Aetiology of Bone Tumours in Children and Young Adults: An Updated Narrative Review

Mr Ahmad Ilyasa Ahmad, Mr Suhash Mahendira Rajan, Dr Adam Errington, Dr Richard McNally
Student number: 220688637 | Degree programme: MB BS | c2068863@newcastle.ac.uk | Population Health Sciences Institute, Newcastle University

Background

Primary bone cancers in **children and young adults** (CYA; 0-24 years) are rare. The two main types are **osteosarcoma (OS)**, a cancer of bone-forming cells, and **Ewing sarcoma (ES)**, which is usually driven by a specific gene fusion. Together, OS and ES make up most bone cancers in this age group.

Across high-income countries, bone tumours represent **3–5%** of cancers in children aged 0–14 and **7–8%** in adolescents aged 15–19. Overall, there are about **5 cases per million** children each year, with rates rising through childhood and peaking around puberty.[3]

Patterns vary by place and population: for example, ES shows marked geographical and ethnic differences, while OS and ES together display global heterogeneity in occurrence.[1]

The causes of these cancers remain uncertain. Current evidence points to a mix of **genetic predisposition** and **environmental influences**, rather than a single explanation.

Aims

This project updates the Newcastle 2009 narrative review—originally covering studies from **1970–2008**—by synthesising new evidence from **2009–2025** and placing it alongside international cancer-registry trends (CI5-Plus).[1,2]

The aim is to clarify which suspected risk factors are consistently supported, which are not, and to highlight priorities for future research.

Methods

1. Updated the 2009 Newcastle review by searching **MEDLINE**, **Embase** and **Web of Science** for 2009–2025 using terms for osteosarcoma, Ewing sarcoma, risk factors and genetics; included human studies in children, adolescents and young adults.
2. Two reviewers screened records and extracted **study design**, **age band**, **exposure definitions** and **effect estimates** (OR/RR/HR with 95% CIs), with brief notes on potential bias.
3. Evidence was summarised narratively; where ≥3 comparable studies existed, results were pooled with simple random-effects and variability described at a high level.
4. CI5-Plus summary data (C40–C41) for ages 0–24 in five registries (1983–2017) were analysed to report **age-standardised rates per million** and the average annual percent change (AAPC: average yearly % change from log-linear models) with 95% CIs.[2]

CI5-Plus Incidence Trends

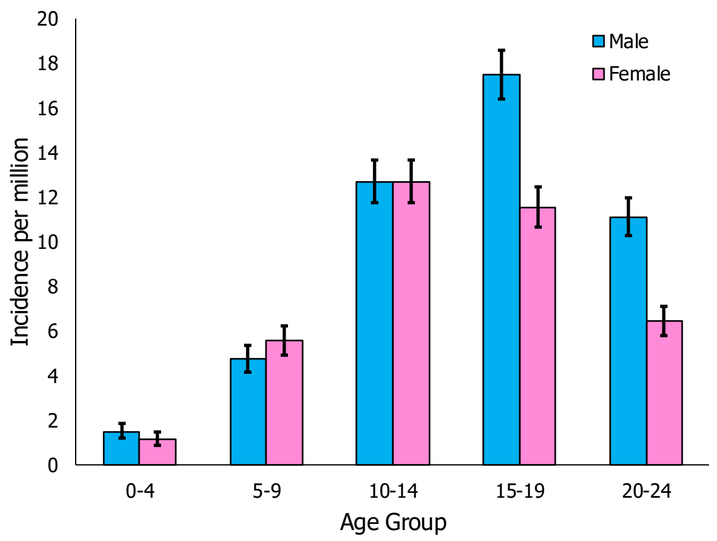
Table 1. Registry dataset selected from the CI5-Plus Summary.[2]

Registry	AAPC (%)	95% CI
Colombia (Cali)	2.25	0.90 – 3.63
Australia (NSW+ACT)	0.60	-0.16 – 1.36
USA (SEER-9)	0.50	0.09 – 0.92
UK (England)	0.40	0.09 – 0.71
Japan, Miyagi Prefecture	-0.99	-3.14 – 1.20

AAPC = **average annual percent change** from log-linear models of ASR; values are percentages with 95% CIs. ASR = age-standardised rate per million.

