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Tinnitus during and after childhood cancer: A systematic review

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ABSTRACT

Background: Tinnitus can occur during and after treatment for childhood cancer. Studies on the occurrence of, and risk factors for tinnitus during and after childhood cancer treatment are scarce. The aim of this study is to get insight into the frequency and risk factors of tinnitus during and after childhood cancer therapy, based on a review of all previously reported literature.

Materials and methods: Systematic electronic literature searches that combined childhood cancer with different treatments and tinnitus terms were performed in the databases EMBASE, Medline, Cochrane, Web of Science, and Google Scholar. Studies were included based on reporting the frequency of tinnitus during and/or after childhood cancer, with 75% of participants being under the age of 25 at time of diagnosis, diagnosed with any type of childhood malignancy and treated with any type of chemotherapy and/or radiotherapy. A risk of bias assessment per research question was performed.

Results: Tinnitus incidence rates were reported up to 15.9 (95% CI 11.8–21.4) during therapy and up to 5.4 (95% CI 4.3–6.9) more than 5 years after diagnosis. The relative risk of developing tinnitus as compared to siblings during and after childhood cancer therapy were reported up to 17.2 (95% CI 11.8–25.0) during therapy and up to 3.7 (95% CI 2.7–5.1) more than 5 years after diagnosis. Independent risk factors for tinnitus development included high dose cranial radiation and platinum based chemotherapy.

Conclusion: The frequency of and risk to develop tinnitus seems to be higher in childhood cancer patients and survivors as compared to the normal population. Regular tinnitus screening before, during and after therapy with standardized questionnaires for early detection seems therefore reasonable in order to identify high-risk patients and eventually develop successful clinical preventive, supportive and management strategies.

1. Introduction

Currently, survival rates of children with cancer have reached up to circa 80% (Netherlands Comprehensive Cancer Organisation, 2018). This is the result of improved stratification, better treatment options and enhanced supportive care regimens over the past decades (Kaatsch, 2010). Due to increased survival, more awareness has been created for adverse events during and after childhood cancer treatment. In total, up to 75% of all childhood cancer survivors (CCS) experience at least one late effect due to their therapy (Geenen et al., 2007; Oeffinger et al., 2006). A serious late effect of childhood cancer treatment includes ototoxicity, which involves the destruction of cochlear structures leading to hearing loss, vertigo, and/or tinnitus (Landier, 2016; Langer et al., 2013).

Tinnitus can occur as a direct, as well as a late toxicity of cancer treatment (Dille et al., 2010). The disorder is characterized by a constant ringing, buzzing or clicking sound, that can be either acute or chronic (i.e. experienced for at least 3–6 months) (Wallhausser-Franke et al., 2017). Most patients suffer from subjective tinnitus, which indicates that the sound can only be heard by an affected individual (Teichroew, 2017). Hence, it can only be reported in a subjective manner (Han et al., 2009). In rare cases of objective tinnitus, on the other hand, the sound that is perceived by the individual can also be perceived by an examiner and is usually caused by muscle spams or problems with vascular flow (Chan, 2009). Tinnitus is considered to be a symptom of various underlying somatic events rather than a disease (Schlee et al., 2017). Such (sudden) events include middle ear pathology, cochlear trauma (e.g. due to loud noise exposure) or

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(iatrogenic) damaging lesions of the central auditory nerve system (Langguth et al., 2013). In children with cancer, subjective chronic tinnitus (from now on called "tinnitus") often accompanies hearing loss, which mainly occurs during and/or after treatment with platinum-based chemotherapy (e.g. cisplatin and carboplatin), cranial and/or local irradiation (Langer et al., 2013; Landier and Merchant, 2005), and occasionally follows local surgery (e.g. stapedectomy, tympanoplasty and mastoid surgery) and/or brain surgery (Enrico and Goodey, 2011). Tinnitus following (childhood) cancer treatment seems hardly reversible (Enrico and Goodey, 2011).

In general, tinnitus varies in severity and in accompanying symptoms. It has been described as a severe problem in more than 4 million individuals in the European Union (1% in the general population) (Schlee et al., 2017; McCormack et al., 2016). Even though the disorder is not life-threatening, it is often experienced as frustrating and very annoying, as it causes considerable distress and consequently reduction of quality of life (Han et al., 2009; Langguth et al., 2013). Accompanying symptoms like sleeping difficulties, anxiety, and depression have been described (Han et al., 2009; Schlee et al., 2017; Lanvers-Kaminsky et al., 2017), even leading sporadically to self harm and even suicide (Aazh and Moore, 2018). In children, tinnitus can cause attention problems and decreased speech discrimination (Han et al., 2009). Consequently, the disorder can affect school and work performances as well as social interactions in a negative manner (Yu-guang et al., 2012). In adults, tinnitus has a serious impact on society and healthcare costs. It is estimated that for instance in a small country as the Netherlands with more than 17 million inhabitants, the economic burden of the occurrence of tinnitus reaches up to €10.8 billion especially due to socio-economic consequences (Schlee et al., 2017; Maes et al., 2013).

