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Auditory Complications in Childhood Cancer Survivors: A Report from the Childhood Cancer Survivor Study^a

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Abstract

Background—Studies have found associations between cancer therapies and auditory complications, but data are limited on long-term outcomes and risks associated with multiple exposures.

Procedure—The Childhood Cancer Survivor Study is a retrospective cohort investigating health outcomes of long-term survivors (5+ years) diagnosed and treated between 1970 and 1986 compared to a randomly selected sibling cohort. Questionnaires were completed by 14,358 survivors of childhood cancer and 4,023 sibling controls. Analysis determined the first occurrence of four auditory conditions in two time periods: diagnosis to ≥ 5 years post diagnosis, and > 5 years post diagnosis. Multivariable analyses determined the relative risks (RR) and 95% confidence interval (CI) of auditory conditions by treatment exposure.

Results—Five or more years from cancer diagnosis, survivors were at increased risk of problems hearing sounds (RR=2.3; 95% CI: 1.8–2.8), tinnitus (RR=1.7; 95% CI: 1.4–2.1), hearing loss requiring an aid (RR=4.4; 95% CI: 2.8–6.9), and hearing loss in 1 or both ears not corrected by a hearing aid (RR=5.2; 95% CI: 2.8–9.5), when compared to siblings. Temporal lobe and posterior fossa radiation was associated with these outcomes in a dose-dependent fashion. Exposure to platinum compounds was associated with an increased risk of problems hearing sounds (RR=2.1;

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95% CI: 1.3–3.2), tinnitus (RR=2.8; 95% CI: 1.9–4.2), and hearing loss requiring an aid (RR=4.1; 95% CI: 2.5–6.7)

Conclusions—Childhood cancer survivors are at risk of developing auditory complications. Radiation and platinum compounds are determinants of this risk. Follow-up is needed to evaluate the impact of auditory conditions on quality of life.

Keywords

late effects of therapy; radiation therapy

Introduction

Due to improvements in therapeutic modalities and supportive care, the overall survival rate for childhood cancer is approximately 80%^{1–2}. Accordingly, there has been an interest in and emphasis on the burden of cure that survivors face. Research has shown that long-term survivors are at increased risk for morbidity and early mortality³. A study by Oeffinger et al. found that approximately two-thirds of childhood cancer survivors report at least one chronic health condition and many have multiple and/or severe chronic conditions⁴. Although the majority of childhood cancer survivors consider their quality of life to be good, some late effects can have an adverse impact.⁵ Development of complications of therapy depends on many factors, including the type and cumulative dose of chemotherapeutic agents, age at therapy, and whether radiation was part of the treatment plan^{2,6}.

Hearing loss is a well-reported complication of cancer treatment^{6–9}. These late complications not only create functional limitation in survivors, but also potentially impact other arenas, such as speech development, educational attainment, and socialization.⁹ Platinum chemotherapy agents may cause hearing deficits, ranging from reversible tinnitus to permanent hearing loss^{8,–10}. Cisplatin ototoxicity is characterized as bilateral, irreversible, and progressive sensorineural hearing loss^{8–9,11–12}. Carboplatin does not routinely cause hearing loss, but may when given in combination with cisplatin or in high doses^{11, 13–16}. Larger individual and cumulative doses, the presence of a brain tumor, and young patient age are considered risk factors for developing cisplatin-induced ototoxicity^{8–9,11,17}. Additionally, studies suggest that prior cranial radiation may enhance the ototoxicity of platinum compounds.^{17–20}

Radiation therapy to the head and/or neck can damage the auditory apparatus, leading to both conductive and sensorineural hearing loss.^{9,21} The severity of radiation-induced ototoxicity is determined by the total dose, with most toxicity seen at doses greater than 30 Gy.^{9,22–23} In addition, patients with ventriculoperitoneal (VP) shunts experience changes in intracranial pressure that can cause or increase the risk of hearing loss²². There is evidence that the incidence of clinically significant hearing loss from radiation is relatively low and manifestation may require long-term follow-up²².

This study from the Childhood Cancer Survivor Study (CCSS) reports the results of an analysis of the long-term effects of cancer and its associated therapies on hearing. Primary aims were to describe the risk of self-reported hearing complications as a function of survivors' clinical and demographic characteristics and time since diagnosis; to compare the rates of these hearing complications in survivors and a sibling control group; and to evaluate the effect of specific cancer treatments on the risk of developing late hearing complications five years post diagnosis.

