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PREVALENCE OF RIB ANOMALIES IN PEDIATRIC CANCER PATIENT

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INTRODUCTION

Every year more than 40000-50000 children in the INDIA are diagnosed with pediatric cancer, which is primary cause of disease –related mortality for children itbetween the age group of 1-14 years.[1].Although a few risk factors have been conclusively identified, including exposure to high dose radiation and certain genetic syndrome, the etiology underlying most cases remains unknown. Compared to current estimates ,a higher proportion of pediatric malignancies may be caused by tumor predisposition syndrome. Such constitutional genetic defects cause abnormal clinical phenotypes in utero such as Down syndrome and Beckwith – Wiedemann syndrome .These genetic defects may cause abnormal cellular proliferation in utero that predisposes the individual to develop cancer postnatally.[2]Many such studies have demonstrated relationship between congenital anomalies like such as supernumerary nipples, cafe` -au-lait spots, abnormal palmar flexion creases , and leg length asymmetry with childhood cancer.[3]

Not only phenotypic abnormalities that are grossly visible but other abnormalities which requires a detailed radiological examination may also be related to underlying constitutional defects.Rib anomalies detected in radiological examination is one of

them.Congenital rib abnormalities are found in approximately 2% of the general population.[4]Usually,they occur in isolation and are rarely symptomatic ,but they can also be associated with other malformations.Rib abnormalities occur in a broad range of morphologic variations,and most of the time it is difficult to distinguish between anatomical variation and malformation.[5]For example there is specific skeletal anomalies in Gorlin syndrome which occur due to mutation in patched gene.Postnatally these patients develop basal cell carcinoma and several other childhood cancers,such as rhabdomyosarcoma and medulloblastoma.[6]

Thus, finding and comprehending links between aberrant development in utero or during childhood of acquiring cancer will have consequences for monitoring prognosis,risk assessment and maybe planned for specific treatments. Tumor predisposition syndromes might account for a larger percentage of childhood cancers than is currently estimated. In such syndromes, like Down syndrome and BeckwithWiedemann syndrome, the same constitutional genetic defects lead prenatally to an abnormal clinical phenotype of the individual patient, while postnatally they may lead to abnormal cellular proliferation, predisposing the individual for cancer development [1,2]. Several studies have shown a relationship between childhood cancer and the presence of major [3] and minor anomalies [4] in children. Recently a large population of childhood cancer patients was submitted to a detailed clinical morphological examination, showing childhood cancer patients to have a strikingly high prevalence of phenotypic abnormalities, such as supernumerary nipples, café-au-lait spots, abnormal palmar flexion creases, and leg length asymmetry (Merks et al, submitted).We reasoned that not only phenotypic abnormalities detectable by clinical examination, but also skeletal anomalies can provide clues for underlying constitutional defects, as has been shown in several conditions [5]. Gorlin syndrome can serve as an example, constitutional mutations in the causative Patched-gene leading prenatally to formation of specific phenotypic abnormalities, including skeletal anomalies (calcification of the falx cerebri, jaw cysts, bifid ribs, and vertebral anomalies) [6]. Postnatally, the same Patched mutations result in abnormal cellular proliferation predisposing the affected individual for basal cell carcinoma [7], and several other childhood cancers, such as rhabdomyosarcoma [8] and medulloblastoma [9]. In children with cancer different radiological techniques are used to establish the diagnosis, the extent of the cancer, or to detect possible complications. These radiological studies can also be used to search for findings that are not directly related to the primary diagnosis, and may provide clues for the etiology of the tumor. Most children with cancer undergo a

chest radiograph as part of their oncological work-up, which makes these available for reviewing. Schumacher and co-workers earlier reported a higher prevalence of rib anomalies in childhood cancer patients, compared to a small group of pediatric controls [10]. They were able to review a large number of childhood cancer patient radiographs. However, several critical remarks can be made. First of all, definitions of the different rib anomalies were unclear. Furthermore nothing is mentioned about blinding of the observers, 'lower thoracic border anomalies' were not scored, and the number of controls is low. Therefore, we decided to firstly generate prevalence figures for the presence of rib anomalies on chest radiographs in control children (normal values), and secondly to analyze chest radiographs of an equal large amount of childhood cancer patients, using a well defined terminology, and a strict scoring methodolog

Multip[le studies have demonstrated an association between morphological abnormalies and paediatric cancer. Associtions between congenital anomalies and cancer predisposition syndrome are noted in single gene disorders such as Gorlin syndrome,Fanconi anemia and Wilms tumor 1 mutation related disorders .Even in absence of single gene disorders, several epidemiological studies have provided data showing an association between childhood cancer and rib anomalies.

Normally, an individual has 12 pairs of ribs with a total of 24 ribs .Abnormalities of ribs can be numerical (e.g.,>24 or <24 ribs) or structural-cervical ribs, bifid ribs, synostoses,and segmentation defects.

The ribs are flats,ribbon like ,elastic bony arches that extends from thoracic vertebrae posteriorly to the lateral border of the sternum anteriorly. Their anterior ends are connected to the costal cartilages .The ribs along its costal cartilage constitute the costa.

The ribs are arranged one below the other, and the gap between the adjacent ribs are called intercostals spaces.The length of ribs increases from the first to seventh ribs and then gradually decreases hence seventh ribs is the longest ribs.The transverse diameter of the thorax increases progressively from the first to eighth rib,the ribs are arranged obliquely, that is their anterior ends lie at the lower level than their posterior ends.

Accordingly, the ribs are 2 types –typical ribs (3^{rd} to 9^{th}),atypical ribs(1^{st}, 2^{nd},10^{th} ,11^{th},12^{th} .To relation with sternum, ribs are true ribs (1^{st} to 7^{th}),false ribs(8^{th} to

12th).True ribs articulates with the sternum anteriorly,whereas false ribs do not articulates with the sternum anteriorly.11th and 12th ribs are called floating ribs.

Typical Ribs-

Parts-each ribs has three parts --- anterior end,posterior end,shaft.

Anterior end bears a concave depression. Posterior end consists of head neck and tubercles.

The shaft is longest parts and extends between the anterior and posterior ends. It is flattened and has inner and outer surfaces and upper and lower borders.It is curved with convexity directed outward and bears a costal groove on its inner surface.Five centimetre away from tubercle it abruptly changes its direction, this is called the angle of the rib.

Features and attachments—

Anterior end---

It bears small cup shaped depression that joins the corresponding costal cartilages.

Posterior end------

It presents head ,neck, tubercle.

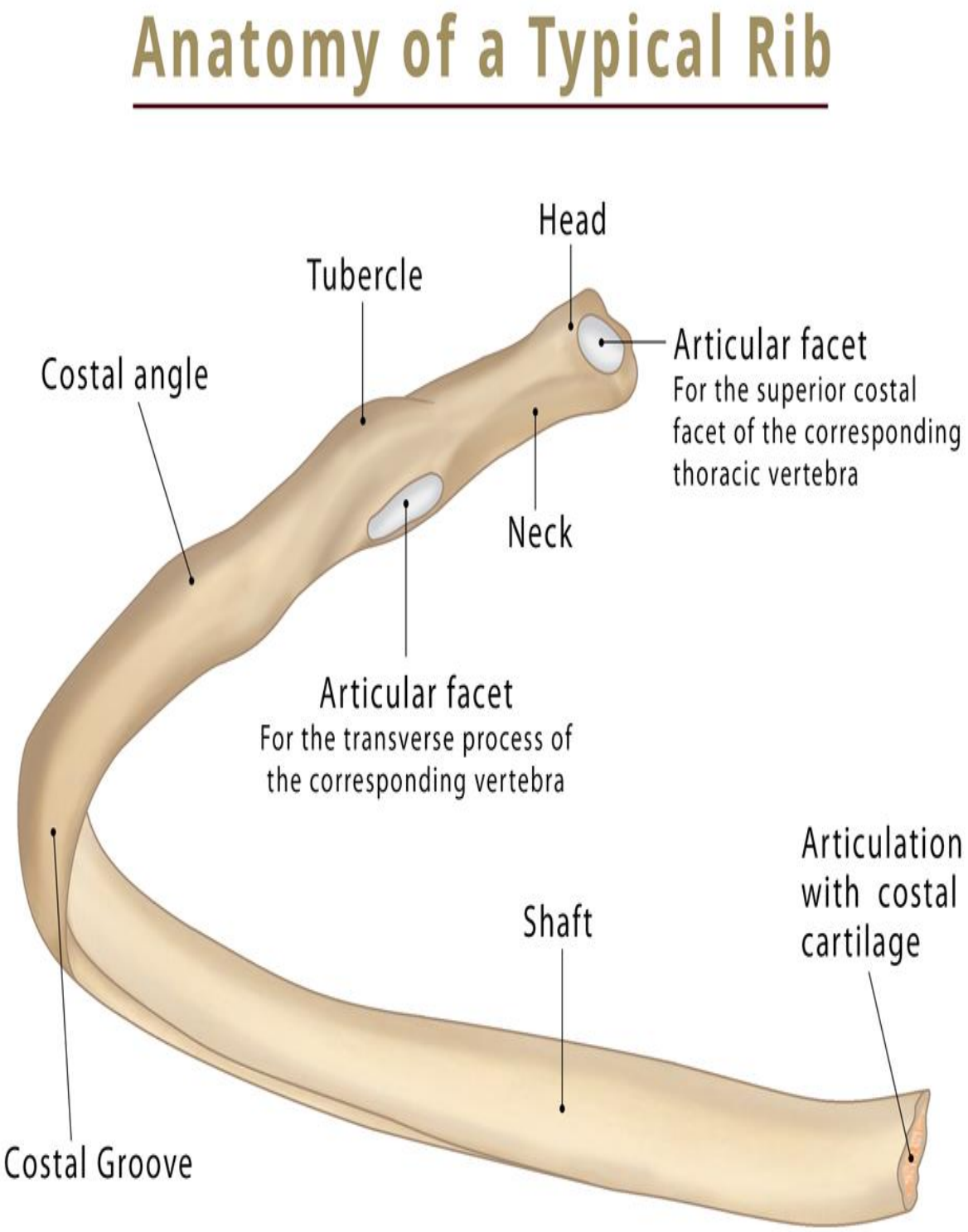
Head ----

It has two facets-lower larger facet and upper smaller facet.

Neck-it has two border –superior and inferior.

Tubercle-two parts- medial articular part an lateral non articular part.

Shaft---two surface,two border, two angles.



Types of rib anomaly may be classified in different categories----

Cervical rib

rib number(<24 or>24)

rib synostosis

bifid ribs

segmentation

aplasia

Cervical Rib-

Cervical rib results from a failure of regression of the costal process of the seventh cervical rib. Cervical rib is an important cause of non traumatic thoracic outlet neurovascular compression.

The following diagnostic criteria for cervical rib

(a) The rib must about the seventh cervical vertebral transverse process which is seen to project horizontally or caudally from the spine ,rather than tranverse process of first thoracic vertebrae

(b) It must have no connection with manubrium sterni.although it may form a synostosis with first rib .

Rib Number -

Normally there is 12 pairs of ribs. The number of ribs in individual are 24.

In some cases it may vary from less than 24 or more than 24.

Bifid Rib-

Sternum bifidum commonly known as bifid rib is an anatomic malformation of the anterior chest wall present since birth. Bifurcated ribs always have a forked sternal end which is often unilateral.this is a rare skeletal abnormality being found in 1.2% of individual.in contrast to other rib malformations, bifid ribs generally occur in absence of vertebral anomalies. Third and fourth ribs are the ones usually involved. Generally the diagnosis is made incidentally on x ray.in most cases it is asymptomatic but previous studies have revealed in presence of genetic syndrome i.e. gorlin syndrome also known as nevoid basal cell carcinoma syndrome which is caused due to mutation of PTCH1. No clinical importance of bifid rib has been established yet

Lumber rib(gorilla rib)-

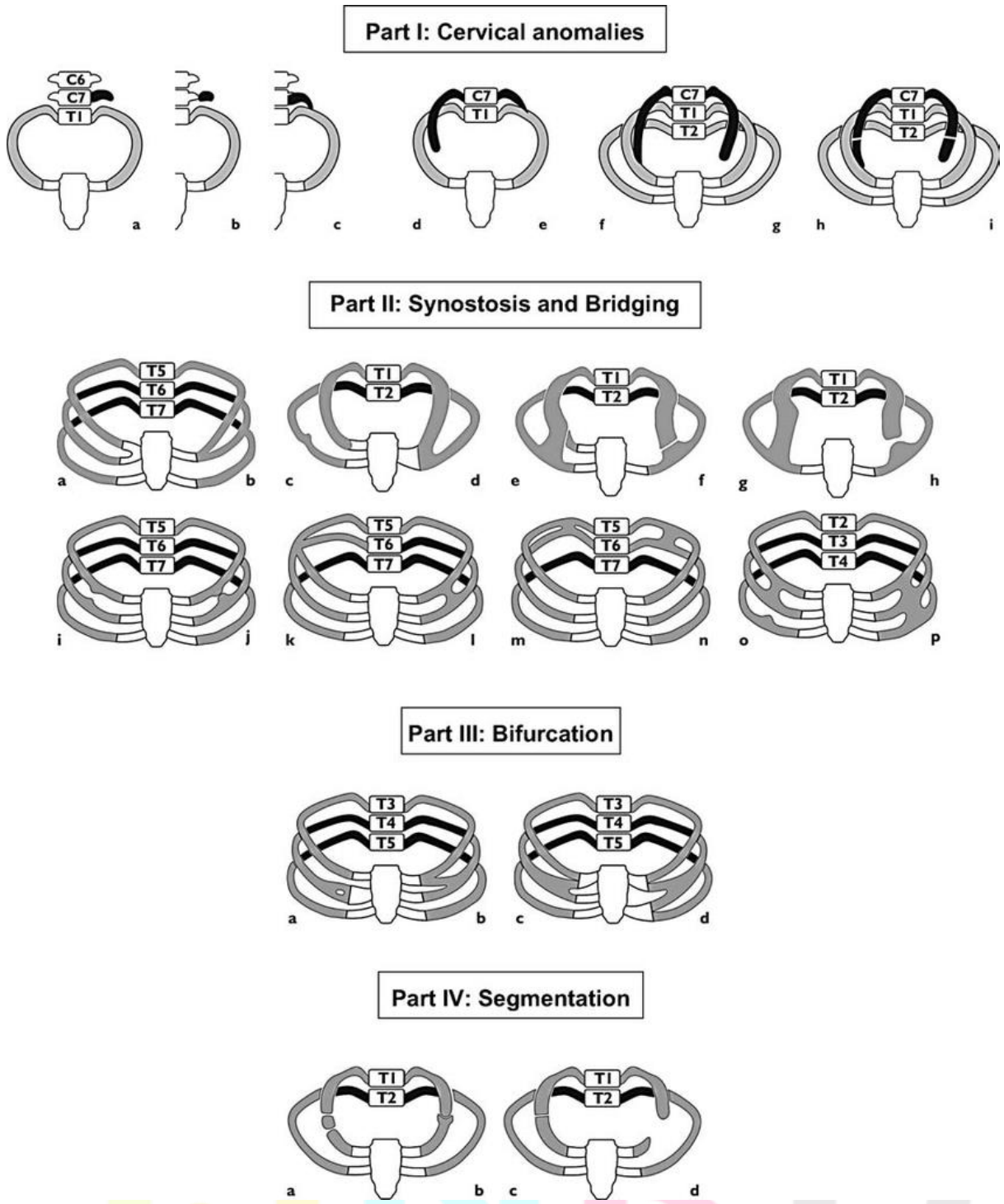
It develops from the costal elements of the L1 vertebrae.Its incidence is more common than cervical rib,but remain undiagnosed as it usually does not cause symptoms.It may be confused with fracture of transverse process of the L1 vertebrae.

