Developmental defects of enamel in childhood cancer survivors: A systematic review and meta-analysis

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DOI 10.23804/ejpd.2024.2256

Abstract

Aim The present systematic review and meta-analysis (Prospero registration number: CRD42023472016) aims to assess the prevalence of developmental defects of enamel (DDEs), qualitatively and/or quantitatively, in childhood cancer survivors (CCS) and evaluate, when possible, these data in comparison with those found in healthy children.

Methods Three electronic databases (PubMed, Embase, Scopus) were searched from January 2003 to January 2024 for studies reporting on DDEs in children with a mean age not exceeding 16 years at the time of the study who underwent antineoplastic therapy. The ROBINS-I and the Joanna Briggs Institute (JBI) tools were used to assess the risk of bias. Included studies with comparable outcomes underwent random effects models meta-analysis using Stata®18.

Results Overall, 807 records were retrieved, 74 studies were selected based on title and abstract, 21 full texts were included in qualitative synthesis, and 18 were included in the meta-analysis. The prevalence of DDEs in CCS varied widely, ranging from 13.16% to 88.30%. The prevalence of qualitative defects ranged from 56.60% to 67.00%, while quantitative defects ranged from 3.10% to 58.20%. From the meta-analyses, the pooled prevalences of CCS with DDEs were as follows: overall DDEs at 0.42 [95% CI: 0.25-0.58], qualitative defects at 0.63 [95% CI: 0.57-0.68], and quantitative defects at 0.23 [95% CI: 0.13-0.34]. Additionally, the log odds ratios for developing DDEs in CCS compared to healthy children were 1.59 [95% CI: 0.7 5-2.42] for overall DDEs, 1.63 [95% CI: 1.09-2.17] for qualitative defects, and 0.72 [95% CI: 0.28-1.17] for quantitative defects. The overall log odds ratio of developing qualitative over quantitative enamel defects in CCS was 1.64 [95% CI: 0.21-3.07], I^2 =92.80%.

Conclusions CCS showed a higher prevalence of DDEs, both qualitative and quantitative, compared to healthy children. The meta-analysis showed higher odds of developing qualitative defects over quantitative defects in CCS. Conclusions regarding the association between the type of therapy administered, age of therapy initiation, and prevalence of DDEs could not be drawn due to insufficient data. A lack of a standardized method of detecting enamel defects posed a challenge in the qualitative and quantitative analysis.

KEYWORDS childhood cancer survivors, developmental defects of enamel, antineoplastic therapy, meta-analysis.

Introduction

Many forms of childhood cancer are observed in children, with leukemia as the most prevalent, followed by central nervous system (CNS) tumors and lymphomas [Steliarova-Foucher et al., 2017]. Survival rates among those diagnosed under 14 years of age have surged to 80% [WHO, 2021]. This augmentation in survival metrics owes primarily to improved therapeutic protocols for chemo and radiotherapy [Siegel et al., 2021]. The treatment modalities for childhood cancer include surgical procedures, chemotherapy, radiation therapy, and, in select instances, hematopoietic stem cell transplantation; more often, a combination of more than one treatment modality is implemented; also, multidrug chemotherapy is a common practice that allows an effective treatment [Kurt et al., 2008]. The inherent lack of specificity and the low therapeutic index of antineoplastic therapy targeting neoplastic cells result in accidental damage to healthy tissues, leading to adverse therapy effects that may include growth disturbances [Goho, 1993]. Early adolescent and young adult cancer survivors are at increased risk of developing health-related problems during their whole life, which encompass cardiac, endocrine, and musculoskeletal sequelae when compared to healthy individuals [Latoch et al., 2022]. Also, a spectrum of oral complications arises following radio/chemotherapeutic interventions that include both short-term and long-term implications. Oral mucositis is a prominently reported short-term effect [de Farias Gabriel et al., 2022; Garrocho-Rangel et al., 2018]. Other short-term manifestations include dry lips, mucosal pallor, mucosal petechiae, ecchymoses, and induced ulcers [Ponce-Torres et al., 2010; Alnuaimi et al., 2018]. Long-term effects include high caries risk, alterations in salivary composition, and dysbiosis of oral microbiota [Wang et al., 2021]. Antineoplastic therapy in growing patients occurs in critical moments of dentofacial maturation, therefore, alterations in craniofacial morphogenesis and developmental disorders of the teeth in terms of both number and shape may occur, including alterations in root development, crown-root ratio, microdontia, hypodontia, dental agenesis and defects in enamel development (DDE)[Busenhart

et al., 2018; Bagattoni et al., 2014]. Although the effects of radiotherapy on dental development are well documented, the minimum toxic dose is still unclear [Thompson et al., 2013; Cossellu et al., 2013]. As for chemotherapy, the implementation of multi-agent therapy makes it difficult to assess the effects of each agent, so its impact has not yet been clarified Jodłowska and Postek-Stefańska, 2022]. For instance, agents like cyclophosphamide, an alkylating agent, and vincristine, a vinca alkaloid, cause disruptions in cell division and growth and have been demonstrated to affect dental development [Hsieh et al., 2011; Näsman et al., 1997].

DDEs are disturbances in hard tissue matrices and mineralisation arising during amelogenesis [FDI, 1992]. Enamel defects comprise a wide range of clinical manifestations classified as quantitative or qualitative, affecting the abundance of enamel structure or its visual attributes and translucency. The enamel development process can be divided into two main phases: secretory and maturation. Within the secretory phase, the enamel matrix formation occurs, which plays a pivotal role in determining the ultimate thickness of the enamel structure. Meanwhile, the maturation phase witnesses a progressive augmentation in the mineral content of the developing enamel, thus shaping the optical attributes of the emerging enamel structure [Robinson, 2014]. Accordingly, quantitative and qualitative defects arise when various insults disrupt the secretory and maturation phases. There is no universal index used for the classification of DDEs. However, several indices have been described to classify different forms of defects, including both qualitative and quantitative, such as the DDE index [FDI, 1992], the modified DDE index (mDDE) [Clarkson and O'Mullane, 1989], Enamel Defect index (EDI) [Elcock et al., 2006] and Aine Index which has been used for classification of enamel defects in celiac patients [Aine, 1986]. Existing literature on the long-term effects of antineoplastic therapy has suggested that CCS are at higher risk of developing dental developmental defects compared to their healthy peers [Avşar et al., 2007; Çetiner et al., 2019; Guagnano et al., 2022; Krasuska-Sławińska et al., 2016]. Systematic reviews addressing the oral health status and long-term effects of CCS are available [Angst et al., 2020; Busenhart et al., 2018; Gawade et al., 2014; Seremidi et al., 2019]. However, DDEs were either not analysed [Angst et al., 2020], or when mentioned [Busenhart et al., 2018; Gawade et al., 2014; Seremidi et al., 2019], the descriptions often lacked detail. One study analysed quantitative enamel defects [Gawade et al., 2014], but a meta-analysis was not performed. In some cases, only quantitative defects in the form of enamel hypoplasia were considered [Seremidi et al., 2019], thereby excluding qualitative assessments. Notably, only one systematic review addressed both types of enamel defects, but data meta-analysis was constrained by a limited pool of only four studies [Busenhart et al., 2018].

Therefore, this systematic review aims to analyse the prevalence of DDEs in CCS and to determine the respective prevalences of qualitative and quantitative defects to assess if there is a potential discrepancy between the two. This analysis will include a comparison with healthy children and explore potential influencing factors, such as the age of therapy initiation and the type of therapy administered.

Materials and Methods

Protocol registration

The systematic review protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42023472016 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023472016). The review adhered to the methodologies outlined in the Cochrane Handbook of Systematic Reviews. It conformed to the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

PICO question

The inquiry addressed in the present review was devised following the PICO model: "What is the prevalence of developmental defects of enamel in childhood cancer survivors who underwent chemo and/or radiotherapy; furthermore, is it higher compared to healthy controls?".

- Participants: children and adolescents cancer survivors who underwent chemotherapy and/or radiotherapy, or a combination of both for treatment of any form of malignancy;
- Intervention: chemotherapy, radiotherapy or both;
- Comparator: healthy children. Studies with no comparison group were considered as well;
- Outcome: prevalence of qualitative and/or quantitative developmental defects of enamel.

Eligibility criteria

Randomised clinical, cross-sectional, observational, retrospective, case-control, and prospective studies were eligible for the present review. The authors examined studies written in English with available full text that reported the prevalence of DDEs in children and adolescents cancer survivors. Studies were excluded whenever effects on enamel development were not among the outcomes, and studies including children with a mean age exceeding 16 years at the time of investigation were excluded. Case reports, review articles, in vitro studies, surveys, and conference abstracts were considered ineligible. DDEs in the studies were evaluated, and qualitative and quantitative enamel defects were considered. Concerning qualitative enamel defects, studies were considered suitable whenever forms of discoloration, diffuse or demarcated opacities, or deviations from the healthy appearance of intact enamel, not associated with any form of structural deficiency, were reported. Concerning quantitative enamel defects, studies were considered suitable whenever structural enamel alterations, in particular enamel hypoplasia, were assessed.