Methods

Patient Selection and Contact

The CCSS is a multi-institutional collaborative retrospective study of individuals who survived at least 5 years after diagnosis of cancer during childhood or adolescence. The current analysis is limited to subjects who met the following criteria: 1.) diagnosis of leukemia, kidney tumor, bone tumor, soft tissue sarcoma, neuroblastoma, Hodgkin disease, non-Hodgkin lymphoma, or primary central nervous system malignancy of any histologic subtype; 2) diagnosis and treatment at one of 26 collaborating institutions; 3) diagnosed between January 1, 1970 and December 31, 1986; 4) age less than 21 years old at diagnosis ; 5) survival greater than or equal to 5 years from diagnosis.^{24–25}

The CCSS research protocol and subject contact documents were approved by the Human Subjects Committees at participating institutions. In 1994, a self-administered baseline questionnaire was sent to eligible participants. This questionnaire contained queries pertaining to demographical information, health habits, medical diagnoses, surgical procedures, and other health outcomes. The survey can be found at the CCSS website (<http://ccss.stjude.org>).

Of the 20,691 eligible 5 year survivors, 3,058 (14.8%) were lost to follow-up. Of the remaining 17,633 cases contacted, 14,358 (81.4%) completed the baseline questionnaire and 3,210 (18.2%) declined participation. Of the participants, 13,247 (92.3%) signed permission to abstract information from their medical records and complete treatment information was obtained for 12,592. Therefore, this report on auditory conditions in childhood cancer survivors is based on 14,358 survivors who completed the baseline questionnaire, with analysis of treatment based on 12,592 survivors with available medical records.

Nearest age siblings of randomly selected participants were invited to participate as the control population. Of the 4,869 siblings contacted, 4023 (82.6%) completed the questionnaire. Table I illustrates the demographic and treatment information for 14,358 survivors and 4023 siblings.

Auditory complications in this analysis included self-reported hearing loss requiring a hearing aid (hearing loss), hearing loss in 1 or both ears not corrected by a hearing aid (deafness), tinnitus or ringing in the ears (tinnitus), and problems hearing sounds, words, or language in crowds (problems hearing sounds). The questions were introduced with "Have you ever been told by a doctor or other health care professional that you have, or have had. . ." Possible responses were "yes", "no", and "not sure". If the respondent answered "yes", they were asked to indicate the age at first occurrence of the condition.

Treatment Information

All participating survivors were asked to sign a consent form allowing information to be obtained from their medical records. For the survivors who returned a signed consent form, information was abstracted from their medical records. The information obtained included chemotherapy, radiation and surgery for their initial therapy, salvage therapy for recurrent disease, and bone marrow transplant preparative regimens (if applicable). Detailed treatment information was abstracted and included exposure to 42 chemotherapeutic agents with cumulative doses for 22 specific agents.

This chemotherapy information was used to assess cisplatin and carboplatinum use as a dichotomous outcome, and as part of a platinum compound cumulative dose. A platinum compound cumulative dose was calculated by summing the cisplatin dose and one-fourth of the carboplatinum dose²⁶.

Within the CCSS, radiation records were obtained for 8507 patients. Details including treatment dose and body area treated were abstracted in the 5 year time period from diagnosis to capture treatment relevant to the primary tumor. Data on the 1% of survivors (n=134) who received some radiation exposure beyond the 5 year cutoff was not included in this analysis. To quantify radiation exposure to the cochlea, maximum treatment doses were summarized for two segments of the brain, posterior fossa and temporal lobe. A brain segment was considered to be in the radiation field if at least half of the segment was included in the primary radiation volume. If there was no direct treatment to the brain segment, dose was classified into high and low scatter categories based on proximity of the treated region to the segment in question. The high scatter category was assigned if the nearest treatment included other regions of the head or brain. The low scatter category was assigned if the nearest treatment was not in the head or brain. Individual scatter doses were not estimated. Based on measurements of radiation falloff with distance and known treatment dose ranges, high scatter doses ranged from approximately 1 to 5 Gy and low scatter doses ranged from approximately >0 to 1 Gy.²⁷

Surgical information from medical records was reviewed for indications of VP shunts (ICD9 codes 2.34, 2.42, or 2.43). The baseline questionnaire also asked if the participant had ever had a VP shunt. This information was used to create a dichotomous VP shunt variable for analysis. The medical record abstraction form is available at <http://ccss.stjude.org>

