Title: Incidence, Predictors and Impact of Hearing Impairment in Long-term Survivors of Childhood Cancer

Working Group: **Primary** Chronic Disease

Secondary: Epidemiology/Biostatistics, Psychology

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Background & Rationale:

Platinum-based chemotherapies, such as cisplatin and carboplatin, are commonly used in the treatment of numerous pediatric malignancies, including neuroblastoma, osteosarcoma, and central nervous system tumors. While platinum therapies are highly effective antineoplastic agents, their use is associated with severe ototoxicity. Platinum toxicity disrupts the outer hair cells, spiral ganglion, and stria vascularis of the organ of Corti, resulting in bilateral, high-frequency sensorineural hearing loss.[1-4] The current clinical approach to reduce treatment-related ototoxicity involves dose reduction or cessation of platinum chemotherapy once hearing impairment is detected. However, once detected, hearing loss is typically permanent, and dose modification will not restore normal hearing.[5, 6] Although ototoxicity and hearing loss are well-established side effects of platinum chemotherapy, the long-term burden of ototoxic therapy remains largely unknown. Specifically, there is a critical need to: 1) characterize the cumulative incidence of hearing impairment among long-term childhood cancer survivors; 2) determine the dose-response relationships of treatment exposures established to be associated with hearing loss (i.e., cisplatin and carboplatin) and identify novel treatment-related factors associated with the development of hearing loss; and 3) determine how hearing impairment may impact academic and psychosocial outcomes among childhood cancer survivors.

Incidence of Platinum Chemotherapy-Associated Ototoxicity: The reported incidence of cisplatin-associated ototoxicity varies greatly, ranging between 20% and 100%.[7-26] While carboplatin is considerably less ototoxic than cisplatin, with a reported incidence of 0% to 17%,[14, 27-35] the use of carboplatin in myelo-ablative conditioning regimens following cisplatin chemotherapy can result in moderate to severe hearing loss in up to 90% of patients.[7, 14, 36, 37] Platinum ototoxicity is often detected within several months of chemotherapy;[6, 10] however, a significant proportion of cases develop late-onset hearing loss or progressive hearing loss that may continue to deteriorate years after platinum therapy.[6, 10, 12, 31, 38-41] Given the progressive nature of treatment-related ototoxicity, extended long-term follow up may be necessary to fully characterize the burden of auditory impairment in survivors of childhood cancer. In fact, a report from the Childhood Cancer Survivor Study (CCSS) Original Cohort revealed the cumulative incidence of auditory complications increased for 15 to 20 years following treatment.[42] This proposal will build upon past research to include participants enrolled in the more contemporary CCSS Expansion Cohort, providing valuable information on the ototoxic effects of modern era therapies.

Treatment-Related Risk Factors for Ototoxicity: Established risk factors for platinum ototoxicity include young age at treatment, exposure to additional ototoxic therapies (i.e., aminoglycosides, other platinum agents, etc.), and cumulative platinum dose;[1, 7, 17, 21, 27, 38, 41, 43-52] however, these factors do not fully account for the considerable variability in individual susceptibility to platinum ototoxicity.[9, 14, 53-55] Independent of platinum-based chemotherapies, radiation to the head and neck exposes the adjacent auditory tissue to potentially harmful doses of radiation,[56] particularly when cochlear doses exceed 30 Gy.[57-59] Additionally, radiation may potentiate the ototoxic effects of subsequent or concomitant platinum chemotherapy at cochlear

doses as low as 10 Gy.[60-63] Notably, in children, prior exposure to cranial radiotherapy appears to reduce the platinum dose necessary to induce significant hearing loss.[64-66] However, many studies have been limited in their ability to describe the interactive effects of radiation and chemotherapy due to smaller sample sizes. Thus, additional research is required to elucidate whether the joint contributions of radiation and platinum therapy exceed the predicted contribution of their individual risks in relation to hearing impairment.

Outcomes in Childhood Cancer Survivors with Hearing Loss: While the long-term academic, economic, and quality of life consequences of childhood cancer therapy have been well described,[67-74] there is growing evidence that a portion of these adverse outcomes may be mediated by treatment-related hearing loss.[75] Among adult survivors of nasopharyngeal carcinoma, hearing loss was correlated with worse cognitive, emotional, and social function as well as lower financial security and quality of life.[76] Hearing impairment may be particularly detrimental in children and has been associated with communication disorders, poor academic performance, social-emotional dysfunction, and decreased quality of life in the general population.[77-79] Limited research in childhood cancer survivors supports a role between ototoxicity and reduced speech intelligibility, cognition, and quality of life.[75, 80-82] Today's advanced hearing aid technology can significantly improve the communication abilities of survivors with ototoxicity. Still, the damaged system cannot be restored to normal and many survivors will continue to experience varying degrees of communication challenges.[83-85] Therefore, determining the long-term complications of treatment-related hearing impairment in survivors of childhood cancer is of considerable importance in their follow up care.

Significance: Striking the appropriate balance between satisfactory survival and toxicity requires a refined understanding of the long-term consequences of treatment-related hearing impairment among survivors of childhood cancer. However, existing research is limited by small sample sizes, lack of data on contemporary populations, and the absence of long-term follow up. To address these limitations, this proposal seeks to determine the long-term burden of ototoxic therapy in the well-characterized Childhood Cancer Survivor Study. This large cohort of childhood cancer survivors with extensive follow-up will facilitate more in-depth analysis and finer stratification of the clinical risk factors that contribute to hearing impairment in this population. This information may inform the development interventions targeting high-risk individuals, while detailing the adverse outcomes of hearing impairment may facilitate the delivery of improved prevention services and supportive follow up care to affected survivors.

We anticipant this project will help to clarify the complex nature of treatment-related hearing impairment in survivors of childhood cancer. The results of this research will also lay the groundwork to explore novel ototoxicity risk factors in future studies. Specifically, the knowledge generated by this study will be used to establish a baseline to: 1) identify genetic variation associated with ototoxicity susceptibility; and 2) integrate treatment and molecular risk factors to develop ototoxicity risk prediction models for this population. Ultimately, we expect this avenue of research will translate to clinical improvements in the treatment and prevention of ototoxicity.

Specific Aims:

1. **Describe the cumulative incidence and rate of hearing impairment among long-term childhood cancer survivors relative to siblings without a history of cancer.**
   Hypothesis: Survivors of childhood cancer will report hearing conditions more frequently than siblings.
2. **Evaluate the joint effects of treatment-related factors on hearing impairment among childhood cancer survivors.**
   Hypothesis: Prior or concomitant exposure to ototoxic therapy will modify the dose-response relationship between subsequent therapy and participant-reported hearing impairment.
3. **Identify academic and psychosocial consequences of hearing impairment among childhood cancer survivors.**
   Hypothesis: Compared to similarly treated survivors without hearing impairments, survivors who report hearing impairment will be more likely to report adverse psychosocial and academic outcomes.

Analysis Framework:

This analysis will leverage existing data within the Childhood Cancer Survivor Study to address each specific aim. While the proposed study population, variables of interest, and analytic plan for each aim are outlined below, a final decision on the methods will be reached with input from CCSS statisticians and collaborators:

Aim 1:

Study Population: This analysis will include all survivors and siblings enrolled in the Overall Cohort who completed the "Hearing/Vision/Speech" section of any questionnaire. Survivors and siblings with a reported diagnosis of hearing impairment at birth (e.g., Expansion Baseline Q3a.d.) or survivors with a reported age at occurrence of hearing impairment less than the age at diagnosis of cancer will be excluded from this analysis.

Study Variables: The outcome of interest is hearing impairment (Original baseline [C.1-7], 2007 FU [D.1-7], Expansion baseline [C.1-7]).