Up until now, tinnitus has not obtained major attention during childhood cancer nor in survivorship care. Given the conceivable impact of tinnitus on socio-economic citizenship and quality of life for survivors, successful clinical preventive, supportive and management strategies need to be urgently developed (Schlee et al., 2017). The aim of the current review is to get insight in the frequency and risk of tinnitus during and shortly after childhood cancer therapy, the long-term frequency and risk of tinnitus after childhood cancer therapy, and the determinants that may influence tinnitus development during and after childhood cancer.

2. Materials and methods

2.1. Literature search strategy

Systematic electronic literature searches were performed in the databases EMBASE, Medline, Cochrane, Web of Science, and Google Scholar up to January 2018. We applied Medical Subject Heading (MeSH) and Title/ Abstract (TiAb) terms in our search strategy to detect references that combine childhood cancer treatments and tinnitus terms. The terms used in our search strategy are listed in Supplementary Table 1. In addition, cross reference checks were performed to identify additional articles that could be potentially relevant.

2.2. Inclusion and exclusion criteria

Studies were included based on reporting of tinnitus occurrence during and/or after childhood cancer, and when they were written in English language. Any type of childhood malignancy and treatment with any type of chemotherapy, radiotherapy and/or surgery was included. Also, ≥75% of the study population was supposed to be below the age of 25 years at time of diagnosis. Book chapters, articles not in full text, and case reports were excluded. Duplicate publications were removed.

2.3. Data extraction

Two reviewers (AJMM and EC) independently screened titles and abstracts of the available publications. Abstracts selected for full text inspection were checked based on inclusion criteria. Disagreements between the reviewers were resolved by consensus and discussed with a third reviewer (MvdHE). From the selected papers, the following data was selected: sample size, patient characteristics (age at diagnosis and age at follow-up), cancer types, cancer treatments (all types of chemotherapy, and/or (cranial) radiation + dose, and/or surgery), follow-up time, and determinants of developing tinnitus. Data on tinnitus occurrence was collected based on the variety of outcomes in available studies, i.e. percentages, prevalence ratios (PR), cumulative incidences of tinnitus (CIT) or incidence rates (IR). Tinnitus risk compared to healthy controls was reported as a relative risk (RR), odds ratio (OR) or hazard ratio (HR).

2.4. Assessment of study quality

A risk of bias assessment was performed to define the quality of the included publications per study question. We therefore used the QUIPS tool previously described by Hayden et al. (2013), which is developed to evaluate the risk of bias in studies that aim to identify prognostic factors. Six different domains were included in the tool: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting (Hayden et al., 2013). As per outcome measurement, the papers were graded for separate domains as having high, moderate or low level of bias. According to the recommendation of Hayden et al., we chose *a priori* the most relevant domains (study participation, prognostic factor measurement, and study confounding) to judge the overall risk of bias in the included studies (Hayden et al., 2013). We considered the performance of multivariate analysis as an important quality criterion for studies that investigated the frequency and/or determinants of tinnitus in childhood cancer patients and survivors. The assessments were taken into account in the interpretation of the results (i.e. conclusions were based on studies with a low risk of bias).

3. Results

In total, 740 publications were identified through database searches, of which 241 duplicate articles were removed. Based on title and abstract screening, 414 manuscripts were excluded. After assessing the full texts of the remaining 85 articles, 10 studies were included based on the inclusion criteria. All 10 studies included tinnitus as outcome after childhood cancer treatment, and of those four also included tinnitus as outcome during childhood cancer treatment. The selection process is shown in Supplementary Figure 1.

3.1. Characteristics of included studies

A summary of four studies on tinnitus onset during and shortly after childhood cancer therapy is depicted in Table 1 (Whelan et al., 2011; Goldsby et al., 2010; Punyko et al., 2005; Packer et al., 2003). All studies were carried out between 2003 and 2011. In total, more than 20,000 participants with different types of childhood cancer were included, and more than 15,000 siblings served as healthy controls. Participants received different types of chemotherapy, such as methotrexate (Goldsby et al., 2010), platinum agents (Whelan et al., 2011), any/unspecified types of chemotherapy (Punyko et al., 2005; Packer et al., 2003). Participants received cranial radiation either as a single treatment or in combined modalities with chemotherapy and/or local surgery. About 62–82% of the participants was younger than 10 years at time of diagnosis.

Table 2 shows a summary of ten studies on tinnitus onset more than five years after childhood cancer diagnosis (Whelan et al., 2011;

Table 1
Summary of studies on early onset tinnitus in childhood cancer patients.