Data Analysis

Multiple imputation methodology was used in the event that a survivor or sibling reported a condition but not the age at first occurrence. Ten imputed values for each missing age were generated via the EM algorithm using a slightly modified version of the technique of Taylor et al.^{28–29} Gender, age, primary diagnosis, radiation therapy, and platinum compound exposure were used in the imputation model for the rate of development of each auditory condition, with the effects of therapy allowed to change across the time periods. The imputation model for siblings did not include diagnosis or treatment information. Reported analytic results were obtained by combining analyses across the imputed data sets using standard formulas.²⁸

The prevalence ratio (PR) at study entry was estimated by dividing the observed count of the condition among survivors by an expected count for the period from diagnosis to 5 years based on rates calculated from same age and gender siblings. Statistical inference was based on bootstrap samples, i.e. using 100 resamples of the observed data (with replacement) to calculate the prevalence ratio 100 times and form an approximate distribution of the estimator. The standard deviation of the distribution was used as the standard error of the PR.

The relative risks (RR) for developing each condition 5 or more years post-diagnosis, comparing the survivors to the siblings, as well as incidence rates per 1000 person-years were estimated by multivariable Poisson regression³⁰. Models were adjusted for gender and for age, with potential within-family correlation accounted for using generalized estimating equations³¹.

To assess the effect of therapy on the risk of developing auditory conditions, multivariable Cox proportional hazard models were used among survivors to determine relative risk for each condition. Models assessed the effect of radiation therapy, use of platinum drugs and VP shunt, adjusting for gender and age at diagnosis. Age was used as the time scale, with subjects entering the risk set at five years post diagnosis.

To determine risk as a function of radiation dose, separate Cox models were fit using maximum dose to the posterior fossa and temporal lobe segments of the brain, adjusting for age at diagnosis, gender, platinum compound use, and VP shunt. Additional models treating platinum compound cumulative dose as categorical (None, 1–349 mg/m², 350 mg/m² or more) revealed interactions between platinum dose and high dose radiation for the conditions ‘hearing loss’ (p-value=.0101) and ‘deafness’ (p-value=.0605). The models were stratified on radiation dose of 50 Gy or more, resulting in two estimates of risk for these conditions. Cumulative incidence curves, starting with the 5-year anniversary of the primary cancer diagnosis, were constructed using the method described in Gooley et al ³² treating death as a competing risk for the outcome.

RESULTS

Table I describes the demographics of the cohorts (eligible survivors and control group siblings) used in this analysis. There was a slight male predominance in the survivor group compared to the sibling control group (53.7% compared with 48.1%). Survivors were younger than siblings, with 77.5% less than 30 years old compared to 62.4%. Over 60% of the survivors were less than 10 years of age at diagnosis. Leukemia was the most common diagnosis among survivors. For cases that survived five years but subsequently died (14.1%), selected baseline information was requested from a family member, usually the parent.

Reported Occurrence of Auditory Conditions and Relative Risk Compared to Siblings

Table II shows the frequencies of auditory complications and comparison to siblings of first occurrence of self-reported auditory conditions by two time periods: prevalence ratio at 5 years post-diagnosis, and the prospective incidence rate and relative risk 5 years or more post-diagnosis. The relative rate of first occurrence of all conditions was greatest in the time period from diagnosis to 5 years post-diagnosis. However, during the period 5 years or more post-diagnosis, the risk among survivors remained significantly higher (p <0.01) relative to siblings for all conditions.

Diagnosis and Treatment-Related Factors for Specific Conditions Occurring 5 Years or More Post-Diagnosis

Problems hearing sounds in crowds was associated with prior treatment with any platinum drug (RR=2.1; 95% CI: 1.3–3.2, Table III) and exposure to posterior fossa or temporal lobe radiation (RR=1.7; 95% CI: 1.3–2.2). All radiation doses other than low scatter to the temporal lobe and the posterior fossa were associated with a statistically significant increased risk of problems hearing sounds compared to those with no radiation to those areas (Table IV). When cumulative dose of platinum compound exposure was explored, there was an increased risk of problems hearing sounds for those treated with 1–349 mg/m² (RR=2.1; 95% CI: 1.1–4.1 Table V) and greater than or equal to 350 mg/m² (RR=1.9; 95% CI: 1.0–3.5). When analyzing the effect of diagnosis on the risk of problems hearing sounds, it was found that the 20 year cumulative incidence was greatest for primary CNS tumor survivors (cumulative incidence= 11.4%; 95% CI: 9.4–13.5) and Hodgkin lymphoma survivors (cumulative incidence= 4.2%; 95% CI: 3.0–5.4) (Table VI). The cumulative incidence of self-reported problems hearing sounds continued to increase up to 20 years after diagnosis for survivors who received radiation to the posterior fossa or temporal lobe (Figure 1) and up to 15 years after diagnosis for those who were treated with platinum chemotherapy agents (Figure 2).