- Hearing impairment will be graded using CTCAE criteria with grade 3 or 4 considered clinically significant: none, mild to moderate (CTCAE Grade 1-2, trouble hearing sounds), severe (CTCAE Grade 3-4, hearing loss requiring a hearing aid, complete deafness in either ear, deafness in one ear not completely corrected by a hearing aid, deafness in both ears not completely corrected by a hearing aid).

Proposed classification of hearing impairment applying CTCAE criteria to CCSS questionnaire responses

Classified as Hearing Impaired	CTCAE	Hearing Impairment Reported	CCSS Questionnaire		
			Original Baseline	2007 Follow-up	Expansion Baseline
No	0	None			
No	1-2	Problems hearing sounds, not requiring a hearing aid	C.6-C.7	D.6-D.7	C.6-C.7
Yes	3	Hearing loss requiring a hearing aid or hearing loss not completely corrected by hearing aid in either ear	C.1-C.3	D.1, D.3	C.1, C.3
Yes	4	Deafness in both ears not completely corrected by hearing aid		D.2	C.2

The primary explanatory variable of interest includes:

- Sibling/Survivor Status

Additional covariates considered in the analysis will include:

- Age during follow up
- Gender
- Race/Ethnicity

Among survivors additional covariates considered will included:

- Cisplatin (none, 1-99 mg/m^2, 100-199 mg/m^2, 200-299 mg/m^2, 300-399 mg/m^2, 400-499 mg/m^2, ≥500 mg/m^2)
- Carboplatin (none, 1-249 mg/m^2, 250-499 mg/m^2, 500-749 mg/m^2, 750-999 mg/m^2, 1,000-1,249 mg/m^2, 1,250-1,500 mg/m^2, >1,500 mg/m^2)
- Radiation dose to the cochlea will be estimated from the maximum treatment dose at the posterior fossa and temporal lobe segments of the brain. Segments will be considered to fall within the radiation field if greater than half of the segment was included in the primary radiation field. In the absence of direct radiation to the segment, radiation exposure will be categorized as high or low-scatter based on proximately of the radiated region to the target segment. For the purposes of this analysis, if the radiated region includes other sections of the head or brain, the dose will be classified high-scatter. Low-scatter dose will be assigned to any instance where the most proximal radiated field did not include the head or brain. Accounting for estimated radiation falloff for known treatment doses, high-scatter dose will range from approximately 1-5 Gy while low-scatter dose will range from approximately 0-1 Gy. Radiation dose (no radiation therapy, low-scatter, high-scatter, and direct radiation [≤10 Gy, 11-20 Gy, 21-30 Gy, 31-40 Gy, ≥41 Gy) will be evaluated in statistical models.

Analysis: Descriptive statistics will be generated and compared between survivor and sibling cohorts. The cumulative incidence of each auditory condition will be calculated with age as the time variable, treating death as a competing risk. The risk of developing each condition among survivors relative to siblings of a similar age, gender, and ethnicity will be estimated using generalized estimating equations assuming a piecewise

exponential model for the hearing impairment, accounting for potential within-family correlation between related individuals.

Aim 2:

Study Population: This analysis will include all survivors enrolled in the Overall Cohort who completed the "Hearing/Vision/Speech" section of any questionnaire. Survivors with a reported diagnosis of hearing impairment at birth (e.g., Expansion Baseline Q3a) or survivors with a reported age at occurrence of hearing impairment less than the age at diagnosis of the primary cancer will be excluded from this analysis.

Study Variables: The outcome of interest is hearing impairment as define previously (Aim 1, Study Variables)

The primary explanatory variables of interest include:

- Cumulative cisplatin dose (cumulative before the cohort entry, i.e., within 5 years of diagnosis)
- Cumulative carboplatin dose (cumulative before the cohort entry, i.e., within 5 years of diagnosis)
- Radiation dose to head/neck region (e.g., temporal lobe, posterior fossa)
- Timing of therapies received before cohort entry (e.g., order of radiation and chemotherapy for testing the specific hypothesis listed above under Specific Aims)

Additional covariates considered in the analysis will include:

- Age at diagnosis
- Age at follow up/time since diagnosis
- Gender
- Race/Ethnicity
- Cancer diagnosis
- Year at diagnosis

Analysis: Summary statistics will be generated across categories of reported hearing impairment. The independent effects of cumulative cisplatin, cumulative carboplatin, and maximum radiation dose to the head and neck region on hearing loss will be assessed with multivariable piecewise exponential models, adjusting for gender, ethnicity, age and year at diagnosis. Interaction terms will be explored in separate models for: cranial radiation and cisplatin; cranial radiation and carboplatin; cisplatin and carboplatin; and cranial radiation, cisplatin, and carboplatin. Interaction results will be presented if there is evidence of significant effect modification (p-value <0.05). Potential non-linear, dose-response associations between treatment factors and auditory complications may be explored using restricted cubic splines. In addition, to further define the dose-response effect for platinum exposure and hearing loss without the confounding effect of RT, an additional model excluding patients with RT exposure will be considered.

Aim 3:

Study Population: Like Aim 2, all survivors enrolled in the Overall Cohort who completed the "Hearing/Vision/Speech" section of any questionnaire will be included in this analysis. Survivors with a reported diagnosis of hearing impairment at birth (e.g., Expansion Baseline Q3a) or prior to the age at diagnosis of the primary cancer will be excluded. Additionally, individuals with a condition associated with developmental delays (Down's syndrome, Klinefelter syndrome, Turner's syndrome) will be excluded from this analysis.

Study Variables: The primary outcomes for this aim include academic and psychosocial variables. The analysis of some outcomes will be stratified by participant age at the time of assessment.

- Academic Outcomes:
  - Entire Cohort:
    - Special Education Programs stemming from learning difficulties (Original baseline [O.3-4], Expansion baseline [R.3-4]) will be coded as present if the participant reports ever being placed in special education programs.
  - ≥18 years of age at assessment:
    - Educational Attainment (Original baseline [O.1-2], 2003 FU [1], 2007 FU [A.3], Expansion baseline [R.1-2]) will be coded as less than high school and completed high school/GED.
- Psychosocial Outcomes:
  - 12-17 years of age at assessment:

- Behavioral Problem Index (Original baseline<18 [J.16-21], Expansion baseline <18 [K.1-6]) is a series of 27 validated questions assessing five behavioral domains: anxiety/depression, headstrong, attention deficit, social withdrawal, and antisocial.[86] Responses to each question will receive a score, with lower scores indicating an absence of the behavior. Individuals with a score placing them in the top 10% of sibling reference scores will be classified as demonstrating behavior/emotional problems consistent with that particular domain.

≥18 years of age at assessment:

- Brief Symptom Inventory (Original baseline [J.16-35], Expansion baseline [K1-18]) is a series of 18 validated questions assessing three emotional domains: anxiety, depression, and somatization. Individuals with a score placing them in the top 10% of sibling reference scores will be classified as demonstrating emotional distress on that particular scale.
- Marital Status (Original baseline [L.1-2], 2003 FU [2], 2007 FU [M.2], Expansion baseline [M.2-3]) will be coded as never or ever married/living with partner.
- Independent Living (Original baseline [A.9], 2003 FU [3], 2007 FU [M.1], Expansion baseline [A.9,M.1]) will be coded present if participant reports living alone or with a spouse/partner.
- Employment Status (Original baseline [O.5-8], 2003 FU [4-5], 2007 FU [A.4-5], Expansion baseline [S.1-3]) will be coded as ever or never employed.
- Personal Income (Original baseline [Q.9], 2003 FU [S.3], 2007 FU [A.8], Expansion baseline [T.3]) will be coded as ≤ $19,999 or ≥ $20,000.