Authors	N	Siblings, N	CC type	CC treatment				Age at diagnosis (%)	MVA	Tinnitus freq. Dx – End treatment	Tinnitus risk Dx – End treatment	Tinnitus freq. End treatment – 5y after Dx	Tinnitus risk End treatment – 5y after Dx	Risk factors for tinnitus
				CT type (%)	*RT type (%)*	*Combined modality (%)*	*RT dose Gy (%)*							
Whelan (2011)	14,358	4,023	LL, ST, BT	CIS (5.1%) CARB (0.5%)	CRT (57%)	NA	<30 Gy: 47% ≥30 Gy: 10% No/UNK: 43%	<10y: 62% ≥10y: 38%	Yes	PR 3.7 (95% CI 2.9-4.7)	NA	PR 3.7 (95% CI 2.9-4.7)	NA	TLI/PFI (≥30Gy) CIS+CARB CNST/STS
Goldsby (2009)	4,151	3,899	HT	MTX, other (94%)	CRT (64.5%)	RC (61%)	<20 Gy: 46% ≥20 Gy: 54%	<10y: 82% ≥10y: 12%	Yes	PR 1.8 (95% CI 1.2-2.8)	NA	PR 1.8 (95% CI 1.2-2.8)	NA	NA
Packer (2003)	1,607	3,418	BT	Any (30%)	CRT (72%)	SR (42%) SRC (28%)	<30 Gy: 33% ≥30 Gy: 67%	<10y: 64% ≥10y: 36%	Yes	IR 15.9 (95% CI 11.8-21.4)	RR 17.2 (95% CI 11.8-25.0)	IR 7.2 (95% CI 5.2-9.8)	RR 7.0 (95% CI 4.8-10.2)	NS
Punyko (2005)	606	3,701	ST	NA	NA	SRC (77%) RC (1%) SC (20%)	NA	<10y: 71% ≥10y: 29%	Yes	IR 5.7 (95% CI 3.1-10.6)	RR 8.0 (95% CI 4.1-15.6)	IR 2.2 (95% CI 0.8-5.9)	RR 2.5 (95% CI 0.9-7.0)	NS

Grey = Studies with a low risk of bias; BT: brain tumors; CC: childhood cancer; CIS: cisplatin; CARB: carboplatin; CI: confidence interval; CNST: central nervous system tumors; CRT: cranial radiotherapy; CT: chemotherapy; Dx: diagnosis; Gy: Gray; HT: hematological tumors; IR: incidence rate; LL: leukemia/lymphoma; MTX: methotrexate; MVA: multivariate analysis; NA: not available; NS: not significant; PFI: posterior fossa irradiation; PR: prevalence ratio; RC: radiotherapy + chemotherapy; RR: relative risk; SC: surgery + chemotherapy; SRC: surgery + cranial radiation + chemotherapy; ST: solid tumors; STS: soft tissue sarcoma; TLI: temporal lobe irradiation; UNK: unknown; Y: years.

Goldsby et al., 2010; Punyko et al., 2005; Packer et al., 2003; Wells et al., 2018; Weiss et al., 2017; King et al., 2017; Kalafatcilar et al., 2014; Ozono et al., 2014; Einar-Jon et al., 2011). The studies were carried out between 2003 and 2017, and included a total of more than 25,000 participants with different types of childhood cancer. About 24,000 siblings and 1000 randomly selected persons from the general population served as control groups. Administered chemotherapy types varied across studies, ranging from methotrexate (Goldsby et al., 2010; Kalafatcilar et al., 2014) to platinum agents (Whelan et al., 2011; Wells et al., 2018; Weiss et al., 2017; King et al., 2017; Einar-Jon et al., 2011), and all types of chemotherapy (Packer et al., 2003; Ozono et al., 2014).

Participants received cranial radiation in nine studies (Whelan et al., 2011; Goldsby et al., 2010; Punyko et al., 2005; Packer et al., 2003; Wells et al., 2018; Weiss et al., 2017; King et al., 2017; Kalafatcilar et al., 2014; Einar-Jon et al., 2011), whereas one study included participants who received radiotherapy at any location (Ozono et al., 2014). Most participants were under the age of 10 at time of diagnosis. At time of follow-up, a large part of the participants was 30 years or younger, and had survived at least 5 years after cancer diagnosis (median time to follow-up 7.5–23 years).

Table 2
Summary of studies on late onset tinnitus in childhood cancer survivors.

