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Review Article

Are Cervical Ribs Indicators of Childhood Cancer? A Narrative Review

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Abstract

A cervical rib (CR), also known as a supernumerary or extra rib, is an additional rib that forms above the first rib, resulting from the overgrowth of the transverse process of a cervical vertebra. Increasingly recognized as a potential marker of developmental disruptions and genetic instability, CRs are believed to arise from mutations in homeobox (Hox) genes that influence axial skeletal development. While often asymptomatic, CRs have been linked to thoracic outlet syndrome and a higher prevalence in individuals with certain childhood cancers. Studies have reported associations between CRs and malignancies such as neuroblastoma, brain tumors, leukemia, sarcomas, Wilms tumor, and germ cell tumors, suggesting possible shared embryological pathways or genetic predispositions. However, conflicting research findings highlight inconsistencies in these associations, underscoring the need for further investigation. This review aims to assess the association between CRs and childhood cancers by examining prevalence rates, exploring genetic and developmental links, evaluating inconsistencies in existing research, and identifying gaps for future study to clarify the clinical significance of CRs in cancer risk assessment.

1. Introduction

A Cervical rib (CR), also known as a "neck rib" or "supernumerary rib," is an extra rib that forms above the first rib, near the collarbone. It develops due to an overgrowth of the transverse process of a cervical spine vertebra. It is thought to result from mutations in homeobox (Hox) genes, which play a role in shaping the axial skeleton in humans and vertebrates. This rib can occur on either side and may be unattached (floating) or fused with the first rib. It can range from a fully formed bone to a delicate fibrous strand [1].

The CRs are present in about 2% of the general adult population. The prevalence is higher in women, who are about twice as likely to have CRs as men. Additionally, ethnic differences have been observed, with one study finding that CRs are more common in African Americans than in whites [2].

Typically, CR is discovered incidentally through radiographic imaging unless it causes symptoms [3]. In some cases, CR can contribute to thoracic outlet syndrome by narrowing the interscalene triangle, leading to pain, weakness, numbness, or cold sensitivity in the affected limb [1, 4, 5]. The first documented clinical signs of neurovascular compression associated with CRs were reported by Cooper in 1818 [6].

Studies have demonstrated a higher prevalence of CRs in individuals with childhood cancers. This association may stem from disruptions in embryonic development during critical stages of blastogenesis, which can simultaneously lead to cervical segmentation defects and increase cancer susceptibility [7, 8].

Moreover, CRs are often regarded as markers of adverse developmental events or genetic instability. Their higher prevalence in stillborn fetuses and individuals with chromosomal abnormalities further underscores their potential role as indicators of systemic vulnerabilities that may contribute to malignancy risk. These findings highlight the importance of understanding rib anomalies (RAs) as anatomical curiosities and potential markers for identifying individuals at increased risk for certain cancers [9]. This study aims to review the association between CRs and cancer, with all referenced articles assessed for eligibility [10].

2. Studies Linking Rib Anomalies to Childhood Cancers

Despite growing awareness of a possible connection between RAs and malignancies, research on this topic remains limited. Only four studies have examined this association, each providing valuable insights into the potential link.

The earliest study by Schumacher et al. (1995) investigated the relationship between RAs and childhood malignancies by reviewing chest X-rays of 1,000 children with cancer and 200 control patients with non-malignant conditions. They found a significantly higher prevalence of RAs, particularly CRs, in children with certain malignancies compared to controls. This suggested that these skeletal abnormalities might be linked to altered morphogenesis in tumor development [7].

A decade later, Merks et al. (2005) conducted a more extensive study analyzing chest radiographs of 906 children with cancer and 881 healthy Caucasian pediatric controls. Their findings confirmed previous reports, demonstrating a higher occurrence of specific RAs in children with certain malignancies. They emphasized the potential role of genetic predisposition in cancer development and suggested that skeletal anomalies could serve as markers for underlying genetic abnormalities [8].

Loder et al. (2007) expanded on these findings by focusing on rib number variations in 218 children with malignancies and 200 control children who had been admitted for polytrauma or suspected child abuse. Their study highlighted a significant difference in rib counts between children with cancer and healthy controls. They speculated that genes involved in vertebral and rib development might also play a role in cancer predisposition, suggesting the possibility of using skeletal anomalies as a screening tool for early cancer detection [11].

