristics of study population

We contacted 2,884 survivors and 1,526 siblings (Supplementary Fig. S1). Questionnaires were returned by 2,061 survivors (response rate 71%) and 864 siblings (response rate 57%).

Of the participating survivors, 54% were male; median (interquartile [IQR]) age at survey was 21 years (6–46) (Table 1). The most common diagnosis among survivors was leukemia (36%), followed by lymphoma (16%) and CNS tumor (14%). Median (IQR) age at cancer diagnosis was 5 years (0–15); median (IQR) time since cancer diagnosis was 15 years (5–38). Of survivors who had received chemotherapy, 6% had been treated with carboplatin, 7% with cisplatin, and 4% with both.Of those who received radiation, 54% had received cranial radiation. Of those who had had surgery, 25% had brain surgery and 7% had a CSF-shunt. Five percent of survivors had received a BMT. Responders were older at survey ($P < 0.001$), more often female ($P < 0.001$), more often diagnosed with leukemia or renal tumor ($P = 0.007$), and had surgery less often than nonresponders ($P = 0.039$) (Table 1).

Prevalence of hearing loss and tinnitus in survivors and siblings

Survivors reported hearing loss more often than siblings did (10 vs. 3%; $P < 0.001$) (Fig. 1). Hearing loss was usually mild (7% in survivors vs. 3% in siblings) and rarely moderate (2% in survivors vs. 0% in siblings) or severe (1% in survivors vs. 0.2% in siblings; $P < 0.001$) (Table 2). Both unilateral (3% in survivors vs. 0.9% in siblings) and bilateral (4% in survivors vs. 1% in siblings) hearing loss were more frequent in survivors than in siblings ($P < 0.001$). The diagnostic groups differed in prevalence of hearing loss (Fig. 1). Survivors with a high prevalence of hearing loss were those with CNS tumor (25%), neuroblastoma (23%), hepatic tumor (21%), bone tumor (16%), soft tissue sarcoma (16%), and germ cell tumor (20%; all $P < 0.001$ compared with siblings). Other diagnostic groups had prevalence of hearing loss comparable to siblings. Prevalence of tinnitus did not differ between survivors and siblings (4 vs. 5%; $P = 0.574$). Prevalence of tinnitus was similar in all diagnostic groups and siblings. Survivors

of CNS tumors showed a non-significant trend toward a slightly increased tinnitus prevalence (P = 0.09; data not shown).

Treatment-related risk factors for hearing loss after cancer diagnosis

In the univariable regression, survivors treated with carboplatin (odds ratio [OR] 3.5), cisplatin (OR 11.0), or both (OR 12.7) more often developed hearing loss after cancer diagnosis than those who were not exposed to platinum compounds ($P < 0.001$) (Table 3). Survivors who had received moderate or high doses of cranial radiation were more likely to report hearing loss after cancer diagnosis (30–49 Gy: OR 2.7; ≥50 Gy: OR 5.5) than those who had not been cranially irradiated ($P < 0.001$). Survivors who had had brain surgery (OR 4.1, $P < 0.001$), CSF-shunt (OR 3.6, $P < 0.001$), or BMT (OR 2.3, P = 0.005) were also more likely to develop hearing loss.

In the multivariable regression, survivors with the following treatments were more likely to develop hearing loss: platinum compounds (carboplatin: OR 2.4; cisplatin: OR 9.4; both combined: OR 8.6; $P <$ 0.001), cranial radiation doses higher than 29 Gy (30–49 Gy: OR 1.7; ≥50 Gy:OR 2.1; $P = 0.016$), brain surgery (OR 2.2; $P = 0.001$), and BMT (OR 2.1; $P = 0.023$) (Table 3 and Supplementary Fig. S2).

Cumulative incidence and onset of hearing loss by treatment group

Cumulative incidence of hearing loss 15 years after cancer diagnosis differed between treatment groups. Survivors treated with both platinum compounds and cranial radiation had the highest cumulative incidence (63%; 95% confidence interval [CI] 40–98%), followed by those treated with only platinum compounds (30%; 95% CI 21–42%), only cranial radiation (9%; 95% CI 6–13%), and those who had had neither of these therapies (5%; 95% CI 4–7%; overall $P < 0.001$) (Fig. 2). In groups treated with platinum compounds, cumulative incidence began to increase in the first year after cancer diagnosis. Survivors treated only with platinum compounds developed hearing loss no later than 7 years after diagnosis, but in survivors with cranial radiation or both, cranial radiation and platinum compounds, cumulative incidence continued to increase until 17 years after diagnosis.