Rib synostosis-

A 5 yr old child came to pedriatic emergency with chest pain and shortness of breath. This case tells about rib synostosis.rib synostosis means fusion of rib with one another.typically rib synostosis may be congenitally fused or can become fused as a result of remote traumatic injury..when congenitally fused they can associated with scoliosis as well as thoracic insufficiency syndrome.

Aplasia -

Congenital absence of the ribs is a relatively rare condition especially for the absence of upper ribs,it can be present as an isolated anomaly or part of many congenital anomalies like in poland syndrome. Defects of the ribs do not occur alone under development.



The term "childhood cancer" encompasses many malipant diseases that occur children and young adults. Unlike the predorninantly epithelial cancers in proportion of which cm be attributed to long-term exposure to environmental risks such as smoking. many childhood neoplasms are ernbryonic and. in some instances. related to the developmental process. (1)

Specific characteristics of neoplasms in children suggest that a significant proportion of childhood cancers are attributed to genetic mutation or genetic predisposition. (2)

Thisrneans that both pre-conceptional and prenatal parental exposures or characteristics may play a causative role. It is now almost clear that the natural history of many cancers in children, similar to congenitai abnomalities, involve interaction between genetic and non-genetic factors. (3)

In addition, the significantly higher than expected occurrence of cancer in children with other genetic and congenital abnormalities sugpsts that children bom with genetic damage are more prone to cancer development than those bom without any genetic mutation. The study of genetic predisposition to cancer in children is still in its early stages. In this regard, congenital abnormalities could provide essential information in mapping the predisposing lesions in cancers. The study of cancer occurrence in children with congenital abnormalities could shed more light on the natural history of malignancies in children and the predisposing factors that may increase the risk of cancer early in life.

Birth defects have been defined as "any abnormality of structure or function, whether inhented or acquired dunng prenatal or perinatal period, and whether it prcsents itself in utero, at birth, or later in life". (4)

This broad definition includes many defects that may not be detected at birth. However, even when limited to abnomalities that are present at or shortiy after birth, binh defects encompass a staggering number of conditions and a multitude of etiological mechanisms. (5)

A congenital malformation develops through the disturbance of a morphogenetic process. It may be located in any organ and it inay Vary considerably in severity and clinical importance. A disturbance of the same developmental process may result in malfornations covenng a wide spectmm from death to conditions that play no functional role for the individual who carries it. (6)

Birth defects epiderniology is a very broad but sparsely explored field. Epidemiological studies of birth defects are harnpered by problems such as lack of a clear definition. And diagnostic variability and inadequacy that produces very incomplete identification of birth defects. Due to variations in definition, follow-up time, diagnostic tools, and the extent to which minor anomalies are included, reported rates of anomalies Vary considerably within and between countnes. The reported rates of malformations in different countnes Vary from 1% to about 10% of births. (7)

Birth defects have now surpassed both prematurity and sudden infant death syndrome as the leading cause of infant mortality and represent a significant source of childhood disability in many countries.(i) Information on the survival rate of children with birth defects is rare. The Iimited data on the survival rates among

specific sub-groups of children with congenital anomalies indicate that survival of children with birth defects is significantly lower than those in children without birth defects. (8)

Childhood cancer is not one disease entity, but nther it is a spectrum of different mdignancies. The biolo$cal nature of tumors in childhood is clinically, histopathologically, and biologically distinct frorn adult-onset mdignancies. Childhood cancers tend to have short latency periods, and are often rapidly growing and aggressivel y invasive. Mile epithelial cancers, such as rhose of hg, breast and prostate, are the most frequent types of cancers in adults. they account for Iess than 10 percent of cancers in children.(l) A recent report indicated that dunng 1989- 1993 in Canada, nearly 9,600 children aged 19 years or less had been diagnosed with cancer and about 2,400 of them died from it dunng the sarne period.(l) Despite al1 efforts at cancer control, there has been a gradua1 increase in the incidence rate of al1 childhood cancers since 1969. The increase in childhood cancers has been seen both in Canada and in other developed and developing counûies. Despite the increase in cancer incidence, childhood cancermortality rates have been steadily declining. One of the early successes of epiderniology in medical genetics was the recognition of the importance of the association between certain childhood cancers and particular patterns of congenital abnormalities. Most of the reported associations were fint recognized through clinical studies that reported a very high incidence of malignancy in patients with a particular congenital abnormality; or, a specific congenital abnormality was found with unusual frequency among patients with a particular malignancy.

Similarities between the epidemiological characteristics of congenital abnormalities and childhood cancer and the higher than expected number of specific birth defects in children with some specific type of mali_miancies. imply the possibility of cornrnon causes for both conditions. It is believed that several genetic conditions predispose children to both congenital anomalies and cancer. (9)

Due to the rarity of both exposure and outcorne, most of the congenital abnormality-cancer associations have been reported based on case series andor small number of cases in clinical settings. Questions regarding the natural history of cancer in children with congenital abnormalities, the levels of cancer risk at different ages, and the pattern of survival in children with both cancer and conpnital abnormalities are still unanswered.

In addition, exploring new associations ador confirming the reported associations between congenital anomalies and childhood cancers through large epidemiological studies in a population-based setting cm be used by other disciplines to investigate the possible cornrnon factors (including genetic ones) in the etiology of these conditions.

The availability of large databases for both congenital abnormalities and childhood cancer in Ontario gave us a unique opportunity to explore the association between these two groups of diseases. This study compared the risk of developing cancer in a cohon of children with congnital abnormalities with the risk in a cohort of normal children,

Etiology of Childhood Cancer-

The above-mentioned problems in definition and classification of birth defects have dso shown their effects in the etiologicd investigations of conpnital anomalies. For exarnple, in most etiological studies, interest focuses on teratogenic events. Also, the malformations should be divided into groups in order to make detection of a change in the rate of one specific category possible. For this, the ideal would be to divide the malformations into pathogenicnlly more homogenous groups. However, such goupscannot be predicted.

Incomplete or non-comparable case ascertainment cm also cause epidemiological studies to produce divergent results.(21)

Thus, it would be possible to mistakenly attribue or rule out, the effect of some risk factors based on a group of cases that havehad better medical attention or those who survive the newborn penod with milder forms of the defect.

Another problem in the etiological investigations of birth defects is the coexistence of more than one malformation in some cases.(71) Tentogens frequently cause multiple malformations. This raises questions such as whether the coexisting defects are causedby some pre-existing genetic or environmental agents, or one of the defects causes another. In general, the issue of whether it is more appropriate to subdivide or to group classes of malformations for epidemiological studies, is still an intuitive issue. (21)

In spite of these problems many epidemiologicd studies have been conducted in order to identify the risk factors for malformations. Unfortunately these efforts have resulted in a small number of definite risk facton.(l)

Malformations can be the result of abnorrnalities in the genetic makeup of the fetus, environmental exposure to tentogens, or caused by a combination of genetic and environmental infiuences.(ll)

Roughly malformations are divided into: those of simple genetic origin (caused by a single major mutant gene); those held to he due to interactions between hereditary tendencies and non-genetic, undefined, factors; those attributed to environmental factors as the major.

Environmental Factors-

Teratogens: These factors can either indirectly affect the unbom child by causing disease in the mother, or alternatively, produce chromosomal damage or mutation in the developing fetus that in tum leads to abnomaIities.(23) The effect and type of anomalies caused by some teratogens depend on the timing ilunng pwgnmsy when exposure occurs. For example, prenatal rubella infection (as a teratogen) during 3 months produces cardiac defects, infection after the fourth month produce deafness, and infection at any time causes growth impairment. (21,33) Tentogenic agents or conditions have been grouped into different categories such as prescription drugs, environmental chemicais, viral infections, matemal exposure to smoking. alcohol consumption and radiation, and materna1 diseases. (21)

More than any other teratogen, the thalidomide tragedy alened the world to the teratogenic potential of prescription drugs. A chemicai with sedative properties thalidomide was marketed in 1956. It was available for four years before its tentognecity was recognized and distribution was halted.(71) While thalidomide caused a wide variety of malformations in limbs, em, and the cardiovascular systern. The mechanism by which this teratogen produced the malformations is entirely unknown. (6) The Iist of the definite or probable tentogenic agents is growing. Prescription drugs (such as diethylstilbestrol, progestin, terimethadione, tetracycline, warfarin, iodides, and thalidomide), matemal exposures (such as smoking, alcohol, and cocaine), chernicd and physical agents (such as mercury, ionizing radiation, and magnetic fields), vitamin supplementation, matemal diseases (such as diabetes mellitus, phenylketonuria, and some tumors) and several viruses (such as rubella, cytomegalovirus, herpes simplex, chickenpox, and influenza) are among the reported teratogens and environmental risk facton for congenital malformations. (21) Although this list is still growing, it accounts for only a small proportion of the birth defects. (21,23) Parental Risk Factors: Some other materna1 and patemal facton have been show to increase the risk of malformation in children. For example, the effect of parental age provides important clues to the causes of birth defects. The most prominent risk factor for Down's Syndrome (TISI is maternai age. (24) The materna1 age effect. An increase in the risk with increasing matemal ag, has been cited as direct evidence for the nonpnetic etiology of birth defects. (31) However. there is not yet a clear etiological explanation for this pattern. Other facton such as the mother's previous live births and stillbirths, and inhnt deaths have also been cited as possible risk facton for congenital anomalies.

Genetic Factors-

It has been estimated that the proposed definite and probable environmentai tentogens account for a small proportion of congenital anomalies (less than one third) and the causative factors for the majority of birth defects remain unknown.(22) Some malformations are thought to be polygenic, that is, the result

of several abnormal genes that are present simultaneously. Other appear to be multifactorial, resulting from abnomal genes interacting with harmful environmental facton. (21,25)

The genesis of many birth defects has been postulated to be related to the action of multiple genetic and environmental factors. As Our undentanding of the mechanisms that give rise to û particular malformation, gradually unfolds, the importance of a multidisciplinary approach to understanding both the genetic and environmental contribution to these conditions become increasingly apparent.

Chromosome abnormalities, single gene defects, and pre mutations are some of the proposed mechanisms involved in genetic causation and familial transmission of congenital malformations. Many mutant genes cause congenital malformations, and although they are individudly rare, together form a considenble sum. It has been specific abnormalities. The role of the above teratogens and risk factors are being investigated for some specific birth defects. including some major anomalies such as DST cleft lip, and neural tube defects.

Down's Syndrome-

Arnong the above listed groups of malformations, DS is different in one major respect from the others. It arises in most cases from a preconceptiond error (the presence of an extra autosome 21 in one garnete), whereas the laying down of the other defects can not be traced back before embryogenesis.

DS is a combination of birth defects including some degree of mental retardation and characteristic facial feanires. About 30 to 50 percent of babies with DS also have congenitai heart defects, and many have some visuai and hearing impairment and other health problems. The severity of dl of these problems varies greatly. DS is one of the most common genetic birth defects. Approximately one in 800 to one in 1,000 babies is born with the disorder, (4)

DS is the most common chromosomal anomaly occumng in the general population. Recent reports suggest that the frequency of DS is increasing with time (30). Older matemal age is one of the strongest reported risk factors for DS with an exponential relationship between the birth prevalence of DS and maternai age. Cuckle et.al. (24) based on the meta-analysis of 8 studies (more than 4500 cases) reported an increasing trend in birth prevalence of DS with increasing matemal age, from a low of 0.6 per Low births for ages 15-20 years to 20 per Low births in ages 45 years and older.

Two explanations have been offered for the association between DS and matemal age. One mode1 is based on the theory that each oocyte is at risk of experiencing deleterious random events of some kind throughout a period lasting from early in the mother's life until the oocyte becomes an ovum. Nondisjunction of the two

autosomes 21 is the outcome for oocytes that have experienced a large number of random events as the mother ages. (32) Another suggestion is that delayed fertilization predisposes to chromosomal damage. Family history of the disorder and male sex are also among the most consistently reported nsk factors for DS. (14)

Neural Tube Defects-

The neural tube is the embryonic structure that develops into the central nervous system and spine. Neural tube defects (NIDS) are serious binh defects, which involve incomplete development of the brain, spinal cord ancilor the protective coverinp of these organs. There are three types of NTDs: spina bifida, anencephaly, and encephdocele. Spina bifida is the most cornrnon. Spina bifida: A birth defect of the spinal column that is sometimes called "cleftor open spine". Spina bifida can range from a mild defect that causes no problem to a serious condition involving muscle paralysis, loss of sensation, infection and loss of bowel and bladder control. Seventy to 90% of children born with the more severe types of spina bifida will also have hydrocephalus, a build up of cerebrospinal fluid in the brain. (4) There are three types of spina bifida: 1) spina bifida occulta; in which an opening in one or more of the vertebra of the spinal column occurs which does not involve my damage to the spinal cord (approximately 40% of al1 Amencans have this mild birth defect without even knowing it); 2) meninpcele, a more serious fom of spina bifida in which the meninges (the protective covenng around the spinal cord). push out through an opening in the spinal colurnn; and, 3) myelomeningocele. the most severe form of spina bifida in which the spinal cord containing the deeper nerves of the spinal column protrudes from the open spine without the protective covenng of the skin. Spinal fluid may leak out and may cause serious infection. This defect usuaily occun at the lower end of the spine resulting in paralysis of the babyTs legs and poor bladder and bowel control. (433)

In North America, NTDs occur in one or two of every 1.000 births. The risk increases to 2% if parents have already had one child born with an NTD. A farnily history of NTDs also increases the possibility of having a child with one of these defects. If either parent has an NTD, their risk of having a child with spina bifida. anencephaly or encephalocele increases to between 3-5percent. (33) Neural tube defects arc in a category of binh defects cailed poZygenic or multifacorial. This means that one or more genes interacting with an environmental factor cause NTDs. Environmentd triggers for NTDs that are being studied include viruses, vitamin and minerd deficiencies, chemicals, and matemal illness such as diabetes. (33) The reported associations between NTDs and socioeconornic status and higher birth order (especially seen in more prevdent areas) have resulted in searching for nutritional deficiencies as one of the causes of NTDs. Vitamin deficiencies in generd and folate deficiency in particular have been tested. Severd studies have shown a

reduced birth prevalence of NTDs was associated with the higher intake of vitamin supplements, especidly folic acid. (33)

Oral Clefts-

Oral clefts are birth defects of the structures that form the mouth. An oral cleft is a split or separation in the baby's lip andfor palate. Cleft lip means that the two sides of the upper lip did not gow together properly. Cleft palate is a split or opening in the roof of the mouth. Although cleft lip and cleft palate may occur in the same baby, both conditions cm happen separately. The baby's mouth forms during the fint three months of prenatal life when parts of the roof of the mouth and upper lip nomally join together.

