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The Influence of Age Factor and Industrial Area on The Malignancy Rate of Bone Tumours

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Abstract

Bone tumour is a term for a group of tumours located in the bones. World Health Organization data in 2020 stated that the incidence rate of bone sarcoma in the Americas and Europe was 0.8 per 100,000 population. Industrial development, especially in areas with high population density, has environmental impacts such as air pollution and contamination of water sources. This has been associated with an increase in the prevalence of bone tumours in children. However, studies on this matter are still limited. This study aims to analyze the effect of industrial areas and age factors on the level of bone tumour malignancy. This study used observational analytics with a case-control design. Osteosarcoma as the case variable and GCT as the control variable. The sample used was 106, consisting of 53 osteosarcoma tumours and 53 GCT tumours. Age classification is divided into 0-18 years and 319 years. Industrial area classification is divided into <2.5 km and 32.5 km. Bivariate analysis using the chi square test. Has obtained approval from the Health Research Ethics Commission (KEPK) of RSUD dr. Moewardi with Number: 1.557/VI/HREC/2024. Results found no significant effect of age factor on the level of bone tumour malignancy (p-value=0.204). Meanwhile, an insignificant effect was also found between the proximity of residence to industrial areas on the level of bone tumour malignancy (p-value=0.121). This study shows that age factor and proximity of residence to industrial areas do not affect the level of bone tumour malignancy.

Introduction

Bone tumours are lumps found in bones due to uncontrolled growth of bone cells (Prabowo, 2023). The prevalence of bone and musculoskeletal tumour malignancy varies across ages with a percentage of 0.2- 0.5% (Bergovec et al., 2015). Data from the World Health Organization (WHO) in 2020 stated that the overall annual incidence rate of bone sarcoma in the Americas and Europe was 0.8 per 100,000 population. This figure is comparable to the incidence rates reported in Argentina and Brazil (1.5-2), as well as in Israel (1.4), especially for two types of tumours namely osteosarcoma and Ewing's sarcoma (WHO, 2020). However, countries in Asia such as India, China, and Japan have a very low incidence of bone tumours (Bergovec et al., 2015). Dr. Cipto Mangunkusumo Hospital (RSCM) stated 16.8 cases of osteosarcoma per year within a period of 13 years (1995-2007) which is the largest number of all bone malignancies (70.59%) (Kamal et al., 2016).

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The cause of bone tumours is still unknown, but several studies have shown a tendency towards genetic factors (Hameed et al., 2018). Osteosarcomagenesis is formed in bone development from unregulated mesenchymal stem cells, osteoblasts and osteoclasts. The tumour suppressor 53 (TP53) and retinoblastoma 1 (RB1) play a role in the development of this tumour. The TP53 gene and protein 53 (p53) products play an important role in regulating the cell cycle and apoptosis. Mutations in the TP53 gene trigger an uncontrolled cell cycle and increase genomic instability (Romadhon & Kurniati, 2024). Research by Perez et al., (2017) stated that osteosarcoma has increased among children with hereditary forms of retinoblastoma, Li-Fraumeni syndrome and other genetic syndromes. Other risk factors such as reproductive, perinatal, developmental, dietary and social do not show consistent findings (García- Pérez et al., 2017).

Age has shown an influence on the incidence of bone tumours and is correlated with the level of bone tumour malignancy. Benign bone tumours are mostly found in those aged <40 years (62.3%) and malignant bone tumours in those aged ≥40 years (70.4%). Patients over the age of 40 years are at risk of developing malignant tumours, increasing 5.345 times compared to those under the age of 40 years (Romadhon et al., 2024). Osteosarcoma often occurs in children and adolescents with an age range of 13-16 years (Purnaning & John, 2023). The peak incidence of osteosarcoma in males occurs at the age of 15-19 years and in females at the age of 10-14 years (Xin & Wei, 2020). Giant cell tumour (GCT) is a benign neoplasm that destroys bones. This tumour is characterized by giant cells that are osteolytic (Kurniati et al., 2023). GCT accounts for 4-10% of all primary bone tumours. The incidence of this disease is 80%, mainly found in the age range of 20-55 years (Arismawati, 2022). Other studies state that GCT has a peak incidence of 25-50 years (Sharma & Mehta, 2013).