Survivors exposed to platinum drugs had an increased risk of tinnitus occurring 5 years or more after diagnosis (RR=2.8; 95% CI: 1.9–4.2). In addition, radiation to the temporal lobe

and posterior fossa in doses of 30 Gy or higher was associated with an increased risk of tinnitus (RR=2.4; 95% CI: 1.6–3.6 and RR=2.6; 95% CI: 1.7–4.1 for 30–49.9 Gy, respectively) as compared to subjects with no radiation to those areas. Platinum compound doses ranging from 1–349 mg/m² as compared to 0 mg/m² were associated with tinnitus (RR=3.8; 95% CI: 2.2–6.8). At 20 years post-diagnosis, self-reported complaints of tinnitus were most frequent in survivors of a primary CNS malignancy (cumulative incidence= 7.4%; 95% CI: 5.7–9.2) and soft tissue sarcoma survivors (cumulative incidence= 4.0%; 95% CI: 2.6–5.3). The cumulative incidence of tinnitus continued to increase up to 20 years post-diagnosis for survivors who received at least 30 Gy of radiation to either the posterior fossa or temporal lobe (Fig 1) and up to 15 years after diagnosis for those who were treated with platinum chemotherapy agents (Fig 2).

Platinum drug exposure increased the risk of hearing loss requiring a hearing aid in survivors (RR=4.1; 95% CI: 2.5–6.7), as did radiation to the posterior fossa or temporal lobe (RR=2.2; 95% CI: 1.4–3.5). The risk of hearing loss increased as dose to the temporal lobe (RR=10.5; 95% CI: 5.9–18.4 for 50+ Gy vs. 0 Gy) and posterior fossa (RR=11.7; 95% CI: 6.5–21.0 for 50+ Gy vs. 0 Gy) increased. In survivors who received < 50 Gy of radiation to the temporal lobe or posterior fossa, exposure to platinum chemotherapy agents increased the risk of hearing loss in a dose-dependent fashion (RR=11.0; 95% CI: 5.2–23.2 for 350+ mg/m² vs. 0 mg/m²). Twenty years after diagnosis, survivors of primary CNS malignancies were most likely to report this condition (cumulative incidence= 6.2; 95% CI: 4.7–7.7). Self-reported hearing loss continued to increase up to 25 years post diagnosis for survivors who received at least 30 Gy of radiation to the posterior fossa or temporal lobe (Fig 1) and up to 15 years after diagnosis for those who were treated with platinum chemotherapy agents (Fig 2). Survivors who were less than 5 years of age at diagnosis were more likely to report hearing loss than subjects age 15–20 (RR 3.1; 95% CI: 1.4–7.1, data not shown).

Hearing loss in one or both ears not corrected by a hearing aid was associated with radiation to the posterior fossa or temporal lobe. Doses of radiation to the temporal lobe that were ≥ 30 Gy were associated with this complication (RR=7.5; 95% CI: 3.6–15.5 for 50+ Gy vs. 0 Gy). In survivors who received radiation to the posterior fossa, the risk of deafness was greatest for those receiving at least 50 Gy (RR 10.7; 95% CI: 5.2–22.2), but was also noted at doses of 30–49.9 Gy compared to no radiation to the posterior fossa. While platinum chemotherapy drug use was not associated with deafness when the entire cohort was analyzed, a sub-group analysis revealed a dose dependent relationship in survivors who received platinum agents and <50 Gy of radiation to the posterior fossa or temporal lobe (RR=5.4; 95% CI: 1.6–18.2 for 350+ mg/m² vs. 0 mg/m²). This condition was reported most frequently by survivors of primary CNS malignancies at 20 years post-diagnosis (cumulative incidence= 5.0; 95% CI: 3.7–6.3). Survivors continued to report deafness up to 15 years after diagnosis for those treated with ≥ 50 Gy of radiation to the posterior fossa or temporal lobe and up to 20 years post diagnosis for those treated with 30–49.9 Gy of radiation to the posterior fossa or temporal lobe (Fig 1) and in survivors who were treated with platinum chemotherapy agents up to 10 years after diagnosis (Fig 2).