Authors	N	Controls, N	CC type	CC treatment				Age at diagnosis (%)	Median time to FU (range)	Median age at FU (range)	MVA	Tinnitus at FU (%)	Tinnitus freq. ≥5 years after diagnosis	Tinnitus risk ≥5 years after diagnosis	Risk factors for tinnitus
				CT type (%)	*RT type (%)*	*Combined modality (%)*	*RT dose Gy (%)*								
Whelan (2011)	14,358	SI: 4,023	LL, ST, BT	CIS (5.1%) CARB (0.5%)	CRT (57%)	NA	<30 Gy: 47% ≥30 Gy: 10% No/UNK: 43%	<10y: 62% ≥10y: 38%	NA	<30y: 77% ≥30y: 33%	Yes	5.6%	IR 2.7 (95% CI 2.3-3.1)	RR 1.7 (95% CI 1.4-2.1)	TLI/PFI (≥30Gy) CIS+CARB CNST/STS
Goldsby (2009)	4,151	SI: 3,899	HT	MTX, other (94%)	CRT (64.5%)	RC (61%)	<20 Gy: 46% ≥20 Gy: 54%	<10y: 82% ≥10y: 12%	14.1y (5.0-29.7)	20.2y (5.9-44.6)	Yes	3.3%	IR 2.5 (95% CI 2.4-2.7)	RR 1.6 (95% CI 1.2-2.1)	NA
Weiss (2017)	2,061	SI: 864	LL, ST, BT	CIS, CARB, other (84%)	CRT (54%)	NA	<30 Gy: 26% ≥30 Gy: 28% No/UNK: 46%	Median: 5.0y (0.0-15.0)	15.0y (5.0-38.0)	21.0y (6.0-46.0)	Yes	CCS: 6% SI: 5%	NA	NA	NS
Wells (2017)	1,876	SI: 4,031	BT	CIS, CARB, VCR, NAA (49%)	CRT alone (1%)	SR (37%) SRC (25%)	NA	<10y: 74% ≥10y: 36%	23.0y (5.1-38.9)	30.3y (6.1-56.4y)	Yes	NA	CIT 8.2-20.8%	NA	Age at Dx <15y FLI/PFI, SMN CIS+CARB
Packer (2003)	1,607	SI: 3,418	BT	Any (30%)	CRT (72%)	SR (42%) SRC (28%)	<30 Gy: 33% ≥30 Gy: 67%	<10y: 64% ≥10y: 36%	NA	<30y: 82% ≥30y: 18%	Yes	11%	IR 5.4 (95% CI 4.3-6.9)	RR 3.7 (95% CI 2.7-5.1)	NS
Punyko (2005)	606	SI: 3,701	ST	NA	NA	SRC (77%) RC (1%) SC (20%)	NA	<10y: 71% ≥10y: 29%	15.7y (5.2-28.8)	<30y: 80% ≥30y: 20%	Yes	CCS: 6% SI: 3%	IR 2.0 (95% CI 1.2-3.5)	RR 1.3 (95% CI 0.7-2.3)	NS
King (2016)	380	SI: 4,031	BT	CIS, CCNU, CPM (59%)	CSRT (94%) CRT (3%)	NA	<30 Gy: 26% ≥30 Gy: 74%	<10y: 73% ≥10y: 27%	NA	30.0y (24.0-36.0)	Yes	17.4%	CIT 10.6-30.1%	HR 4.8 (95% CI 3.5-6.8)	TLI/FLI (≥50Gy) CIS+CARB
Ozono (2014)	185	SI: 72 GP:1,000	LL, ST, BT	Any (98%)	Any location (61%)	RC (40%)	NA	Mean: 8.3y ± 4.8	Mean: 15.3y ± 5.8	Mean: 23.6y ± 4.6	No	CCS: 26% SI: 11% GP: 17%	NA	OR 1.5[a] (95% CI 1.1-2.0) OR 2.3[b] (95% CI 1.1-4.6)	NA
Kalafatçilar (2014)	44	SI: 14	LL	MTX, other (100%)	CRT (41%)	NA	18 Gy: 44% 12 Gy: 66%	Median: 5.5y (3.0-16.0)	7.5y (2.0-18.0)	16.4y (8.0-31.0)	No	13.6%	NA	NA	Age at Dx ≥6y
Einar-Jon (2011)	15	None	ST, BT	CIS, CARB (100%)	CRT (20%)	NA	NA	Median: 4.3y (0.4-18.0)	9.1y (0.8-16.5)	14.1y (11.0-30.1)	No	60%	NA	NA	NA

Grey = Studies with a low risk of bias; Age at Dx: age at diagnosis; BT: brain tumors; CC: childhood cancer; CCNU: lomustin; CCS: childhood cancer survivors; CI: confidence interval; CIT: cumulative incidence tinnitus; CIS: cisplatin; CNST: central nervous system tumors; CPM: cyclophosphamide; CARB: carboplatin; CSRT: craniospinal radiotherapy; CRT: cranial radiotherapy; CT: chemotherapy; FLI: frontal lobe irradiation; FU: follow-up; GP: general population; Gy: Gray; HR: hazard ratio; HT: hematological tumors; IR: incidence rate; LL: leukemia/lymphoma; MTX: methotrexate; MVA: multivariate analysis; NA: not available; NAA: nonplatinum alkylating agent; NS: not significant; OR: odds ratio; PFI: posterior fossa irradiation; RC: radiotherapy + chemotherapy; RR: relative risk; SC: surgery + chemotherapy; SI: siblings; SMN: subsequent malignant neoplasms; SRC: surgery + cranial radiation + chemotherapy; ST: solid tumors; STS: soft tissue sarcoma; TLI: temporal lobe irradiation; UNK: unknown; VCR: vincristine; Y: years; [a]CCS versus controls; [b]CCS versus siblings.