A cleft lip and/or palate results when this joining does not occur. (4) Oral clefts are among the most common birth defects, affecting one of every 700 newboms. More than 250,000 people in the USA have a cleft condition with 25% of them having a cleft palate. 35% having cleft lip, and 50% having both cleft Iip and palote. (33)

Families that have a history of oral clefts in a parent, another child. or close relative, are more likely to have a baby with a cleh Iip andlor palate, but oral clefts can also occur in families without such a background. For cleft lip, the proponion affected among monozygotic twins and first-, second-, and third -degree relatives of the affected subject are reported to be 4O%, 4%, 0.7%, and 0.25% respectively.

Leukemia-

The leukemias of childhood are cancers of the hematopoietic system. They account for the largest nurnber of cases of childhood cancers and are the primary cause of cancer related mortality. Approximately 350 children younger than 20 years of age are diagnosed with leukemia each year in Canada, of which more than 265 are acute lymphoblastic leukemia (AU). Leukemias represent 32% of all 1 cm per cases occur among children younger than 15 years of age and 27% of cancer cases occurring mon; those younger than 20 years of age. However, the relative contribution of leukemia to the total childhood cancer burden varied markedly with age. being 17% in the first year of life, increasing to 46% in 2-3 year olds, and then decreasing to only 9% for 19 year olds.

ALL is the most common type of leukemia accounting for more than 75% percent ofchildhood leukemia cases in children. Acute myeloblastic leukemia (AML) and chronic myeloid leukemia (CML) are among the other diagnostic categories that account for only 20% of total Ieukemia cases in children. (1,31)

There is a sharp peak in AIL incidence among 2-3 years old (>80 per 1,000,000) which decreases to a rate of 20 per million for 8-10 years old. The incidence of AU

in 2-3 year olds is approximately four-fold greater than that for infants and is nearly 10-fold greater than that for 19 year olds. (JI)

Leukemia rates are substantially higher for white children youngr than 15 years of age than for black children. The difference between white and black children is most apparent when examining rates by single year of age, with a nearly three-fold higher incidence at 2-3 yean of age for white children compared to black children. This difference is primarily the result of lower ALL rates among black children. (JI)

The incidence of leukernia among children younger than 15 years of age has increased in the past 20 years. The estimated annuai percentage change for total leukemia during the last 20 yean is 0.9% per year. This increase is primady due to an increase in ALL incidence during this period. (1)

Central Nervous System Tumors-

Central nervous system (CNS) cancer as a group is the second most frequent malignancy of childhood and the most common of the solid tumor. The CNS malignancies represent more than 16% of dl malignancies during childhood. Asuocytoma is the most frequent type of CNS tumor accounting for 52% of CNS malignancies. Intracranid neuroblastoma, medulloblastoma, other gliomas, and ependymomas are other types of CNS tumors. Unlike adults and older children, young children have a relatively high occurrence of malignancies in the cerebellum and the brain stem. In fact, in children younger than 10 years of age, brain stem malignancies are nearly as cornrnon as cerebrd malignancies. The average annual incidence of CNS tumon varied only slightly by age of diagnosis from infancy (36.1 per million) through age seven years (35.2 per million). From age seven to 10, O% drop in incidence rate is obsewed and remains fairly consistent through the next seven years until another substantial decrease at age 18. The incidence of CNS tumors is approximately 14% higher in males than Females and about 18% higher in white children than black children.(1.4 1)

Lymphomas-

The lymphomas, combining Hodgkin's diseose and the non-Hodgkin's lymphomas (NHL), are the third most frequent type of cancer in children accounting for approximately 15% of childhood maligrmcies. The percentage of childhood cancer that is lymphoma varied by age from about 3% for children younger than five years of age to24% for 15- 19 year olds. The incidence of NHL varies much less by age than Hodgkin's disease. NHL incidence increases up until age four where it reaches a plateau and remains almost constant drug the next 10 year. The incidence of NHL is higher in males than females and higher among whites than blacks.

There are few clues to underlying reasons for the distinct pattern of childhood cancer with respect to race, sex and age groups observed in epiderniological studies. For example, it is not clear whether the racial differences indicate racial variability in genetic susceptibility or differential exposure to unidentified environmental agents.

Mortality and Survival-

The cancer survival rate for children has gradually improved over time. Since mid-1970s there has been a large improvement in short term and long term survival. The improvements have been seen in survivd for many types of childhood cancers. The principal reason for the gain for total childhood cancer sumival is due to improvement in the sumival of leukemia.(42)

The five-year survival rate for al1 cancers combined is 71%.(1) Age at diagnosis is a significant predictor of survival among children with cancer, especially leukemia. Infants have a substantially poorer prognosis than older children. Sumival for children with ALL has markedly improved since the early 1970s and overall survival for al1 children with ALL is now approximately 80%. Survival for children with AU is very dependent upon age at diagnosis, with the most favorable outcome observed for children older than one year of age and younger than 10 years of age at the time of diagnosis. In children with ALL, five-year survival rates are highest for the one to four year age group and the five to nine year age group (85% and 80%, respectively). Infants have the poorest outcome (37% 5-year survival rate), followed by the 15-19 year age group (51% 5-year. survival rate). The occurrence of a high proportion of favorable subtypes of AU, in the one to nine year ag goup is said to be one of the main reasonsfor their higher survival rates.(41,*43)*

Survival rate for children with other leukemia types (AML or CML) is substantially lower than that for children with ALL. While outcome for children with AML has improved significantly during the 1st two decades their five-year survival rates are only 41% for the younger than 20 year age group.(41) Among children diagnosed with lymphoma survival rates are also high. The five-year survival rate for cancer cases in this group has increased considenbly during the last two decades. It is now 91% for Hodgkin's disease and 72% for non-Hodgkin's lymphomas.(1.4 1)

Although survival differs by histology, size and location of the malignancy, in general children with CNS cancer do not share the favorable prognosis of those with many other common pediatnc neoplasms, such as leukemias. Additionally, for chi ldren who do survive CNS cancer, long-term morbidity can be substantial. Survival probabilities have improved somewhat over the last two decades. Nevertheless, survival probability for the majority of CNS cancer cases remains less than 60%.

For al1 CNS cancer combined. survival probabi li ty increases with increasing age. Very young children. Especially infants, are at particularly high risk of mortality.($l)

Among cancer cases in other groups. those with liver cancer and sympathetic nervous system tumors had the wont survival. shows the survival rates for children diagnosed with cancer in Canada. 2.3.2 Other Neoplasms and Congenital Anomalies.

Among other cancers with a probable link to birth defects is Wilm's tumour (WT). About 6% of al1 childhood tumours in Canada (73) are WT , making it the second most common neoplasm in the first year of life and the fourth most common cancer in children. The association between WT and congenital anomalies has been reported in somestudies. (46,74) Abnormalities of the genitourinary tract, microcephaly and mental retardation, anindia, and some chromosomal abnomalities have been reported as possible malformations with association to WT. (46,74)

Retinoblastoma and neuroblastoma are among other childhood cancers with possible inhented links. Neuroblastoma is the most frequent cancer in children of less than one year in Canada (more than 22% of cases are in this age group).(73) Because of its early occurrence and dso because of its occurrence in more than one generation, ffiudson et al. has suggested that a significant fraction of these cancers are inhented. (75)

Retinoblastoma is the classic inherited tumour. In more than 40% of the cases, it is hereditary. The hereditary form of this cancer is attributed in part to a chromosomal abnonnality, i.e., the long arm of chromosome 13 being deleted in patients with retinoblastoma and associated congenital malformations. (49)

A hospitd-based study in Montreal (76) reported a two-fold higher rate of congenital anomalies in children with neuroblastoma as compared to population rates. No association between a specific congenital anomaly and neuroblastoma was found in this study. Recently, in a multi-national study in Europe (77) that includes more than 6700 infants with neuroblastoma, no case of DS was found; based on population rates five cases were expected. In addition to the above-mentioned associations, Narod (3) also reported an excess of spinal and rib malformations among children with cancer. Overall, 2 1.8% of children with cancer where found to have minor rib anomalies compared with a 5.5% rate in the gneral population. The highest rates of rib anomalies where found among children withWT, neuroblastoma,, AU. and Ewing's sarcoma.

Review of literature-

In a study done by Merk JH et al in 2005 cervical rib anomalies were present in 6.1% of controls ,aplasia of 12th ribs in 6.6%lumbar ribs in 0.9%,bifurcations in 0.7%synostosis –bridging in 0.3% and segmentation were not found. The overall prevalence of total rib anomalies in cases and controls was equal(14.9% and 14.2% respectively). Cervical rib anomalies were found significantly more often in cases (8.6%)compared to control (p-value=0.047),three groups accounting for this higher prevalence: 12.1% of acute lymphoblastic leukemia patients (p=0.011),18.2% of astrocytoma patients(p=0.023),and 14.7% of germ cell tumor patients (p=0.046)had a cervical rib anomaly.[7]

A retrospective review was done in 2007 of 218 children with malignancy and a control group of 200 children with polytrauma or suspected child abuse .Chest radiographs were reviewed to determine the number of ribs, and the presence of rib anomalies.It was found that Neural malignancies had a higher incidence of rib abnormalities compared with lymphoproliferative or solid malignancies(p=0.01).Relative to the control group ,those with a neural and lymphoproliferative malignancy were 6.23(95%cl,2.7-14.5)and 2.0(95%cl,1-4.1)times more likely to have an abnormal rib count.[8]

In a study conducted by Zierhut H et al; at University of Minnesota Medical Center on 2011 significant difference in the number of cases vs controls with RIB abnormalities were found after controlling for age and sex, specifically for acute myelogenous leukemia, renal tumors and hepatoblastoma[9]

Multiple studies have demonstrated an association between morphological abnormalities and paediatric cancer (Evans et al,Narod et al,Merks et al in 2013).Association between congenital anomalies and cancer predisposition syndrome are noted in single gene disorders such as gorlin syndrome, fanconi anemia,wilms tumor.Even in absence of single gene disorders,several

epidemiological studies have provided data showing an association between childhood cancer and rib anomalies.(Loder et al 2007).Normally an individual has 12 pairs of ribs total 24 ribs.Abnormalities of the ribs can be numerical or structural.All three previous studies examining RAs have reported an association with childhood cancer,however the studies differed in the specific type of RAs implicated**.**

Zapiz et al in 2003 found the relationship that exists between tumors and malformations both generally and in particular combination.This is also valid for minor error of morphogenesis suggesting that embryonic tumors are an expression of aberrant intra uterine morphogenesis.we speculated that these minor aberrations might also manifest in other morphological defects.chest radiograph of 1000 children with malignancies for rib anomalies and compared them to 200 patients with mainly infectious disease.242 rib anomalies in 218 children with tumors (21.8%) and 11(5.5%) in children with malignancies.This difference was statistically highly significant($p<0.001$).A high incidence of cervical ribs was found in neuroblastoma (33%),brain tumor(27.4%),leukemia,soft tissue sarcoma(24.5%).

We have generated normal values for rib anomalies in a large group of Caucasian control children (Table 2). The overall prevalence of rib anomalies in the cohort of 881 pediTable 3 Prevalence of cervical anomalies in 12 larger tumor groups (n>20) compared to their prevalence in 881 controls Tumor Number of patients Frequency (%) p-value (v2) Neuroblastoma 61 6 9.8 0.252 Germ cell tumor 34 5 14.7 0.046 Rhabdomyosarcoma 68 5 7.4 0.687 Nephroblastoma 133 13 9.8 0.115 Osteosarcoma 48 3 6.3 0.973 Ewing sarcoma 39 3 7.7 0.692 Medulloblastoma 21 2 9.5 0.524 Astrocytoma 22 4 18.2 0.023 Hodgkin Disease 92 5 5.4 0.791 Acute myeloid leukemia 26 0 0.0 0.193 Acute lymphoblastic leukemia 132 16 12.1 0.011 Non-Hodgkin lymphoma 106 8 7.5 0.570 Other malignancies 124 8 6.5 0.889 Total 906 78 8.6 0.047 122

J.H.M. Merks et al. / European Journal of Medical Genetics 48 (2005) 113–129 atric controls was 14.2% (125/881), which is higher than reported in the major reference adult control population (5.72%) from 1956 by Pionnier and Depraz [15] (Table 4). Patients with asthma or an atopic constitution form a considerable part of the present controls (44/165, Table 1), and one may wonder about a possible relation between the conditions and the presence of rib anomalies. However, despite the frequent use of chest radiography in asthma patients such relation between asthma and rib anomalies has never been reported. Furthermore, in the present cohort, no differences in the prevalence of rib anomalies were found between asthma patients and other controls (data not shown). As radiographs in the Swiss study [15] did not permit an adequate judgment of aplasia of the 12th thoracic ribs or presence of lumbar ribs (together 51.2% of the total number of anomalies in the present study), this most likely explains the difference in overall prevalence figures: if we exclude

anomalies of the lower thoracic ribs in the present study, the prevalence of anomalies in controls is similar to the Swiss study (i.e. 7.2%) [15]. There are several other control studies [18–20] (Table 4), often lacking clear definitions of the anomalies, or without a clear description of their review methods and population characteristics. This precludes a more detailed comparison. The ideal control group for the evaluation of rib anomalies in children would be a large set of radiographs made in school children without any medical problem. However, such a study would be unethical, as it would mean to make radiographs only for research purposes in otherwise healthy children. The next best study design is in our view a study performed in children referred by general practitioners and general pediatricians for chest radiographs on a common indication, in order to minimize the contribution of special patient groups visiting a tertiary center like our Center. In order to further minimize the contribution of patients with special disorders all patient with more than one radiograph were also excluded. As several studies have shown a high prevalence of cervical rib anomalies in specific patient groups [21,22], prevalence figures of our carefully selected 'hospital controls' might still overestimate the prevalence of cervical anomalies in healthy children. However, they are the best available controls, and the association between cervical ribs and childhood cancer might only prove stronger when radiographs of school children would have been used. To prevent a large disturbance by ethnic background, we excluded all patients with clearly non-Caucasian names. It should be realized that people from former Dutch colonies can have Dutch names too, and people from mixed descent will not be recognized this way too. However, as registration of ethnicity is not allowed in the Netherlands, as in many other Western-European countries, the presently used method was the best available. It may be rightfully reasoned that digital radiography would have allowed a superior evaluation of rib anomalies. However, digital radiography was only introduced as the standard method for children at our center very recently, preventing such a study in our center, as it will in many other centers around the world. The normal values presented here only apply for conventional radiography. We encourage future, similar studies using digital radiography. We also demonstrate a significantly higher prevalence of cervical rib anomalies in a large cohort of childhood cancer patients compared to controls. The difference was found only in patients with acute lymphoblastic leukemia, astrocytoma, and germ cell tumor, suggesting that cervical rib anomalies are tumor specific. These results support our hypothesis, that constitutional genetic defects, environmental factors, or combinations of these, are more frequently involved in pediatric oncogenesis than currently estimated.