Cumulative incidence of hearing loss by period of cancer diagnosis

Cumulative incidence differed between periods of cancer diagnosis (Fig. 3). We first looked at all survivors together (panel A). The risk of hearing loss was low for survivors diagnosed 1976–1985, increased in 1986–1995 with widespread use of platinum compounds in Switzerland, and decreased again in 1996–2005. Cumulative incidence of hearing loss 15 years after diagnosis was 4% in those diagnosed in 1976–1985, 12% in those diagnosed in 1986–1995, and 9% in those diagnosed 1996–2005. Accordingly, HRs were 0.41 (95% CI 0.22–0.75) in 1976–1985 and 0.79 (95% CI 0.48–1.30; P = 0.017) in 1996–2005 compared with that in 1986–1995 (HR=1.00, Reference). Second, we looked at survivors treated with cranial radiation only (panel B). There, cumulative incidence after 15 years was 6% for those diagnosed 1976–1985, increased to 13% for those diagnosed in the second period, and was lowest (2%) in those diagnosed most recently (1996–2005). Corresponding HRs were 0.45 (95% CI 0.19–1.07) in 1976–1985 and 0.32 (95% CI 0.07–1.49; P = 0.089) in 1996–2005, compared with that in 1986–1995. For survivors treated with platinum compounds only (panel C), cumulative incidence after 15 years was 42% for those diagnosed 1986–1995 and 12% for those diagnosed 1996–2005, with an HR of 0.27 (95% CI 0.08–0.86; *P* = 0.027). Finally, we looked at survivors treated with both cranial radiation and platinum compounds (panel D). In this group, cumulative incidence was 62% for those diagnosed in 1986–1995 and 39% for those diagnosed in 1996–2005, with a corresponding HR of 0.56 (95% CI 0.23–1.40; P = 0.219).

DISCUSSION

This comprehensive national survey of hearing loss after childhood cancer found that prevalence of self-reported hearing loss was significantly higher in childhood cancer survivors than in siblings and varied between diagnostic groups, with the highest prevalence in survivors of CNS tumors. Incidence of hearing loss increased significantly after platinum compounds were introduced in the 1980s, but tended to decrease again in 1996–2005. Prevalence of tinnitus was similar in survivors and siblings.

We found a high prevalence of hearing loss (10%) among childhood cancer survivors. The U.S. Childhood Cancer Survivor Study found lower prevalence of self-reported hearing loss (5%) among survivors of childhood cancer than we did.[12] The discrepancy between the two studies may result from differences in study period and length of observation: The U.S. study did not include survivors diagnosed after 1986, when platinum compounds came into common use, while we included all survivors diagnosed up to 2005. Also, the U.S. study assessed prevalence of hearing loss up to 5 years after diagnosis only, while our mean follow-up time was 15 years. We have shown that cumulative incidence continues to increase well beyond 5 years from diagnosis particularly for those treated with cranial radiation.

When we looked at single diagnostic groups, we found that every fourth survivor of CNS tumor or neuroblastoma reported hearing loss, which is similar to the findings of Christopherson et al.[16] in survivors with CNS tumors (21%) and Gurney et al.8 in survivors of neuroblastoma (31%).

Prevalence of tinnitus was relatively low in our study, in both survivors (4%) and siblings (5%). The U.S. study found a higher 5-year prevalence in survivors (6%), and differences to siblings (1%).[12]

We identified platinum compounds, cranial radiation at doses 30 Gy or higher, brain surgery, and BMT as risk factors for hearing loss. A large body of literature shows the effect of cumulative dose of platinum compounds on hearing loss.1 Several studies have reported a dose-dependent relationship between cochlear radiation and hearing loss, with a threshold dose in the range of 35–45 Gy.[6,27] Survivors with BMT are at notably increased risk of hearing loss,[19,28] but BMT has no ototoxic effect and is a surrogate for accompanying pre-treatments that include total body irradiation or myeloablative chemotherapy with high-dose platinum compounds. We found high prevalence of hearing loss in survivors who had had brain surgery. Brain surgery may lead to auditory complications when the tumor is located near auditory structures.[27,29] We found no association between hearing loss and CSF-shunt, even though two U.S. studies in children with brain tumors found that rapid changes in intracranial pressure from hydrocephalus itself or from subsequent shunting affect

cochlear physiology and can cause hearing loss.[27,30] Our study might have underestimated the effect of CSF shunt, since we had no detailed information on changes in intracranial pressure.