DISCUSSION

Previous studies have investigated ototoxicity in children who received platinum chemotherapy and/or cranial radiation.^{8–9,11,19,20,22,23} Many have been limited to certain diseases, such as nasopharyngeal carcinoma, neuroblastoma, and brain tumors.^{16,22,23,33,34} In part due to different grading systems and variability in reporting hearing loss, there has been a great deal of variation in estimates of the incidence of hearing loss after cisplatin therapy in the pediatric population, with ranges in the literature from 11–97%¹⁴. In addition, the majority of reported studies regarding ototoxicity have relatively short follow-up and

there is evidence that hearing deficits from therapy may worsen with time or have a latency period prior to manifestation^{11,15,22,23,35}. The current study, while relying on self-reported auditory outcomes, adds to current knowledge by providing estimates from a large and diverse cohort of survivors who reported a first occurrence of auditory complications 5 years or greater post-diagnosis, and with follow-up spanning up to 25 years.

The CCSS is an invaluable resource for the identification of late effects that first occur many years after the original diagnosis. The make-up of this cohort is representative of the cancer incidence and 5 year survival rates of the eight major pediatric cancers eligible and treated during the treatment era (1970–1985). Due to limited resources, however, survivors of more rare malignancies, such as germ cell tumors and nasopharyngeal carcinomas, were not included in the CCSS cohort. It is important to note that the new CCSS cohort is currently accruing patients who were treated between 1987–1999 and will allow further investigation into sequelae faced by survivors treated with more current treatment regimens. This will be especially important in studying the late effects in survivors of primary CNS malignancies, as their regimens have been modified and survival rates have improved.

This study confirmed that treatment with platinum compounds has adverse effects on hearing, as it was associated with a risk of problems hearing sounds, tinnitus, and hearing loss requiring a hearing aid. The mechanism of cisplatin toxicity involves deterioration of the outer hair cells of the Organ of Corti in the cochlea^{15,36}, while carboplatin affects the inner hair cells of the Organ of Corti¹³. This progressive loss of hair cells occurs due to intracellular production of reactive oxygen species and iron-induced free radicals, which deplete the cells of anti-oxidants¹⁵. Sensorineural hearing loss is a known complication of platinum drugs, but hearing loss affecting only the higher frequencies is difficult to appreciate as it manifests with impaired recognition of high frequency consonants (such as s, f, k) and difficulty in hearing the plural forms of words^{9, 11}. Problems hearing sounds and tinnitus may be surrogate markers of sensorineural hearing loss, as they are often symptoms of the underlying damage to the auditory apparatus^{37–39}. Although cumulative platinum compound dosing was analyzed in relation to auditory complications, with the exception of hearing loss requiring a hearing aid and deafness in a subset of survivors who received <50 Gy of radiation to the temporal lobe or posterior fossa, there was no dose response in the risk of late-occurring hearing conditions. This study supports earlier reports that indicate that while ototoxicity secondary to platinum compounds often develops soon after treatment³⁶, there is a risk of progression or new onset ototoxicity greater than 5 years after therapy^{11,15}.

Not unexpectedly, radiation to the temporal lobe and/or posterior fossa resulted in an increased risk of problems hearing sounds, tinnitus, hearing loss requiring a hearing aid, and hearing loss in 1 or both ears not corrected by a hearing aid. Radiation may affect the external ear, causing otitis externa and stenosis of the external auditory canal. The middle ear can manifest radiation toxicity through eustachian tube dysfunction, leading to chronic otitis media with effusion. In addition, perforation or sclerosis of the tympanic membrane may occur. These changes can cause transient or permanent conductive hearing loss. Radiation effects on the inner ear may lead to tinnitus, labyrinthitis, vertigo, and sensorineural hearing loss due to damage to the cochlea and retro-cochlear component of the auditory apparatus^{7,21}. Radiation damage often occurs within 6–12 months of treatment³³, but this study shows that survivors more than 5 years post-diagnosis remain at risk for the development of ototoxicity. In addition, although the majority of toxicity seen with radiation occurred at doses ≥ 30 Gy, problems hearing sounds was seen at doses <30 Gy, indicating that close audiologic follow-up is called for in all survivors who received radiation to the posterior fossa or temporal lobe.