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Table 4 Literature overview of prevalences of rib anomalies in controls and pediatric cancer patients (CA: Cervical Anomaly, TA: Transverse Apophysomegaly, CR: Cervical Rib, LR: Lumbar Rib, AT: Aplasia of Twelfth rib, BI: Bifurcation, B-S: Bridging-Synostosis, S: Segmentation, F: review focused on rib anomalies, D:

definitions clear, B: blinding of observers, C: central review, O: number of observers, AC: Adult Controls, PC: Pediatric Controls, PCP: Pediatric Cancer Patients, *)radiographs in this study did not allow adequate judgment of the lower thoracic border) Study Population Cases with anomalies (%) CA (%) TA (%) CR (%) LR (%) AT (%) BI (%) B-S (%) S (%) Quality assessment F D B CO Steiner [18] 38,105 AC 0.16 0.05 - 0.05 0.04 - 0.01 0.01 - - +

/- ? - ? Etter [19] 40,000 AC 1.36 0.17 - 0.17 - - 0.64 0.27 - - +/- ? - ? Sycamore [20] 2,000 AC 2.8 0.5 - 0.5 - - 1.0 0.2 - + +/- ? –Pionnier [15] 10,000 AC 5.72 2.34 1.89 0.84

We detected a moderate but fairly consistent association of RAs and childhood cancer, which remained despite several sensitivity analyses that we performed to compensate for limitations. The findings further appeared to be strongest in AML, renal tumours, and hepatoblastoma. Our results offer partial confirmation of three previous studies on the topic.

Loder et al (2007) and Schumacher et al (1992) reported an association of RAs with abnormal rib number whereas Merks et al (2005) failed to confirm this association. Merks et al and Schumacher et al (1992) found an association of cervical ribs and overall childhood cancer, but the studies showed discrepant results between which childhood cancers were associated with cervical ribs. It should be noted that transverse apophysomegalies were not included in our definition of cervical ribs, which may account for the lack of a positive association found in our study. Our results are similar to Loder et al (2007) with a small percentage of identifiable cervical ribs and Table 4 Description of rib anomalies in paediatric cancer cases and controls Total cases (N ¼ 455) Total controls (N ¼ 1133) Crude ORa (95% CI), P-value Adjusted ORb (95% CI), P-value Adjusted ORb without BMT (95% CI), P-value Any rib anomalies 31 (6.8%) 51 (4.5%) 1.55 (0.98, 2.46), P ¼ 0.06 1.60 (1.00, 2.65), P ¼ 0.05 1.81 (1.05, 3.10), P ¼ 0.03 Rib number (o24 or 424) 29 (6.4%) 47 (4.1%) 1.57 (0.98, 2.53), P ¼ 0.06 1.66 (1.00,2.74), P ¼ 0.05 1.78 (1.01, 3.12), P ¼ 0.05 Cervical ribs 6 9 1.67 (0.60, 4.72), P ¼ 0.13 1.63 (0.55, 4.80), P ¼ 0.38 2.61 (0.89, 7.68), P ¼ 0.08 Abbreviations: OR ¼ odds ratio; 95% CI ¼ 95% confidence interval; BMT ¼ bone marrow transplantation. Any rib anomaly including abnormal rib number, cervical ribs, bifid ribs, and rib synostoses. The total rib anomalies are not the sum of abnormal rib number and rib abnormalities due to some individuals who had both abnormal rib number and abnormality. Each case was only counted once. Any noticeable surgical alterations were excluded from the analysis (control ¼ 2 and cases ¼ 4). a Fisher's exact test was used to determine the P-value for cervical ribs in the crude analysis. b Adjusted for sex and age at first chest imaging.

Table 5 Rib anomalies identified by individual cancer types Normal ribs Abnormal ribs Crude OR (95% CI) Adjusted OR (95% CI) Total cancers 455 424 (93.2%) 31 (6.8%) 1.55 (0.98, 2.46) 1.60 (1.0, 2.65) Leukaemias, myeloproliferative diseases, and myelodysplastic 221 206 (93.2%) 15 (6.8%) 1.54 (0.85, 2.80) 1.55 (0.84, 2.88) Lymphoid leukaemias 105 99 (94.3%) 6 (5.7%) 1.40 (0.58, 3.36) 1.27 (0.51, 3.11) Acute myeloid leukaemias 78 70 (89.7%) 8 (10.3%) 2.42 (1.11, 5.31) 2.29 (1.02, 5.13) Chronic myeloproliferative diseases 20 20 (100%) 0 (0.0%) — — Other specified or unspecified leukaemias 18 17 (94.4%) 1 (5.6%) 1.36 (0.18, 10.44) 1.16 (0.15, 8.98) Lymphomas and reticuloendothelial neoplasms 50 49 (98.0%) 1 (2.0%) 0.47 (0.06, 3.49) 0.37 (0.05, 2.89) Hodgkin lymphomas 29 29 (100%) 0 (0%) — — Non-Hodgkin lymphomas (except Burkitt's lymphoma) 12 11 (91.7%) 1 (8.3%) 2.10 (0.27, 16.63) 1.67 (0.21,13.41) Other specified or unspecified lymphomas 9 9 (100%) 0 (0%) — — CNS and miscellaneous intracranial and intraspinal neoplasms 34 31 (91.2) 3 (8.8%) 2.24 (0.66, 7.59) 2.00 (0.59, 6.77) Neuroblastoma and other peripheral nervous cell tumours 31 29 (93.6%) 2 (6.4%) 1.46 (0.34, 6.30) 1.48 (0.34, 6.40) Renal tumours 20 17 (85.0%) 3 (15.0%) 3.74 (1.06, 13.19) 3.73 (1.05, 13.22) Malignant bone tumours 39 37 (94.9%) 2 (5.1%) 1.15 (0.27, 4.89) 0.95 (0.21, 4.31) Osteosarcomas 21 19 (90.4%) 2 (9.5%) 2.23 (0.51, 9.85) 1.81 (0.38, 8.53) Ewing tumour and related sarcomas of bone 15 15 (100%) 0 (0%) — — Other specified and unspecified malignant bone tumours 3 3 (100%) 0 (0%) — — Soft tissue and other extraosseous sarcomas 30 29 (96.7%) 1 (3.3%) 0.73 (0.10, 5.41) 0.64 (0.08, 4.91) Rhabdomyosarcomas 15 14 (93.3%) 1 (6.7%) 1.52 (0.20, 11.75) 1.35 (0.17, 10.62) Other specified or unspecified soft tissue sarcomas 15 15 (100%) 0 (0%) — — Controls 1133 1082 (95.5%) 51 (4.5%) — — Abbreviations: OR ¼ odds ratio; 95% CI ¼ 95% confidence interval; CNS ¼ central nervous system. Association of rib anomalies and childhood cancers

H Zierhut et al 1394 British Journal of Cancer (2011) 105(9), 1392 – 1395 & 2011 Cancer Research UK Epidemiology a significant association of abnormal rib number with paediatric cancer. We did not see significant associations with other cancers previously reported with the exception of Wilm's tumour (Schumacher et al, 1992). Our results exhibited an increased number of RAs in CNS neoplasms but the result was not significant. A reduced number of CNS and miscellaneous intracranial and intraspinal neoplasms in our analysis may have prohibited power to detect a significant association.

The US study by Loder et al (2007) is closest to our population and may account for the similarity of results between the studies. Data on RAs may not be generalisable

to all ethnic populations. To the extent that we could rely on the data supplied and examine ethnicity (Caucasian and non-Caucasian), we found an association limited to non-Caucasians although this is not a large percentage of our study population. Future studies may help to better understand the role of ethnicity on RAs and the association with childhood cancer. The hospital-based case – control study design had several limitations. The study population was created from a convenience sample which to some extent limited our analyses. Case and control selection has the potential to introduce bias. Cases in our study were obtained from a tertiary care centre. Cases were likely unaware of RAs and therefore unlikely to be differentially ascertained based on this basis. The underlying cohort that gave rise to the cases in our study would be difficult to define. In an attempt to best replicate the cohort, controls were obtained from a hospital-based clinic to better represent the paediatric population of Minnesota, but we cannot rule out bias due to mi Several reports of costal abnormalities exist in the literature [7, 14, 15]. In cervical ribs known to be caused by hox gene mutations [16], there is a long history of diagnosis from Galen and Vesalius to surgical excision of a symptomatic cervical rib by Cote [17]. Later cervical rib was classified into five types based on its development and attachment to the sternum [18]. The clinical significance of the cervical rib is that it may cause thoracic outlet syndromes, including vascular or neurogenic symptoms caused by compression of great vessels and brachial nerve plexus [15]. The pooled prevalence estimate of the cervical rib is 0.9%-1.4%, and it is more common in females (0.9-1.7%) than in males (0.5%-1%) [15]. As mentioned in the literature, cervical ribs are often asymptomatic and considered incidental findings in standard radiology procedures [19]. In Chang et al.'s study, 23 patients with thoracic outlet syndrome who developed subclavian artery thrombosis or aneurysm and ischemic upper extremity underwent cervical rib resections [20]. Their study also mentioned a female dominance of cervical rib presence, and cervical ribs with large size and fusion to the first rib cause significant symptoms [20]. The prevalence and female dominance of cervical ribs is reported in our study, as well. Bifid ribs usually occur at the end of sternal ends and are reported to be asymptomatic and found incidentally [21]. The general Prevalence of bifid rib is 1.7 to 6.75% [8, 21]. In most cases, there are unilateral bifid ribs on the left [7] or right [21] with male dominance [7]. However, bilateral or multiple bifid ribs on the same side have also been reported, which may be associated with Gorlin syndrome [10, 22]. Although rib abnormality is considered a minor criterion for diagnosis of Gorlin syndrome, it has to be considered for possible co-occurrence of the disease [12]. This syndrome is caused by activation of the hedgehog signaling pathway due

to loss of function mutations in the patched (PTCH1) receptor [23]. This leads to smoothened (SMO) co-receptor activation, which causes activation of downstream transcription factors and target genes [24]. Activating this signaling pathway leads to cell proliferation, migration, and differentiation, resulting in several conditions, including basal cell carcinoma, medulloblastoma, and skeletal malformations [12]. In this study, the Prevalence of bifid ribs was 3%, with male dominance (66.7%) and left side occurrence of 100% (all the cases were on the left side) involving second to fifth ribs. One hundred percent (12 cases) of left side occurrence of bifid ribs in this study is a rare report because the literature implies that this anomaly is usually located on the right side [21]. No specific explanation was stated in the literature on the cause of the side-specific occurrence of bifid ribs.

In a study done by jukerberk JH et al in 2009 cervical rib anomalies were present in 6.1% of controls ,aplasia of 12^{th} ribs in 6.6%lumbar ribs in 0.9%,bifurcations in 0.7%synostosis –bridging in 0.3% and segmentation were not found. The overall prevalence of total rib anomalies in cases and controls was equal(14.9% and 14.2% respectively). Cervical rib anomalies were found significantly more often in cases (8.6%)compared to control (p-value=0.047),three groups accounting for this higher prevalence: 12.1% of acute lymphoblastic leukemia patients (p=0.011),18.2% of astrocytoma patients(p=0.023),and 14.7% of germ cell tumor patients (p=0.046)had a cervical rib anomaly.[7]

Serial no	*Name*	*Age year*	*Sex*	*Religion*	*Type of family*	*Family income per month*	*Any surgical history*	*Residential status*	*Type of rib anomaly*
1	*Sk saidul*	*6*	*M*	*muslim*	*joint*	*10000/*	*no*	*local*	*Bifid rib*
2	*Mrinal shibastava*	*7*	*M*	*Hindu*	*Nuclear*	*12000/*	*no*	*local*	*Rib synostosis*