We found the highest cumulative incidence of hearing loss 15 years post-diagnosis in survivors who had been treated with both platinum compounds and cranial radiation (63%). A U.S. study by Knight et al.[9] found that 80% of patients with medulloblastoma and osteosarcoma, who are often treated with both cranial radiation or platinum compounds developed hearing loss within 200 days after diagnosis. When we looked at time intervals between diagnosis and onset of hearing loss, we saw that auditory complications that followed treatment with platinum compounds always appeared within 7 years of diagnosis. Onset of auditory complications after radiotherapy could occur much later (up to 17 years after diagnosis). Two U.S. studies reported similar time intervals between platinum administration and detection of hearing loss: 6–82 months in Qaddoumi et al.[31] and 12–98 months in Kolinsky et al.[32] The U.S. childhood cancer survivor study reported that survivors who had had cranial radiation developed hearing loss as late as 15 years after diagnosis.[12] We found no other study that compared cumulative incidence curves between different periods of cancer diagnosis because previous studies had investigated shorter time periods after cancer diagnosis (e.g., 1970–1986,[12,15] 1974–1998,[19] 1995–2008[23]).

In our study, the incidence of hearing loss increased with the widespread introduction of platinum compounds from 1985 onward, but tended to decrease again for patients diagnosed in the last period, 1996–2005. The decrease in hearing loss after 1995 could be explained by more recent clinical protocols, which recommend to replace cisplatin with the less toxic carboplatin at the first sign of auditory complications.[33,34] The incidence of hearing loss in survivors who had received only cranial radiation also tended to decrease after 1996, perhaps because modern protocols use new radiation techniques like three-dimensional conformal or intensity-modulated radiation therapy.[13,14,35] The decrease in incidence of hearing loss after 1996 could also be caused by the shorter follow-up time between diagnosis and questionnaire survey in the last period, as it is well known that hearing loss after cranial radiation may begin many years after treatment. We are currently contacting survivors

with a second follow-up questionnaire. These data will then allow further investigation of this potential bias. The consistent results for survivors treated with both cranial radiation and platinum compounds might be explained by changes in treatment regimens for CNS tumor patients, who made up a large proportion of our participants. Until the end of the 1980s, these patients had been treated with radiotherapy instead of chemotherapy. When platinum compounds became available, treatment regimens changed: CNS tumor patients were prescribed both craniospinal radiation and platinum compounds.[16,36]

In the late 1990s, when it became obvious that cranial radiation caused neurocognitive effects, new protocols reduced radiation doses but intensified platinum chemotherapy.[37,38]

In summary, most patients diagnosed with CNS tumors, neuroblastomas, hepatic tumors, bone tumors, soft tissue sarcomas, and germ cell tumors receive ototoxic treatments like platinum compounds, cranial radiation, or brain surgery. These diagnostic groups are at high risk of hearing loss and should be closely monitored with audiological tests during, and for many years after cancer treatment. If auditory complications are detected early, physicians can counsel patients, offer them hearing aids, and perhaps prevent the progress of hearing loss and secondary effects like impaired speech development or neurocognitive functioning.[10,11,39]

Our study has some limitations. First, numbers of survivors with auditory complications were relatively small in some diagnostic groups and we may have missed some effects because CIs were large. We used self-reported information on auditory complications, so complications could have been underreported, especially when hearing was affected only in the high frequencies and did not affect survivor's daily life, or when tinnitus after cancer treatment disappeared. However, an Australian study suggests that self-reports have a reasonable sensitivity (78–100%) for detecting hearing loss when pure-tone audiometry was used as the gold standard.[40] Incidence of hearing loss in the early period (1976–1985) might be underestimated. Survival rate in this period was lowest, while time lag between diagnosis and questionnaire mailing was longest. A larger proportion of these survivors may have died and not been reached by the survey compared with survivors of other decades.Our study

may also be limited by the fact that we could not narrow the radiation area to the cochlea, though our approach is supported by earlier studies that report that cochlear doses of radiation are not the exclusive reason for hearing loss; other head and neck sites are also associatedwith hearing loss.[12,41] We could not determine if the effect of platinum compoundswas dose-dependent, as we did not have exact cumulative doses of platinum compounds. Finally, it remains unclear if other ototoxic drugs (e.g., aminoglycoside antibiotics or loop diuretics) contribute to the auditory damage, as that information was not available to us.