Information sources and search strategy

Three electronic databases, PubMed, Embase, and Scopus, were searched from January 2003 to January 2024. The following search strings were used for each database search:

- PubMed: ("Neoplasms" [Mesh] OR "leukemia" [Mesh] OR "pediatric cancer" [tiab] OR "pediatric oncology"[tiab] OR "radiotherapy" [Mesh] OR "Chemotherapy, Cancer, Regional Perfusion" [Mesh] OR "antineoplastic agents" [Mesh] OR "childhood cancer survivors" [tiab]) AND ("enamel hypoplasia" [tiab] OR "dental hypoplasia" [tiab] OR "tooth hypoplasia" [tiab] OR "enamel hypomineralisation" [tiab] OR "enamel defects" [tw] OR "dental defects" [tw] OR "tooth abnormalities"[Mesh] OR "pediatric dentistry" [Mesh]).
- Embase: ('malignant neoplasm' OR 'childhood cancer' OR 'radiotherapy':ti,ab,kw OR 'chemotherapy':ti,ab,kw) AND ('pediatric dentistry' OR 'developmental defects of enamel' OR 'enamel hypoplasia' OR 'dental enamel hypomineralisation' OR 'tooth malformation'/exp OR 'tooth malformation')
- Scopus: (ALL (*malignant AND neoplasm OR *childhood AND cancer OR *leukemia OR *cancer AND radiotherapy OR chemotherapy)) AND (ALL("tooth anomalies" OR "enamel hypoplasia" OR "dental hypoplasia" OR "enamel defects" OR "dental hypomineralisation" OR "developmental defects of enamel" OR "DDE"OR "dental anomalies" OR "dental defects" OR "dental anomalies").

No restrictions on country or publication status were adopted. Articles were then cross-checked by two independent authors (AA, NC).

Study selection and data extraction

After removing duplicates, records were assessed based on title and abstract. Disagreement was solved by discussion, and when it was not possible, a third author (MGC) was consulted. Subsequently, the same two authors proceeded to full-text analysis. Full texts of the included articles were analysed, and data extraction was performed independently by the two reviewers (AA, NC). Disagreements were resolved by debate or involvement, where needed, with the same third author (MGC). The following data were collected and inserted in an Excel® extraction form: bibliographic information (authors, publication year, country), type of the study, outcome assessed (quantitative or qualitative enamel developmental defects), participants characteristics (sample size, mean age, sex distribution), cancer information (age at diagnosis, type of tumor, follow-up period), implemented therapy (mean age at therapy initiation, kind of therapy, duration, agents, dosage), dental examination (index used, type of dentition, tooth type, prevalence of DDEs).

Risk of bias assessment

The Cochrane Collaboration's ROBINS-I and Joanna Briggs Institute (JBI) tools were used to assess bias. The ROBINS-I tool was used for non-randomised studies. The tool includes the use of seven distinct domains for the evaluation of the risk of bias. For each domain, the authors had to answer signaling questions aiming at giving an overall estimation of the risk of bias, which ranged from "Low" to "Critical" [Sterne et al., 2016]. Studies were judged to have a low risk of bias if they met all seven domains, moderate if at least one domain was rated as moderate risk, serious if any domain was rated as serious risk, and critical if any domain was rated as critical risk. The following variables were evaluated in the included studies regarding the first domain, which assesses possible confounding factors: type of antineoplastic therapy, age at therapy initiation, and duration of treatment. Regarding the sixth domain, which evaluates outcomes measurement, studies that used an index to detect enamel development defects were considered to have a low risk of bias. Likewise, studies that provided detailed descriptions of reported enamel defect patterns received a favorable rating even without using an index. Studies that differentiated between qualitative and quantitative enamel defects were assigned a moderate risk of bias, while those that did not make this distinction were classified as having a 'severe' risk of bias. The JBI Appraisal checklist for cross-sectional studies was used to evaluate the quality of studies without a control group. The tool comprises eight key questions designed to evaluate methodological quality. To each question, one of the following answers could be assigned: "Yes", "No", "Unclear", or "Not applicable" [Munn et al., 2019]. The risk of bias was considered low when all criteria were met, or no more than 1 criterion was judged unclear; moderate if 2 criteria were judged unclear and the others were met, or 1 criterion was not met, and the others were met; or high if 3 or more criteria were judged unclear and the others were met, or 2 criteria were not met, and the others were met.

Statistical analysis

The meta-analysis was conducted using Stata®18 SE for Mac. Only those studies were included in the meta-analysis that reported the final sample size, the prevalence of DDEs as a single metric, or the categorisation of enamel defects into qualitative, quantitative, or exclusively qualitative or quantitative in the form of percentages or the number of affected children in both the CCS group and the healthy children group, when present. Studies with commensurate data were then used to conduct different meta-analyses according to the type of outcome reported. Due to high heterogeneity, metaregression (according to age at inclusion) and subgroup meta-analyses (according to type of therapy) were conducted. The random effects model was used to evaluate the pooled prevalence of the outcomes in the CCS; the log odds ratio was used as effect size to compare each of the analysed outcomes in CCS and healthy subjects whenever a group of healthy controls was available. The results of each meta-analysis were graphically represented in forest plots. Furthermore, funnel plots were generated to assess potential publication biases within the included studies. Inter-authors reliability was assessed as the percentage of agreement using Cohen's Kappa statistics.

Results

Search results

The database search yielded a total of 807 articles and, after removal of duplicates, 713 records were analysed according to title and abstract. Subsequently, 74 studies were assessed for eligibility according to the inclusion/exclusion criteria; the results

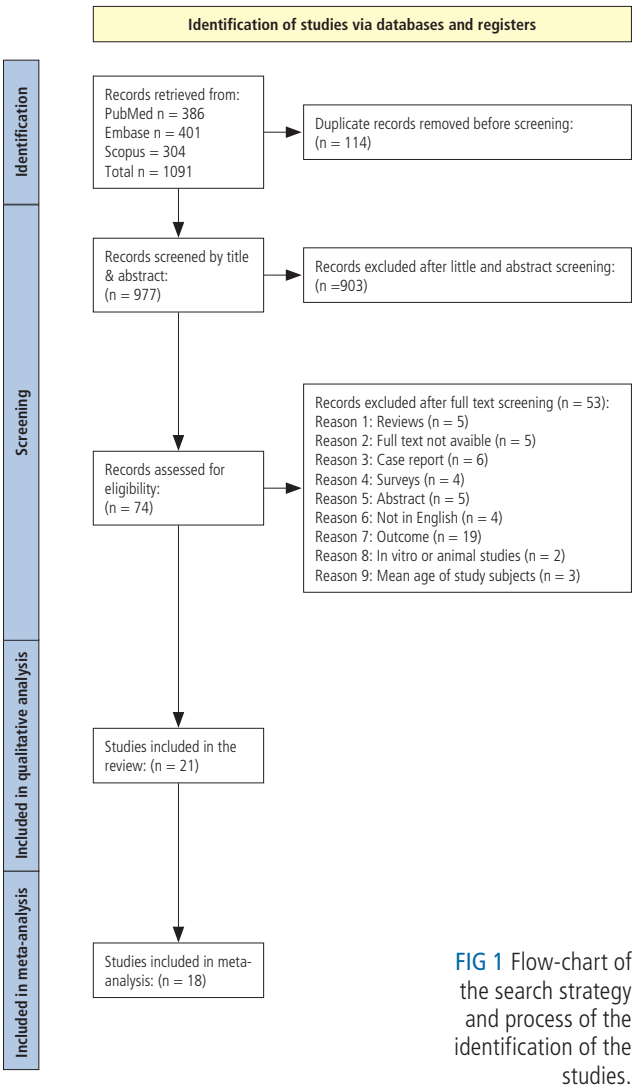

FIG 1 Flow-chart of the search strategy and process of the identification of the studies.

are presented in the flow-chart shown in (Fig. 1). After full-text evaluation, 21 studies were included in the qualitative synthesis and 18 in the meta-analysis. Cohen's Kappa value for inter-reviewers agreement was 0.57 at the title and abstract screening (95.50% agreement) and 0.83 at full-text screening (96.1%).