It is important to note that two demographic groups stood out as particularly vulnerable to audiologic complications: survivors of primary CNS malignancies and those survivors who were diagnosed at less than 5 years of age. Radiation is often part of the therapy for primary CNS malignancies and now platinum compounds are often utilized, exposing survivors to multiple ototoxic treatments. It is also possible that the hearing loss is in addition to cognitive late effects of therapy, thereby putting the survivor at increased risk of impaired quality of life. In addition, survivors who were less than 5 years of age at diagnosis were found to have an increased risk of hearing loss requiring a hearing aid. This fact stresses the need for close audiologic follow-up in survivors who were treated at a very young age and who may be at increased risk for adverse educational and psychosocial sequelae.

It is also notable that survivors of Hodgkin lymphoma had an increased cumulative incidence of problems hearing sounds at 20 years post diagnosis. With the exception of certain salvage therapies, this population is not routinely exposed to platinum chemotherapy agents. It is likely that the report of problems hearing sounds is related to neck radiation that some survivors received. This finding is worth further follow-up, as some response based treatment protocols for Hodgkin lymphoma are intensifying therapy with the addition of cisplatin to slow responders.

There is evidence that pre-irradiation cisplatin is associated with less risk of ototoxicity than when cisplatin is given during or after radiation^{17,19}. We attempted to confirm that finding; however, few patients during the time period from 1970–1986 were treated with pre-irradiation cisplatin. It was not until later years that cisplatin was routinely used in brain tumor patients.

This study is not without limitations. The use of temporal lobe and posterior fossa radiation dosage as a surrogate for dosage to the cochlea is not ideal and more precise information about the dosage the cochlea received would have been preferred. Some of the auditory conditions studied could overlap, resulting in a survivor answering yes to multiple conditions. The data available on this large cohort is limited to self-reported auditory outcomes, which may result in either under or over-reporting of some conditions. However, reliability of selected self-reported conditions among stem cell transplant survivors has been demonstrated to be good⁴⁰.

In summary, survivors of childhood cancer are at increased risk for auditory late effects. This risk is multifactorial, based in part on treatment factors, age at diagnosis, and the underlying diagnosis. This report documents that hearing loss can occur or progress more than 5 years after diagnosis and supports continued audiologic follow-up of survivors who were treated with platinum compounds or radiation, especially those who were less than 5 years of age at diagnosis and those treated for primary CNS malignancies. Hearing loss is not only a medical complication, but may influence speech development, educational achievement, and social-emotional maturation.^{11,41} Early detection of auditory impairment and intervention may decrease the risk of adverse psychosocial outcomes. Continued follow-up of childhood cancer survivors is needed to evaluate the future occurrence of auditory impairment among an aging population and to evaluate the impact of complications on quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Cumulative incidence (%) of conditions based on maximum radiation to temporal lobe or posterior fossa.

Figure 2.
Cumulative incidence (%) of conditions by use of platinum drugs (cisplatin or carboplatin).

Table I

Characteristics of Survivors and Siblings

Characteristic	Survivor		Sibling	
	N	%	N	%
Total	14358		4023	
Gender *				
Female	6645	46.3	2086	51.9
Male	7713	53.7	1937	48.1
Age at questionnaire (yrs) *				
<18	3960	27.6	817	20.3
18–29	7161	49.9	1693	42.1
30–39	2905	20.2	1170	29.1
40–49	332	2.3	328	8.2
50+	0	0	15	0.4
Vital Status				
Alive	12339	85.9	4023	100
Dead	2019	14.1	0	0
Age at diagnosis				
0–4	5753	40.1	NA	NA
5–9	3201	22.3	NA	NA
10–14	2913	20.3	NA	NA
15–20	2491	17.3	NA	NA
Year of diagnosis				
1970–1973	1923	13.4	NA	NA
1974–1977	2913	20.3	NA	NA
1978–1981	3757	26.2	NA	NA
1982–1986	5765	40.2	NA	NA
Diagnosis				
Leukemia	4830	33.6	NA	NA
Hodgkin Disease	1927	13.4	NA	NA
CNS Tumor	1877	13.1	NA	NA