Finally, Zierhut et al. (2011) reinforced the association between RAs and childhood cancers through a hospital-based case-control study of 459 pediatric cancer patients and 1,135 controls who had undergone chest X-rays for non-cancer-related reasons. Their research confirmed that children with cancer were more likely to have RAs, particularly those diagnosed with specific malignancies. They underscored the need for further studies to determine the biological mechanisms linking RAs to cancer development [12].

3. Cancers Linked to CRs

3.1. Neuroblastoma

Neuroblastoma is a highly aggressive tumor that develops from neural crest cells and is the most common cancer in infants under one year old worldwide [13]. It represents about 10% of all pediatric cancers and primarily affects children within their first five years of life [14].

A defining characteristic of neuroblastoma is its highly variable clinical behavior. In approximately 50% of affected infants, the tumor regresses spontaneously, whereas in others, it advances into an aggressive, metastatic disease that is often resistant to standard treatments like chemoradiotherapy, stem cell transplantation, and immunotherapy [15]. This unpredictability complicates treatment, especially for high-risk patients who experience chemo-resistant relapse, with survival rates remaining below 40% [14].

The initiation and progression of neuroblastoma are driven by genetic abnormalities that interfere with cell division, proliferation, and apoptosis [15]. Significant genetic factors include MYCN amplification, TP53 deletions, ALK mutations or amplifications, TERT rearrangements, ATRX deletions or mutations, and segmental chromosomal aberrations. However, whole-genome sequencing studies have identified only a limited number of recurrent somatic mutations, making the development of targeted therapies challenging. Consequently, a precise understanding of the biological complexity and diversity of neuroblastoma is crucial for improving diagnostic and treatment approaches [15].

Schumacher et al. (1992) identified a strong correlation between neuroblastoma and CRs, reporting that 33% of children with neuroblastoma had CRs, a markedly higher prevalence than in the general population. This notable disparity suggests a potential developmental or genetic connection between neuroblastoma and skeletal anomalies. Furthermore, neuroblastoma was the only malignancy in their study to exhibit a significantly increased incidence of rib bifurcation (4.5%), a rate nearly four times higher than expected, reinforcing the possibility of disrupted skeletal development linked to the disease [7].

In contrast, Merks et al. (2005) analyzed 61 neuroblastoma patients and found that 9.8% had CRs, compared to 6.1% in the control group. While this suggests a slightly increased prevalence, the difference was not statistically significant ($p = 0.252$). This discrepancy with Schumacher et al. (1992) may be due to differences in sample size, diagnostic criteria, or population characteristics [7, 8].

Loder et al. (2007) took a broader approach by grouping neuroblastoma with other neural malignancies. Their findings showed a higher incidence of RAs (35%) in children with neural tumors compared to those with other malignancies. However, they did not specifically find an association between neuroblastoma and CRs. Among the eight neuroblastoma patients in their study, RAs were present, but no cases of CRs were observed. Instead, the most common skeletal abnormality was a reduced rib count, with affected children having 22 or 23 ribs instead of the typical 24. This suggests that while RAs may be linked to neuroblastoma, the specific presence of CRs may not be a defining characteristic [11].

Similarly, Zierhut et al. (2011) analyzed 31 neuroblastoma cases and found that 6.4% had RAs. However, the study did not report how many of these cases involved CRs specifically. The statistical analysis yielded an odds ratio (OR) of 1.46 (95% CI: 0.34–6.30) for any rib anomaly in neuroblastoma patients, indicating a slightly higher occurrence of skeletal abnormalities but without statistical significance. The lack of a significant association between RAs and neuroblastoma may be due to the study's small sample size, which could have limited its ability to detect a stronger relationship [12].

Overall, while Schumacher et al. (1992) identified a strong association between neuroblastoma and CRs, subsequent studies, including those by Merks et al. (2005), Loder et al. (2007), and Zierhut et al. (2011), reported weaker or non-significant links [7, 8, 11, 12]. The inconsistencies across studies highlight the need for further research with larger sample sizes and more detailed skeletal analyses to determine whether CRs represent a meaningful developmental marker for neuroblastoma or if their observed association is due to broader skeletal anomalies.

