

## Clinical and Genetic Risk Factors for Radiation-Associated Ototoxicity: A Report from the Childhood Cancer Survivor Study and the St. Jude Lifetime Cohort

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**Background:** Cranial radiation therapy (CRT) for pediatric cancer often results in ototoxicity in the form of hearing loss and tinnitus. We sought to identify clinical determinants and genetic risk factors for ototoxicity among adult survivors of pediatric cancer treated with cranial radiation.

**Methods:** Relationships between age at last observation, sex, cumulative CRT dose and self-reported ototoxicity were evaluated for hearing loss and tinnitus among 1,991 (tinnitus) and 2,198 (hearing loss) survivors in the Childhood Cancer Survivor Study who received CRT. Logistic regression evaluated associations with non-genetic risk factors and comorbidities as well as SNP dosages in GWAS of CRT-related tinnitus (cases: 146; controls: 1,845) and hearing loss (cases: 270; controls: 1,928).

**Results:** Males were more likely to report CRT-related tinnitus (9.4% vs. 5.4%;  $p=5.81 \times 10^{-4}$ ) and hearing loss (14.0% vs. 10.7%;  $p=0.02$ ) than females after adjusting for dose and age at last observation. Survivors with tinnitus or hearing loss were more likely to experience persistent dizziness or vertigo (tinnitus:  $p<2.00 \times 10^{-16}$ ; hearing loss:  $p=6.35 \times 10^{-9}$ ), take antidepressants (tinnitus:  $p=0.02$ ; hearing loss:  $p=0.01$ ) and report poorer overall health (tinnitus:  $p=9.40 \times 10^{-7}$ ; hearing loss:  $p=1.30 \times 10^{-6}$ ) compared to survivors without tinnitus or hearing loss after age-adjustment. GWAS of CRT-related tinnitus revealed a prominent signal in chromosome 1 led by rs203248 ( $p=1.50 \times 10^{-9}$ ), while GWAS of CRT-related hearing loss identified rs332013 ( $p=5.79 \times 10^{-7}$ ) in chromosome 8 and rs67522722 ( $p=7.78 \times 10^{-7}$ ) in chromosome 6 as approaching genome-wide significance. Replication analysis in an independent cohort of pediatric cancer survivors (SJLIFE) indicated that rs67522722, intronic to *ATXN1*, a gene associated with the neurodegenerative disorder spinocerebellar ataxia type 1, was significantly associated with CRT-related hearing loss ( $p=0.03$ ). Enrichment analysis and LD score regression with previous GWAS results of cisplatin-related hearing loss and tinnitus in testicular cancer survivors showed no detectable enrichment in genetic architecture with CRT-related hearing loss and tinnitus, respectively.

**Conclusions:** Radiation-associated ototoxicity was associated with sex, several neurological symptoms, increased antidepressant use and poorer self-reported health. GWAS of CRT-related hearing loss identified rs67522722 that was replicated in an independent cohort of pediatric cancer survivors.