Our study was strengthened by its large representative population based sample of childhood cancer survivors. We followed survivors over a long period of time, covered all diagnostic groups, and also included survivors who had been diagnosed in different time periods. Our study is the first to investigate the prevalence of auditory complications among all diagnostic groups of childhood cancer and to compare incidence between different periods of cancer diagnosis. Few other studies investigated tinnitus in addition to hearing loss in long-term childhood cancer survivors.

Our findings show that survivors treated with platinum compounds, cranial radiation, or brain surgery have a higher risk of developing hearing loss. Even though use of platinum compounds with ototoxic properties has increased in recent years, the burden of hearing loss appears to have stabilized. This suggests that survivors have benefited from new treatment regimens that use less ototoxic radiation and more carefully dosed platinum compounds.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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461 **TABLES**

462 **Table 1**

463 Characteristics of childhood cancer survivors and siblings

	Survivors					Siblings[a]		
	Responders, N = 2,061		Nonresponders, N = 816			N = 864		
Characteristics	n	%	n	%	*P*[b]	n	%	*P*[c]
Sex					0.001			<0.001
Female	952	46	309	38		498	58	
Male	1,109	54	507	62		366	42	
Age at survey, years					<0.001			<0.001
5–15	455	22	161	20		127	15	
16–20	587	29	302	37		159	18	
21–40	976	47	339	42		514	59	
41–60	43	2	14	2		64	7	
Age at diagnosis, years					0.832			
<1	202	10	75	9				
1–4	734	36	281	34				
5–9	537	26	216	26				
10–16	588	29	244	30				
Period of cancer diagnosis					0.206			
1976–1985	401	20	144	18				
1986–1995	731	36	275	34				
1996–2005	929	45	397	49				
Cancer diagnosis (ICCC3)					0.007			
I: Leukemia	745	36	258	32				
II: Lymphoma	334	16	149	18				
III: CNS tumor	285	14	125	15				
IV: Neuroblastoma	114	6	43	5				
V: Retinoblastoma	70	3	22	3				
VI: Renal tumor	143	7	36	4				
VII: Hepatic tumor	19	1	5	1				
VIII: Bone tumor	83	4	36	4				
IX: Soft tissue sarcoma	115	6	50	6				
X: Germ cell tumor	54	3	32	4				
XI and XII: Other rare tumors[d]	21	1	18	2				
Langerhans cell histiocytosis	78	4	42	5				
Treatments[e]								
Chemotherapy	1,733	84	655	80	0.069			
No platinum	1,442	82	–[f]					
Carboplatin	99	6	–					
Cisplatin	126	7	–					
Both	64	4	–					
Unknown platinum use	2	1	–					
Radiotherapy	703	34	286	35	0.578			
No cranial radiation	300	43	–					
Cranial radiation <30 Gy	182	26	–					
Cranial radiation 30–49 Gy	48	7	–					
Cranial radiation ≥50 Gy	148	21	–					
Unknown cranial radiation	25	4	–					

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	Survivors					Siblings[a]		
	Responders, N = 2,061		Nonresponders, N = 816			N = 864		
Characteristics	n	%	n	%	P[b]	n	%	P[c]
Surgery	1,189	58	491	62	0.039			
Brain surgery	292	25	–[f]					
CSF-shunt	79	7	–					
BMT	112	5	46	6	0.723			

ICCC3, International Classification of Childhood Cancer, 3rd edition; N, number; P, P value.

[a]For analysis, siblings were standardized on sex and age at study according to the survivors.

[b]P values calculated from chi-square statistics comparing responding to nonresponding survivors.

[c]P values calculated from chi-square statistics comparing survivors to siblings.

[d]Other malignant epithelial neoplasms, malignant melanomas, and other or unspecified malignant neoplasms.

[e]Each subject could have had more than one treatment.

[f]Detailed treatment information not available for nonresponding survivors.

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Table 2

Severity and laterality of self-reported hearing loss in survivors and siblings

[a]"No" column contains missing.

[b]Prevalence in siblings is standardized on sex and age at study according to the survivor population.

[c]P-values calculated from chi-square statistics comparing prevalence in survivors to siblings.

[d]Percentages are based upon available data.