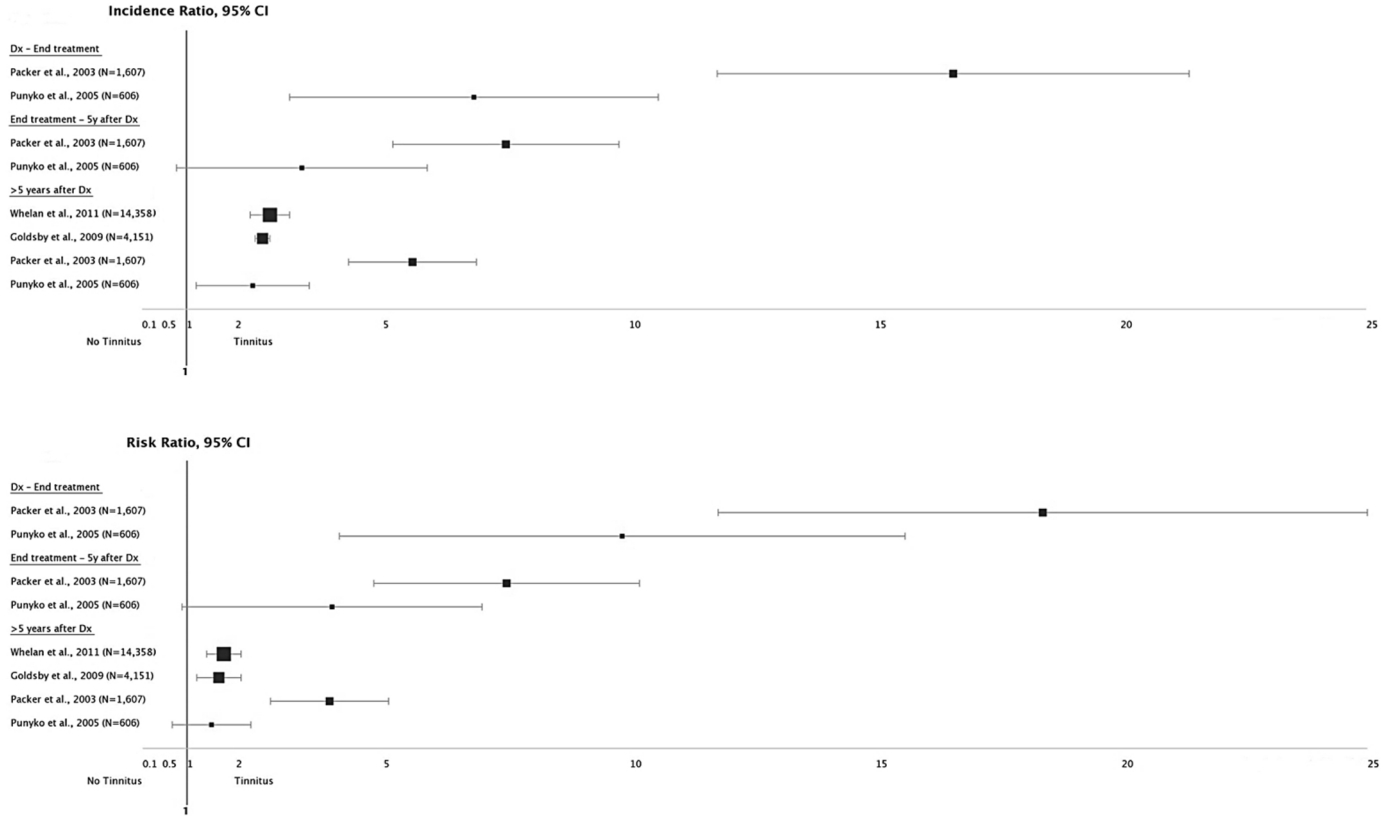

Fig. 1. Forest plots showing the tinnitus incidence and risk ratios during and after childhood cancer therapy.

3.2. Tinnitus occurrence and risk during and shortly after childhood cancer treatment

Four studies included the occurrence of tinnitus during and shortly after childhood cancer treatment (Whelan et al., 2011; Goldsby et al., 2010; Punyko et al., 2005; Packer et al., 2003), of which two also reported the relative risk (RR) of tinnitus (Punyko et al., 2005; Packer et al., 2003). All studies performed multivariate analyses. The risk of bias in these publications was rated as low (Supplementary Table 2 and 3).

In two studies, the prevalence ratios (PR) from diagnosis to 5 years after diagnosis were 1.8 (95% CI 1.2–2.8) and 3.7 (95% CI 2.9–4.7) (Whelan et al., 2011; Goldsby et al., 2010). The tinnitus incidence rates (IRs) from diagnosis to end of treatment were 5.7 (95% CI 3.1–10.6) and 15.9 (95% CI 11.8–21.4), and IRs from end of treatment to 5 years after diagnosis were 2.2 (95% CI 0.8–5.9) and 7.2 (95% CI 5.2–9.8) (Fig. 1) (Punyko et al., 2005; Packer et al., 2003). The reported RRs of developing tinnitus from diagnosis to end of treatment were 8.0 (95% CI 4.1–15.6) and 17.2 (95% CI 11.8–25.0), and from end of treatment up to 5 years after diagnosis 2.5 (95% CI 0.9–7.0) and 7.0 (95% CI 4.8–10.2) as compared to siblings (Punyko et al., 2005; Packer et al., 2003) (Fig. 1).