3	*Rahul tribedi*	*5*	*M*	*Hindu*	*Nuclear*	*10500/*	*no*	*local*	*Cervical rib*
4	*Ajoy tripathi*	*5*	*M*	*Hindu*	*Nuclear*	*20000/*	*no*	*local*	*Lumber rib*
5	*Sabnam sultana*	*6*	*F*	*Muslim*	*Nuclear*	*15000/*	*no*	*local*	*Rib segmentation*
6	*Yamin begam*	*7*	*F*	*Muslim*	*Nuclear*	*20000/*	*no*	*local*	*aplasia*
7	*Jamini roy*	*6*	*F*	*Hindu*	*Nuclear*	*20000/*	*no*	*local*	*Rib number reduced*
8	*Joyita tripathi*	*6*	*F*	*Hindu*	*Nuclear*	*15000/*	*no*	*local*	*synostosis*
9	*Ruma gupta*	*6*	*F*	*Hindu*	*Nuclear*	*15000*	*no*	*local*	*Rib segmentation*
10	*Tribid verma*	*6*	*M*	*Hindu*	*Nuclear*	*12000/*	*No*	*local*	*Bifid rib*
11	*Ram verma*	*6*	*M*	*Hindu*	*Nuclear*	*12000/*	*No*	*Local*	*aplasia*
12	*Binod patel*	*6*	*M*	*Hindu*	*Nuclear*	*12000/*	*No*	*Local*	*Lumber rib*
13	*Gopal verma*	*5*	*M*	*Hindu*	*Nuclear*	*20000/*	*No*	*Local*	*Cervical rib*
14	*Atul verma*	*5*	*M*	*Hindu*	*Nuclear*	*20000/*	*No*	*Local*	*Rib aplasia*
15	*Pradip ojha*	*6*	*M*	*Hindu*	*Nuclear*	*20000/*	*No*	*Local*	*Cervical rib*
16	*Pushpa mandi*	*8*	*F*	*Hindu*	*Nuclear*	*30000/*	*No*	*Local*	*Normal*
17	*Manju patel*	*7*	*M*	*Hindu*	*Nuclear*	*10000/*	*No*	*Local*	*Normal*
18	*Naman ojha*	*6*	*M*	*Hindu*	*Nuclear*	*20000/*	*No*	*Local*	*Normal*
19	*Parthi goyel*	*7*	**M**	*Hindu*	*Nuclear*	*30000/*	*No*	*Local*	*Normal*
20	*Kajal agarwal*	*8*	*F*	*Hindu*	*Nuclear*	*20000/*	*No*	*Local*	*Normal*
21	*Ram agarwal*	*9*	**M**	*Hindu*	*Nuclear*	*10000/*	*No*	*Local*	*Rib aplasia*
22	*Rumji goel*	*10*	*M*	*Hindu*	*Nuclear*	*10000/*	*No*	*Local*	*Normal*
23	*Anankha khandelwal*	*7*	*F*	*Hindu*	*Nuclear*	*10000/*	*No*	*Local*	*Normal*
24	*Pawan kumar*	*6*	*M*	*Hindu*	*Nuclear*	*20000/*	*No*	*Local*	*Normal*
25	*Rakshit pawal*	*8*	*M*	*Hindu*	*Nuclear*	*20000/*	*No*	*Local*	*Normal*
26	*Rishi goel*	*9*	*M*	*Hindu*	*Nuclear*	*20000/*	*No*	*Local*	*Normal*
27	*Anand patel*	*10*	*M*	*Hindu*	*Nuclear*	*10000/*	*No*	*Local*	*Normal*
28	*Honey singh*	*6*	*M*	*Hindu*	*Nuclear*	*20000/*	*No*	*Local*	*Normal*
29	*Farid ali*	*7*	*M*	*Muslim*	*Nuclear*	*10000/*	*No*	*Local*	*Normal*
30	*Rahmat shah*	*87*	*M*	*Muslim*	*Nuclear*	*10000/*	*No*	*Local*	*Normal*
31	*Ram jain*	*9*	*M*	*Hindu*	*Nuclear*	*10000/*	*No*	*Local*	*Normal*
32		*10*			*Nuclear*		*No*	*Local*	*Normal*
33		*7*			*Nuclear*		*No*	*Local*	*Normal*
34		*8*			*Nuclear*		*No*	*Local*	*Normal*
35		*9*			*Nuclear*		*No*	*Local*	*Normal*
36		*10*			*Nuclear*		*No*	*Local*	*Normal*
37		*6*			*Nuclear*		*No*	*Local*	*Normal*
38		*7*			*Nuclear*		*No*	*Local*	*Normal*
39		*8*			*Nuclear*		*No*	*Local*	*Normal*
40		*7*			*Nuclear*		*No*	*Local*	*Normal*
41		*6*			*Nuclear*		*No*	*Local*	*Normal*
42		*10*			*Nuclear*		*No*	*Local*	*Normal*
43		*9*			*Nuclear*		*No*	*Local*	*Normal*
44		*8*			*Nuclear*		*No*	*Local*	*Normal*
45		*7*			*Nuclear*		*No*	*Local*	*Normal*
46		*6*			*Nuclear*		*No*	*Local*	*Normal*
47		*7*			*Nuclear*		*No*	*Local*	*Normal*
48		*8*			*Nuclear*		*No*	*Local*	*Normal*
49		*9*			*Nuclear*		*No*	*Local*	*Normal*

50		8			Nuclear		No	Local	Normal
51		7			Nuclear		No	Local	Normal
52		6			Nuclear		No	Local	Normal
53		9			Nuclear		No	Local	Normal
54		10			Nuclear		No	Local	Normal
55		11			Nuclear		No	Local	Normal
56		9			Nuclear		No	Local	Normal
57		7			Nuclear		No	Local	Normal
58		8			Nuclear		No	Local	Normal
59		5			Nuclear		No	Local	Normal
60		6			Nuclear		No	Local	Normal
61		4			Nuclear		No	Local	Normal
62		3			Nuclear		No	Local	Normal
63		2			Nuclear		No	Local	Normal
64		1			Nuclear		No	Local	Normal
65		9			Nuclear		No	Local	Normal
66		8			Nuclear		No	Local	Normal
67		7			Nuclear		No	Local	Normal
68		9			Nuclear		No	Local	Normal
69		10			Nuclear		No	Local	Normal
70					Nuclear		No	Local	Normal
71					Nuclear		No	Local	Normal
72					Nuclear		No	Local	Normal
73					Nuclear		No	Local	Normal
74					Nuclear		No	Local	Normal
75					Nuclear		No	Local	Normal
76					Nuclear		No	Local	Normal
77					Nuclear		No	Local	Normal
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79					Nuclear		No	Local	Normal
80					Nuclear		No	Local	Normal
81					Nuclear		No	Local	Normal
82					Nuclear		No	Local	Normal
83					Nuclear		No	Local	Normal
84					Nuclear		No	Local	Normal
85					Nuclear		No	Local	Normal
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87					Nuclear		No	Local	Normal
88					Nuclear		No	Local	Normal
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95					Nuclear		No	Local	Normal
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108					Nuclear		No	Local	Normal
109					Nuclear		No	Local	Normal
110					Nuclear		No	Local	Normal
111					Nuclear		No	Local	Normal
112					Nuclear		No	Local	Normal
113					Nuclear		No	Local	Normal
114					Nuclear		No	Local	Normal

115					*Nuclear*		*No*	*Local*	*Normal*
116					*Nuclear*		*No*	*Local*	*Normal*
117					*Nuclear*		*No*	*Local*	*Normal*
118					*Nuclear*		*No*	*Local*	*Normal*
119					*Nuclear*		*No*	*Local*	*Normal*
120					*Nuclear*		*No*	*Local*	*Normal*
121					*Nuclear*		*No*	*Local*	*Normal*
122					*Nuclear*		*No*	*Local*	*Normal*
123					*Nuclear*		*No*	*Local*	*Normal*
124					*Nuclear*		*No*	*Local*	*Normal*
125					*Nuclear*		*No*	*Local*	*Normal*
126					*Nuclear*		*No*	*Local*	*Normal*
127					*Nuclear*		*No*	*Local*	*Normal*
128					*Nuclear*		*No*	*Local*	*Normal*
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131					*Nuclear*		*No*	*Local*	*Normal*
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133					*Nuclear*		*No*	*Local*	*Normal*
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135					*Nuclear*		*No*	*Local*	*Normal*
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166					*Nuclear*		*No*	*Local*	*Normal*
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174					*Nuclear*		*No*	*Local*	*Normal*
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193					*Nuclear*		*No*	*Local*	*Normal*
194					*Nuclear*		*No*	*Local*	*Normal*
195					*Nuclear*		*No*	*Local*	*Normal*

Material and method-

Rib anomalies were assessed in a hospital-based case – control studyCases consisted of all paediatric haematology and oncology and bone marrow transplantation (BMT) patients treated at the University of kgmu Medical Center—lucknow, MN for malignancy during2023-2024. Cases must have been diagnosed between the ages of 0 –19 years and had been imaged during the study period. Children with a known syndrome (e.g., bone marrow failure syndromes, Down's syndrome, and muccopolysaccaridoses) identified through our database were excluded; we expect that only very minimal number of syndromic cases were missed. Controls were randomly selected paediatric patients who received a chest X-ray at kgmu,lucknow during June and October of 2023-2024. Controls were chosen from this community hospital as they more likely represent the general Twin Cities paediatric population. Indications for chest X-rays in controls included asthma or shortness of breath, bronchitis, chest pain, possible pneumonia, trauma, and others (e.g., foreign body). The study was approved by the University kgmu Institutional review boardControls For the control group we selected all chest radiographs made in children (age 0 – 18 years) at our hospital between January 1, 1992 and September 31, 2002 (flow-chart: Fig. 1). In order to prevent the inclusion of unusual and selected patients referred to our tertiary center, we selected from the total radiographs only those that were ordered by general practitioners, the general pediatricians at the outpatient ward of our hospital, and physicians at the emergency department. In order to prevent recognition of controls by the observers, we selected for patients with asthma or infectious diseases without other major pulmonary or cardiac abnormalities on their radiographs, by searching all radiology reports for the words: 'asthma', 'bronchitis', 'airway', 'COPD' (in former times commonly used in the Netherlands as a general term for asthma and bronchitis), 'no', or 'clear'. The words 'no' and 'clear' were selected for they were found to be most specific in describing normal chest

radiographs in radiology reports. Using the above selection criteria 17,245 chest radiographs were selected. Subsequently all patients with more than one radiograph (either chest radiographs or other imaging studies, n=14,319) were excluded, again to prevent the inclusion of unusual and selected patients. It is well known that phenotypic characteristics vary considerably depending on ethnic background [11]. Indeed several larger studies on phenotypic characteristics focused on single ethnic groups [12–14]. Although never specifically investigated it is very likely that the same differences hold for abnormalities involving ribs. Differences found in prevalence figures for rib anomalies among subjects from different European countries are in concert with this assumption [15]. Registration of ethnicity is not allowed in the Netherlands, so this information was not available. Therefore, to prevent a large disturbance by the ethnic background, we excluded all patients with clearly non-Caucasian names (n=1,519). All names were independently reviewed by two observers; all Western-European names were included, while all names with clearly another background, for example African and Asian, were excluded. In case of doubt the patient was excluded. Subsequently, the radiology reports were again screened, but this time for describing abnormalities other than rib anomalies (e.g. cardiomegaly, or signs of previous surgery), excluding 361 radiographs. A further 119 radiographs were untraceable, and 46 radiographs could not be evaluated because of technical reasons; radiographs were only included if all ribs were visible, the vertebral column was depicted from at least C6 until L1, and radiographic techniques were adequate. This way a total of 881 chest radiographs of normal pediatric controls remained available. To check whether this strategy was correct, diagnoses of 200 randomly selected controls were retrieved from their patient charts. Of the 200 patients 35 were referred by their general practitioner for a radiograph only, and never had a chart; diagnoses of the other 165 control. 2.2. Cases We reviewed chest radiographs of two patient cohorts: the first cohort consisted of all Caucasian patients who visited the clinic for Late Effects of Childhood Cancer at our center. This outpatient clinic follows all persons treated as a child for cancer and in complete remission for at least five years. The second cohort consisted of all Caucasian children newly diagnosed with malignancies at our center between January 1, 1998 and December 31, 2002. All available chest radiographs of these patients were retrieved. If more than one chest radiographs of a patient were available, the first radiograph taken at diagnosis was selected for review. In total, 906 chest radiographs were reviewed, 582 from the Late Effects Clinic, and 324 from newly diagnosed patients. Permission for the study was obtained from the Medical Ethical Committee of our hospital2.3. Definitions Definitions of rib anomalies were based on two major reference studies [15,16], and a reference chart was developed depicting schematically all possible rib anomalies that can be scored on a chest radiograph (Fig. 2). Only aplasia of 12th ribs and presence of lumbar ribs were not depicted, as these anomalies needed no further clarification. Six major groups of rib anomalies were defined: 1. Cervical anomalies,

including Transverse Apophysomegalies (TA) and true Cervical Ribs (CR), 2. Aplasia of the 12th ribs (AT), 3. Lumbar ribs (LR), 4. Bifid ribs or bifurcations, 5. Synostosis or bridging of ribs, and 6. Segmentations. TA of C7 were diagnosed if the processus transversus of C7 extended more laterally than the processus transversus of T1 on a radiograph with the head of the patient not turned sideward. CR were registered only if also an articulation was visible (Fig. 2), the same principle applying for LR. Representative radiographs from the present study showing th

2.4. Radiologic Techniques As this is a retrospective study chest radiographs from different clinical settings were used. Therefore a mix of radiographic techniques ranging from AP bed radiographs to upright PA chest radiographs was available for review. Digital radiography was only introduced as the standard method for children at our center In order to limit the influence of digital radiography, i.e. the possibility to change window and level width on the screening console, digital radiographs were evaluated from hard copy

2.5. Reviewing Radiographs Chest radiographs from cases and controls were randomly mixed, and any patient identity information visible on the radiographs was blocked, in order to prevent recognition (Fig. 1). The panel of observers consisted of two pediatric radiologists, a musculoskeletal radiologist and a pediatrician-clinical geneticist, all skilled in evaluating skeletal anomalies. Each radiograph was independently reviewed by two of these observers, each working independently from one another. Radiographs which were scored as abnormal .

Study design-cross sectional observational study.

Study settings-the study will be conducted in dept. of anatomy in collaboration with dept. of peadiatrics.,kgmu,lko

Study duration-one year.

Sample size-the sample size for the proposed study was calculated using the prevalence (p=14.9%) of anomalies among peadiatrics cancer patients,type one error rate (q=5%)and the marjin of error (d=5%)by means of following formula-
N=------Z2*P*Q---

D^2-------- thus the required sample iz is 195

Study population .-----pediatric patients with confirmed childhood malignancies like leukemia ,neuroblastoma, nephroblastoma, and wilms tumor in the age group of 6 months -12 years in the dept of pediatrics ,kgmu , up.

Participant selection

Inclusion criteria for cases pediatric patients with confirmed childhood malignancies like leukemia, neuroblastoma, nephroblastoma and wilms tumor. In the age group of 6 month -12 yrs in the dept. of pediatrics.

Inclusion criteria for control----children who were advised for chest radiograph for asthma, bronchitis, chest pain, pneumonia,trauma,other non malignant conditions.