3.2. Brain Tumors

A brain tumor forms when cells grow irregularly and multiply uncontrollably. These tumors may arise from brain cells, the meninges (the membranes surrounding the brain), glands, or nerves. They can cause direct damage to brain cells and elevate pressure within the skull, resulting in harmful effects [16].

Due to their severity, brain tumors are classified into different grades. Grade 1 tumors are the least aggressive, typically associated with more prolonged survival. They grow slowly, resemble normal cells under a microscope, and can often be effectively treated with surgical removal. Examples include pilocytic astrocytoma, ganglioglioma, and gangliocytoma. Grade 2 tumors also grow slowly but appear abnormal under a microscope. Some may invade nearby tissues and tend to recur, occasionally progressing to a higher grade [16].

Grade 3 tumors are malignant and share similarities with grade 2 tumors but are more likely to recur as grade 4 tumors. Grade 4 tumors are the most aggressive, growing rapidly and appearing highly abnormal under a microscope. They invade surrounding brain tissue, form new blood vessels, and contain areas of dead cells at their core. Glioblastoma Multiforme is a well-known example of a grade 4 tumor [16].

Brain tumors develop due to a combination of genetic, environmental, and molecular factors. Genetic predisposition plays a key role, with inherited syndromes such as neurofibromatosis and Li-Fraumeni syndrome increasing the risk. Environmental exposures, particularly ionizing radiation, are well-established contributors, while occupational exposure to chemicals and electromagnetic fields remains inconclusive. Viral infections, immune dysfunction, and chronic inflammation may also influence tumor development [17, 18].

The study by Schumacher et al. (1992) found that 27.4% of children with brain tumors had CRs, compared to only 5.5% in the control group ($p < 0.001$). This substantial difference suggests a potential developmental link between CRs and brain tumors, possibly due to shared embryological pathways affecting both skeletal and neural development. The high prevalence reported in this study indicates that CRs might serve as an anatomical marker for underlying genetic or developmental disruptions associated with brain tumor formation [7].

Merks et al. (2005) further supported this hypothesis by identifying a significant association between CR anomalies and astrocytomas. Their study reported that 18.2% of childhood cancer patients with astrocytomas had CRs, compared to 6.1% in the control group. This finding suggests that certain subtypes of brain tumors, particularly astrocytomas, may have a stronger developmental association with CR anomalies [8].

However, Loder et al. (2007) did not find a strong link between brain tumors and CRs. While RAs were more frequent in children with neural malignancies (35%), none of these anomalies were identified as CRs. Instead, children with neural malignancies were found to be 6.23 times more likely to have an abnormal rib count compared to the control group. This suggests that while skeletal anomalies may be associated with neural tumors in general, CRs specifically may not be a consistent marker [11].

Zierhut et al. (2011) also provided a more tempered perspective. Their study examined 34 pediatric cases of central nervous system tumors, including brain tumors, and found that 8.8% ($n = 3$) had some form of rib anomaly. However, they did not identify a statistically significant association between CRs and

brain tumors. This finding further weakens the case for a direct link and suggests that broader skeletal anomalies may be involved rather than CRs specifically [12].

Overall, while Schumacher et al. (1992) and Merks et al. (2005) suggest a possible association between CRs and brain tumors, the findings from Loder et al. (2007) and Zierhut et al. (2011) cast doubt on the specificity of this relationship [7, 8, 11, 12]. The inconsistencies across studies highlight the need for further research to determine whether CRs are a true marker for brain tumor risk or if their association is due to broader developmental abnormalities affecting multiple organ systems.

3.3. Leukemia

Leukemia is a frequently occurring cancer in both children and adults. It results from disruptions in normal cell regulation that lead to the uncontrolled growth of hematopoietic stem cells in the bone marrow. It is more commonly found in males and individuals of white ethnicity, with its prevalence increasing with age. On average, about one in 70 people will develop leukemia during their lifetime. The four main types of leukemia, each with unique characteristics, are acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), chronic lymphocytic leukemia, and chronic myelogenous leukemia [19].

Leukemia occurs worldwide, with a higher prevalence and overall mortality in more developed countries. However, the mortality rate tends to be greater in developing nations [20]. The development of leukemia results from a complex interaction between genetic predisposition and environmental influences, with neither factor alone provides a complete explanation. While significant strides have been made in identifying risk factors and potential disease mechanisms, the exact causes of most leukemia cases remain uncertain. Known risk factors include genetic syndromes, chromosomal abnormalities, radiation exposure, specific chemicals, certain viral infections, and prior cancer treatments, but these account for only a fraction of cases [20, 21].