The primary explanatory variable of interest is hearing impairment.

- Hearing impairment will be categorized as previously defined (Aim 1, Study Variables)

Additional covariates considered in the analysis will include:

- Age at diagnosis
- Age at questionnaire
- Gender
- Race/Ethnicity
- Cancer diagnosis
- Year at diagnosis
- Treatment (e.g., cranial radiation dose, cumulative platinum dose)

Analysis: This cross-sectional analysis will compare academic and psychosocial outcomes between survivors with auditory condition and similarly treated survivors without hearing impairments. Logistic regression models will be used to evaluate the association between auditory complications and each outcome. Models will be adjusted for age, gender, ethnicity, cancer diagnosis. The potential modifying effect of age at first occurrence of hearing impairment may be explored in subsequent models.

All statistical analyses will be performed at a 5% significance level. For each research aim, we will conduct regression diagnostics to evaluate the assumptions and overall goodness of fit for each model. Appropriate steps will be taken to address multiple comparisons (i.e., Bonferroni-adjusted p-values), influential observations, and violations of the regression model assumptions. Individuals missing information on one or more of the variables included in a model will be excluded from the analysis. Variables with >5% missing data will be excluded from regression models except for variables deemed highly important (e.g., age at occurrence of hearing impairment), in which case standard methods will be used to average regression estimates across multiple imputed data sets.

References:

1. Skinner R, Pearson AD, Amineddine HA, Mathias DB, Craft AW. Ototoxicity of cisplatinum in children and adolescents. Br J Cancer. 1990;61(6):927-31. Epub 1990/06/01. PubMed PMID: 2372498; PubMed Central PMCID: PMCPMC1971678.
2. Schaefer SD, Post JD, Close LG, Wright CG. Ototoxicity of low- and moderate-dose cisplatin. Cancer. 1985;56(8):1934-9. Epub 1985/10/15. PubMed PMID: 4040801.
3. Brock PR, Knight KR, Freyer DR, Campbell KC, Steyger PS, Blakley BW, et al. Platinum-induced ototoxicity in children: a consensus review on mechanisms, predisposition, and protection, including a new International Society of Pediatric Oncology Boston ototoxicity scale. J Clin Oncol. 2012;30(19):2408-17. Epub 2012/05/02. doi: 10.1200/jco.2011.39.1110. PubMed PMID: 22547603; PubMed Central PMCID: PMCPMC3675696.
4. Grewal S, Merchant T, Reymond R, McInerney M, Hodge C, Shearer P. Auditory late effects of childhood cancer therapy: a report from the Children's Oncology Group. Pediatrics. 2010;125(4):e938-50. Epub 2010/03/03. doi: 10.1542/peds.2009-1597. PubMed PMID: 20194279; PubMed Central PMCID: PMCPMC3106205.
5. Brock PR, Bellman SC, Yeomans EC, Pinkerton CR, Pritchard J. Cisplatin ototoxicity in children: a practical grading system. Med Pediatr Oncol. 1991;19(4):295-300. Epub 1991/01/01. PubMed PMID: 2056973.
6. Knight KR, Kraemer DF, Neuwelt EA. Ototoxicity in children receiving platinum chemotherapy: underestimating a commonly occurring toxicity that may influence academic and social development. J Clin Oncol. 2005;23(34):8588-96. Epub 2005/11/30. doi: 10.1200/jco.2004.00.5355. PubMed PMID: 16314621.
7. Landier W, Knight K, Wong FL, Lee J, Thomas O, Kim H, et al. Ototoxicity in children with high-risk neuroblastoma: prevalence, risk factors, and concordance of grading scales--a report from the Children's Oncology Group. J Clin Oncol. 2014;32(6):527-34. Epub 2014/01/15. doi: 10.1200/jco.2013.51.2038. PubMed PMID: 24419114; PubMed Central PMCID: PMCPMC3918536.
8. Bass JK, Huang J, Onar-Thomas A, Chang KW, Bhagat SP, Chintagumpala M, et al. Concordance between the chang and the International Society of Pediatric Oncology (SIOP) ototoxicity grading scales in patients treated with cisplatin for medulloblastoma. Pediatr Blood Cancer. 2014;61(4):601-5. Epub 2014/02/08. doi: 10.1002/pbc.24830. PubMed PMID: 24504791; PubMed Central PMCID: PMCPMC4371725.
9. Nitz A, Kontopantelis E, Bielack S, Koscielniak E, Klingebiel T, Langer T, et al. Prospective evaluation of cisplatin- and carboplatin-mediated ototoxicity in paediatric and adult soft tissue and osteosarcoma patients. Oncol Lett. 2013;5(1):311-5. Epub 2012/12/21. doi: 10.3892/ol.2012.997. PubMed PMID: 23255940; PubMed Central PMCID: PMCPMC3525486.
10. Yasui N, Adachi N, Kato M, Koh K, Asanuma S, Sakata H, et al. Cisplatin-induced hearing loss: the need for a long-term evaluating system. J Pediatr Hematol Oncol. 2014;36(4):e241-5. Epub 2013/09/28. doi: 10.1097/mph.0000000000000028. PubMed PMID: 24072246.
11. Abujamra AL, Escosteguy JR, Dall'Igna C, Manica D, Cigana LF, Coradini P, et al. The use of high-frequency audiometry increases the diagnosis of asymptomatic hearing loss in pediatric patients treated with cisplatin-based chemotherapy. Pediatr Blood Cancer. 2013;60(3):474-8. Epub 2012/06/30. doi: 10.1002/pbc.24236. PubMed PMID: 22744939.
12. Al-Khatib T, Cohen N, Carret AS, Daniel S. Cisplatinum ototoxicity in children, long-term follow up. Int J Pediatr Otorhinolaryngol. 2010;74(8):913-9. Epub 2010/09/18. doi: 10.1016/j.ijporl.2010.05.011. PubMed PMID: 20846503.
13. Cheuk DK, Billups CA, Martin MG, Roland CR, Ribeiro RC, Krasin MJ, et al. Prognostic factors and long-term outcomes of childhood nasopharyngeal carcinoma. Cancer. 2011;117(1):197-206. Epub 2010/08/26. doi: 10.1002/cncr.25376. PubMed PMID: 20737561; PubMed Central PMCID: PMCPMC2994981.
14. Dean JB, Hayashi SS, Albert CM, King AA, Karzon R, Hayashi RJ. Hearing loss in pediatric oncology patients receiving carboplatin-containing regimens. J Pediatr Hematol Oncol. 2008;30(2):130-4. Epub 2008/04/01. doi: 10.1097/MPH.0b013e31815d1d83. PubMed PMID: 18376265.
15. Coradini PP, Cigana L, Selistre SG, Rosito LS, Brunetto AL. Ototoxicity from cisplatin therapy in childhood cancer. J Pediatr Hematol Oncol. 2007;29(6):355-60. Epub 2007/06/07. doi: 10.1097/MPH.0b013e318059c220. PubMed PMID: 17551394.
16. Knight KR, Kraemer DF, Winter C, Neuwelt EA. Early changes in auditory function as a result of platinum chemotherapy: use of extended high-frequency audiometry and evoked distortion product otoacoustic