Other factors associated with bone tumours are environmental factors such as carcinogenic chemicals and industrial pollution. Industrial development, especially in areas with high population density, has environmental impacts such as air pollution and contamination of water sources (García-Pérez et al., 2017). Pollutants generated by industrial estates are various. The International Agency for Research on Cancer (IARC) categorizes types of pollutants based on their carcinogenic properties in humans. Substances that are carcinogenic include arsenic, chromium, lead, dichloromethane, chlordane, and dichloromethane (García-Pérez et al., 2016). Another study stated that the majority of malignant bone tumour cases occurred in respondents who lived near the coastline with a distance of less than 14 km from the sea (Romadhon et al., 2024). Inversely proportional to the study by Edwards et al. (2021) which assessed that there was no relationship between exposure to agricultural herbicides phenoxy and chlorophenol and the incidence of sarcoma (Edwards et al., 2021). Research on bone tumours in childhood and their proximity to industrial areas is still very rare (García-Pérez et al., 2019).

A simple bibliometric analysis was conducted using the PUBMED database with the keywords ("age") AND ("industry") AND ("bone tumours") obtained 4 documents from 2015 to 2024. A search using Google Scholar yielded 2,640 documents. Meanwhile, a search using Google Scholar from 2015 to 2024 only yielded 63 with the addition of the keyword "Indonesia".

Methodology

Research design

The method used is observational analytic with a case control approach. This study was conducted in the Anatomical Pathology Laboratory, Faculty of Medicine, Muhammadiyah University of Surakarta.

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Population

The population of this study was medical records of histopathology preparations with a final diagnosis of bone tumours in the Anatomical Pathology Laboratory, Faculty of Medicine, Muhammadiyah University of Surakarta. The sample used in this study was medical records of histopathology preparations with a diagnosis of bone tumours in 2019 to 2020.

Sampling Technique and Sample Size Determination

The sample size was calculated using a hypothesis test for unpaired variables used for the ordinal scale (categorical scale). The sample size formula used adheres to Dahlan (2010) using the unpaired categorical analysis formula. A total of 106 samples were obtained for two variables, where the P1 and P2 values must be known from previous research. Sampling was carried out using the principle of the non-probability sampling method, consecutive sampling type, which is based on inclusion and exclusion criteria.

In the study of Romadhon et al., (2024), the prevalence of benign bone tumour sufferers aged less than 40 years was 62.3%, while the prevalence of malignant bone tumour sufferers aged less than 40 years was 37.7%. The Odds Ratio (OR) on the data was 5.345 and p-value = 0.000.

Restriction criteria

The inclusion criteria are medical records equipped with basic respondent data (date of birth, gender, complete address, and lesion predilection), addresses visible on the Google Maps application, and have a Pathology Anatomy diagnosis of osteosarcoma or GCT bone tumour with complete data.

The exclusion criteria include histopathology preparations that find malignant cancer from other organs (asynchronous), intensive radiation exposure, a history of Paget's bone disease, a history of bone marrow transplantation, and incomplete medical records.

Measurement

The data used are secondary data. The variables studied were age with categories from infants to adolescents (0-18 years) and adults to the elderly (≥19 years) as well as industrial areas with distance criteria of more than or equal to 2.5 km (≥2.5 km) and less than 2.5 km (<2.5 km).

Statistical analysis

Data analysis was carried out univariate and bivariate. Univariate analysis was used to determine the distribution of sample characteristics. Bivariate analysis to determine the effect between case variables and control variables. The statistical test used is the Chi-Square test with a 95% confidence level (p value <0.05) which refers to a significant correlation.

Ethical clearance

The researcher has obtained approval from the Health Research Ethics Commission (KEPK) of Dr. Moewardi Hospital with Number: 1.557 / VI / HREC / 2024.

Results and Discussion

Univariate Analysis Results

Univariate analysis to determine the distribution of characteristics of benign bone tumour and malignant bone tumour samples divided into variables of age, gender, distance of residence from industrial area, and type of industrial area.

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Table 1. Characteristics of benign bone tumour research sample

Variable	(n)	(%)
Benign (n=53)		
Age		
Infants to adolescents (0-18 years)	19	35,8
Adults to elderly (≥19 years)	34	64,2
Gender		
Male	23	43,4
Female	30	56,6
Distance Industrial Area		
≥2,5 km	6	11,3
<2,5 km	47	88,7
Type of Industrial Area		
Factory and company	35	66
Farm and agriculture	18	34

Based on Table 1, respondents with benign bone tumours were mostly found at a distance of less than 2.5 km (88.7%) from the industrial area with the type of industrial area of factories and companies (66%). This table also shows the age, the majority in the adult to elderly age category (64.2%) with female gender (56.6%).