Exclusion criteria -----bone marrow failure syndrome, down syndrome

Data collection------ethical clearance

Has obtained from institutional ethical review board.following parameters has observed in chest radiograph-----

Rib number

Cervical ribs

Lumber ribs

Bifid ribs

Ribs synostosis

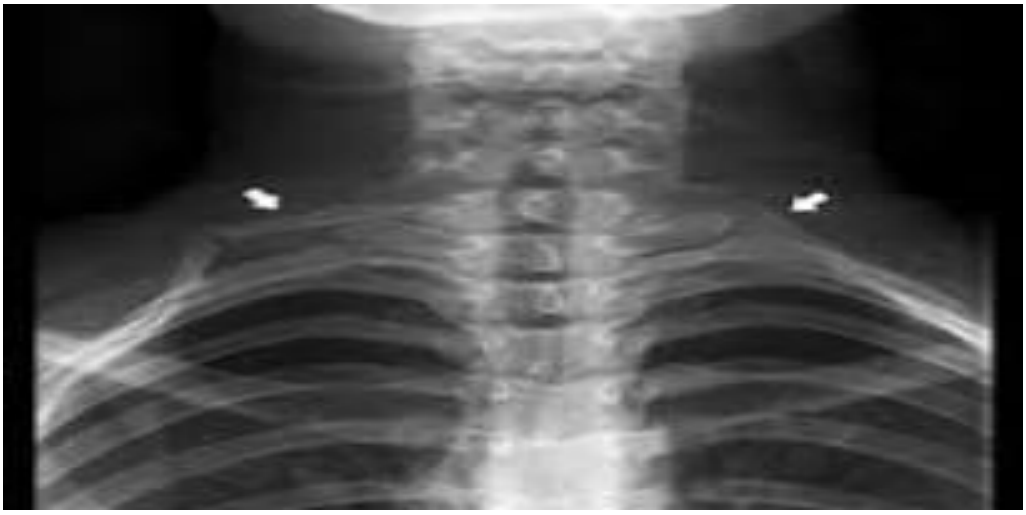
Vertebral segmentation

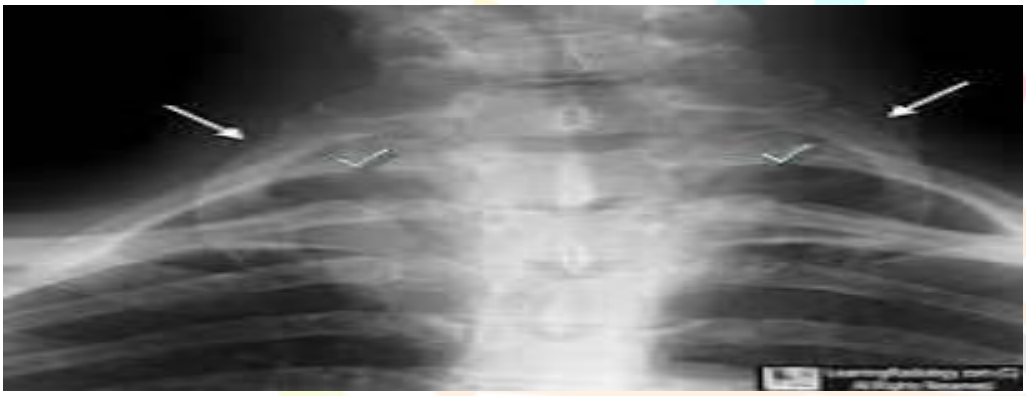
Post surgical repair

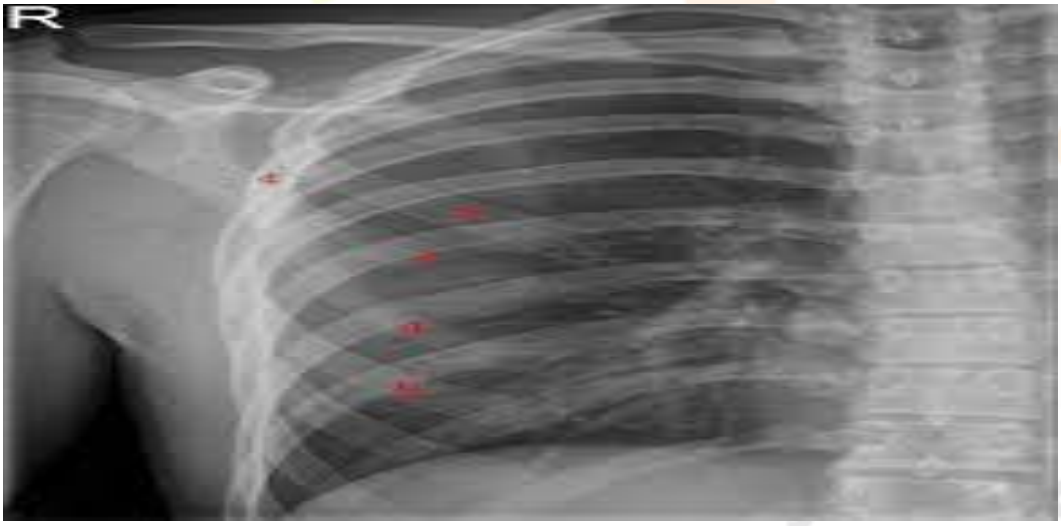
Statistical analysis---the continuous variables will be evaluated by means or range value.the dichotomous variable will be presented in number or frequency and will be analysed using chi square or fisher extract test.for comparison of the means between two group analysis by students t test mann whitney u test and spearman correlation with 95%confidence .