emissions. J Clin Oncol. 2007;25(10):1190-5. Epub 2007/04/03. doi: 10.1200/jco.2006.07.9723. PubMed PMID: 17401008.
17. Stohr W, Langer T, Kremers A, Bielack S, Lamprecht-Dinnesen A, Frey E, et al. Cisplatin-induced ototoxicity in osteosarcoma patients: a report from the late effects surveillance system. Cancer Invest. 2005;23(3):201-7. Epub 2005/06/11. PubMed PMID: 15945505.
18. Hale GA, Marina NM, Jones-Wallace D, Greenwald CA, Jenkins JJ, Rao BN, et al. Late effects of treatment for germ cell tumors during childhood and adolescence. J Pediatr Hematol Oncol. 1999;21(2):115-22. Epub 1999/04/17. PubMed PMID: 10206457.
19. Berg AL, Spitzer JB, Garvin JH, Jr. Ototoxic impact of cisplatin in pediatric oncology patients. Laryngoscope. 1999;109(11):1806-14. Epub 1999/11/24. doi: 10.1097/00005537-199911000-00016. PubMed PMID: 10569412.
20. Brock PR, Yeomans EC, Bellman SC, Pritchard J. Cisplatin therapy in infants: short and long-term morbidity. Br J Cancer Suppl. 1992;18:S36-40. Epub 1992/08/01. PubMed PMID: 1323992; PubMed Central PMCID: PMCPMC2149657.
21. Pasic TR, Dobie RA. cis-platinum ototoxicity in children. Laryngoscope. 1991;101(9):985-91. Epub 1991/09/01. doi: 10.1288/00005537-199109000-00001. PubMed PMID: 1886448.
22. Ruiz L, Gilden J, Jaffe N, Robertson R, Wang YM. Auditory function in pediatric osteosarcoma patients treated with multiple doses of cis-diamminedichloroplatinum(II). Cancer Res. 1989;49(3):742-4. Epub 1989/02/01. PubMed PMID: 2910492.
23. Kretschmar CS, Warren MP, Lavally BL, Dyer S, Tarbell NJ. Ototoxicity of preradiation cisplatin for children with central nervous system tumors. J Clin Oncol. 1990;8(7):1191-8. Epub 1990/07/01. PubMed PMID: 2358836.
24. Lafay-Cousin L, Purdy E, Huang A, Cushing SL, Papaioannou V, Nettel-Aguirre A, et al. Early cisplatin induced ototoxicity profile may predict the need for hearing support in children with medulloblastoma. Pediatr Blood Cancer. 2013;60(2):287-92. Epub 2012/09/25. doi: 10.1002/pbc.24307. PubMed PMID: 23002030.
25. Gupta AA, Capra M, Papaioannou V, Hall G, Maze R, Dix D, et al. Low incidence of ototoxicity with continuous infusion of cisplatin in the treatment of pediatric germ cell tumors. J Pediatr Hematol Oncol. 2006;28(2):91-4. Epub 2006/02/08. doi: 10.1097/01.mph.0000199586.98926.8e. PubMed PMID: 16462581.
26. Sivaprakasam P, Gupta AA, Greenberg ML, Capra M, Nathan PC. Survival and long-term outcomes in children with hepatoblastoma treated with continuous infusion of cisplatin and doxorubicin. J Pediatr Hematol Oncol. 2011;33(6):e226-30. Epub 2011/07/28. doi: 10.1097/MPH.0b013e31821f0eaf. PubMed PMID: 21792028.
27. Musial-Bright L, Fengler R, Henze G, Hernaiz Driever P. Carboplatin and ototoxicity: hearing loss rates among survivors of childhood medulloblastoma. Childs Nerv Syst. 2011;27(3):407-13. Epub 2010/10/12. doi: 10.1007/s00381-010-1300-1. PubMed PMID: 20931205.
28. Qaddoumi I, Bass JK, Wu J, Billups CA, Wozniak AW, Merchant TE, et al. Carboplatin-associated ototoxicity in children with retinoblastoma. J Clin Oncol. 2012;30(10):1034-41. Epub 2012/03/01. doi: 10.1200/jco.2011.36.9744. PubMed PMID: 22370329; PubMed Central PMCID: PMCPMC3341147.
29. Ji S, Chueh HW, Kim JY, Lim SJ, Cho EJ, Lee SH, et al. Responses and adverse effects of carboplatin-based chemotherapy for pediatric intracranial germ cell tumors. Korean J Pediatr. 2011;54(3):128-32. Epub 2011/07/09. doi: 10.3345/kjp.2011.54.3.128. PubMed PMID: 21738543; PubMed Central PMCID: PMCPMC3120999.
30. Fouladi M, Gururangan S, Moghrabi A, Phillips P, Gronewold L, Wallace D, et al. Carboplatin-based primary chemotherapy for infants and young children with CNS tumors. Cancer. 2009;115(14):3243-53. Epub 2009/06/02. doi: 10.1002/cncr.24362. PubMed PMID: 19484793; PubMed Central PMCID: PMCPMC4307774.
31. Jehanne M, Lumbroso-Le Rouic L, Savignoni A, Aerts I, Mercier G, Bours D, et al. Analysis of ototoxicity in young children receiving carboplatin in the context of conservative management of unilateral or bilateral retinoblastoma. Pediatr Blood Cancer. 2009;52(5):637-43. Epub 2009/01/17. doi: 10.1002/pbc.21898. PubMed PMID: 19148943.
32. Bergeron C, Dubourg L, Chastagner P, Mechinaud F, Plouvier E, Desfachelles AS, et al. Long-term renal and hearing toxicity of carboplatin in infants treated for localized and unresectable neuroblastoma: results