Table 2. Characteristics of malignant bone tumour research samples

Variable	(n)	(%)
Malignant (n=53)		
Age		
Infants to adolescents (0-18 years)	13	24,5
Adults to elderly (≥19 years)	40	75,5
Gender		
Male	27	50,9
Female	26	49,1
Distance Industrial Area		
≥2,5 km	12	22,6
<2,5 km	41	77,4
Type of Industrial Area		
Factory and company	35	66
Farm and agriculture	18	34

Table 2 shows the characteristics of malignant bone tumour respondents were mostly found at a distance of less than 2.5 km (77.4%) from industrial areas with the type of industrial areas of factories and companies (66%). This table shows the majority of ages in the adult to elderly age category (75.5%) with male gender (50.9%).

Bivariate Analysis Results

Bivariate analysis to determine the effect of osteosarcoma tumour case variables (malignant bone tumours) and GCT control variables (benign bone tumours). The statistical test used was the Chi-Square test with a 95% confidence level (p value <0.05) which refers to a significant correlation.

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Table 3. Influence of age factor on the malignancy rate of bone tumours

Age	Benign		Malignant		OR	CI 95%		P
	F	(%)	F	Lower		Lower	Upper	
Infants to adolescents	19	35,9	13	24,5	0,582	0,251	1,348	0,204
Adults to elderly	34	64,1	40	75,5				
Total	53	100	53	100				

Table 3 shows the results of the bivariate analysis of the characteristics of the influence of age factors on malignancy rate of bone tumours obtained a Chi-square p-value of 0.204. This indicates that there is no significant influence between age factors on the level of bone tumour malignancy. This table shows the results that in both samples, both benign (64.1%) and malignant (75.5%) types of malignancy were mostly in adulthood to the elderly, namely in the age category of 19 to over 60 years.

Table 4. Influence of residential proximity to industrial areas on the malignancy rate of bone tumours

Distance	Benign		Malignant		Distance	Benign		P
	F	(%)	F	(%)		Lower	Upper	
<2,5 km	6	11,3	12	22,7	0,436	0,150	1,266	0,121
≥2,5 km	47	88,7	41	77,3				
Total	53	100	53	100				

Based on Table 4, the results of the bivariate analysis of the characteristics of the influence of residential proximity to industrial areas on the malignancy rate of bone tumours obtained a Chi-square p-value of 0.121. This indicates that there is no significant influence between industrial areas and the level of bone tumour malignancy. This table shows the results that in both samples, both benign (88.7%) and malignant (77.3%) types of malignancy were mostly located at a distance of residence close to the industrial area of less than 2.5 km.

Medical record data covering the period 2019 to 2020, along with the geographical distribution depicted, were also included in the analysis. This study included 106 cases of bone tumours categorized into benign bone tumours 53 cases in Figure 1 and malignant bone tumours 53 cases in Figure 2.