3.3. Tinnitus occurrence and risk more than 5 years after childhood cancer treatment

The frequency of tinnitus, 5 years after treatment was analyzed in all ten studies. The risk of bias was low in seven articles (Whelan et al., 2011; Goldsby et al., 2010; Punyko et al., 2005; Packer et al., 2003; Wells et al., 2018; Weiss et al., 2017; King et al., 2017), moderate in one article (Ozono et al., 2014), and high in two articles (Kalafatcilar et al., 2014; Einar-Jon et al., 2011) (Supplementary Table 2). Six out of ten studies also included results on the risk of very long-term tinnitus development, of which five had a low risk of bias (Whelan et al., 2011; Goldsby et al., 2010; Punyko et al., 2005; Packer et al., 2003; Wells et al., 2018; King et al., 2017) and one a high risk of bias (Ozono et al., 2014) (Supplementary Table 3).

The estimated IRs ranged from 2.0 (95% CI 1.2–3.5) to 5.4 (95% CI 4.3–6.9) (Fig. 1) (Whelan et al., 2011; Goldsby et al., 2010; Punyko et al., 2005; Packer et al., 2003). Reported CITs were 8.2% and 10.6% five years after diagnosis, and ranged up to 20.8% and 30.1% thirty years after diagnosis, respectively (Wells et al., 2018; King et al., 2017).

The RR of developing tinnitus more than 5 years after diagnosis ranged from 1.3 (95% CI 0.7–2.3) to 3.7 (95% CI 2.7–5.1) (Fig. 1) (Whelan et al., 2011; Goldsby et al., 2010; Packer et al., 2003). One study reported the OR for tinnitus occurrence in CCS at time of follow-up compared to siblings (OR 1.5, 95% CI 1.1–2.0) as well as to the general population (OR 2.3, 95% CI 1.1–4.6) (Ozono et al., 2014). The hazard rate for tinnitus development was issued in one study (HR 4.8, 95% CI 3.5–6.8) (King et al., 2017).

The frequency of tinnitus at time of follow-up in childhood cancer survivors varied from 3.3% to 60% (Whelan et al., 2011; Goldsby et al., 2010; Punyko et al., 2005; Packer et al., 2003; Weiss et al., 2017; King et al., 2017; Kalafatcilar et al., 2014; Ozono et al., 2014; Einar-Jon et al., 2011). In studies with a low risk of bias, the range was 3.3% to 17.4% (Whelan et al., 2011; Goldsby et al., 2010; Punyko et al., 2005; Packer et al., 2003; Wells et al., 2018; King et al., 2017; Weiss et al., 2018).

3.4. Determinants of tinnitus development during and shortly after childhood cancer treatment

One study with a low risk of bias reported risk factors for tinnitus development during and shortly after childhood cancer therapy (Supplementary Table 4). The multivariate analysis revealed administration of platinum drugs (RR 2.8, 95% CI 1.9–4.2), cranial radiation ≥ 30 Gy on the temporal lobe (RR up to 2.6, 95% CI 1.7–4.1) and/or posterior fossa (RR up to 2.9, 95% CI 1.8–4.6), central nervous system

tumors (CIT 7.4%, 95% CI 5.7–9.2), and soft tissue sarcomas (CIT 4.0%, 95% CI 2.6–5.3) as independent risk factors for early onset tinnitus (Whelan et al., 2011).

3.5. Determinants of tinnitus development more than 5 years after childhood cancer treatment

Four studies, of which one had a high risk of bias (Kalafatcilar et al., 2014), and three had a low risk of bias (Whelan et al., 2011; Wells et al., 2018; King et al., 2017) (Supplementary Table 4), reported factors that influence tinnitus development after childhood cancer treatment. Three higher quality studies that performed multivariate analyses identified platinum agents (HRs 2.1, 95% CI 1.2–3.9 (Wells et al., 2018) and 2.6, 95% CI 1.2–5.5 (King et al., 2017); RR up to 2.8, 95% CI 1.9–4.2 (Whelan et al., 2011)), high radiation dose (≥30 Gy or ≥50 Gy) on the temporal lobe (Whelan et al., 2011; King et al., 2017), frontal lobe (King et al., 2017) and/or posterior fossa (Whelan et al., 2011; Wells et al., 2018) (HR up to 2.3, 95% CI 1.4–3.8; RR up to 2.9, 95% CI 1.8–4.6), and the occurrence of second malignant neoplasms (HR 2.9, 95% CI 1.2–6.5) (Wells et al., 2018)as independent risk factors. The cumulative incidence of tinnitus was highest in central nervous system tumors (CIT 7.4%, 95% CI 5.7–9.2), and soft tissue sarcomas (CIT 4.0%, 95% CI 2.6–5.3) (Whelan et al., 2011). A younger age at diagnosis (under the age of 15 years) was reported as a protective factor for late-onset tinnitus (HR up to 0.4, 95% CI 0.2-0.8) (Wells et al., 2018), in multivariate analysis.