Studies and sample characteristics

Characteristics of the selected studies are shown in (Table 1). The selected studies were conducted in Turkey [Avşar et al., 2007; Çetiner et al., 2019; Kılınç et al., 2019; Oğuz et al., 2004], Poland [Jodłowska and Postek-Stefańska, 2021, 2022; Krasuska-Sławińska et al., 2016], Italy [Defabianis et al., 2023; Guagnano et al., 2022; Lauritano and Petruzzi, 2012], India [Atif et al., 2022; Talekar et al., 2022], Spain [Rabassa-Blanco et al., 2024], USA [Owosho et al., 2016] UK [Hutton et al., 2010], France [Marec-Berard et al., 2005], Brazil [Maciel et al., 2009; Minicucci et al., 2003], South Korea [Kang et al., 2018], Greece [Seremidi et al., 2023], and Israel [Halperson et al., 2022]. Papers were published between 2003 and 2024. Of the included papers, eight studies were case-control [Avşar et al., 2007; Çetiner et al., 2019; Hutton et al., 2010; Kılınç et al., 2019; Krasuska-Sławińska et al., 2016; Maciel et al., 2009; Marec-Berard et al., 2005; Oğuz et al., 2004], five studies were cross-sectional [Atif et al., 2022; Defabianis et al., 2023; Guagnano et al., 2022; Halperson et al., 2022; Jodłowska and Postek-Stefańska, 2022], seven studies were retrospective [Jodłowska and Postek-Stefańska, 2021; Kang et al., 2018; Minicucci et al., 2003; Owosho et al., 2016; Rabassa-Blanco et al., 2024; Seremidi et al., 2023; Talekar et al., 2022] and one prospective controlled study [Lauritano and Petruzzi, 2012]. The total sample sizes of the included studies ranged from 13 [Owosho et al., 2016] to 241 [Atif et al., 2022] subjects. All studies included children of both sexes, with a mean age at the time of the study that ranged from 7.10 [Halperson et al., 2022] to 15.50 [Rabassa-Blanco et al., 2024] years. Regarding the timing of dental examinations, four studies reported that the examinations were conducted at least 2 years after antineoplastic therapy was completed [Defabianis et al., 2023; Guagnano et al., 2022; Jodłowska and Postek-Stefańska, 2022; Lauritano and Petruzzi, 2012]. Nine studies [Avşar et al., 2007; Çetiner et al., 2019; Hutton et al., 2010; Jodłowska and Postek-Stefańska, 2021; Kang et al., 2018; Krasuska-Sławińska et al., 2016; Minicucci et al., 2003; Oğuz et al., 2004; Seremidi et al., 2023] reported the mean elapsed time from the completion of treatment to the time of dental examination, which ranged from 2.30 [Çetiner et al., 2019] to 6.90 [Kang et al., 2018] years. In one study [Owosho et al., 2016] the examination was conducted at least 5 years after the antineoplastic treatment, while in another [Krasuska-Sławińska et al., 2016] a time interval between 5 and 8 years from cessation of therapy to oral examination was reported. Six studies [Atif et al., 2022; Halperson et al., 2022; Maciel et al., 2009; Marec-Berard et al., 2005; Rabassa-Blanco et al., 2024; Talekar et al., 2022] didn't provide information on the timing of dental examination. A spectrum of diversity regarding the types of tumors from which the subjects included were affected is reported, as shown in (Table 2). Only five studies were conducted on subjects exclusively affected by distinct malignancies, namely non-Hodgkin lymphoma [Oğuz et al., 2004], rhabdomyosarcoma [Owosho et al., 2016], acute lymphoblastic leukemia [Maciel et al., 2009; Minicucci et al., 2003] and nephroblastoma (Wilm's tumor) [Marec-Berard et al., 2005].

A heterogeneity in the type of therapy administered to subjects was noted, as shown in (Table 2). Nine studies included subjects

Study ID	Country	Type of study	Sample size (CCS/CTR)	CCS (M/F)	CCS age at oral exam in years[a]	Time between cancer treatment and oral evaluation (mean in years)	Dentition type
[Minicucci et al., 2003]	Brazil	Retrospective	76	76: 43/33	10.70 (NR)	NR	NR
[Oğuz et al., 2004]	Turkey	Case-Control	72 (36/36)	36: 29/7	10.00 (4.20-17.60)	2.60	NR
[Marec-Berard et al., 2005]	France	Case-Control	105 (27/78)	27: 11/16	7.50 median (3.00-12.70)	NR	Permanent & Deciduous
[Avşar et al., 2007]	Turkey	Case-Control	192 (96/96)	96: 50/46	10.80 (NR)	2.50	Permanent
[Maciel et al., 2009]	Brazil	Case-Control	112 (56/56)	56: 32/24	11.80 (NR)	NR	NR
[Hutton et al., 2010]	United Kingdom	Retrospective	120	120: 69/51	NR (1.00-17.00)	4.33	Permanent
[Lauritano and Petruzzi, 2012]	Italy	Prospective controlled	104 (52/52)	52: 25/27	11.50 (8.00-15.00)	≥2	NR
[Krasuska- Sławińska et al., 2016]	Poland	Case-Control	120 (60/60)	NR	11.81 (NR)	4.90	Permanent
[Owosho et al., 2016]	United states of America	Retrospective	13	13: 5/8	NR (NR)	≥ 5 years	NR
[Kang et al., 2018]	South Korea	Retrospective	196	196: 127/69	15.60 (4.60-33.90)	6.90 median	Permanent
[Çetiner e al., 2019]	Turkey	Case-Control	93 (53/40)	53: 41/12	10.30 (NR)	2.30	Permanent & Deciduous
[Kilinç et al., 2019]	Turkey	Case-Control	165 (93/72)	93: 48/45	9.54 (8.00-13.00)	5-8	NR
[Jodłowska and Postek-Stefańska, 2021]	Poland	Retrospective	38	NR	NR (5.00-18.00)	5.17	NR
[Atif et al., 2022]	India	Cross-sectional	241 (120/121)	120: 81/39	14.30 (NR)	NR	Permanent
[Guagnano et al., 2022]	Italy	Cross-sectional	104 (52/52)	52: 31/21	10.60 (4.00-22.00)	≥ 2	Permanent
[Halperson et al., 2022]	Israel	Cross-sectional	121	NR	7.1 (0.1-17.7)	NR	Permanent
[Jodłowska and Postek-Stefańska, 2022]	Poland	Cross-sectional	37	NR	NR (6.00-17.00)	≥ 2	NR
[Talekar et al., 2022]	India	Retrospective	81	81: 49/32	10.32 (4-17)	NR	N R
[Defabianis et al., 2023]	Italy	Cross-sectional	88	88: 51/37	11.4 (NR)	≥ 2	Permanent
[Seremidi et al., 2023]	Greece	Retrospective	70	70: 32/38	11.2 (5.4-20)	5.48	Permanent & Deciduous
[Rabassa-Blanco et al., 2024]	Spain	Retrospective	109	NR	15.50 (12.00-22.00)	NR	Permanent

CCS: Childhood Cancer Survivors, CTR: Controls, M/f: Male/Female, NR: Not reported, a Values are given in mean. Age ranges are given in parenthesis when available.

TAB 1 General characteristics of the included studies.