The study by Schumacher et al. (1992) found a significant association between CRs and leukemia, with 26.8% (n = 227) of leukemia patients exhibiting CRs compared to only 5.5% (n = 11) in the control group ($p < 0.001$). This finding suggests a potential developmental or genetic link between skeletal anomalies and leukemia, possibly due to disruptions in early embryonic development affecting both hematopoietic and skeletal systems [7].

Similarly, Merks et al. (2005) identified a significant association between CR anomalies and ALL, with a prevalence of 12.1% in ALL patients compared to 6.1% in controls ($p = 0.011$). This reinforces the idea that skeletal anomalies may serve as a marker for certain pediatric malignancies, though the underlying mechanisms remain unclear [8].

Loder et al. (2007) further examined RAs in leukemia patients. Among 218 children with malignancies, 75 had leukemia (64 with ALL and 11 with AML) [11]. The incidence of abnormal rib counts in children with lymphoproliferative malignancies (which includes leukemia and lymphoma) was 15%, compared to 8% in the control group. Logistic regression analysis revealed that children with leukemia and other lymphoproliferative malignancies were twice as likely to have an abnormal rib count compared to controls. While this supports a broader association between RAs and leukemia, the study did not specifically focus on CRs, making direct comparisons with Schumacher et al. (1992) and Merks et al. (2005) more challenging [7, 8].

In contrast, Zierhut et al. (2011) provided a more nuanced perspective. While their study confirmed an overall link between RAs and an increased risk of childhood cancers, the specific association between CRs and leukemia did not reach statistical significance. Notably, children with AML had a significantly higher likelihood of RAs, with an adjusted OR of 2.29 (95% CI: 1.02–5.13). However, when CRs were analyzed separately, the association weakened (adjusted OR = 1.63, 95% CI: 0.55–4.80), failing to reach statistical significance. This suggests that while RAs in general may be linked to leukemia, CRs alone may not be a consistent marker for the disease [12].

Overall, the studies by Schumacher et al. (1992) and Merks et al. (2005) suggest a potential association between CRs and leukemia [7, 8, 11]. However, Zierhut et al. (2011) cast doubt on the specificity of this relationship, indicating that while RAs may be more common in leukemia patients, CRs alone may not be a reliable marker [12]. Further research is needed to clarify whether CRs are a developmental indicator of leukemia risk or if their observed association is due to broader skeletal anomalies linked to pediatric malignancies.

3.4. Sarcomas

Sarcomas comprise a diverse group of mesenchymal tumors, with over 100 distinct diagnostic types. This variability is evident through both light microscopy and gene expression analysis. Even within the same histological category, there can be substantial differences in biological behavior [22].

Sarcomas are generally classified into two main types: soft tissue sarcomas and primary bone sarcomas, each requiring unique staging and treatment strategies. Soft tissue sarcomas are typically categorized based on genetic alterations and microscopic examination of hematoxylin-eosin–stained tissue, where morphological features resembling normal tissues are identified. Additionally, sarcomas are further assessed by histologic grade. The three key prognostic factors are the tumor's grade, size, and primary location [22].

Sarcomas usually arise spontaneously, but certain risk factors have been identified. Exposure to ionizing radiation, often from cancer treatments, increases the likelihood of sarcomas, typically appearing 7-10 years after exposure. Other risk factors include chronic lymphedema, exposure to chemicals like vinyl chloride, and infection with human herpesvirus 8, which is linked to Kaposi sarcoma [22].

Several genetic syndromes also elevate sarcoma risk. Neurofibromatosis type 1 leads to benign and malignant nerve sheath tumors, while neurofibromatosis type 2 is associated with meningiomas and cranial nerve schwannomas. Gardner syndrome increases the risk of desmoid tumors, and hereditary retinoblastoma raises the likelihood of osteosarcoma and soft

tissue sarcomas later in life. Li-Fraumeni syndrome, caused by TP53 mutations, also predisposes individuals to sarcomas [22].