of the SFOP NBL90 study. Pediatr Blood Cancer. 2005;45(1):32-6. Epub 2005/03/16. doi: 10.1002/pbc.20379. PubMed PMID: 15768383.
33. Stern JW, Bunin N. Prospective study of carboplatin-based chemotherapy for pediatric germ cell tumors. Med Pediatr Oncol. 2002;39(3):163-7. Epub 2002/09/05. doi: 10.1002/mpo.10134. PubMed PMID: 12210444.
34. Heideman RL, Kovnar EH, Kellie SJ, Douglass EC, Gajjar AJ, Walter AW, et al. Preirradiation chemotherapy with carboplatin and etoposide in newly diagnosed embryonal pediatric CNS tumors. J Clin Oncol. 1995;13(9):2247-54. Epub 1995/09/01. PubMed PMID: 7666082.
35. Friedman HS, Krischer JP, Burger P, Oakes WJ, Hockenberger B, Weiner MD, et al. Treatment of children with progressive or recurrent brain tumors with carboplatin or iproplatin: a Pediatric Oncology Group randomized phase II study. J Clin Oncol. 1992;10(2):249-56. Epub 1992/02/11. PubMed PMID: 1732426.
36. Parsons SK, Neault MW, Lehmann LE, Brennan LL, Eickhoff CE, Kretschmar CS, et al. Severe ototoxicity following carboplatin-containing conditioning regimen for autologous marrow transplantation for neuroblastoma. Bone Marrow Transplant. 1998;22(7):669-74. Epub 1998/11/18. doi: 10.1038/sj.bmt.1701391. PubMed PMID: 9818694.
37. Kushner BH, Budnick A, Kramer K, Modak S, Cheung NK. Ototoxicity from high-dose use of platinum compounds in patients with neuroblastoma. Cancer. 2006;107(2):417-22. Epub 2006/06/17. doi: 10.1002/cncr.22004. PubMed PMID: 16779793.
38. Kolinsky DC, Hayashi SS, Karzon R, Mao J, Hayashi RJ. Late onset hearing loss: a significant complication of cancer survivors treated with Cisplatin containing chemotherapy regimens. J Pediatr Hematol Oncol. 2010;32(2):119-23. Epub 2010/01/26. doi: 10.1097/MPH.0b013e3181cb8593. PubMed PMID: 20098336.
39. Weissenstein A, Deuster D, Knief A, Zehnhoff-Dinnesen AA, Schmidt CM. Progressive hearing loss after completion of cisplatin chemotherapy is common and more pronounced in children without spontaneous otoacoustic emissions before chemotherapy. Int J Pediatr Otorhinolaryngol. 2012;76(1):131-6. Epub 2011/11/23. doi: 10.1016/j.ijporl.2011.10.020. PubMed PMID: 22104469.
40. Einarsson EJ, Petersen H, Wiebe T, Fransson PA, Grenner J, Magnusson M, et al. Long term hearing degeneration after platinum-based chemotherapy in childhood. Int J Audiol. 2010;49(10):765-71. Epub 2010/09/30. doi: 10.3109/14992027.2010.485595. PubMed PMID: 20874050.
41. Bertolini P, Lassalle M, Mercier G, Raquin MA, Izzi G, Corradini N, et al. Platinum compound-related ototoxicity in children: long-term follow-up reveals continuous worsening of hearing loss. J Pediatr Hematol Oncol. 2004;26(10):649-55. Epub 2004/09/30. PubMed PMID: 15454836.
42. Whelan K, Stratton K, Kawashima T, Leisenring W, Hayashi S, Waterbor J, et al. Auditory complications in childhood cancer survivors: a report from the childhood cancer survivor study. Pediatr Blood Cancer. 2011;57(1):126-34. Epub 2011/02/18. doi: 10.1002/pbc.23025. PubMed PMID: 21328523; PubMed Central PMCID: PMCPMC3091978.
43. Gurney JG, Bass JK, Onar-Thomas A, Huang J, Chintagumpala M, Bouffet E, et al. Evaluation of amifostine for protection against cisplatin-induced serious hearing loss in children treated for average-risk or high-risk medulloblastoma. Neuro Oncol. 2014;16(6):848-55. Epub 2014/01/15. doi: 10.1093/neuonc/not241. PubMed PMID: 24414535; PubMed Central PMCID: PMCPMC4022215.
44. Li Y, Womer RB, Silber JH. Predicting cisplatin ototoxicity in children: the influence of age and the cumulative dose. Eur J Cancer. 2004;40(16):2445-51. Epub 2004/11/03. doi: 10.1016/j.ejca.2003.08.009. PubMed PMID: 15519518.
45. Weatherly RA, Owens JJ, Catlin FI, Mahoney DH. cis-platinum ototoxicity in children. Laryngoscope. 1991;101(9):917-24. Epub 1991/09/01. doi: 10.1288/00005537-199109000-00001. PubMed PMID: 1886439.
46. Cohen BH, Zweidler P, Goldwein JW, Molloy J, Packer RJ. Ototoxic effect of cisplatin in children with brain tumors. Pediatr Neurosurg. 1990;16(6):292-6. Epub 1990/01/01. PubMed PMID: 2134738.
47. Reddel RR, Kefford RF, Grant JM, Coates AS, Fox RM, Tattersall MH. Ototoxicity in patients receiving cisplatin: importance of dose and method of drug administration. Cancer Treat Rep. 1982;66(1):19-23. Epub 1982/01/01. PubMed PMID: 7198012.
48. Laurell G, Jungnelius U. High-dose cisplatin treatment: hearing loss and plasma concentrations. Laryngoscope. 1990;100(7):724-34. Epub 1990/07/01. doi: 10.1288/00005537-199007000-00008. PubMed PMID: 2362532.

49. Lewis MJ, DuBois SG, Fligor B, Li X, Goorin A, Grier HE. Ototoxicity in children treated for osteosarcoma. Pediatr Blood Cancer. 2009;52(3):387-91. Epub 2008/12/09. doi: 10.1002/pbc.21875. PubMed PMID: 19061216.
50. Yancey A, Harris MS, Egbelakin A, Gilbert J, Pisoni DB, Renbarger J. Risk factors for cisplatin-associated ototoxicity in pediatric oncology patients. Pediatr Blood Cancer. 2012;59(1):144-8. Epub 2012/03/21. doi: 10.1002/pbc.24138. PubMed PMID: 22431292; PubMed Central PMCID: PMCPMC3767972.
51. Vermorken JB, Kapteijn TS, Hart AA, Pinedo HM. Ototoxicity of cis-diamminedichloroplatinum (II): influence of dose, schedule and mode of administration. Eur J Cancer Clin Oncol. 1983;19(1):53-8. Epub 1983/01/01. PubMed PMID: 6682776.
52. Pollera CF, Marolla P, Nardi M, Ameglio F, Cozzo L, Bevere F. Very high-dose cisplatin-induced ototoxicity: a preliminary report on early and long-term effects. Cancer Chemother Pharmacol. 1988;21(1):61-4. Epub 1988/01/01. PubMed PMID: 3342465.
53. Buhrer C, Weinel P, Sauter S, Reiter A, Riehm H, Laszig R. Acute onset deafness in a 4-year-old girl after a single infusion of cis-platinum. Pediatr Hematol Oncol. 1990;7(2):145-8. Epub 1990/01/01. PubMed PMID: 2206855.
54. Lanvers-Kaminsky C, Krefeld B, Dinnesen AG, Deuster D, Seifert E, Wurthwein G, et al. Continuous or repeated prolonged cisplatin infusions in children: a prospective study on ototoxicity, platinum concentrations, and standard serum parameters. Pediatr Blood Cancer. 2006;47(2):183-93. Epub 2005/11/23. doi: 10.1002/pbc.20673. PubMed PMID: 16302218.
55. Rademaker-Lakhai JM, Crul M, Zuur L, Baas P, Beijnen JH, Simis YJ, et al. Relationship between cisplatin administration and the development of ototoxicity. J Clin Oncol. 2006;24(6):918-24. Epub 2006/02/18. doi: 10.1200/jco.2006.10.077. PubMed PMID: 16484702.
56. Mujica-Mota MA, Lehnert S, Devic S, Gasbarrino K, Daniel SJ. Mechanisms of radiation-induced sensorineural hearing loss and radioprotection. Hear Res. 2014;312:60-8. Epub 2014/03/22. doi: 10.1016/j.heares.2014.03.003. PubMed PMID: 24650954.
57. Merchant TE, Gould CJ, Xiong X, Robbins N, Zhu J, Pritchard DL, et al. Early neuro-otologic effects of three-dimensional irradiation in children with primary brain tumors. Int J Radiat Oncol Biol Phys. 2004;58(4):1194-207. Epub 2004/03/06. doi: 10.1016/j.ijrobp.2003.07.008. PubMed PMID: 15001264.
58. Hua C, Bass JK, Khan R, Kun LE, Merchant TE. Hearing loss after radiotherapy for pediatric brain tumors: effect of cochlear dose. Int J Radiat Oncol Biol Phys. 2008;72(3):892-9. Epub 2008/04/09. doi: 10.1016/j.ijrobp.2008.01.050. PubMed PMID: 18395355.
59. Vieira WA, Weltman E, Chen MJ, da Silva NS, Cappellano AM, Pereira LD, et al. Ototoxicity evaluation in medulloblastoma patients treated with involved field boost using intensity-modulated radiation therapy (IMRT): a retrospective review. Radiat Oncol. 2014;9:158. Epub 2014/07/22. doi: 10.1186/1748-717x-9-158. PubMed PMID: 25041714; PubMed Central PMCID: PMCPMC4118158.
60. Hitchcock YJ, Tward JD, Szabo A, Bentz BG, Shrieve DC. Relative contributions of radiation and cisplatin-based chemotherapy to sensorineural hearing loss in head-and-neck cancer patients. Int J Radiat Oncol Biol Phys. 2009;73(3):779-88. Epub 2008/08/19. doi: 10.1016/j.ijrobp.2008.05.040. PubMed PMID: 18707819.
61. Warrier R, Chauhan A, Davluri M, Tedesco SL, Nadell J, Craver R. Cisplatin and cranial irradiation-related hearing loss in children. Ochsner J. 2012;12(3):191-6. Epub 2012/10/11. PubMed PMID: 23049454; PubMed Central PMCID: PMCPMC3448239.
62. Zuur CL, Simis YJ, Lansdaal PE, Hart AA, Rasch CR, Schornagel JH, et al. Risk factors of ototoxicity after cisplatin-based chemo-irradiation in patients with locally advanced head-and-neck cancer: a multivariate analysis. Int J Radiat Oncol Biol Phys. 2007;68(5):1320-5. Epub 2007/04/10. doi: 10.1016/j.ijrobp.2007.01.042. PubMed PMID: 17418969.
63. Bhandare N, Antonelli PJ, Morris CG, Malayapa RS, Mendenhall WM. Ototoxicity after radiotherapy for head and neck tumors. Int J Radiat Oncol Biol Phys. 2007;67(2):469-79. Epub 2007/01/24. doi: 10.1016/j.ijrobp.2006.09.017. PubMed PMID: 17236969.
64. Schell MJ, McHaney VA, Green AA, Kun LE, Hayes FA, Horowitz M, et al. Hearing loss in children and young adults receiving cisplatin with or without prior cranial irradiation. J Clin Oncol. 1989;7(6):754-60. Epub 1989/06/01. PubMed PMID: 2715805.