RESULT-

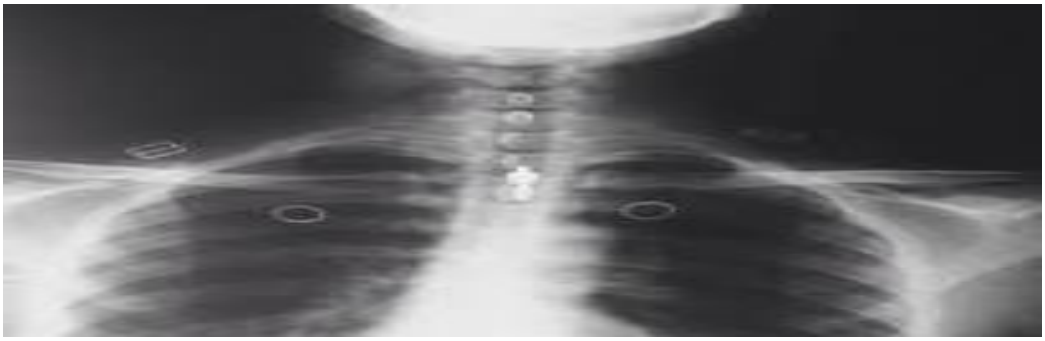
Cervical rib

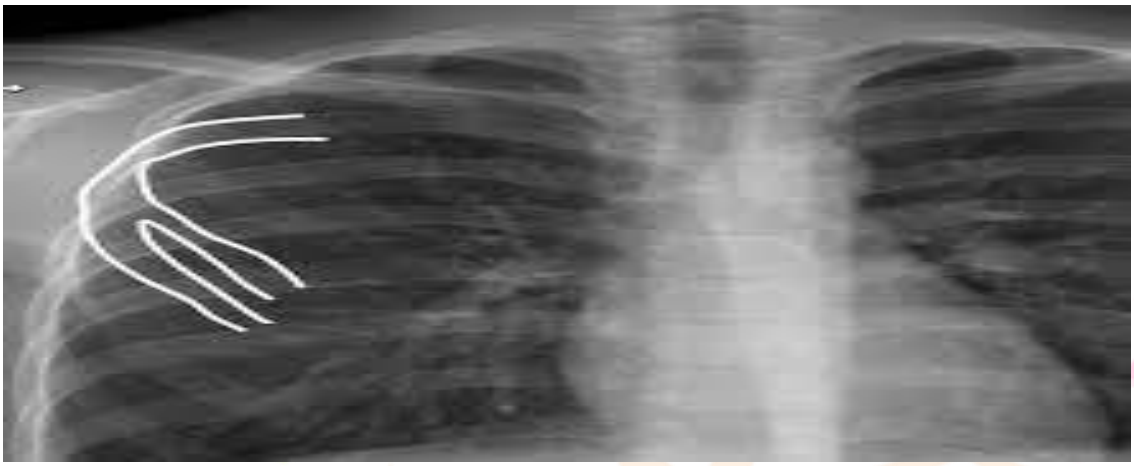


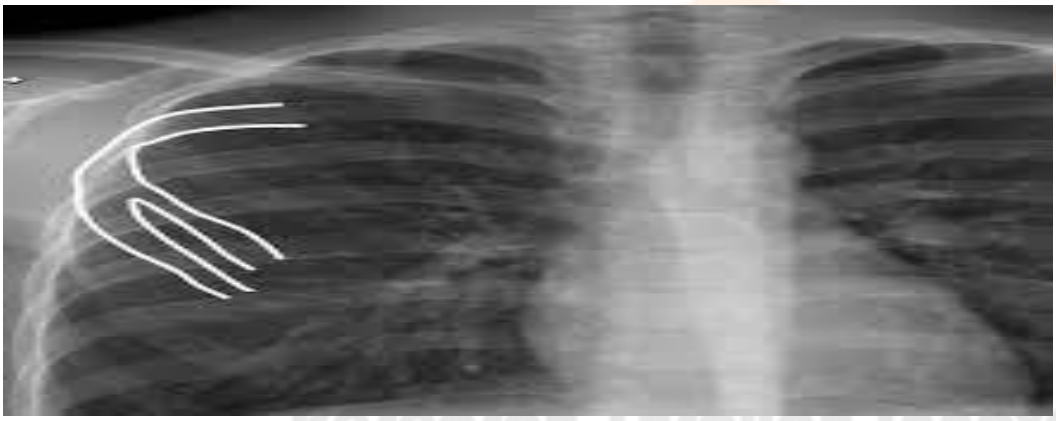


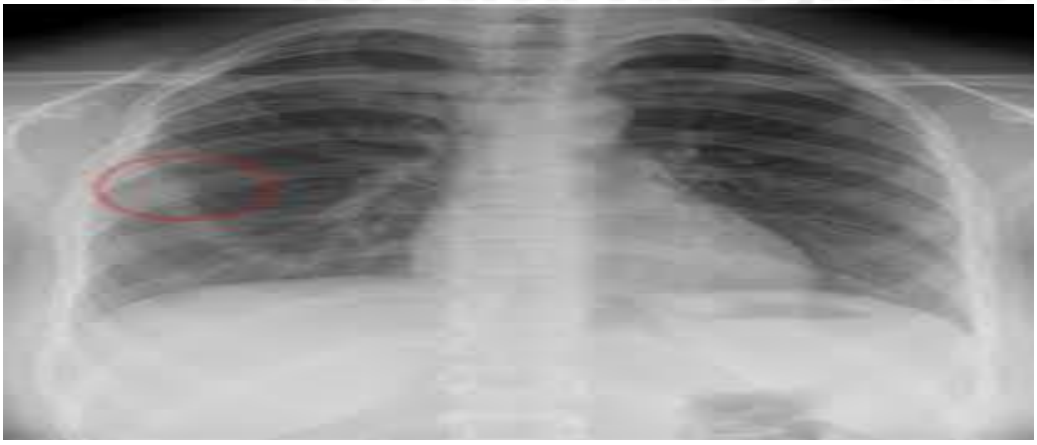


Bifid ribs----------

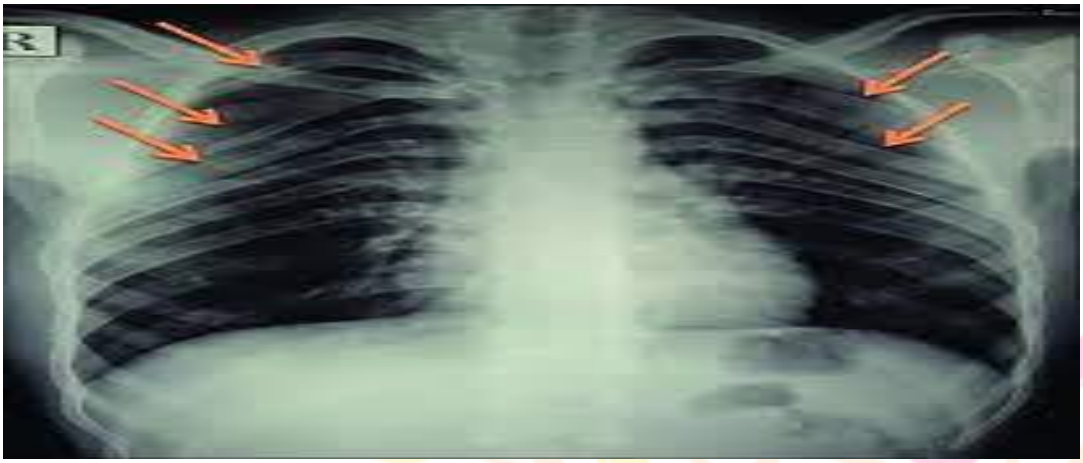


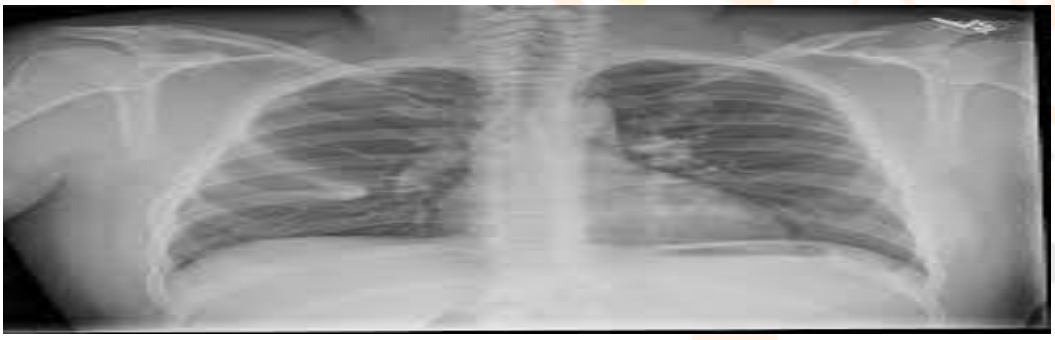


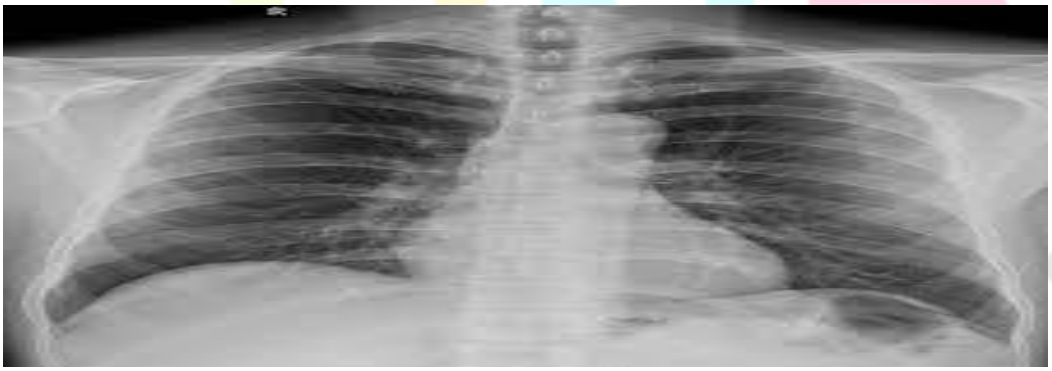


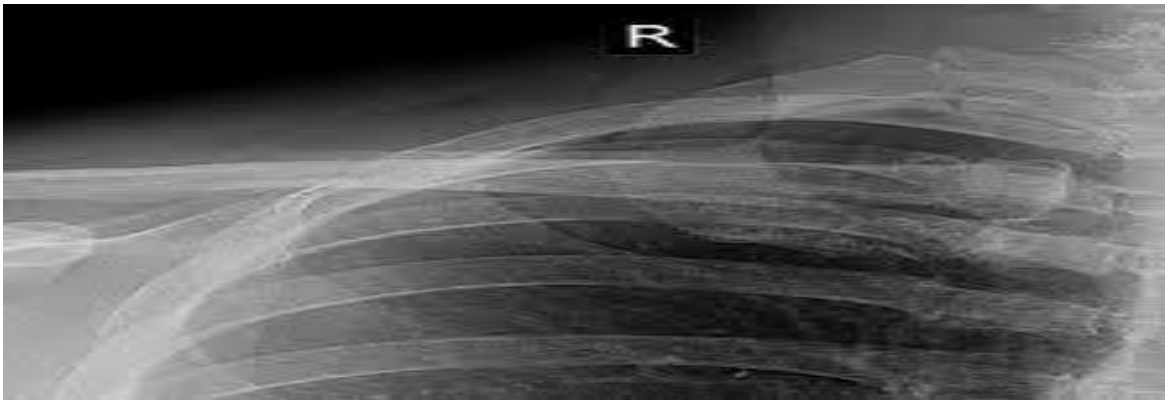


Rib synostosis

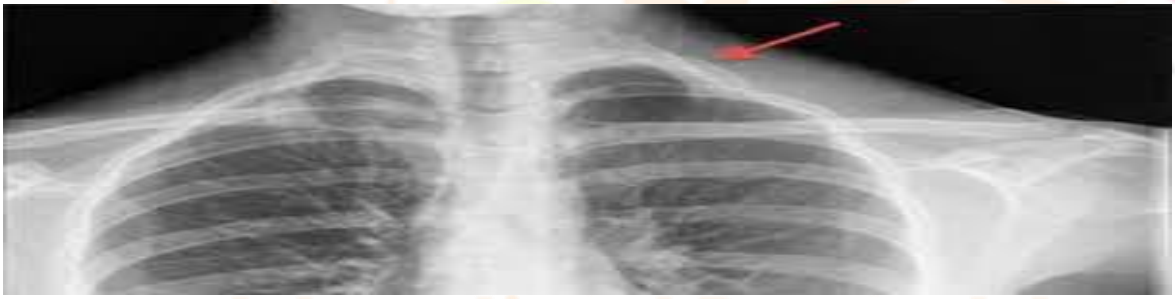




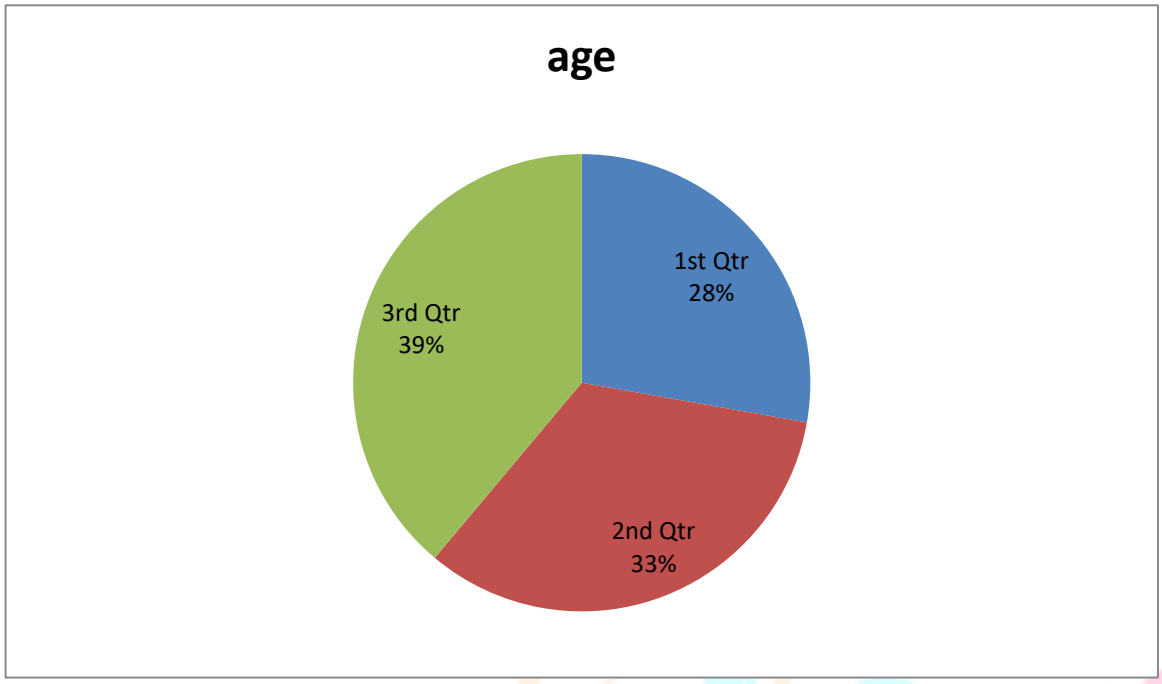




Aplasia of rib----------

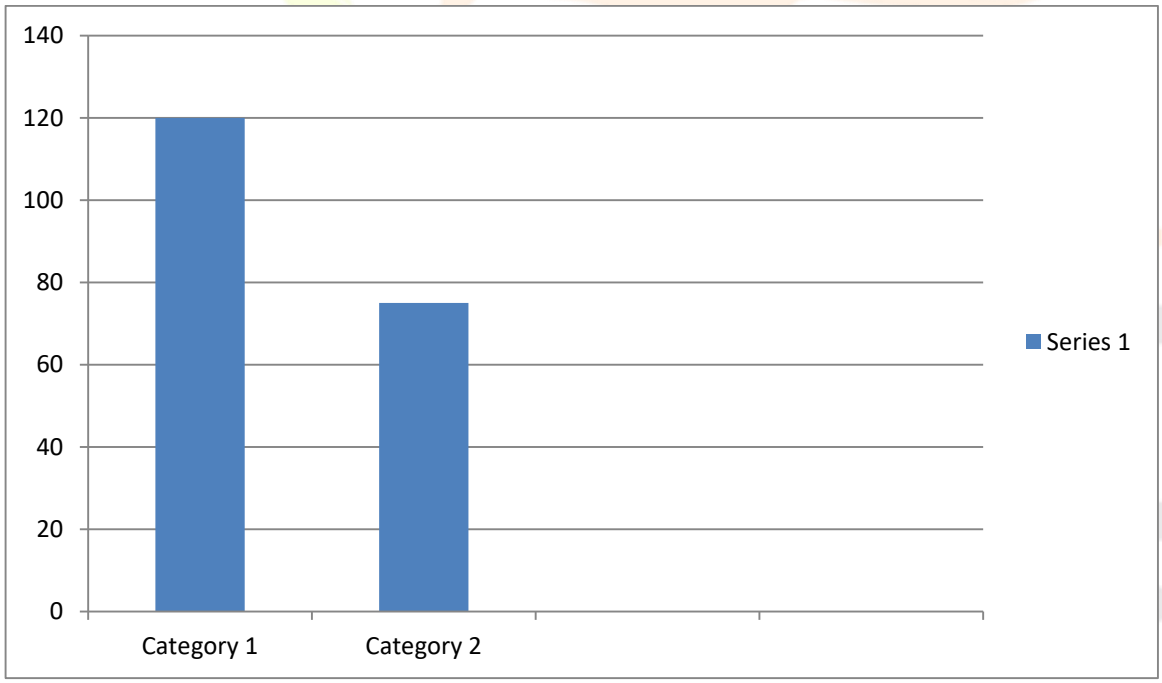


For age of the cases of draw a chart-



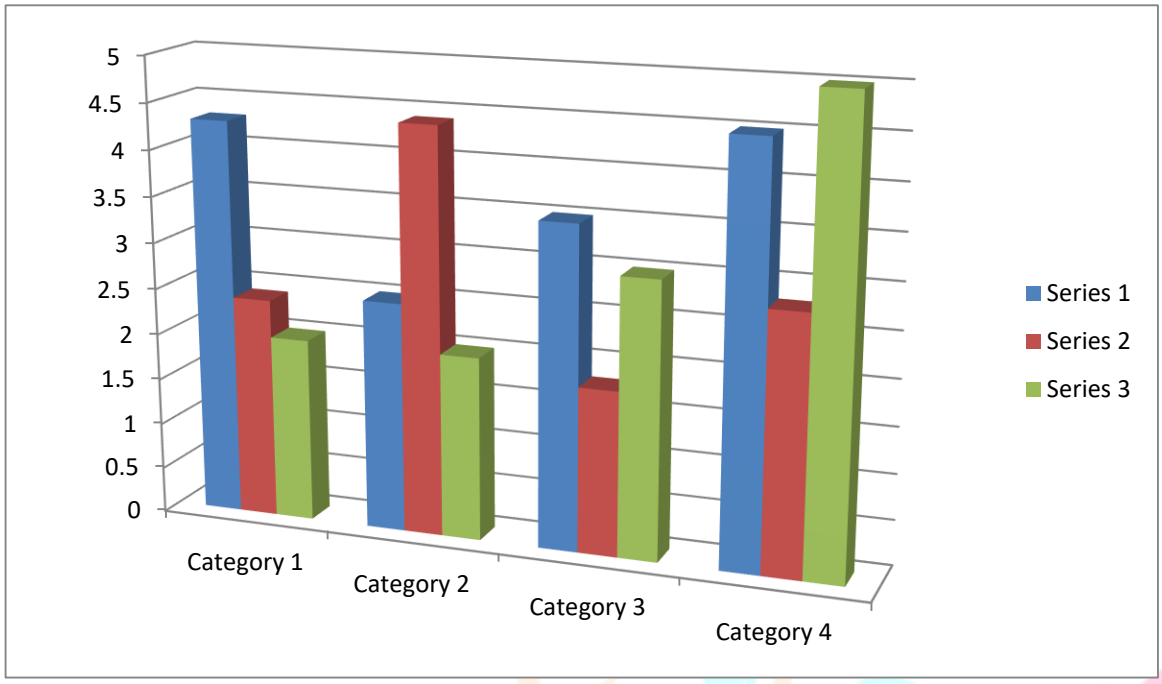
Age green 1-5 yr, 6-9 yr red, 10-12 yr blue