Characteristic	Survivor		Sibling	
	N	%	N	%
Kidney Tumor	1256	8.7	NA	NA
Soft Tissue Sarcoma	1246	8.7	NA	NA
Bone Tumor	1188	8.3	NA	NA
NHL	1080	7.5	NA	NA
Neuroblastoma	954	6.6	NA	NA
Radiation: Post Fossa				
None	4134	28.8	NA	NA
<30 Gy	7105	49.5	NA	NA
30–49 Gy	504	3.5	NA	NA
50+ Gy	588	4.1	NA	NA
Unknown	2027	14.1	NA	NA
Radiation: Temporal Lobe				
None	4134	28.8	NA	NA
<30 Gy	6820	47.5	NA	NA
30 Gy–49 Gy	672	4.7	NA	NA
50+ Gy	705	4.9	NA	NA
Unknown	2027	14.1	NA	NA
Radiation: Max dose to post fossa or temporal lobe				
None	4134	28.8	NA	NA
<30 Gy	6721	46.8	NA	NA
30–49 Gy	568	4.0	NA	NA
50+ Gy	908	6.3	NA	NA
Unknown	2027	14.1	NA	NA
Chemotherapy:				
Carboplatin				
No	12498	87.0	NA	NA
Yes	76	0.5	NA	NA
Unknown	1784	12.4	NA	NA
Cisplatin				
No	11836	82.4	NA	NA

Characteristic	Survivor		Sibling	
	N	%	N	%
Yes	738	5.1	NA	NA
Unknown	1784	12.4	NA	NA
Platinum drugs cumulative area dose				
None	11800	82.2	NA	NA
1–349 mg/m2	243	1.7	NA	NA
350+ mg/m2	447	3.1	NA	NA
Unknown	1868	13.0	NA	NA
Ventriculoperitoneal shunt				
No	11490	80.0	NA	NA
Yes	775	5.4	NA	NA
Unknown	2093	14.6	NA	NA

NA: not applicable;

* p value <0.0001; NHL: Non Hodgkin Lymphoma

Table II
Self-Reported Auditory Conditions in Survivors- Prevalence Ratios Compared to Sibling Cohort

Auditory Condition	No.		Diagnosis to 5 years post diagnosis		5+ years post diagnosis	
	No ^a	Yes ^b	Yes	Prevalence Ratio (95% CI)	Yes	Incidence Rate [*] 5% CI Relative Risk ^{**} (95% CI)
Problems hearing sounds	13338	1020	410	4.6(3.7–5.8) ^c	483	2.8 (2.4–3.3) 2.3 (1.8–2.8) ^c
Tinnitus	13560	798	280	3.7(2.9–4.7) ^c	415	2.7 (2.3–3.1) 1.7 (1.4–2.1) ^c
Hearing loss	13965	393	191	10.3 (6.2–17.2) ^c	154	0.8 (0.6–1.1) 4.4 (2.8–6.9) ^c
Deafness	14057	301	153	10.7(6.3–18.3) ^c	108	0.8 (0.6–1.1) 5.2 (2.8–9.5) ^c

^{*} among survivors, per 1000 person-years;

^{**} adjusted for age and gender;

^a the “No” column also contains counts for “not sure” and missing;

^b the “Yes” column includes those who developed the condition before diagnosis of malignancy and those who were unsure of when the condition first occurred;

^c p value<0.01;

Summary of Treatment factors and Relative Risk of Late Auditory Conditions 5+ Years Post-Diagnosis

Table III

Auditory Condition	Treatment Factor Relative Risk* (95% CI)	
	Any platinum drug use vs none	Any radiation to posterior fossa or temporal lobe vs none
Problems hearing sounds	2.1 (1.3–3.2) **	1.7 (1.3–2.2) **
Tinnitus	2.8 (1.9–4.2) **	1.2 (0.9–1.6)
Hearing loss	4.1 (2.5–6.7) **	2.2 (1.4–3.5) **
Deafness	1.7 (0.8–3.5)	2.3 (1.2–4.2) **

* Models for platinum drug adjusted for age at diagnosis, gender, VP shunt, and maximum radiation dose levels; Models for posterior fossa/temporal lobe radiation adjusted for any platinum drug use, gender, age at diagnosis, and VP shunt;

** p value <0.01

Table IV
Radiation Dose to Temporal Lobe and Risk of Late Auditory Conditions 5+ Years Post-Diagnosis