	Survivors				Siblings				
	N = 2,061				N = 864				
	Prevalence				Prevalence				
	No[a]	Yes	%	95% CI	No[a]	Yes	%[b]	95% CI	P[c]
Hearing loss	1,854	207	10	9–11	834	30	3	2–5	<0.001
Severity									<0.001
Mild		138	7	6–8		28	3	2–5	
Moderate		49	2	2–3		–	–	–	
Deafness		20	1	1–2		2	0.2	0–1	
Laterality[d]									<0.001
Unilateral		55	3	2–3		7	0.9	0–2	
Bilateral		90	4	4–5		10	1	1–2	

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Table 3

Effect of treatment-related factors on hearing loss after cancer diagnosis

N, number; P, P values.

[a]Absolute numbers of survivors reporting hearing loss after diagnosis.

[b]Row percentages.

[c]Global P value was calculated with likelihood ratio tests.

[d]Odds ratios comparing exposed to non exposed childhood cancer survivors, adjusted for use of platinum compounds, cranial radiation, CSF-shunt, BMT, brain surgery, sex, and age at diagnosis.

[e]Univariable analysis restricted to n = 2,059 because of missing values.

[f]Univariable analysis restricted to n = 2,036 because of missing values.

	Univariable regression					Multivariable regression		
	N = 2,061					N = 2,034		
	n[a]	%[b]	OR	95%CI	P[c]	OR[d]	95%CI	P[c]
Age at diagnosis, years					0.059			0.016
<1	19	9	1.0			1.0		
1–4	57	8	0.8	0.5–1.4		1.2	0.7–2.3	
5–9	57	11	1.1	0.7–2.0		1.3	0.7–2.5	
10–16	37	6	0.6	0.4–1.2		0.7	0.3–1.3	
Sex					0.174			0.057
Male	83	8	1.0			1.0		
Female	87	9	1.2	0.9–1.7		1.4	1.0–2.0	
Chemotherapy[e]					<0.001			<0.001
No platinum	85	5	1.0			1.0		
Carboplatin	15	15	3.5	2.0–6.4		2.4	1.3–4.5	
Cisplatin	45	36	11.0	7.2–16.8		9.4	5.8–15.0	
Both	25	39	12.7	7.4–22.9		8.6	4.8–15.7	
Cranial radiation[f]					<0.001			0.016
No cranial radiation	113	7	1.0			1.0		
<30 Gy	5	3	0.4	0.2–1.0		0.5	0.2–1.3	
30–49 Gy	8	17	2.7	1.3–6.0		1.7	0.7–4.0	
≥50 Gy	42	29	5.5	3.6–8.2		2.1	1.2–3.7	
Brain surgery					<0.001			0.001
No brain surgery	109	6	1.0			1.0		
Brain surgery	61	21	4.1	2.9–5.7		2.2	1.4–3.5	
CSF-shunt					<0.001			0.547
No shunt	152	8	1.0			1.0		
Shunt	18	23	3.6	2.0–6.2		1.2	0.6–2.4	
BMT					0.005			0.023
No BMT	155	8	1.0			1.0		
BMT	15	19	2.3	1.3–3.8		2.1	1.1–4.0	

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FIGURES

Figure 1

Prevalence of self-reported hearing loss and tinnitus in survivors and siblings

CI, confidence interval; CNS, central nervous system.

[a](survivors or siblings with hearing loss or tinnitus/total number of persons in this group)

[b]Prevalence in siblings is standardized on sex and age at study according to survivor population.

P values calculated from chi^2-statistics comparing prevalence between survivors of all or of separate diagnostic groups to siblings.