Study ID	Cancer type	Therapy type	Mean age at therapy and/or diagnosis	Outcome	Index	Reported defects	Enamel defects prevalence	P value (CCS/CTR)
[Minicucci et al., 2003]	ALL	CH, R	5.10 (T)	Quantitative	NR	Hypoplasia	32.89%	NR
[Oğuz et al., 2004]	NHL	CH	7.10 (D)	Quantitative & Qualitative	DDE Index	Enamel discolorations and defects	67.00% (Ql) 56.00% (Qn)	0.0001 (Ql) 0.34 (Qn)
[Marec-Berard et al., 2005]	Wilm's tumor	CH	3.60 (D)	Quantitative	NR	Enamel hypoplasia	22.00%	NR
[Avşar et al., 2007]	Various	CH, R	6.40 (T)	Quantitative & Qualitative	DDE Index	White/cream & yellow/brown opacities, fine white lines and hypoplasia	69.80%(DDEs) 66.70% (Ql) 3.10% (Qn)	NR
[Maciel et al., 2009]	ALL	CH, R	5.30 (T&D)	Quantitative	NR	Hypoplasia	41.00%	0.324
[Hutton et al., 2010]	Various	CH	NR	Quantitative & Qualitative	mDDE Index	Demarcated, diffuse or both opacities, Hypoplasia only, hypoplasia with demarcated opacities, other defects.	62.5% (DDEs)	NR
[Lauritano and Petruzzi, 2012]	ALL & AML	CH	NR	Quantitative	NR	Enamel hypoplasia	17.30%	0.02
[Krasuska- Sławińska et al., 2016]	Various	CH	5.90 (T)	Quantitative & Qualitative	mDDE Index	Opacities, hypoplasia and combination of both	88.30%(DDEs) 56.60% (Ql) 11.60% (Qn) 20.00%(Comb)	0.000(DDEs) 0.006 (Ql) 0.10 (Qn) 0.068(Comb)
[Owosho et al., 2016]	RMS	CH, R	5.00 (T)	Quantitative	NR	Enamel hypoplasia	23.07%	NR
[Kang et al., 2018]	Various	CH, R, HSCT	4.70 (D)	Quantitative	MDDI	Mild and severe enamel hypoplasia	12.20%	NR
[Çetiner e al., 2019]	Various	CH	NR	Quantitative & Qualitative	NR	Hypoplasia & discoloration	56.60% (Ql) 58.20% (Qn)	< 0.001 (Ql) 0.131 (Qn)
[Kilinç et al., 2019]	Various	CH, R	3.75 (T)	Quantitative & Qualitative	NR	Enamel defect	23.70% (DDEs)	0.009
[Jodłowska and Postek-Stefańska, 2021]	Various	CH,S	3.17 (D)	NR	NR	Enamel anomalies	13.16% (DDEs)	NR
[Atif et al., 2022]	Various	CH, R	5.67 (D)	Quantitative & Qualitative	mDDE Index	Developmental defects of enamel	37.50% (DDEs)	0.01
[Guagnano et al., 2022]	Various	CH, R, HSCT	NR	Quantitative & Qualitative	Aine index	Grade I (qualitative defects), Grade II, III, IV (quantitative defects)	28.1%* (DDEs)	<0.001
[Halperson et al., 2022]	Various	CH, R, HSCT	NR	Quantitative & Qualitative	NR	Hypocalcification or hypoplasia (in one value)	17.00% (DDEs)	NR
[Jodłowska and Postek-Stefańska 2022]	Various	CH	NR	Quantitative & Qualitative	NR	Enamel abnormalities (Opacities, Deep perikymata & hypoplasia)	8.80%* (Ql) 3.80%*(Qn)	NR
[Talekar et al., 2022]	Various	CH	NR	Quantitative	NR	Enamel hypoplasia	6.17%	NR
[Defabianis et al., 2023]	Various	CH, R	5.10 (D) 3.80(T:CH) 8.40 (T:R)	Quantitative & Qualitative	Aine index	Grade I (qualitative defects), Grade II, III, IV (quantitative defects)	21.6%*	NR
[Seremidi et al., 2023]	Various	CH, R, HSCT	4.20 (T)	Quantitative & Qualitative	NR	Demarcated & diffuse opacities, Hypoplasia and combination.	54.00%(DDEs) 64.00% (Ql) 25.00%(Qn) 5.00% (Comb)	NR
[Rabassa-Blanco et al., 2024]	Various	CH, R, HSCT	2.90 (T)	NR	NR	Developmental defects of enamel	31.20% (DDEs)	NR

ALL: Acute Lymphoblastic Leukaemia; AML: Acute Myeloblastic Leukaemia, NHL: Non-Hodgkin Lymphoma, RMS: Rhabdomyosarcoma; CH: Chemotherapy; R: Radiotherapy; S: Surgery, HSCT: Hematopoietic Stem Cell Transplantation; DDE index: Developmental Defects of Enamel index, mDDE index: modified Developmental Defects of Enamel index; MDDI: Modified Dental Defects Index, NR: Not Reported; D: Diagnosis; T: Therapy; DDEs: Developmental defects of enamel, Ql: Qualitative, Qn: Quantitative, Comb: Combination of qualitative & quantitative * Percentages reporting teeth affected

TAB 2 Main characteristics and results of the studies regarding the type of cancer, treatment received, and enamel defects developed.

who had undergone chemotherapy [Çetiner et al., 2019; Hutton et al., 2010; Jodłowska and Postek-Stefańska, 2021, 2022; Krasuska-Sławińska et al., 2016; Lauritano and Petruzzi, 2012; Marec-Berard et al., 2005; Oğuz et al., 2004; Talekar et al., 2022] Only in one study [Oğuz et al., 2004] is stated that subjects had undergone only chemotherapy without receiving any form of radiation. The remaining studies stated that subjects didn't receive any form of head and neck radiation without specifying whether other forms of radiation were used or the dosages administered [Çetiner et al., 2019; Hutton et al., 2010; Jodłowska and Postek-Stefańska, 2021, 2022; Krasuska-Sławińska et al., 2016; Lauritano and Petruzzi, 2012; Marec-Berard et al., 2005; Talekar et al., 2022]. Seven studies included subjects who had undergone both chemotherapy and/or radiotherapy [Atif et al., 2022; Avşar et al., 2007; Defabianis et al., 2023; Kılınç et al., 2019; Maciel et al., 2009; Minicucci et al., 2003; Owosho et al., 2016]. In particular, five studies stated that children received maxillofacial radiotherapy [Halperson et al., 2022; Kılınç et al., 2019; Minicucci et al., 2003; Owosho et al., 2016; Seremidi et al., 2023]. One study included subjects undergoing surgical intervention [Jodłowska and Postek-Stefańska, 2021]. Five studies included subjects who had undergone hematopoietic stem cell transplantation [Guagnano et al., 2022; Halperson et al., 2022; Kang et al., 2018; Rabassa-Blanco et al., 2024; Seremidi et al., 2023]. Seven studies [Avşar et al., 2007; Kılınç et al., 2019; Krasuska-

Sławińska et al., 2016; Maciel et al., 2009; Minicucci et al., 2003; Owosho et al., 2016; Rabassa-Blanco et al., 2024] provided information regarding the age of therapy initiation, which ranged from 2.90 [Rabassa-Blanco et al., 2024] to 8.40 years [Defabianis et al., 2023]. Regarding preventive oral care programs, one study stated children did not receive any oral prophylaxis during or after therapy [Lauritano and Petruzzi, 2012]; meanwhile, three studies [Avşar et al., 2007; Çetiner et al., 2019; Oğuz et al., 2004] reported chlorhexidine mouth rinses were prescribed during and after hospitalisation. None of the included studies provided information on whether dental check-ups were also conducted before the initiation of therapy. Additionally, no studies have reported whether regular dental follow-ups were performed after the conclusion of the neoplastic therapy.

Detection of developmental enamel defects

Indices and assessment approaches

A wide variability regarding the method of defects evaluation was observed across the studies (Table. 2). Most studies didn't provide details regarding the index used to assess enamel defects [Çetiner et al., 2019; Jodłowska and Postek-Stefańska, 2021, 2022; Kılınç et al., 2019; Lauritano and Petruzzi, 2012; Maciel et al., 2009; Marec-Berard et al., 2005; Minicucci et al., 2003; Owosho et al., 2016; Rabassa-Blanco et al., 2024]. Two studies used the Developmental Defects of Enamel index (DDE Index) [Avşar et al., 2007; Oğuz et al., 2004]; meanwhile, two studies reported employing the modified Developmental Defects of Enamel index (mDDE) [Atif et al., 2022; Hutton et al., 2010; Krasuska-Sławińska et al., 2016] The Aine index was used in two studies [Defabianis et al., 2023; Guagnano et al., 2022]. One study [Kang et al., 2018] adopted the Modified Dental Defect Index (MDDI) to evaluate dental and crown and root defects. With this index, the defects of the crown, only quantitative defects, were assessed; these defects were classified according to severity into mild and severe. In all studies except five [Atif et al., 2022; Hutton et al., 2010; Jodłowska and Postek-Stefańska, 2022; Seremidi et al., 2023; Talekar et al., 2022], a radiographic examination was used to identify dental developmental defects.

Type of enamel defects and dentition

Fourteen of the included studies evaluated both qualitative and quantitative defects of enamel [Atif et al., 2022; Avşar et al., 2007; Çetiner et al., 2019; Defabianis et al., 2023; Guagnano et al., 2022; Halperson et al., 2022; Hutton et al., 2010; Jodłowska and Postek-Stefańska, 2021; Kılınç et al., 2019; Krasuska-Sławińska et al., 2016; Oğuz et al., 2004; Rabassa-Blanco et al., 2024; Seremidi et al., 2023], and five studies [Atif et al., 2022; Halperson et al., 2022; Jodłowska and Postek-Stefańska, 2021; Kılınç et al., 2019; Rabassa-Blanco et al., 2024] reported the overall prevalence of DDEs without reporting the respective prevalence of each type of defect. Two studies reported the respective prevalences without reporting the total prevalence [Çetiner et al., 2019; Oğuz et al., 2004]. Seven studies analysed only quantitative defects of enamel [Kang et al., 2018; Lauritano and Petruzzi, 2012; Maciel et al., 2009; Marec-Berard et al., 2005; Minicucci et al., 2003; Owosho et al., 2016; Talekar et al., 2022]. The overall prevalence of DDEs ranged from 13.16% [Jodłowska and Postek-Stefańska, 2021] to 88.30% [Krasuska-Sławińska et al., 2016]. The prevalence of qualitative enamel defects ranged from 56.60% [Çetiner et al., 2019; Jodłowska and Postek-Stefańska, 2022] to 67.00% [Oğuz et al., 2004], while the prevalence of such defects in the control groups, if present, varied from 18.70% [Avşar et al., 2007] to 32.30% [Krasuska-Sławińska et al., 2016]. Regarding the quantitative defects of enamel, the prevalence in CCS ranged from 3.10% [Avşar et al., 2007] to 58.20% [Çetiner et al., 2019], while in the control group it ranged from 1.00% [Avşar et al., 2007] to 42.50% [Çetiner et al., 2019]. Nine studies [Atif et al., 2022; Avşar et al., 2007; Defabianis et al., 2023; Guagnano et al., 2022; Halperson et al., 2022; Hutton et al., 2010; Kang et al., 2018; Krasuska-Sławińska et al., 2016; Rabassa-Blanco et al., 2024] reported the assessment of enamel defects focusing solely on permanent dentition, two of which [Atif et al., 2022; Rabassa-Blanco et al., 2024] did not include the third molar from the examination. Three studies [Çetiner et al., 2019; Marec-Berard et al., 2005; Seremidi et al., 2023] examined both the primary and permanent dentition; a higher prevalence of enamel defects in patients with permanent dentition (68.00%) compared to mixed dentition (19.00%) was reported [Seremidi et al., 2023]. A higher prevalence of qualitative defects has been found in central incisors [Kılınç et al., 2019] and a higher prevalence of both qualitative and quantitative defects in maxillary anterior teeth and upper first premolars [Hutton et al., 2010]. A higher prevalence of quantitative defects has been described in upper and lower premolars [Minicucci et al., 2003]. Finally, a difference in the extent of defects per tooth was described, with defects most commonly covering 1/3 to 2/3 of the crown surface in children who survived cancer compared to less than 1/3 in healthy controls [Atif et al., 2022].