Radiation Site	Auditory Condition	Relative Risk* (95% CI)			
		1–29.9 Gy	30–49.9 Gy	50+ Gy	low scatter
Temporal Lobe					
	Problems hearing sounds	1.6 (1.2–2.2) ^b	3.8 (2.6–5.5) ^b	4.2 (2.9–6.2) ^b	1.8 (1.1–3.0) ^a
	Tinnitus	1.2 (0.9–1.7)	2.4 (1.6–3.6) ^b	2.6 (1.7–4.1) ^b	1.3 (0.7–2.2)
	Hearing loss	1.2 (0.6–2.3)	6.2 (3.4–11.2) ^b	10.5 (5.9–18.4) ^b	2.0 (0.7–5.3)
	Deafness	1.2 (0.5–2.8)	7.6 (3.7–15.8) ^b	7.5 (3.6–15.5) ^b	1.4 (0.3–6.3)
Posterior Fossa					
	Problems hearing sounds	1.6 (1.2–2.2) ^b	3.6 (2.4–5.4) ^b	5.9 (4.0–8.7) ^b	1.8 (1.2–2.9) ^b
	Tinnitus	1.2 (0.9–1.7)	2.6 (1.7–4.1) ^b	2.9 (1.8–4.6) ^b	1.4 (0.9–2.1)
	Hearing loss	1.3 (0.7–2.4)	5.4 (2.8–10.4) ^b	11.7 (6.5–21.0) ^b	3.7 (1.9–7.1) ^b
	Deafness	1.0 (0.4–2.5)	7.1 (3.2–15.6) ^b	10.7 (5.2–22.2) ^b	2.8 (1.1–6.9) ^a

* Relative risks for doses shown vs no radiation. Models adjusted for age at diagnosis, gender, any platinum drug use, and VP shunt

^a p value <0.05;

^b p value <0.01

Platinum Compound Dose and Relative Risk of Late Auditory Conditions > 5 Years Post-Diagnosis

Table V

Auditory Condition	Radiation strata	Platinum Dose Relative Risk* (95% CI)	
		1–349mg/m2	350+mg/m2
Problems hearing sounds		2.1 (1.1–4.1) ^a	1.9 (1.0–3.5) ^a
Tinnitus		3.8 (2.2–6.8) ^b	2.1 (1.1–4.2) ^a
Hearing loss	50+ Gy	1.4 (0.3–5.7)	1.5 (0.5–4.7)
	< 50 Gy	4.2 (1.3–14) ^a	11.0 (5.2–23.2) ^b
Deafness	50+ Gy	---	0.5 (0.1–3.6)
	< 50 Gy	2.7 (0.6–11.8)	5.4 (1.6–18.2) ^b

* Relative risks for doses shown vs no platinum. Models adjusted for age at diagnosis, gender, and maximum radiation dose to posterior fossa or temporal lobe and VP shunt placement;

---: not estimable;

^a p value <0.05;

^b p value <0.01

Cumulative Incidence (%) and 95% C.I. for Self-Reported Auditory Conditions at 20 Years Post-Diagnosis by Diagnosis Group

Table VI

Auditory Condition	Diagnosis*						
	Leukemia	CNS Tumor	Hodgkin Disease	NHL	Kidney Tumor	NB	STS
Problems hearing sounds	3.8 (3.0-4.6)	11.4 (9.4-13.5)	4.2 (3.0-5.4)	3.5 (2.1-4.9)	2.6 (1.3-3.9)	2.7 (1.3-4.2)	3.5 (2.2-4.8)
Tinnitus	3.7 (2.8-4.5)	7.4 (5.7-9.2)	3.8 (2.7-4.8)	3.3 (1.9-4.6)	2.2 (1.2-3.3)	2.0 (0.8-3.2)	4.0 (2.6-5.3)
Hearing loss	0.8 (0.4-1.2)	6.2 (4.7-7.7)	0.4 (0.1-0.8)	0.3 (0.0-0.7)	0.4 (0.0-0.8)	1.1 (0.3-1.8)	1.1 (0.4-1.8)
Deafness	0.4 (0.1-0.6)	5.0 (3.7-6.3)	0.4 (0.1-0.7)	0.2 (0.0-0.6)	0.3 (0.0-0.7)	0.3 (0.0-0.9)	0.6 (0.0-1.2)

* NHL: Non-Hodgkin Lymphoma; NB: neuroblastoma; STS: soft tissue sarcoma