4. Discussion

Tinnitus can occur as an adverse event during or after childhood cancer treatment. To date, the prevalence of, and risk factors for hearing loss after treatment in childhood cancer survivors have been investigated, but the occurrence of tinnitus is not being registered in many upfront childhood cancer studies. Through this systematic review, we aimed to get insight into the occurrence, risk and determinants of tinnitus during and after childhood cancer therapy based on all previously reported literature, thereby including the quality of the studies. The tinnitus incidence rate reached up to 15.9 per 1000 population (95% CI 11.8–21.4) during childhood cancer treatment, and up to 5.4 per 1000 population (95% CI 4.3–6.9) more than 5 years after treatment. We observed a large variation in tinnitus frequency rates at time of follow-up in CCS, even ranging up to 60%. In studies with a low risk of bias, however, the observed frequency rate of tinnitus at time of follow-up ranged from 3 to 17%. This is important since tinnitus remains a rather poorly understood side effect but a clinical relevant childhood cancer toxicity.

In total, four studies with a low risk of bias in our systematic review that reported on tinnitus frequency during and shortly after childhood cancer treatment, showed that the frequency of tinnitus in childhood cancer patients and survivors is higher compared to healthy peers. Two out of four studies also revealed that the higher risk of developing tinnitus is already present at young age, during and shortly after treatment (Punyko et al., 2005; Packer et al., 2003). This is important as this most certainly will affect the child's development early in life, and it is conceivable that the disorder can contribute to serious learning and behavioral difficulties in children. Subsequently, this can negatively influence their social interactions, cognitive and psycho-emotional properties (Yu-guang et al., 2012; Kim et al., 2012).

Based on the results of four reliable studies, it seems that tinnitus occurs frequently in survivors of childhood cancer (Whelan et al., 2011; Goldsby et al., 2010; Punyko et al., 2005; Packer et al., 2003). This may be important, since adults with intolerable tinnitus have been shown to experience sleeping difficulties and concentration problems (Henry et al., 2005), and as a consequence, higher probability of depression, anxiety, mental distress and disability (Crocetti et al., 2009; Krog et al., 2010; Shargorodsky et al., 2010). It is known, that this ultimately influences work performances and participation in society (Moroe and Khoza-Shangase, 2014). No studies are available on the course of tinnitus over time after childhood cancer, nor on the reversibility of tinnitus after ototoxic childhood cancer therapy. This underscores the need for future prospective studies as chronic tinnitus most likely will contribute highly to the burden of disease and consequently will significantly impact the quality of life in adult long term CCS (Nondahl et al., 2007).

Three studies revealed that platinum-based chemotherapy and high dose cranial radiation (> 30 Gy) are serious independent risk factors for tinnitus development during and after childhood cancer therapy. These cancer therapies have shown to cause destruction of outer hair cells in rodent models, by increasing the generation of reactive oxygen species (ROS), leading to apoptotic cell death in the cochlea (Lanvers-Kaminsky et al., 2017; Sheth et al., 2017; Karasawa and Steyger, 2015; Low et al., 2009). Changes in outer hair cells can lead to a mismatch between excitatory and inhibitory networks in the central auditory system in the brain, which results in an excessive increase of spontaneous activity of neurons underlying sound perception leading to the presence of tinnitus in ear or head (Henry et al., 2014; Frisina et al., 2016). The findings of the studies in this systematic review indicate that children and survivors treated with platinum-based chemotherapy and/or cranial radiation above 30 Gy, may be considered a high-risk population, for which increased awareness of tinnitus in clinical practice is needed and regular audiological evaluations during and after childhood cancer therapy are necessary.

It seems that the subset of children that suffer from CNS tumors are extra prone for developing tinnitus (Packer et al., 2003; King et al., 2017). In these patients the central auditory nerve system may be affected, and hence, tinnitus and hearing loss can be directly related to the disease (Foley et al., 2017). In addition, these patients often receive maximally tolerated doses of cranial radiation (Wells et al., 2018) and/or platinum-based agents (Gupta et al., 2017), underscoring the often multifactorial origin of tinnitus in these cases. One study in our systematic review showed that a younger age at diagnosis was a protective factor for long-term tinnitus occurrence (Wells et al., 2018). This may be partly due to underreporting in clinical practice, as very young children may not be able to describe subjective tinnitus (Kentish et al., 2014). In addition, previous studies state that the risk of tinnitus perception and annoyance increases once an individual becomes older (Coelho, 2011; Al-Swiahb and Park, 2016), due to the fact that inhibition of the nervous system reduces over the years, leading to more excitation of neurons that subsequently can cause tinnitus (Caspary et al., 2005; Møller, 2011a). On the contrary, it is known that treatment-related hearing loss often develops at a very young age (Clemens et al., 2016). Thus, tinnitus and hearing loss onset seem to differ between age categories, which is important to consider during audiological monitoring in childhood cancer patients and survivors.