Schumacher et al. (1992) found a significant association between CRs and sarcomas, reporting their presence in 24.5% of patients with soft tissue sarcomas ($p < 0.001$) and 17.1% of those with Ewing sarcoma ($p < 0.01$), compared to only 5.5% in the control group. These findings suggest a potential developmental or genetic link between CR anomalies and sarcomas, possibly due to early mesodermal development disruptions, which influences skeletal and soft tissue formation [7].

However, later studies did not consistently replicate these findings. Merks et al. (2005) found much lower rates of CRs in sarcoma patients, with 7.4% of rhabdomyosarcoma cases (5/68, $p = 0.687$), 6.3% of osteosarcoma cases (3/48, $p = 0.973$), and 7.7% of Ewing sarcoma cases (3/39, $p = 0.692$). None of these differences were statistically significant, suggesting that the initial association reported by Schumacher et al. (1992) may have been due to sample variation or other confounding factors. The stark contrast between these two studies raises questions about whether the observed link is truly biologically relevant or if it was an artifact of study design or population differences [8].

Loder et al. (2007) examined RAs in solid tumors, including osteosarcoma, rhabdomyosarcoma, and Ewing sarcoma, finding that 13% of cases exhibited RAs. However, this association was not statistically significant ($p = 0.15$), suggesting that while RAs may be more common in children with cancer, they do not appear to be strongly associated with sarcomas specifically [11].

Similarly, Zierhut et al. (2011) identified a general link between RAs and childhood cancers but did not find a significant correlation between CRs and sarcomas. This further weakens the hypothesis that CRs are a marker for sarcoma risk [12].

Overall, while the Schumacher et al. (1992) study initially suggested a strong association between CRs and sarcomas, more recent studies, including those by Merks et al. (2005), Loder et al. (2007), and Zierhut et al. (2011), have not confirmed this relationship [7, 8, 11, 12]. The inconsistencies in findings suggest that if a link does exist, it may be weaker than initially thought or influenced by confounding factors. Further research with larger sample sizes and refined methodologies is needed to clarify whether CRs have any true predictive value for sarcoma development.

3.5. Wilms tumor

Wilms tumor (WT), or nephroblastoma, is a malignant solid tumor that arises from the primitive renal bud. It is the most common primary renal tumor in the urogenital tract of children and typically occurs unilaterally in 90–95% of cases. However, it can also present bilaterally or multicentrically, particularly in cases associated with genetic factors, occurring either simultaneously (synchronously) or at different times (metachronously). WT accounts for approximately 2% to 6% of all childhood cancers [23].

Both genetic and environmental factors influence the development of WT. Genetic mutations play a crucial role, particularly in the WT1 and WT2 genes, which are vital for kidney development [23]. WT1 mutations are linked to syndromic forms of WT, such as WAGR and Denys-Drash syndromes, while WT2 abnormalities are associated with Beckwith-Wiedemann syndrome. Additionally, mutations in CTNNB1 (β-catenin), TP53, and microRNAs contribute to tumor development. Environmental factors, including parental exposure to pesticides before conception or during pregnancy, may increase the risk, though their precise impact remains unclear. WT is frequently associated with congenital syndromes involving developmental abnormalities [23].

Schumacher et al. (1992) identified a significant association between CRs and WT, reporting that 23.5% of children with WT had CRs, compared to only 5.5% in the control group ($p < 0.001$). This strong statistical significance suggests a potential developmental link between skeletal anomalies and WT [7].

However, Merks et al. (2005) found that 9.8% of children with WT had CRs, compared to 6.1% in the control group, but the difference was not statistically significant ($p = 0.115$). This suggests that while CRs may be more common in WT patients, the association is not robust enough to be considered a reliable marker [8]. Similarly, Zierhut et al. (2011) reported a statistically significant increase in overall RAs among children with renal tumors, including WT. However, when analyzing CRs specifically, they did not find a significant association, further casting doubt on their role as a consistent indicator of WT [12].

Loder et al. (2007) provided additional support for a general link between RAs and pediatric malignancies but did not specifically analyze CRs in WT patients. This broader pattern suggests that skeletal anomalies may be associated with childhood cancers but does not confirm a direct link between CRs and WT [11].

These findings indicate that while there is some evidence of a relationship between skeletal anomalies and WT, the inconsistent association with CRs suggests that other factors may be at play. Additional research is needed to explore the genetic and developmental mechanisms underlying these observations, which could provide further insights into the etiology of WT and its potential links to congenital anomalies.