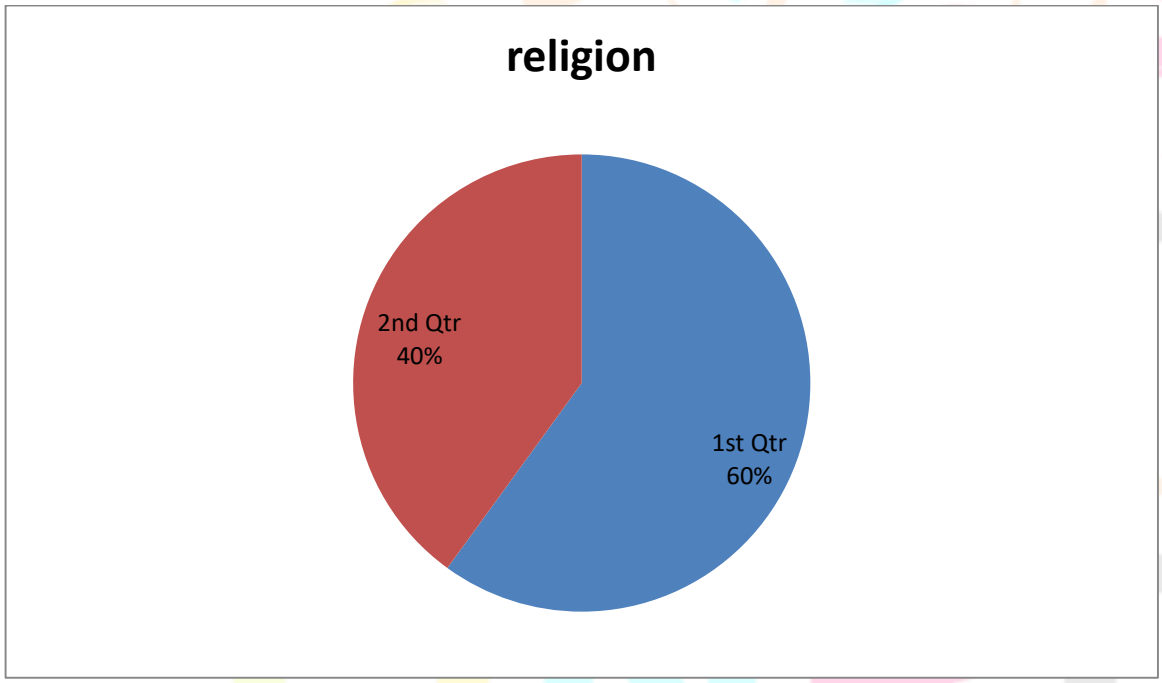
Sex of individual---------



Male cat 1, female cat 2

Religion of individuals-





Hindu- blue , muslim –red

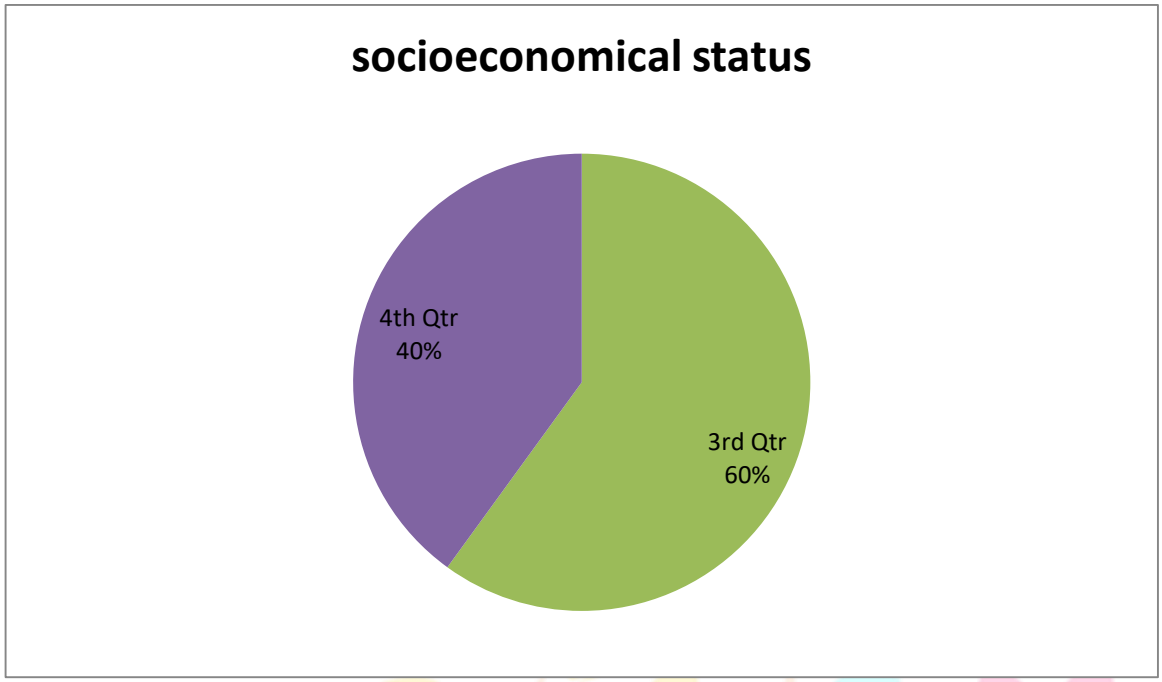
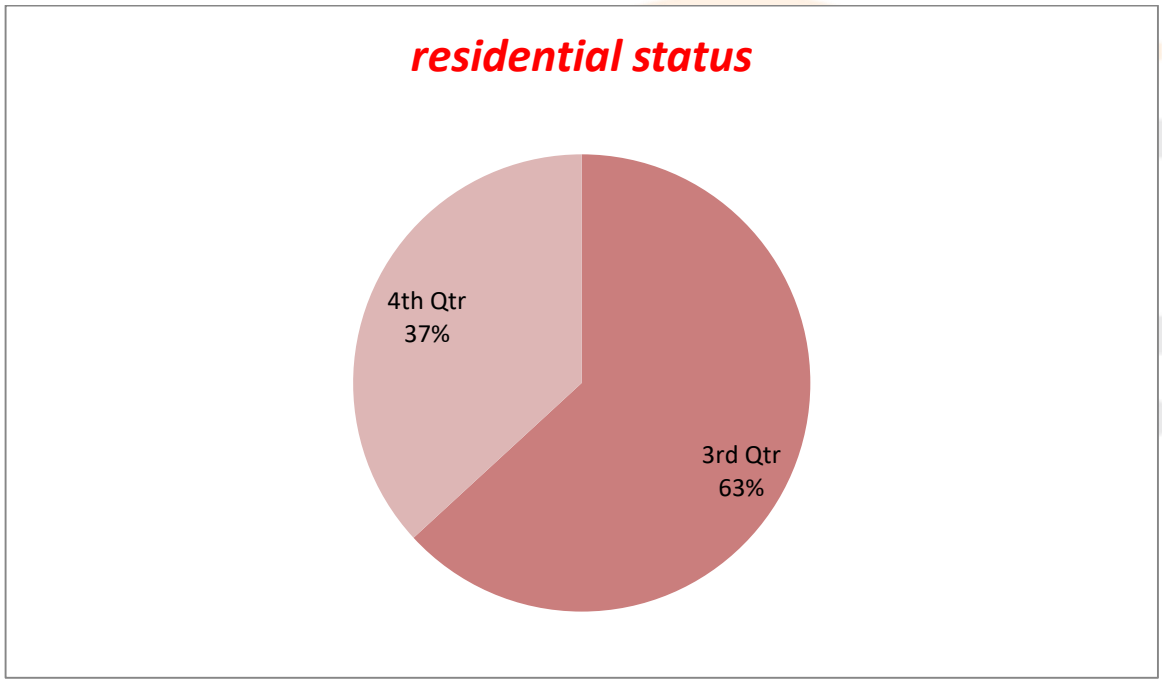
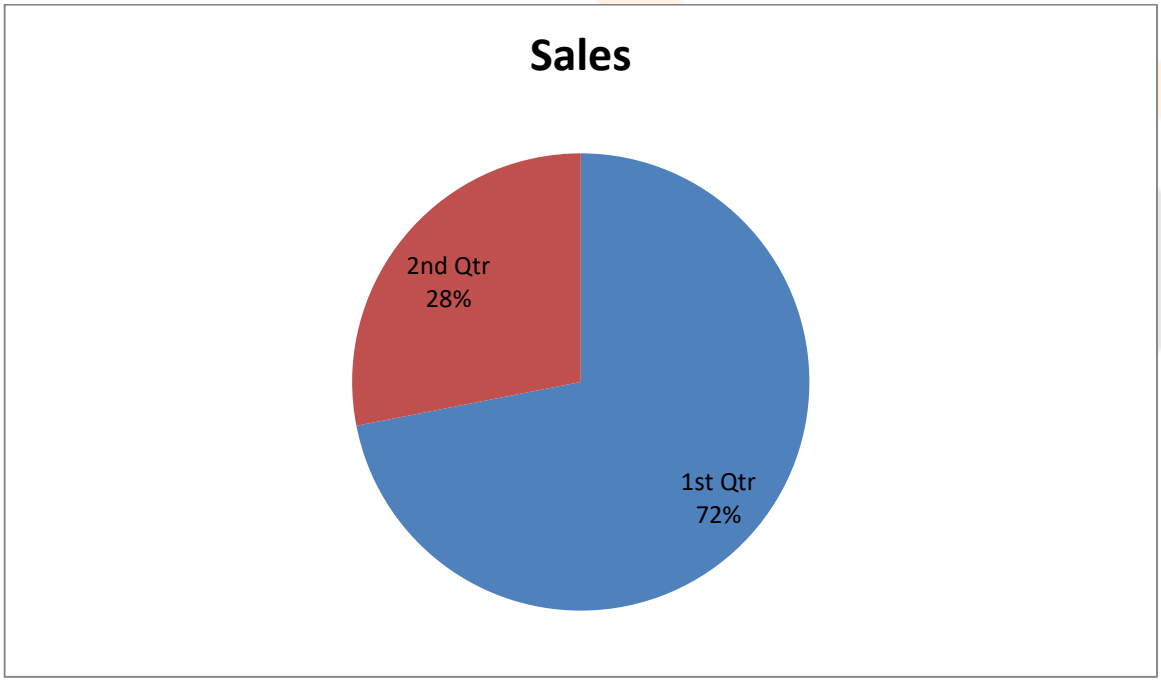


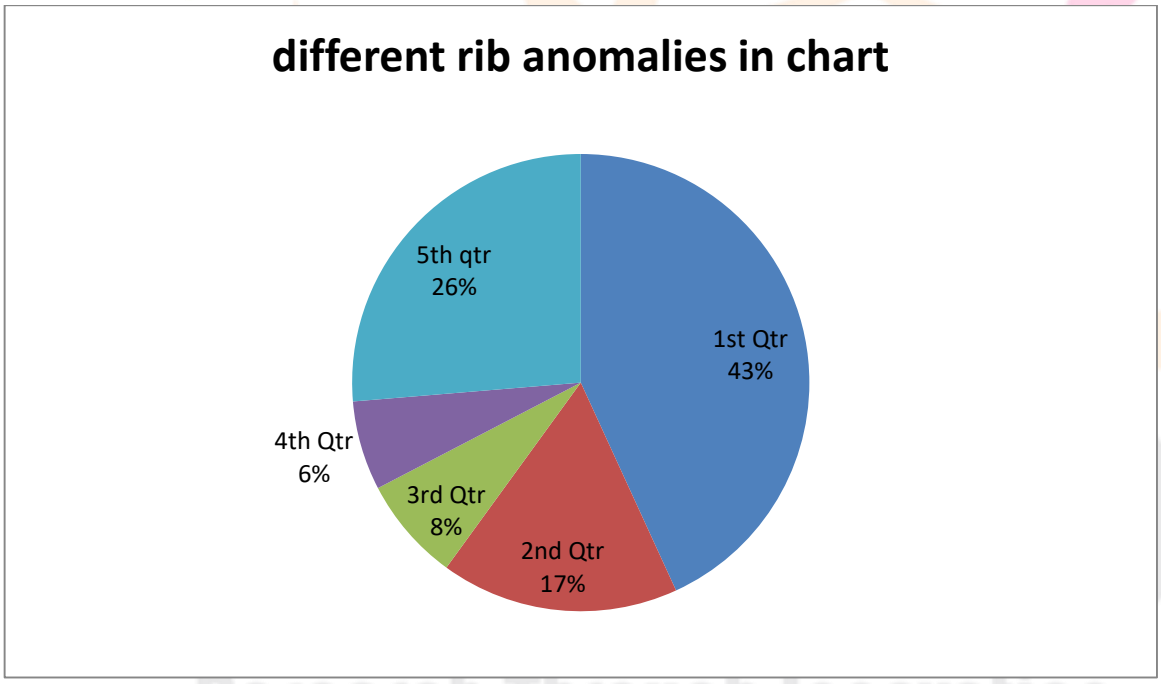
Figure 5 upper middle blue , lower green



Red states- local, white state- others residents



Surgical history, blue denote no surgical history



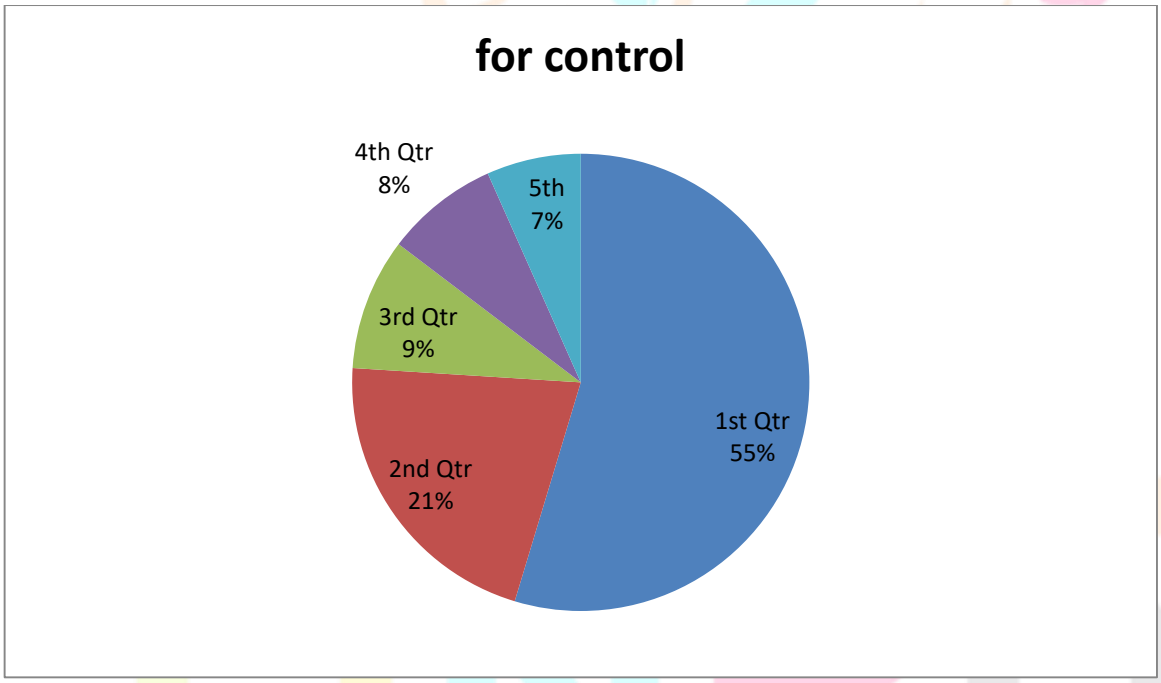
1st quarter denotes cervical rib

2nd denotes lumber rib

3rd denotes rib synostosis

4th denotes bifid rib

5th denotes aplasia



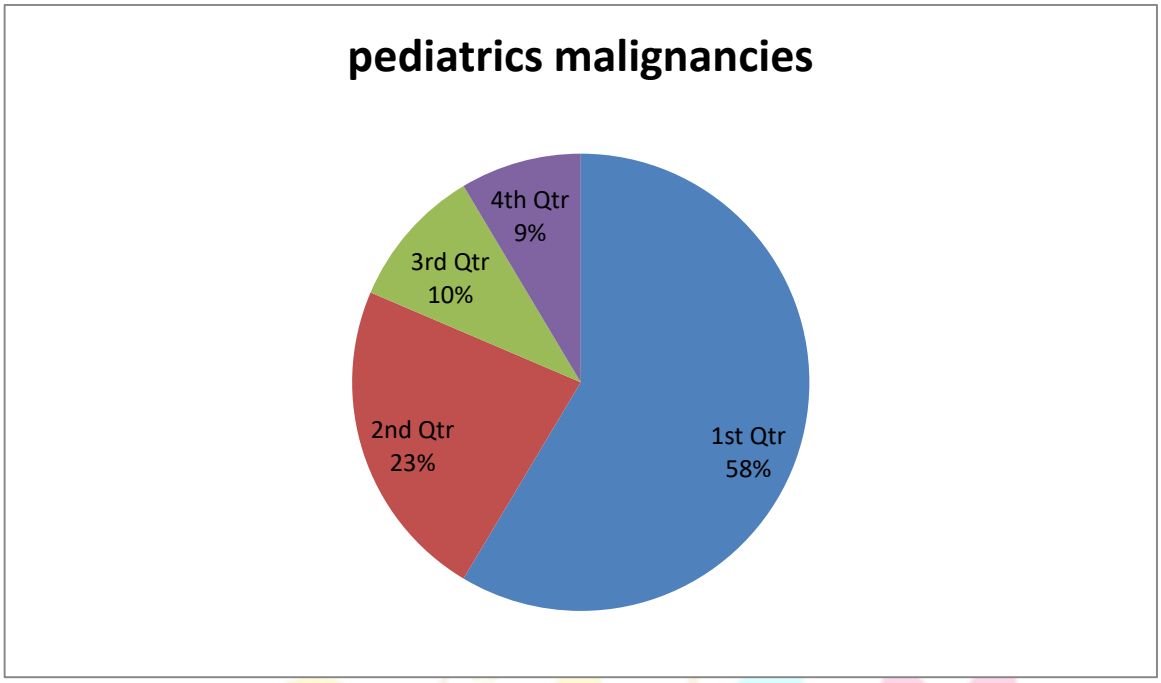
Bronchial asthma 1st tier

Bronchitis 2nd tier

Trauma 3rd tier

Tb lung 4th tier

Other non malignancies 5th tier



1st quar –leukemia

2nd quar-neuroblastoma

3rd –nephroblastoma

4th other childhood malignancies