65. Walker DA, Pillow J, Waters KD, Keir E. Enhanced cis-platinum ototoxicity in children with brain tumours who have received simultaneous or prior cranial irradiation. Med Pediatr Oncol. 1989;17(1):48-52. Epub 1989/01/01. PubMed PMID: 2913475.
66. Miettinen S, Laurikainen E, Johansson R, Minn H, Laurell G, Salmi TT. Radiotherapy enhanced ototoxicity of cisplatin in children. Acta Otolaryngol Suppl. 1997;529:90-4. Epub 1997/01/01. PubMed PMID: 9288280.
67. Jain N, Krull KR, Brouwers P, Chintagumpala MM, Woo SY. Neuropsychological outcome following intensity-modulated radiation therapy for pediatric medulloblastoma. Pediatr Blood Cancer. 2008;51(2):275-9. Epub 2008/04/19. doi: 10.1002/pbc.21580. PubMed PMID: 18421716.
68. Ris MD, Walsh K, Wallace D, Armstrong FD, Holmes E, Gajjar A, et al. Intellectual and academic outcome following two chemotherapy regimens and radiotherapy for average-risk medulloblastoma: COG A9961. Pediatr Blood Cancer. 2013;60(8):1350-7. Epub 2013/02/28. doi: 10.1002/pbc.24496. PubMed PMID: 23444345.
69. Krull KR, Huang S, Gurney JG, Klosky JL, Leisenring W, Termuhlen A, et al. Adolescent behavior and adult health status in childhood cancer survivors. J Cancer Surviv. 2010;4(3):210-7. Epub 2010/04/13. doi: 10.1007/s11764-010-0123-0. PubMed PMID: 20383785; PubMed Central PMCID: PMCPMC3098531.
70. Janson C, Leisenring W, Cox C, Termuhlen AM, Mertens AC, Whitton JA, et al. Predictors of marriage and divorce in adult survivors of childhood cancers: a report from the Childhood Cancer Survivor Study. Cancer Epidemiol Biomarkers Prev. 2009;18(10):2626-35. Epub 2009/10/10. doi: 10.1158/1055-9965.epi-08-0959. PubMed PMID: 19815636; PubMed Central PMCID: PMCPMC2768276.
71. Mulhern RK, Merchant TE, Gajjar A, Reddick WE, Kun LE. Late neurocognitive sequelae in survivors of brain tumours in childhood. Lancet Oncol. 2004;5(7):399-408. Epub 2004/07/03. doi: 10.1016/s1470-2045(04)01507-4. PubMed PMID: 15231246.
72. Mulhern RK, Palmer SL, Merchant TE, Wallace D, Kocak M, Brouwers P, et al. Neurocognitive consequences of risk-adapted therapy for childhood medulloblastoma. J Clin Oncol. 2005;23(24):5511-9. Epub 2005/08/20. doi: 10.1200/jco.2005.00.703. PubMed PMID: 16110011.
73. Armstrong GT, Jain N, Liu W, Merchant TE, Stovall M, Srivastava DK, et al. Region-specific radiotherapy and neuropsychological outcomes in adult survivors of childhood CNS malignancies. Neuro Oncol. 2010;12(11):1173-86. Epub 2010/08/19. doi: 10.1093/neuonc/noq104. PubMed PMID: 20716593; PubMed Central PMCID: PMCPMC3098024.
74. Gurney JG, Krull KR, Kadan-Lottick N, Nicholson HS, Nathan PC, Zebrack B, et al. Social outcomes in the Childhood Cancer Survivor Study cohort. J Clin Oncol. 2009;27(14):2390-5. Epub 2009/02/20. doi: 10.1200/jco.2008.21.1458. PubMed PMID: 19224833; PubMed Central PMCID: PMCPMC2677924.
75. Schreiber JE, Gurney JG, Palmer SL, Bass JK, Wang M, Chen S, et al. Examination of risk factors for intellectual and academic outcomes following treatment for pediatric medulloblastoma. Neuro Oncol. 2014;16(8):1129-36. Epub 2014/02/06. doi: 10.1093/neuonc/nou006. PubMed PMID: 24497405; PubMed Central PMCID: PMCPMC4096173.
76. Tsai WL, Huang TL, Liao KC, Chuang HC, Lin YT, Lee TF, et al. Impact of late toxicities on quality of life for survivors of nasopharyngeal carcinoma. BMC Cancer. 2014;14:856. Epub 2014/11/22. doi: 10.1186/1471-2407-14-856. PubMed PMID: 25413127; PubMed Central PMCID: PMCPMC4247772.
77. Kushalnagar P, Topolski TD, Schick B, Edwards TC, Skalicky AM, Patrick DL. Mode of communication, perceived level of understanding, and perceived quality of life in youth who are deaf or hard of hearing. J Deaf Stud Deaf Educ. 2011;16(4):512-23. Epub 2011/05/04. doi: 10.1093/deafed/enr015. PubMed PMID: 21536686; PubMed Central PMCID: PMCPMC3202327.
78. Bess FH, Dodd-Murphy J, Parker RA. Children with minimal sensorineural hearing loss: prevalence, educational performance, and functional status. Ear Hear. 1998;19(5):339-54. Epub 1998/10/31. PubMed PMID: 9796643.
79. Wake M, Hughes EK, Collins CM, Poulakis Z. Parent-reported health-related quality of life in children with congenital hearing loss: a population study. Ambul Pediatr. 2004;4(5):411-7. Epub 2004/09/17. doi: 10.1367/a03-191r.1. PubMed PMID: 15369416.
80. Liberman PH, Schultz C, Goffi-Gomez MV, Lopes LF. Speech recognition and frequency of hearing loss in patients treated for cancer in childhood. Pediatr Blood Cancer. 2013;60(10):1709-13. Epub 2013/06/15. doi: 10.1002/pbc.24560. PubMed PMID: 23765953.
81. Gurney JG, Tersak JM, Ness KK, Landier W, Matthay KK, Schmidt ML. Hearing loss, quality of life, and academic problems in long-term neuroblastoma survivors: a report from the Children's Oncology Group.