Risk of bias assessment

Ten of the selected studies [Atif et al., 2022; Avşar et al., 2007; Çetiner et al., 2019; Guagnano et al., 2022; Hutton et al., 2010; Kılınç et al., 2019; Krasuska-Sławińska et al., 2016; Lauritano and Petruzzi, 2012; Maciel et al., 2009; Oğuz et al., 2004] had a control group of healthy participants, thus prompting the use of the ROBINS-I tool for risk of bias assessment, while for the remaining eleven studies [Defabianis et al., 2023; Halperson et al., 2022; Jodłowska and Postek-Stefańska, 2021, 2022; Kang et al., 2018; Marec-Berard et al., 2005; Minicucci et al., 2003; Owosho et al., 2016; Rabassa-Blanco et al., 2024; Seremidi et al., 2023; Talekar et al., 2022] lacking a control group in their design, the JBI tool was used. The results of the risk of bias assessment using the ROBINS-I are presented in (Fig. 2). One article [Guagnano et al., 2022] was deemed to have a low risk of bias as it satisfied all seven domains. Four articles [Atif et al., 2022; Avşar et al., 2007; Krasuska-Sławińska et al., 2016; Oğuz et al., 2004] were rated at moderate risk of bias, as they presented some concerns over one or more domains; four articles [Çetiner et al., 2019; Kılınç et al., 2019; Lauritano and Petruzzi, 2012; Maciel et al., 2009] were judged to be at serious risk of bias, and one study (Hutton et al., 2010) at critical risk of bias, as they raised significant concerns on more than one domain. In particular, two domains, bias due to confounding and bias in outcome measurement, showed the highest risk among the included studies. Results of risk of bias assessment using JBI tool are shown in (Fig. 3). One study was found to have a low risk of bias [Defabianis et al., 2023], one study showed a medium risk of bias [Talekar et al., 2022] and nine studies were deemed to have a high risk of bias [Halperson et al., 2022; Jodłowska and Postek-Stefańska, 2021, 2022; Kang et al., 2018; Marec-Berard et al., 2005; Minicucci et al., 2003; Owosho et al., 2016; Rabassa-Blanco et al., 2024; Seremidi et al., 2023].

Meta-analysis

The pooled prevalence of CCS with DDEs was 0.42 [95% CI: 0.25-0.58], I^2 =96.76%; meanwhile, when comparing CCS with healthy controls, the overall log odds ratio was 1.59 (odds ratio: 4.90) [95% CI:0.75-2.42], I^2 =79.83% (Fig. 4 A-B). The pooled prevalence of CCS with qualitative enamel defects was 0.63 [95%

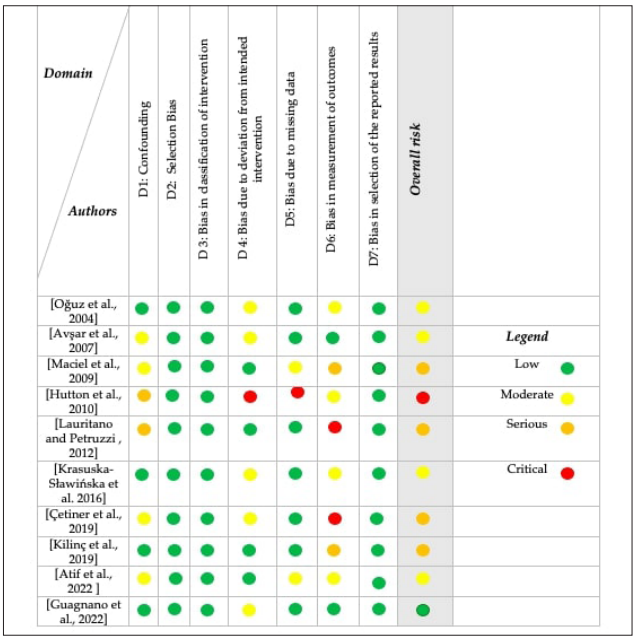

FIG. 2 Risk of bias using ROBINS-I tool for the non-randomized studies included in the review.

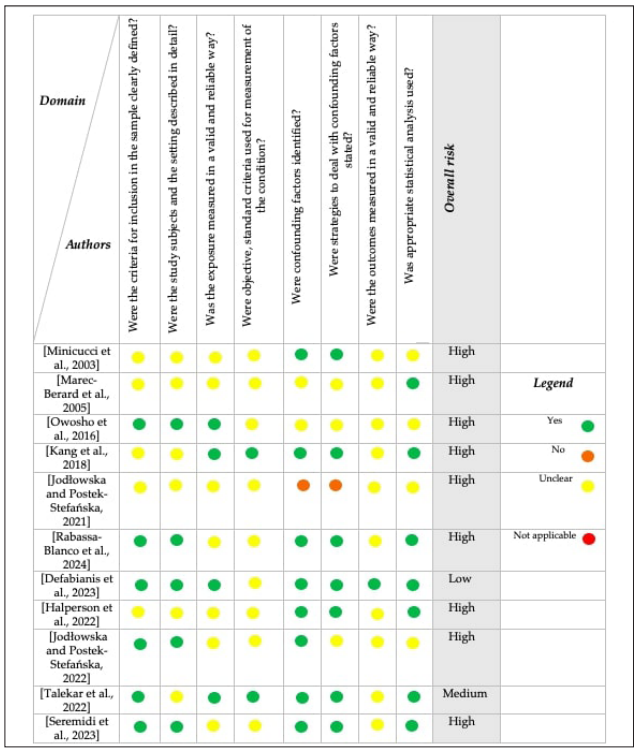

FIG. 3 Risk of bias using Joanna Briggs Institute tool for the included studies without a control group.

CI: 0.57-0.68], I² =0.00% and, when comparing CCS with healthy controls, log odds ratio was 1.63 (odds ratio: 5.10) [95%CI:1.09-2.17], I² =42.36% (Fig. 5 A-B). The pooled prevalence of CCS with quantitative enamel defects was 0.23 [95% CI:0.13-0.34], I² =96.63%; meanwhile, when comparing CCS with healthy controls the log odds ratio was 0.72 (odds ratio: 2.05) [95% CI: 0.28-1.17], I² =0.00% (Fig. 6 A-B).Additionally, the overall log odds ratio of developing qualitative over quantitative defects of enamel in CCS was 1.64 (odds ratio: 5.16) [95% CI: 0.21-3.07], I² =92.80% (Fig.

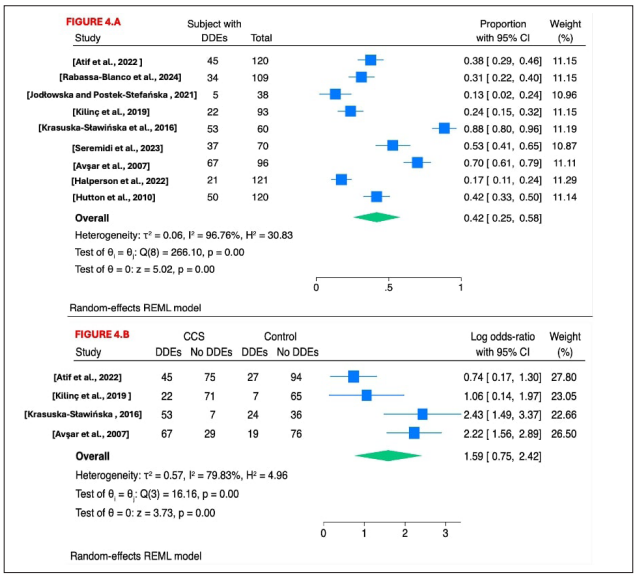

FIG. 4A, 4B Metanalysis: forest plot for DDEs prevalence in childhood cancer survivors (A) and in childhood cancer survivors compared to control groups (B).