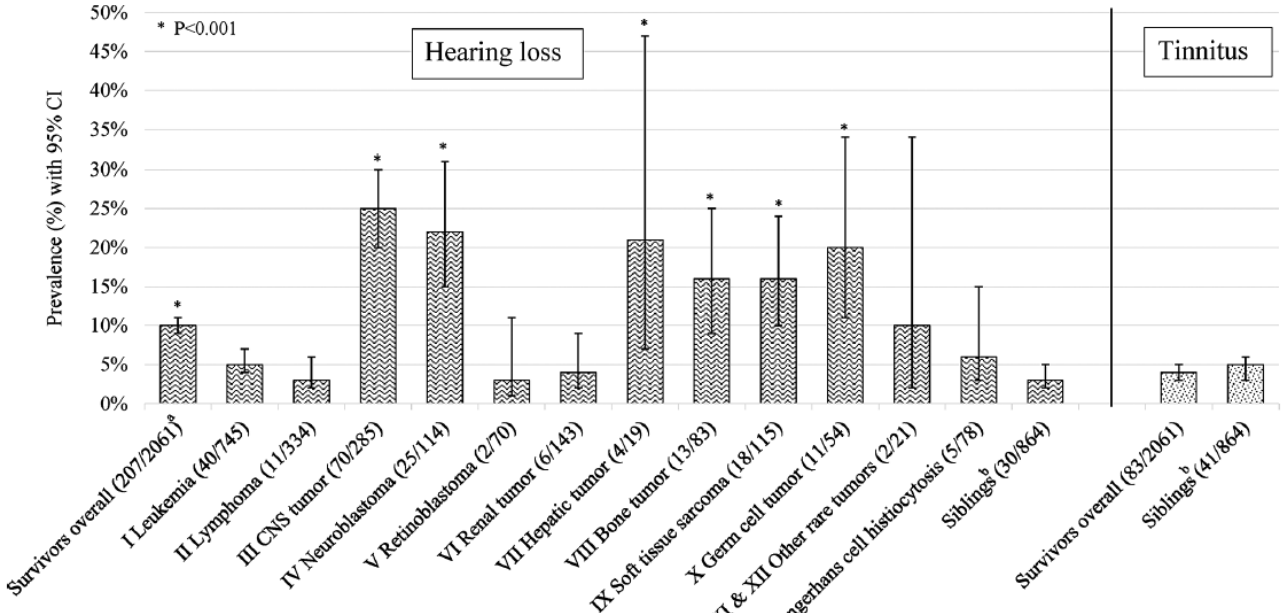

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Figure 2

Cumulative incidence of hearing loss since year of diagnosis, by treatment groups

P, P value.

Analysis is restricted to questionnaires answered by adolescents and adults (n = 1,606). Multiple imputation was used to impute missing values for year of onset of hearing loss in n = 43. P-value is calculated with log-rank test. Time of onset of hearing loss was reported in years.

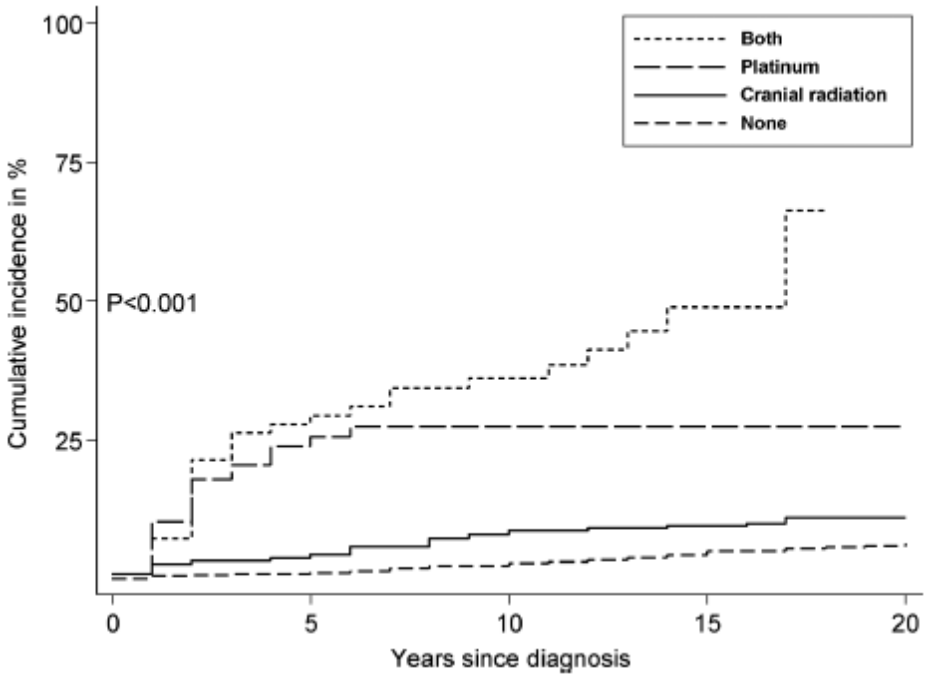

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Figure 3

Cumulative incidence of hearing loss after cancer diagnosis based on treatment groups stratified by period of cancer diagnosis, adjusted for diagnostic group

P, P value.

Analysis is restricted to questionnaires answered by adolescents and adults (n = 1,606). Multiple imputation was used to impute missing values for year of onset of hearing loss in n = 43. Time of onset of hearing loss was reported in years. Global P-values are calculated with log-rank tests.

*Since approval for cisplatin was in 1979 and for carboplatin in 1986 in Switzerland, the time period 1976–1985 was not computed.