Pediatrics. 2007;120(5):e1229-36. Epub 2007/11/03. doi: 10.1542/peds.2007-0178. PubMed PMID: 17974716.
82. Brinkman TM, Bass JK, Li Z, Ness KK, Gajjar A, Pappo AS, et al. Treatment-induced hearing loss and adult social outcomes in survivors of childhood CNS and non-CNS solid tumors: Results from the St. Jude Lifetime Cohort Study. Cancer. 2015. Epub 2015/08/20. doi: 10.1002/cncr.29604. PubMed PMID: 26287566.
83. Russ SA, Kenney MK, Kogan MD. Hearing difficulties in children with special health care needs. J Dev Behav Pediatr. 2013;34(7):478-85. Epub 2013/09/18. doi: 10.1097/DBP.0b013e3182a39878. PubMed PMID: 24042079.
84. Einar-Jon E, Trausti O, Asgeir H, Christian M, Thomas W, Mans M, et al. Hearing impairment after platinum-based chemotherapy in childhood. Pediatr Blood Cancer. 2011;56(4):631-7. Epub 2011/02/08. doi: 10.1002/pbc.22876. PubMed PMID: 21298751.
85. Einarsson EJ, Petersen H, Wiebe T, Fransson PA, Magnusson M, Moell C. Severe difficulties with word recognition in noise after platinum chemotherapy in childhood, and improvements with open-fitting hearing-aids. Int J Audiol. 2011;50(10):642-51. Epub 2011/08/05. doi: 10.3109/14992027.2011.585667. PubMed PMID: 21812630.
86. Schultz KA, Ness KK, Whitton J, Recklitis C, Zebrack B, Robison LL, et al. Behavioral and social outcomes in adolescent survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol. 2007;25(24):3649-56. Epub 2007/08/21. doi: 10.1200/jco.2006.09.2486. PubMed PMID: 17704415.

Table 1. Characteristics of childhood cancer survivors and siblings enrolled in the Childhood Cancer Survivor Study

	Survivors (n=)		Siblings (n=)	
	Auditory Complications		Auditory Complications	
	CTCAE Grade 0-2 (n=)	CTCAE Grade 3-4 (n=)	CTCAE Grade 0-2 (n=)	CTCAE Grade 3-4 (n=)
Gender, n(%)				
Male				
Female				
Race/Ethnicity, n(%)				
Non-Hispanic White				
Non-Hispanic Black				
Hispanic				
Other				
Age at Questionnaire, n(%)				
<18 years				
18-29 years				
30-39 years				
≥40 years				
Cancer Diagnosis, n(%)			NA	NA
Bone Tumor				
CNS Tumor				
Kidney Tumor				
Leukemia				
Hodgkin Lymphoma				
Non-Hodgkin Lymphoma				
Neuroblastoma				
Age at Diagnosis, n(%)			NA	NA
<5 years				
5-9 years				
10-14 years				
15-20 years				
Year at Diagnosis, n(%)			NA	NA
1970-1979				
1980-1989				
1990-1999				
Cumulative Cisplatin Dose, mean (sd)			NA	NA
Cumulative Carboplatin Dose, mean (sd)			NA	NA
Radiation Dose to Posterior Fossa, mean (sd)			NA	NA
Radiation Dose to Temporal Lobe, mean (sd)			NA	NA

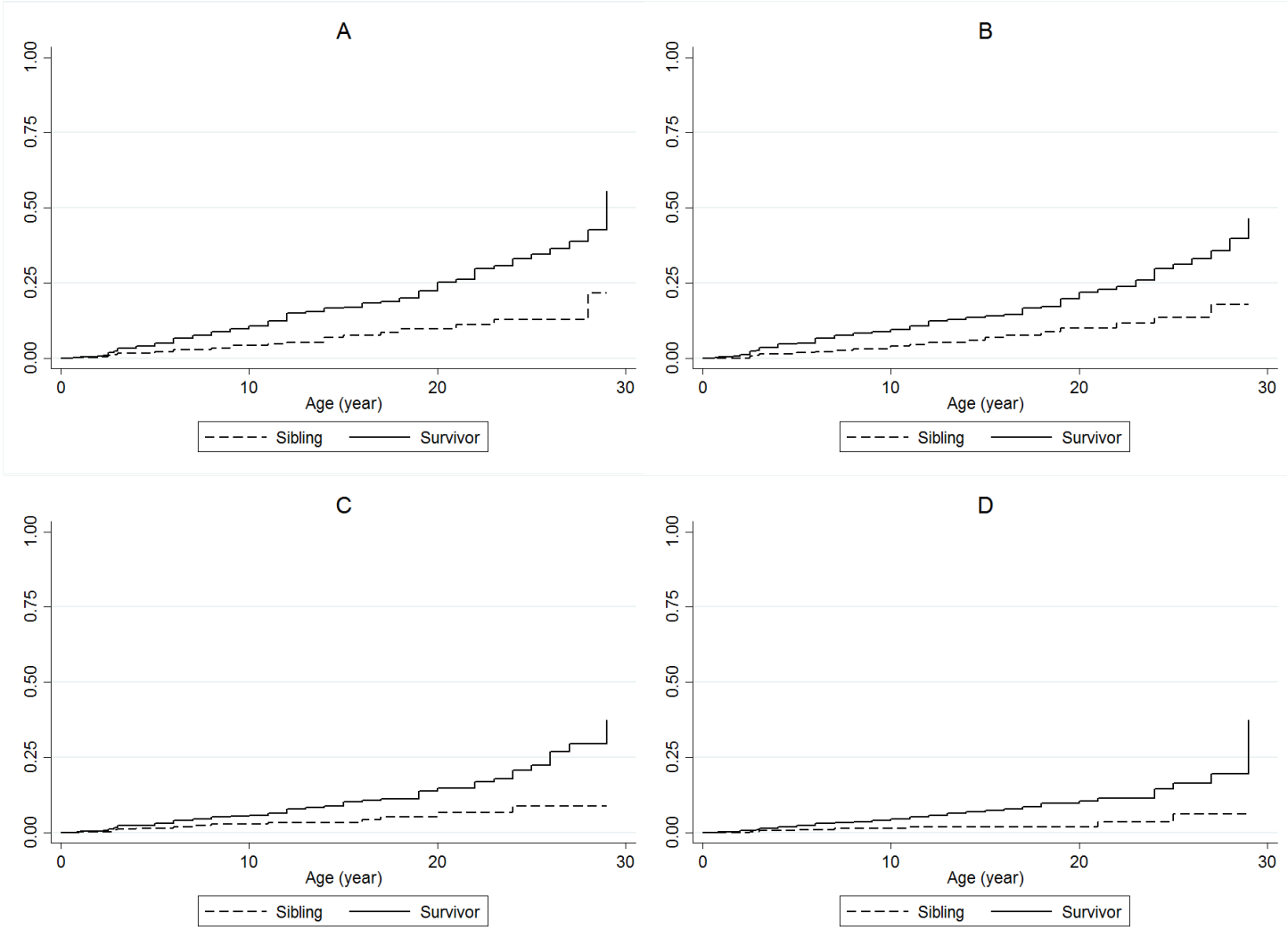

Figure 1. Cumulative incidence of CTCAE grade 3-4 hearing impairment among childhood cancer survivors and siblings enrolled in the CCSS (A), childhood cancer survivors treated with cisplatin chemotherapy (no carboplatin or cranial radiation exposure) and siblings enrolled in the CCSS (B), childhood cancer survivors treated with carboplatin chemotherapy (no cisplatin or cranial radiation exposure) and siblings enrolled in the CCSS (C), and childhood cancer survivors exposed to direct cranial radiation (no cisplatin or carboplatin exposure) and siblings enrolled in the CCSS