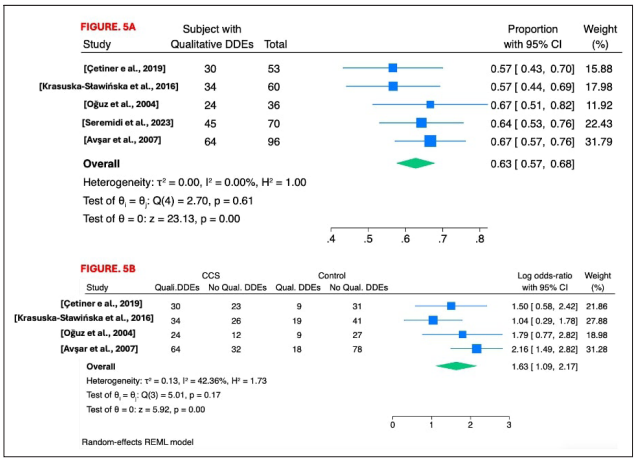

FIG. 5A, 5B Metanalysis: forest plot for the prevalence of qualitative DDEs in childhood cancer survivors (A) and in childhood cancer survivors compared to control groups (B).

7A). Subgroup analyses were also performed to analyze variables such as type of therapy administered and mean age at therapy initiation. Only four studies [Halperson et al., 2022; Kılınç et al., 2019; Minicucci et al., 2003; Seremidi et al., 2023] provided data regarding the number of subjects that developed developmental defects of enamel when chemotherapy alone or associated with radiotherapy was administered. The overall log odds ratio was -0.22 (odds ratio: 0.8) [95% CI:0.21-3.07] (Fig. 7B). As for the mean age at therapy initiation, no association was found. An assessment of the publication bias for each outcome was made and the funnel plots are illustrated in Figure 8. For the case-control studies, no asymmetry emerges; the funnel plots on the prevalence of DDEs and of quantitative defects in CCS (Fig. 8A, E) reflect the high heterogeneity of the results.

Discussion

Oral health status and implications of antineoplastic therapy in CCS have been extensively examined in previous systematic reviews

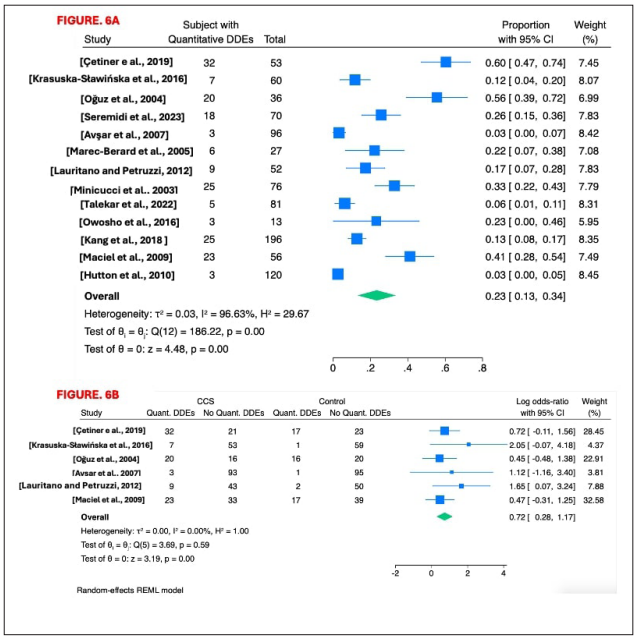

FIG. 6A, 6B Metanalysis: forest plot for the prevalence of quantitative DDEs in childhood cancer survivors (A) and in childhood cancer survivors compared to control groups (B).

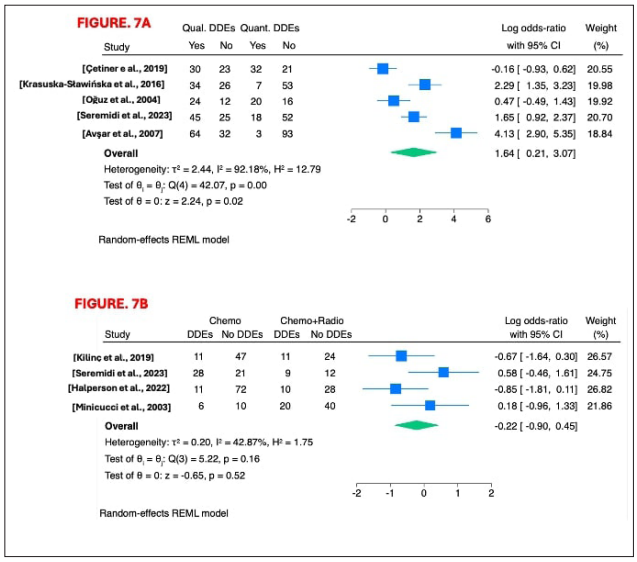

FIG. 7A, 7B Metanalysis: forest plot for the prevalence of qualitative DDEs vs quantitative DDEs in childhood cancer survivors (A) and for the overall prevalence of DDEs in relation to the type of therapy administered (chemotherapy vs chemotherapy in addition to radiotherapy).

[Angst et al., 2020; Busenhart et al., 2018; Gawade et al., 2014; Seremidi et al., 2019], DDEs have not previously been the main focus of such investigations. Specifically, in one systematic review, enamel defects were not analysed [Angst et al., 2020]. While in one study [Gawade et al., 2014], authors analysed studies that reported on either enamel defects or enamel hypoplasia offering only descriptions of the respective prevalences in each study without aggregating data through meta-analysis to establish the pooled prevalence; it's worthy noting that enamel defects reported encompassed both quantitative and qualitataive defects that were considered under one category. In one study [Seremidi et al., 2019], authors analysed only quantitative defects particularly enamel hypoplasia, odds ratios in relation to age, for each dental developmental defect were reported, demonstrating higher odds of developing enamel hypoplasia with higher dosages of radiation. On the other hand, only one study [Busenhart et al., 2018], differentiated between the main categories of enamel defects qualitative and quantitative, analysing enamel discolorations and hypoplasia respectively; the authors performed a meta-analysis that included a restricted pool of literature comprising only four studies,two of which analysed hypoplasia, while the remaining two studies assessed tooth discolorations, results showed a slightly higher relative risk of developing tooth discoloration over enamel hypoplasia which is consistent with the results of the current review. The current review makes an effort to distinguish between the various types of enamel defects, both qualitative and quantitative; eighteen studies were included in the meta-analysis, contributing to a comprehensive understanding of the existing literature. Quality assessment of the included studies revealed that most were at moderate to high risk of bias, potentially impacting the conclusions drawn from this review. This risk is largely due to the systematic lack of data on the number of subjects affected by DDEs in relation to the type of therapy, age at therapy, and duration of therapy, which may represent confounding factors. Additionally, the absence of a standardised definition, description, and evaluation of DDEs could introduce bias into the reported results of each included study. The results of the meta-analysis provide evidence that CCS have a higher prevalence of DDEs than healthy children. The estimated pooled prevalence obtained through the random effects model indicates that a significant proportion of CCS developed these defects. It appears that CCS are approximately five times more likely to develop DDEs than healthy children; additionally CCS were approximately five times and two time more likely to develop qualitative and quantitative enamel defects, respectively, when compared to healthy controls. The results also showed a higher probability of developing qualitative enamel defects over quantitative ones. This finding could be explained by the fact that the enamel matrix was already formed at the time of therapy administration, thus mainly influencing the maturation phase of enamel formation and leading to a higher prevalence of qualitative enamel defects. Qualitative defects were reported less frequently than quantitative ones in the included studies. In particular, among the eighteen studies included in the meta-analysis, thirteen reported the prevalence of quantitative defects, while only five reported the prevalence of qualitative defects. This discrepancy may be explained by the fact that quantitative defects were recognised and reported as long-term effects of cancer therapy much earlier than qualitative defects and that the latter have only recently become the subject of interest in the scientific literature, perhaps due to the great interest in a specific form of enamel hypomineralisation that is molar and incisional enamel (MIH) [Giuca et al., 2020]. As developmental defects of enamel are inherently multifactorial [Seow, 2014], based on the type of studies available and included, it is difficult to establish a clear cause-and-effect relationship in CCS. Several factors, including the type of cancer, the treatment modalities employed, and patient demographic variables, may affect the development of DDEs. Therefore, discerning the precise influence of the different factors on the occurrence of DDEs is complex, also due to the inconsistency and frequent absence of reported data, as the authors of the included studies often neglected to report the respective prevalence rates in relation to the age at the start of therapy, the type of therapy