3.6. Germ Cell Tumors

Germ cell tumors (GCTs) are the most diverse childhood neoplasms. The majority are benign teratomas, presenting as heterogeneous masses with cystic and solid components. However, approximately 20% of GCTs are malignant, accounting for 3% of pediatric cancers. Malignant GCTs can occur at any age but follow a bimodal distribution, primarily affecting infants and adolescents [24].

These tumors can develop in various anatomical locations, including the gonads, sacrococcygeal region, mediastinum, retroperitoneum, and other para-axial sites. They are believed to originate from a common progenitor germ cell but exhibit diverse histologies, such as endodermal sinus tumor (yolk sac tumor), germinoma (dysgerminoma or seminoma), embryonal carcinoma, and choriocarcinoma. Different histological types often coexist within a single tumor, with approximately 25% of pediatric GCTs containing multiple histologic components [24].

Malignant GCTs have specific genetic predispositions, and genome-wide association studies (GWAS) have identified single-nucleotide polymorphisms (SNPs) in genes such as KITLG, SPRY4, DMRT1, and TERT, which are linked to the development of testicular GCTs [25].

Schumacher et al. (1992) investigated the relationship between CR anomalies and yolk sac tumors, a type of GCT, but did not find a significant association. The prevalence of RAs in patients with yolk sac tumors was 3.4%, which was not significantly different from the normal population (5.5%). This finding suggests that, unlike other pediatric malignancies, GCTs may not share a strong developmental link with skeletal anomalies [7].

In contrast, Merks et al. (2005) reported a statistically significant association between CR anomalies and GCTs, with 14.7% of GCT patients exhibiting CRs compared to 6.1% in controls ($p = 0.046$). This suggests a potential genetic or developmental link between GCTs and skeletal anomalies, though the mechanisms underlying this association remain unclear. The higher prevalence observed in this study raises the possibility that certain genetic mutations or disruptions in embryonic development may predispose individuals to both conditions [8].

Loder et al. (2007) did not specifically analyze CRs in relation to GCT. However, their study demonstrated a broader statistically significant association between RAs and childhood malignancies. Children with cancer had a higher prevalence of RAs (18%) compared to the control group (8%), with a p-value of 0.003. While this finding supports a general link between skeletal anomalies and pediatric cancers, it does not establish a direct connection between CRs and GCTs [11].

Similarly, Zierhut et al. (2011) did not specifically report a link between CR and GCTs. The absence of a reported association with GCTs suggests that these tumors may not be as strongly linked to skeletal anomalies as other childhood malignancies [12].

Overall, while some studies indicate a potential link between CR anomalies and GCTs, the evidence remains inconsistent. Merks et al. (2005) provided the most substantial support for an association, but findings from Schumacher et al. (1992) and Zierhut et al. (2011) did not confirm this relationship [7, 8, 12]. Additional research is needed to determine whether CR anomalies can serve as a marker for GCTs or if the observed association is due to other underlying developmental factors.

4. Other RAs Associated with Cancer

Numerical RAs, such as having fewer than 24 ribs, were also found to be more common in children with malignancies. Loder et al. (2007) reported that 18% of children with malignancies had an abnormal rib number compared to 8% of controls. Among specific cancer types, neural tumors had the highest incidence of abnormal rib counts (35%), followed by lymphoproliferative malignancies (15%) and solid tumors (13%) [11]. Similarly, Zierhut et al. (2011) found that children with AML, renal tumors, and hepatoblastoma had a significantly higher likelihood of having an abnormal rib count ($p = 0.008$) [12].

Rib bifurcations, which involve rib splitting into two separate structures, have also been linked to certain malignancies. Schumacher et al. (1992) reported that 4.5% of neuroblastoma patients exhibited rib bifurcations, a rate four times higher than that of the normal population (1.07%). This suggests that developmental abnormalities affecting rib segmentation may be related to tumorigenesis in neural crest-derived cancers such as neuroblastoma [7].

Rib synostosis, or rib fusion, has also been observed in childhood malignancies. Though relatively rare, this anomaly was documented in some studies. Schumacher et al. (1992) found that 0.5% of cancer patients had rib synostosis compared to none in the control group, while Merks et al. (2005) identified synostosis in 0.2% of cancer patients. Notably, leukemia and brain tumor patients were more likely to present with this anomaly [7, 8].