In the normal population, hearing loss (Sliwinska-Kowalska and Zaborowski, 2017), noise exposure (Ralli et al., 2017), and female gender (Seydel et al., 2013) are reported risk factors for tinnitus onset. Hearing loss and noise exposure were also confirmed risk factors for tinnitus in survivors of adult-onset cancer (Frisina et al., 2016), but not addressed in the retrieved literature on childhood cancer patients and survivors. It is acknowledged that hearing loss causes reduced input of sound to the auditory system. This can consequently induce neural plasticity, subsequently leading to alterations in the processing of sounds, including increased excitement of neurons in the CNS, leading to tinnitus. However, not all individuals with hearing loss experience tinnitus, which indicates that neural plasticity is not always induced by deprivation of sound (Møller, 2011a). Individuals exposed to a sudden noise can be affected by acute tinnitus, which usually resolves over time but this can also become irreversible (Gilles et al., 2013). A higher frequency of tinnitus in women may seem to be caused by female reproductive hormones that play a role in reducing activity of the neural transmitter gamma amino butyric acid (GABA) (Tremere et al., 2009).

Reduced GABA activity promotes neural excitability in neurons, leading to hyperactivity that triggers tinnitus (Møller, 2011b). Hence, hearing loss, noise exposure and gender might be taken into consideration as possible risk factors for tinnitus development in childhood cancer patients and survivors.

A representative, national health survey on tinnitus epidemiology and impact showed that 10% of 222 million American adults experience tinnitus, and that only 50% of them report tinnitus symptoms to a healthcare provider (Bhatt and Lin, 2016). Their step towards consultation seems to depend on the severity of accompanying psychological symptoms (e.g. anxiety, depression, concentration problems) and somatic problems (e.g. headache, muscle tension, high blood pressure) (Scott and Lindberg, 2000). Circa 85% of the patients has never tried any type of therapy for their tinnitus (Bhatt and Lin, 2016). Also, awareness of the disorder in clinical practice is sometimes still lacking (Fackrell et al., 2012), and patients with tinnitus are often told to integrate the condition in their daily life (Newman et al., 2011). This is bothersome, since patients with intolerable tinnitus can profit from support of multiple disciplines (the audiologist, neurologist, otolaryngologist, psychologist, etc.) to successful manage their complaints (Newman et al., 2011; Searchfield and Baguley, 2011; Láinez et al., 2011; Kleinjung, 2011; Greimel and Kröner-Herwig, 2011). Examples of beneficial therapies for tinnitus are Cognitive Behavioral Treatment (CBT), Tinnitus Retraining Therapy (TRT), and use of hearing aids or cochlear implants (Hesse, 2016). As tinnitus can have considerable impact on the quality of life, surveillance for the disorder should become part of standard care during treatment and during regular checkups of survivors in late effects clinics.

The diagnosis of tinnitus in young children is challenging, since they seem to be able to ignore the sound due to distraction of external influences (Kim et al., 2012). Also, children are not always capable to report tinnitus (Yu-guang et al., 2012). A suggestion to overcome this problem would be to implement regular tinnitus screening along with audiometric checkups during childhood cancer treatment, including detailed case history, otoscopy, and questionnaires on tinnitus severity. It is important that information is obtained from both child and parent. A questionnaire for parents can include queries on changes in the child's behavior that may be a sign of tinnitus, such as sleeping difficulties, avoidance of quiet or noisy environments, and problems with listening and speech perception in class. In young children, the use of toys or drawing material can help to get insight in the presence of tinnitus. In addition, communication at the child's level of cognitive and linguistic understanding is essential (Kentish et al., 2014). Therefore, standardization of appropriately phrased questions per age category would be helpful to develop suitable tinnitus questionnaires for children (Rosing et al., 2016).

In conclusion, this systematic review reveals a high occurrence and risk of tinnitus in childhood cancer patients and survivors compared to healthy controls. Overall, patients and survivors that suffered from CNS tumors, platinum treatment, and/or high dose cranial radiation seem to be at higher risk of developing tinnitus. Future prospective studies in childhood cancer patients and survivors are needed to confirm these results, with additional focus on identification of genetic risk factors that explain increased individual susceptibility to chronic tinnitus. Based on evidence from the available studies, we feel that increased awareness for tinnitus in childhood cancer patients and survivors should be created in clinical practice. Therefore, regular screening and information providing before, during and after childhood cancer therapy with standardized questionnaires per age category for early detection seems an important aspect. Continuing prospective, complete and systematic registration is necessary to determine the frequency and impact of tinnitus and to identify high-risk patients.

Contributions

AM, EC, and MvdHE contributed to the conception and design of the study. AM and EC were responsible for data acquisition. All authors were involved in analysis and interpretation of the data. AM and MvdHE wrote the manuscript. EC, MvG, and AH critically read and revised the content of the manuscript. All authors approved the final version of the article.

Conflict of interest

The authors have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.critrevonc.2019.01.004.

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