From 1983–2017, incidence rose modestly but significantly in **Cali, SEER-9, and England**; **Australia** shows no clear change; **Miyagi** trends downward but **not significantly**.

Figure 1. Incidence of Primary Bone Tumours by Age Group, England (1983–2017)[2]



Across England (1983–2017), incidence climbs from early childhood to a clear **adolescence peak**, then falls. Rates are similar for boys and girls to 10–14; a marked male excess emerges at 15–19 (≈17.5 vs 11.6 per million) and persists into 20–24.

Since 2009, registry data show modest rises and a clear adolescence peak in CYA bone tumours—prompting this update.

Narrative Review Results & Conclusion

Growth & stature (OS) — Strong/consistent
Children who are taller or grow faster have a higher chance of osteosarcoma; those in the tallest group have about **2–3×** the risk of average-height children. Genetic studies point the same way, supporting a growth-related explanation.

Early-life hernias (ES) — Consistent
Children with certain hernias (e.g., inguinal or diaphragmatic) are more likely to develop Ewing sarcoma. This pattern is not seen in osteosarcoma, suggesting different early-life biology.

Inherited predisposition (OS) — High but uncommon
About **1 in 10** young people with osteosarcoma carry a TP53 change. Other inherited syndromes (RB1, rare helicase disorders) together account for <2%. Most children and young adults do not have a recognised inherited cause.

Table 2. Aetiological risk factors of bone tumours.

Factor	Cancer	Risk estimate	95% CI
Taller stature (≥90th centile)	OS	OR = 2.6	—
Height (per 1 SD, genetic MR)	OS	OR = 1.10	1.01–1.19
Inguinal hernia	ES	OR = 1.27	1.01–1.59
Diaphragmatic hernia	ES	OR = 2.27	1.30–3.95
TP53 pathogenic variant	OS	9–10% of cases	—
RB1 / rare helicase syndromes	OS	<2% of cases	—

OS = osteosarcoma; **ES** = Ewing sarcoma; **MR** = Mendelian randomisation; "—" indicates CIs vary across pooled studies or are not consistently reported.

Large, fair-comparison studies show **no link** between community water fluoridation and **bone tumours**; common childhood infections show no consistent pattern. Apparent **"injury causes cancer"** signals are usually **reverse causation**. Modern data show **no specific association** between routine diagnostic **CT imaging** and **osteosarcoma** or **Ewing sarcoma**.

Other hints are **small or mixed**—for example, **higher birth weight** (modest for osteosarcoma), **older parental age** (often fades after adjustment), and **proximity/occupational exposures** (inconsistent due to rough exposure measures).

Further Investigations

Larger **pooled studies** in **children and young adults (CYA)** are needed to detect modest risks and confirm which early-life factors matter.

For **osteosarcoma**, confirming the growth-related signal by linking puberty-timed markers and long-term growth records to further stratify risk. For **Ewing sarcoma**, replicate the hernia finding with detail on type, timing, and surgical repair to potentially clarify early-life pathways.

Across both cancers, improve exposure measurement from pregnancy through childhood using standardised definitions so results can be combined, and study genes and environment together (e.g., **Mendelian randomisation**) to test causality and clarify interactions.

References
1. **Eyre R, et al.** Epidemiology of bone tumours in children and young adults. *Pediatr Blood Cancer*. 2009;53(6):941-952. doi:10.1002/pbc.22194.
2. **Ferlay J, Colombet M, Bray F.** Cancer Incidence in Five Continents, CI5plus: IARC CancerBase No. 9 [Internet]. Lyon: International Agency for Research on Cancer; [cited 2025 Oct 22]. Available from: https://ci5.iarc.who.int
3. **Cancer Research UK**. **Bone sarcoma statistics: incidence and survival** [Internet]. London: Cancer Research UK; [cited 2025 Oct 22]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bone-sarcoma

Acknowledgements

This project was supported by the **Newcastle University Research Scholarship**. Grateful thanks to **Professor Richard McNally** (project supervisor) for guidance on research direction and oversight, and to **Dr Adam Errington** for his analytical advice and feedback.