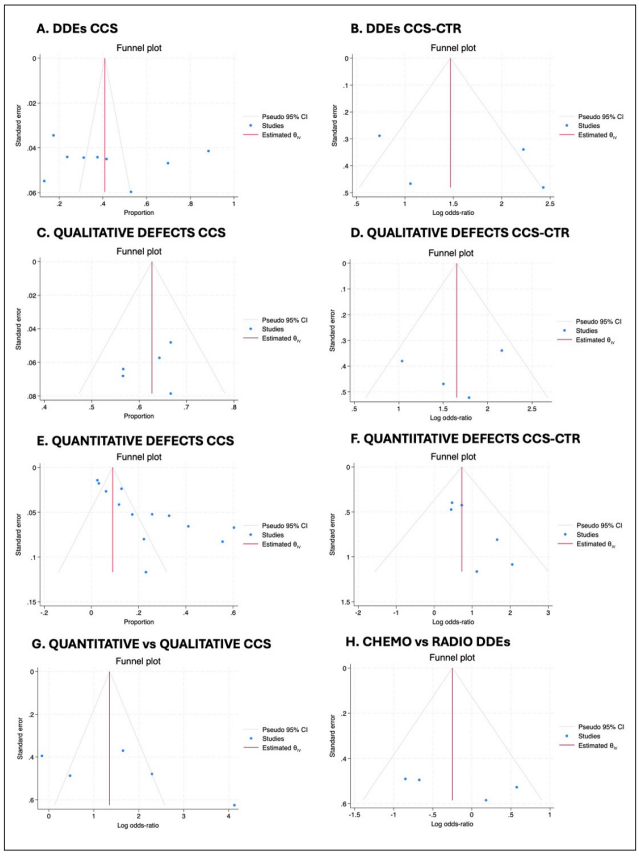

FIG. 8 Funnel plots of publication bias for each outcome (A-H). An asymmetry emerges for the overall prevalence of DDEs in childhood cancer survivors and for quantitative defects (A, E).

implemented and, in particular, the type of tumor. This omission may be explained by the fact that all the included studies evaluated various aspects of oral health in cancer survivors, with enamel defects not being the primary outcome of interest. However, subgroup meta-analyses were performed to explore the role of the type of therapy implemented and the age of onset of treatment on the prevalence of enamel development defects. The results showed a lack of statistical significance when comparing two treatment approaches, chemotherapy alone or chemotherapy combined with radiotherapy. It is crucial to note the paucity of studies providing such data; only four studies were included in the analysis [Halperson et al., 2022; Kılınç et al., 2019; Minicucci et al., 2003; Seremidi et al., 2023]. This limitation underlines the need to interpret these results with caution. Only a minority of studies have used a standardised index to classify enamel developmental defects; furthermore, the lack of a precise definition of the type of defect has been a challenge that has often led to overlapping data. In particular, there has been confusion over the differentiation between enamel hypomineralisation, hypocalcification, and hypoplasia. This confusion could be caused by not using a standardised index and having a limited understanding of classifying enamel defects [Villani et al., 2023]. This limitation may be due to the recent attention given to this topic, which has only gained importance in the scientific literature in the last decade. In contrast, most studies were conducted before this period. Moreover, two studies have utilized the Aine Index [Defabianis et al., 2023; Guagnano et al., 2022], created for enamel defect classification in celiac patients. Paradoxically, in the studies in which the authors indicated using an index, they often did not specify the individual prevalence of each class, type, or severity of defects. Instead, they reported only the overall prevalence of enamel defects. This omission created difficulties in discerning discrepancies between the prevalences of quantitative and qualitative defects. Another critical aspect was the lack of information on whether these defects manifested as hypomineralisation of the molar incisors (MIH) or presented post-eruptive breakdown. This absence of specific details regarding the presentation of these defects complicates the comprehensive understanding of their nature and progression. Although some studies have analysed both primary and permanent dentition, authors have often neglected to report the respective prevalence of DDEs in each dentition. This oversight hampers the ability to fully understand the distribution and impact of enamel defects at different stages of dental development. A significant gap was also identified in most studies regarding the reporting of dental check-ups conducted before the initiation of therapy and the regular dental follow-ups during and after the treatment period. In addition, a lack of implementation of preventive dental programs for children during hospitalization and after discharge was noted. Therefore, there is a need for greater collaboration between dental and medical professionals to ensure comprehensive care for children with various forms of cancer.

Conclusion

CCS showed a higher prevalence of qualitative and quantitative DDEs than healthy children. A strong association was found between childhood cancer survival and qualitative enamel defects, while the correlation with quantitative enamel defects was moderate. Due to insufficient data, it is difficult to assess a cause-effect relationship between antineoplastic therapy and the prevalence of DDE. Furthermore, the lack of a standardized index for their detection complicates the comparison of results between studies. Consequently, further research is needed to obtain more reliable data and draw definitive conclusions.

Competing interests

The authors declare no competing interests in relation to the present review.

Author contributions

MGC and GC designed and planned the search strategies; CS and NC created the strings and performed the search; AA, NC, and SC searched the articles and wrote the manuscript draft; CS performed the analysis; AA and SC created the tables; MGC, AA, NC wrote the manuscript; MGC and GC revised the manuscript and checked the tables.

Funding

This study did not receive any funding.

References

› A review of the developmental defects of enamel index (DDE Index). Commission on Oral Health, Research & Epidemiology. Report of an FDI Working Group. Int Dent J, 1992; 42:411–426.
› Aine L. Dental enamel defects and dental maturity in children and adolescents with coeliac disease. Proc Finn Dent Soc, 1986; 82 Suppl 3: 1–71.
› Alnuaimi E, Al Halabi M, Khamis A, Kowash M. Oral health problems in leukaemic paediatric patients in the United Arab Emirates: a retrospective study. Eur J Paediatr Dent, 2018; 19:226-232.
› Angst PDM, Maier J, Dos Santos Nogueira R, Manso I.S, Tedesco T. K. Oral health status of patients with leukemia: a systematic review with meta-analysis. Arch Oral Biol, 2020; 120:104948.
› Atif M, Mathur VP, Tewari N, Bansal K, Rahul M, Bakhshi S. Long-Term Effect of Anticancer Therapy on Dentition in Childhood Cancer Survivors: An