Table 2. Estimated association[1] between treatment factors and reported auditory complication among childhood cancer survivors enrolled in the Childhood Cancer Survivor Study

	CTCAE Grade 3-4 Hearing Impairment			
	Overall (n=) HR(95%CI)	Cisplatin Only (n=) HR(95% CI)	Carboplatin Only (n=) HR(95% CI)	Radiation Only (n=) HR(95% CI)
Cumulative Cisplatin, mg/m^2				
None	Ref.	Ref.	--	--
1-99				
100-199				
200-299				
300-399				
400-499				
≥500				
Cumulative Carboplatin, mg/m^2				
None	Ref.	--	Ref.	--
1-249				
250-499				
500-749				
750-999				
1,000-1,249				
1,250-1,499				
≥1,500				
Cranial Radiation Dose				
None	Ref.	--	--	Ref.
Low-Scatter				
High-Scatter				
Direct Dose ≤10 Gy				
Direct Dose 11-20 Gy				
Direct Dose 21-30 Gy				
Direct Dose 31-40 Gy				
Direct Dose ≥41 Gy				
Age at Diagnosis, year				
Age at Follow up, year				
Gender				
Male	Ref.	Ref.	Ref.	Ref.
Female				
Race/Ethnicity				
Non-Hispanic White	Ref.	Ref.	Ref.	Ref.
Non-Hispanic Black				
Hispanic				
Other				
Year at Diagnosis				
1970-1979	Ref.	Ref.	Ref.	Ref.
1980-1989				
1990-1999				

[1]Models adjusted for and other variables in the table

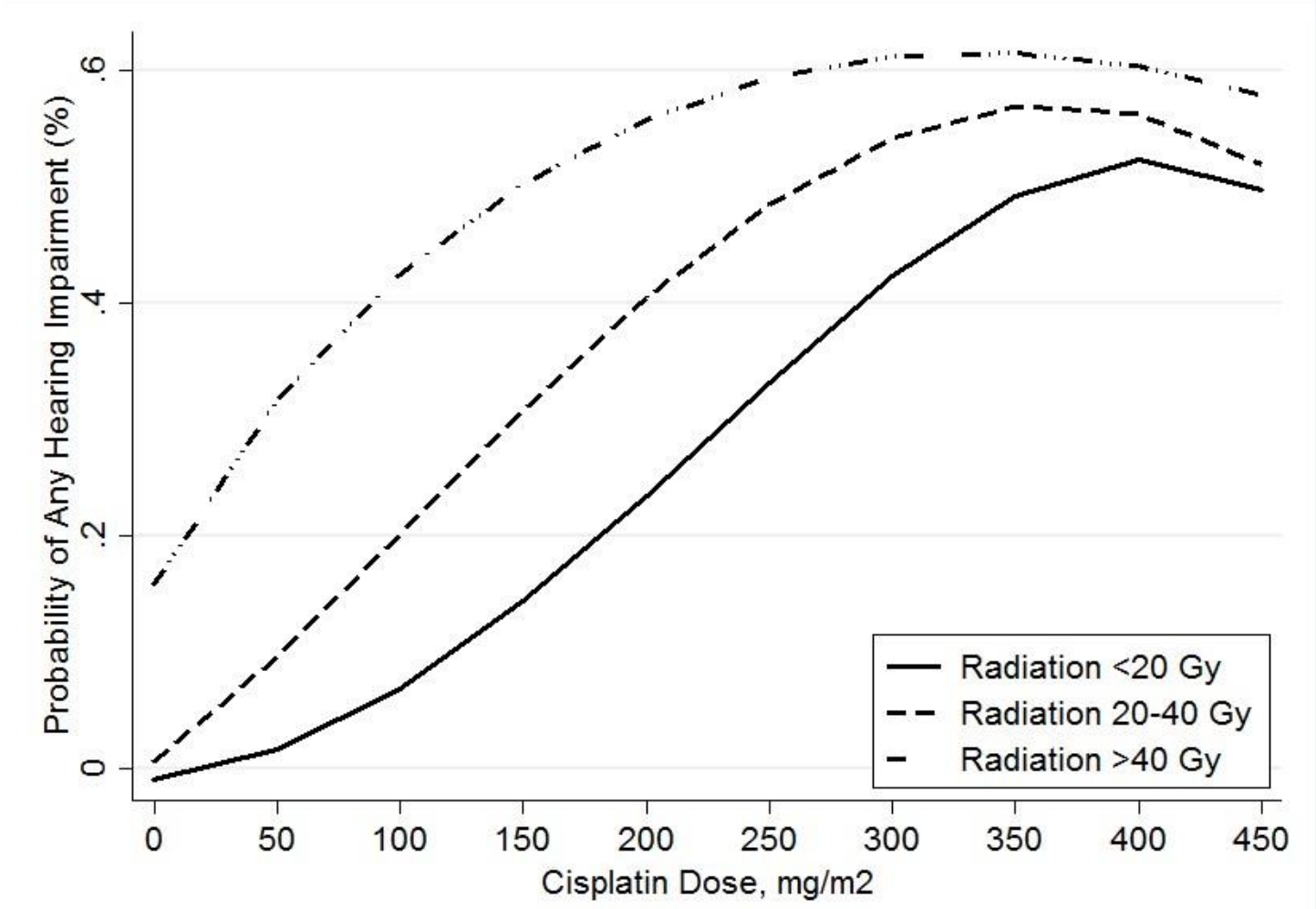

Figure 2. Fractional polynomial plot for cumulative cisplatin dose and predicted probability of any reported hearing impairment among cancer survivors enrolled in the Childhood Cancer Survivor Study by maximum radiation dose to the posterior fossa

Table 3. Association[1] between auditory complications and academic outcomes among survivors of childhood cancer enrolled in the Childhood Cancer Survivor Study

	N	Use of Special Education OR (95% CI)	Less Than High School Graduate OR (95% CI)
Hearing Loss[2]			
Grade 0-2		Ref.	Ref.
Grade 3-4			
Age at Diagnosis, year			
Age at Follow up, year			
Gender			
Male		Ref.	Ref.
Female			
Race/Ethnicity			
Non-Hispanic White		Ref.	Ref.
Non-Hispanic Black			
Hispanic			
Other			
Year at Diagnosis			
1970-1979		Ref.	Ref.
1980-1989			
1990-1999			
Cranial Radiation Dose			
None		Ref.	Ref.
Low-Scatter			
High-Scatter			
Direct Dose ≤10 Gy			
Direct Dose 11-30 Gy			
Direct Dose ≥31 Gy			

[1]Models adjusted cancer diagnosis, and other variables in the table

[2]Hearing impairment defined as CTCAE grade 3-4 reported hearing loss

Table 4. Association[1] between auditory complications and psychosocial outcomes among survivors of childhood cancer enrolled in the Childhood Cancer Survivor Study

	Behavioral Problem Domains				
	Anxiety	Headstrong	Attention Deficit	Social Withdrawal	Antisocial
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Hearing Loss[2]					
Grade 0-2	Ref.	Ref.	Ref.	Ref.	Ref.
Grade 3-4					
	Social Domains				
	Never Married	Non-independent Living	Never Employed	Personal Income <$20,000	
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	
Hearing Loss[2]					
Grade 0-2	Ref.	Ref.	Ref.	Ref.	
Grade 3-4					

[1]Models adjusted for age at diagnosis, age at questionnaire, gender, race/ethnicity, year of diagnosis, cranial radiation therapy, cancer diagnosis, and other variables in the table

[2]Hearing impairment defined as CTCAE grade 3-4 reported hearing loss