Additionally, rib hypoplasia (underdeveloped ribs) and aplasia (missing ribs) have been reported in association with various malignancies. Loder et al. (2007) found that children with malignancies were more likely to have fewer ribs, with 44 cases of 22 ribs and 10 cases of 23 ribs, compared to just 16 cases in the control group ($p = 0.003$) [11]. Schumacher et al. (1992) also reported that 1.2% of cancer patients had rib aplasia or hypoplasia, compared to 0.5% in controls (Table 1) [7].

5. Future Perspectives

Future research should focus on large-scale, multicenter studies to validate these findings and establish whether RAs, particularly numerical variations, bifurcations, synostoses, and hypoplasia, can be predictive markers for specific cancers. Advances in imaging technologies, such as high-resolution computed tomography and magnetic resonance imaging, may enhance the accuracy of rib anomaly detection and contribute to more precise correlations with cancer risk.

Genetic and molecular studies are also needed to explore the role of Hox genes and other developmental pathways in skeletal formation and oncogenesis. Identifying genetic mutations contributing to RAs and tumor development could lead to novel insights into cancer predisposition syndromes. Additionally, investigating the role of environmental and epigenetic factors in the occurrence of RAs and malignancies may provide a more comprehensive understanding of their shared etiology.

From a clinical perspective, integrating rib anomaly screening into routine pediatric check-ups for high-risk populations could help in early cancer detection. However, before implementing such screening, further studies must determine the predictive value of RAs and whether they can be used as independent risk markers.

Ultimately, interdisciplinary collaboration between geneticists, radiologists, oncologists, and developmental biologists will be crucial in advancing understanding of the link between RAs and childhood cancer. As research continues, these efforts may pave

Table 1. Association Between Rib Anomalies and Childhood Malignancies

Study	Year	Sample Size	Key Findings	Cancer Types	Types of Rib Anomalies	Conclusion
Schumacher et al. [7]	1992	1000 cancer, 200 controls	Rib anomalies more common in cancer patients (21.8% vs. 5.5% in controls). Neuroblastoma had the highest rate (33%).	Neuroblastoma, Brain tumors, Leukemia, Soft tissue sarcoma, Wilms' tumor, Ewing sarcoma	CRs, Bifurcations, Synostoses, Aplasia/Hypoplasia	Rib anomalies may be linked to tumor development. Further research needed.
Merks et al. [8]	2005	906 cancer, 881 controls	CRs were more common in cancer patients (8.6% vs. 6.1% in controls), particularly in leukemia and astrocytoma.	ALL, Astrocytoma, Germ Cell Tumors	CRs, Bifid ribs, Rib synostosis	Rib anomalies could indicate genetic mutations linked to cancer.
Loder et al. [11]	2007	218 cancer, 200 controls	Rib anomalies were more frequent in cancer patients (18% vs. 8%). Neural tumors had the highest incidence (35%).	Neural tumors, Lymphoproliferative malignancies, Solid tumors	Fewer than 24 ribs, Rib fusions, Bifurcations	Possible link between rib anomalies and homeobox gene mutations.
Zierhut et al. [12]	2011	625 cancer, 1499 controls	Significant association found between rib anomalies and leukemia, renal tumors, and hepatoblastoma.	AML, Renal tumors, Hepatoblastoma	Fewer or more than 24 ribs, CRs, Bifurcations	Rib anomalies could be a marker for cancer predisposition. More research needed.

ALL: Acute Lymphoblastic Leukemia, AML: Acute Myelogenous Leukemia, CR: Cervical rib

the way for novel diagnostic strategies and targeted therapies for pediatric malignancies.

6. Conclusion

CRs may serve as valuable indicators of underlying genetic and developmental abnormalities linked to pediatric cancers. Understanding these connections could ultimately contribute to improved cancer screening, early diagnosis, and personalized treatment strategies for children at risk.

Declarations

Conflicts of interest: The authors have no conflicts of interest to disclose.

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Use of AI: Perplexity (Deep Research) and ChatGPT (GPT-4.5) were used to assist in language editing and improving the clarity of the manuscript. All content was reviewed and verified by the authors. Authors are fully responsible for the entire content of their manuscript.

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