Observational, Cross-Sectional Study. Indian J Pediatr,2022; 89:327–332.
› Avşar A, Elli M, Darka O, Pinarli G. Long-term effects of chemotherapy on caries formation, dental development, and salivary factors in childhood cancer survivors. Oral Surg Oral Med Oral Pathol Oral Radiol Endod, 2007; 104:781–89.
› Bagattoni S, D'Alessandro G, Prete A, Piana G, Pession A. Oral health and dental late adverse effects in children in remission from malignant disease. A pilot case-control study in Italian children. Eur J Paediatr Dent, 2014; 15:45-50.
› Busenhart DM, Erb J, Rigakos G, Eliades T, Papageorgiou S N. Adverse effects of chemotherapy on the teeth and surrounding tissues of children with cancer: A systematic review with meta-analysis. Oral Oncol, 2018; 83:64–72.
› Çetiner D, Çetiner S, Uraz A, Alpaslan GH, Alpaslan C, Toygar Memikoğlu TU, Karadeniz C. Oral and dental alterations and growth disruption following chemotherapy in long-term survivors of childhood malignancies. Support Care Cancer, 2019; 27:1891–99
› Clarkson J, O'Mullane D. A modified DDE Index for use in epidemiological studies of enamel defects. J Dent Res, 1989; 68:445–450.
› Cossellu G, Seramondi R, Benedicenti S, Farronato G, Olivi G, Angiero F. Tooth developmental anomalies in severe combined immunodeficiency disease and juvenile myelomonocytic leukemia: common clinical features and treatment outcomes. Eur J Paediatr Dent, 2013; 14:328-332.
› de Farias Gabriel A, Silveira FM, Curra M, Schuch LF, Wagner VP, Martins MAT, da Silveira Matte U, Siebert M, Botton MR, Brunetto AT, Gregianin LJ, Martins MD. Risk factors associated with the development of oral mucositis in pediatric oncology patients: Systematic review and meta-analysis. Oral Dis,2022; 28:1068–1084.
› Defabianis P, Bocca N, Romano F. Prevalence and association of dental anomalies and tooth decay in Italian childhood cancer survivors. J Clin Pediatr Dent, 2023; 47:81–87.
› Elcock C, Lath DL, Luty JD, Gallagher MG, Abdellatif A, Bäckman B, Brook AH. The new Enamel Defects Index: testing and expansion. Eur J Oral Sci, 2006, 114 Suppl 1:35–38; discussion 39-41, 379.
› Garrocho-Rangel JA, Herrera-Moncada M, Márquez-Preciado R, Tejeda-Nava F, Ortiz-Zamudio JJ, Pozos-Guillén A. Oral mucositis in paediatric acute lymphoblastic leukemia patients receiving methotrexate-based chemotherapy: case series. Eur J Paediatr Dent, 2018; 19:239-242.
› Gawade PL, Hudson MM, Kaste SC, Neglia JP, Constine LS, Robison LL, Ness KK. A systematic review of dental late effects in survivors of childhood cancer. Pediatr Blood Cancer, 2014; 61:407–416.
› Giuca MR, Lardani L, Pasini M, Beretta M, Gallusi G, Campanella V. State-of-the-art on MIH. Part. 1 Definition and aepidemiology. Eur J Paediatr Dent, 2020; 21: 80–82.
› Goho C. Chemoradiation therapy: effect on dental development. Pediatr Dent, 1993; 15: 6–12.
› Guagnano R, Romano F, Berger M, Fagioli F, Vallone V, Bello L, Vitale MC, Defabianis P. Long-term effect of anticancer therapy on dentition of Italian children in remission from malignant disease: A cross-sectional study. Eur J Paediatr Dent, 2022; 23:131–36.
› Halperson E, Matalon V, Goldstein G, Saieg Spilberg S, Herzog K, Fux-Noy A, Shmueli A, Ram D, Moskovitz M. The prevalence of dental developmental anomalies among childhood cancer survivors according to types of anticancer treatment. Sci Rep, 2022; 12:4485.
› Hsieh G-S S, Hibbert S, Shaw P, Ahern V, Arora M. Association of cyclophosphamide use with dental developmental defects and salivary gland dysfunction in recipients of childhood antineoplastic therapy. Cancer, 2011; 117: 2219–2227.
› Hutton A, Bradwell M, English M, Chapple I. The oral health needs of children after treatment for a solid tumour or lymphoma. Int J Paediatr Dent,2010; 20:15–23.
› Jodłowska A, Postek-Stefańska L. Tooth development in the light of chemotherapy-induced agenesis in cancer survivors. J Stoma,2021; 74:28–33.
› Jodłowska A, Postek-Stefańska L. Systemic Anticancer Therapy Details and Dental Adverse Effects in Children. Int J Environ Res Public Health, 2022; 19: 6936.
› Kang C-M, Hahn SM, Kim HS, Lyu CJ, Lee J-H, Lee J, Han JW. Clinical Risk Factors Influencing Dental Developmental Disturbances in Childhood Cancer Survivors. Cancer Res Treat, 2018; 50: 926–935.
› Kılınç G, Bulut G, Ertuğrul F, Ören H, Demirağ B, Demiral A, Aksoylar S, Kamer ES, Ellidokuz, H, Olgun N. Long-term Dental Anomalies after Pediatric Cancer Treatment in Children. Turk J Haematol, 2019; 36:155–161.
› Krasuska-Sławińska E, Brożyna A, Dembowska-Bagińska B, Olczak-Kowalczyk D. Antineoplastic chemotherapy and congenital tooth abnormalities in children and adolescents. Contemp Oncol (Pozn), 2016; 20:394–401.
› Kurt BA, Armstrong GT, Cash DK, Krasin MJ, Morris EB, Spunt SL, Robison LL, Hudson MM. (2008). Primary care management of the childhood cancer survivor. J Pediatr, 2008; 152:458–466.
› Latoch E, Zubowska M, Młynarski W, Stachowicz-Stencel T, Stefanowicz J, Sławińska D, Kowalczyk J, Skalska-Sadowska J, Wachowiak J, Badowska W, Czajńska-Deptuła A, Dembowska-Bagińska B, Garus K, Skoczeń S, Pobudejska-Pieniążek A, Szczepański T, Machnik K, Panasiuk A, Sęga-Pondel D, Krawczuk-Rybak M. Late effects of childhood cancer treatment in long-term survivors diagnosed before the age of 3 years – A multicenter, nationwide study. Cancer Epidemiol, 2022; 80:102209.
› Lauritano D, Petruzzi M. Decayed, missing and filled teeth index and dental anomalies in long-term survivors leukaemic children: a prospective controlled study. Med Oral Patol Oral Cir Bucal, 2012; 17: e977-80.
› Maciel JCC, de Castro CG, Brunetto AL, Di Leone LP, da Silveira HED. Oral health and dental anomalies in patients treated for leukemia in childhood and adolescence. Pediatr Blood Cancer, 2009; 53:361–65.
› Marec-Berard P, Azzi D, Chaux-Bodard AG, Lagrange H, Gourmet R, Bergeron C. Long-term effects of chemotherapy on dental status in children treated for nephroblastoma. Pediatr Hematol Oncol, 2005; 22:581–88.
› Minicucci EM, Lopes LF, Crocci AJ. Dental abnormalities in children after chemotherapy treatment for acute lymphoid leukemia. Leuk Res,2003; 27:45–50.
› Munn Z, Aromataris E, Tufanaru C, Stern C, Porritt K, Farrow J, Lockwood C, Stephenson M, Moola S, Lizarondo L, McArthur A, Peters M, Pearson A, Jordan Z. The development of software to support multiple systematic review types: the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI). Int J Evid Based Healthc, 2019; 17:36–43.
› Näsman M, Forsberg CM, Dahllöf G. Long-term dental development in children after treatment for malignant disease. Eur J Orthod, 1997; 19: 151–59.
› Oğuz A, Cetiner S, Karadeniz C, Alpaslan G, Alpaslan C, Pinarli G. Long-term effects of chemotherapy on orodental structures in children with non-Hodgkin's lymphoma. Eur J Oral Sci, 2004; 112:8–11.
› Owosho AA., Brady P, Wolden SL, Wexler LH, Antonescu CR, Huryn JM, Estilo CL. Long-term effect of chemotherapy-intensity-modulated radiation therapy (chemo-IMRT) on dentofacial development in head and neck rhabdomyosarcoma patients. Pediatr Hematol Oncolo,2016; 33:383–392.
› Ponce-Torres E, Ruíz-Rodríguez M del S, Alejo-González F, Hernández-Sierra JF, Pozos-Guillén A de J. Oral manifestations in pediatric patients receiving chemotherapy for acute lymphoblastic leukemia. J Clin Pediatr Dent, 2010; 34: 275–79.
› Rabassa-Blanco J, Brunet-Llobet L, Marcote-Sinclair P, Balsells-Mejía S, Correa-Llano MG, Miranda-Rius J.Prevalence of, and risk factors for, dental sequelae in adolescents who underwent cancer therapy during childhood. Oral Dis, 2024; 30:604–14.
› Robinson C. Enamel maturation: a brief background with implications for some enamel dysplasias. Front Physiol, 2014, 8:388.
› Seow WK. Developmental defects of enamel and dentine: challenges for basic science research and clinical management. Aust Dent J, 2014; 59 Suppl 1:143–154.
› Seremidi K, Kavvadia K, Kattamis A, Polychronopoulou A. Dental caries and dental developmental defects as adverse effects of antineoplastic treatment in childhood cancer survivors. Eur Arch Paediatr Dent,2023; 24:357–365.
› Seremidi K, Kloukos D, Polychronopoulou A, Kattamis A, Kavvadia K. Late effects of chemo and radiation treatment on dental structures of childhood cancer survivors. A systematic review and meta-analysis. Head Neck, 2019; 41:3422–3433.
› Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin, 2021; 71: 7–33.
› Steliarova-Foucher E, Colombet M, Ries LAG, Moreno F, Dolya A, Bray F, Hesseling P, Shin HY, Stiller CA, IICC-3 contributors. International incidence of childhood cancer, 2001-10: a population-based registry study. Lancet Oncol,2017; 18:719–731.
› Sterne JA, Hernán MA, Reeves BC, Savović, J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Higgins JP. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ, 2016; 355: i4919.
› Talekar AL, Musale PK, Kothare SS. Dental Caries and Dental Anomalies in Children Undergoing Chemotherapy for Malignant Diseases. Int J Clin Pediatr Dent, 2022; 15:428–332.
› Thompson RF, Schneider RA, Albertini F, Lomax AJ, Ares C, Goitein G, Hug EB. Dose to the developing dentition during therapeutic irradiation: organ at risk determination and clinical implications. Int J Radiat Oncol Biol Phys, 2013; 86:108–113.
› Villani FA, Aiuto R, Dioguardi M, Paglia L, Caruso S, Gatto R, Re D, Garcovich D. Caries prevalence and molar incisor hypomineralisation (MIH) in children. Is there an association? A systematic review. Eur J Paediatr Dent, 2023; 24:312-320.
› Wang Y, Zeng X, Yang X, Que J, Du Q, Zhang Q, Zou J. Oral Health, Caries Risk Profiles, and Oral Microbiome of Pediatric Patients with Leukemia Submitted to Chemotherapy. Biomed Res Int, 2021; 6637503
› World Health Organization. CureAll framework: WHO global initiative for childhood cancer: increasing access, advancing quality, saving lives. World Health Organization, 2021 (available at https://www.who.int/publications/i/item/9789240025271).