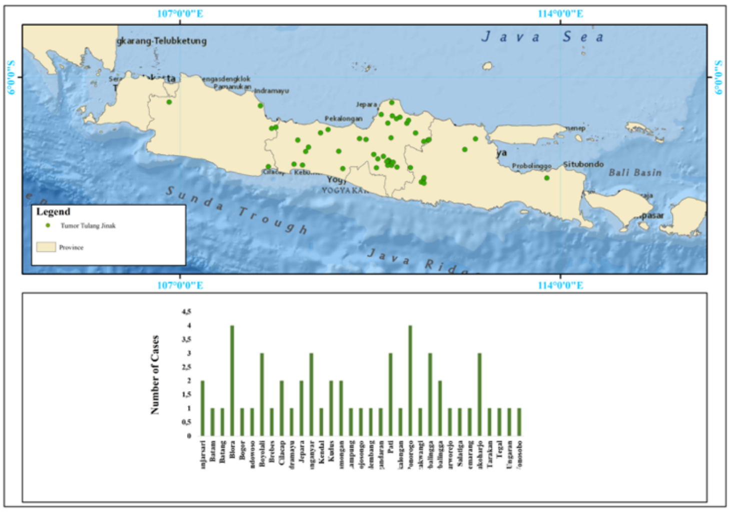

Figure 1. The distribution of benign bone tumour cases from 2019 to 2020

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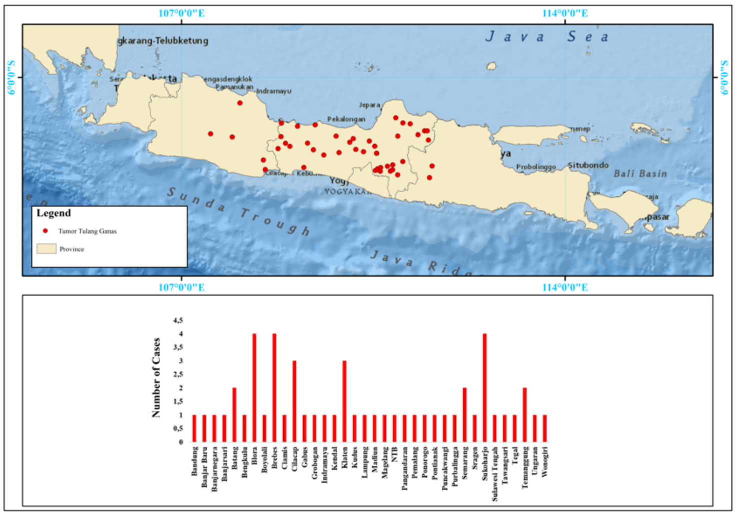

Figure 2. The distribution of malignant bone tumour cases from 2019 to 2020

The influence of age factor on the malignancy rate of bone tumours

Based on Table 3 shows the characteristics of the influence of age factors on malignancy rate of bone tumours, the Chi-square p-value of 0.204 is obtained, indicating an insignificant effect. Benign bone tumour respondents are in the adult to elderly age category in the age range more than 19 years (64.1%), while malignant bone tumour respondents are in the same age category (75.5%).

These results are not in accordance with the research conducted by Romadhon et al., (2024) in Indonesia at the age of less than 40 years and more than or equal to 40 years. Benign bone tumours are mostly found at the age less than 40 years, amounting to 66 respondents (62.3%) and malignant bone tumours are mostly found at the age of more than or equal to 40 years, amounting to 38 respondents (70.4%). Based on the results of multivariate testing with logistic regression, there is a significant age variable with an odds ratio of 5.345 and a p-value <0.05. This shows that the risk of sufferers more than or equal to 40 years of age to experience malignant tumours increases 5.345 times compared to the age of less than 40 years. This study analyzed respondents including individuals, environment and demographics. (Romadhon et al., 2024).

Other supporting findings are based on the study of Kurniati et al., (2023) in Java, Indonesia. The results of this study stated that age factors have a significant influence on the incidence of Giant Cell Tumours (GCT) with a p-value of 0.007. The majority of respondents were in the 20-50 year age category (67.3%). The study involved respondents with respondent criteria with age variable data with an age category of 20-50 years and a place of residence with rural and urban categories listed in medical records (Kurniati et al., 2023). Other findings are based on the study of Zhang et al., (2024) in Wuhan, China at the ages of 25 and 45 years. The results of the study presented significant results related to osteosarcoma and the elderly with a p-value of 0.0002. This study reveals a new molecular mechanism that links cellular aging and cancer development through methylmalonic acid (MMA)-driven transcriptional reprogramming of the Maf Bzib Transcription Factor B NOTCH3 (MAFB-NOTCH3) axis. This study involves the mechanism of osteosarcoma development in the elderly, especially regarding the MAFB/NOTCH3 axis and the role of MMA in tumour development, but does not mention the geographic location or specific population of origin of the respondent sample (Zhang et al., 2024).

The age of patients with bone tumours correlates with tumour aggressiveness. Younger patients (less than 50 years) with bone tumours show different molecular profiles compared to older

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patients. This is due to different genomic changes and pathways such as higher KRT2 mutations in the younger age group and increased TP53 gene mutations in the elderly group. The aggressiveness of malignant bone tumours is indicated by Ki-67 protein levels playing an important role in predicting the risk of metastasis and local recurrence. Higher Ki-67 values are associated with an increased risk of adverse outcomes (Japie et al., 2019).

This study focused on 106 respondents with 53 osteosarcoma case variables and 53 GCT control variables. Age classification in this study used the categories of infants to adolescents (0-18 years) and adults to the elderly (≥19 years). The table below is a summary of previous research related of the age factors on malignancy rate of bone tumours.

Table 5. Summary of previous research of the age factor on the malignancy rate of bone tumours

Research	Research Methods	Sample	Age Category	Results
Romadhon et al., (2024)	cross sectional	106 samples at age less than 40 years and 54 samples at age more than or equal to 40 years	less than 40 years and more than or equal to 40 years	In cases of benign bone tumours, a diagnosis of GCT was obtained in 33 cases out of 82 cases, while in malignant bone tumours, a diagnosis of osteosarcoma was obtained in 28 cases out of 78 cases.
Kurniati et al., (2023)	analytical observational cross sectional	47 GCT samples and 60 non GCT samples	the high-risk age category is 20-50 years while the low-risk age is <20 years and >50 years	The highest frequency of bone tumours was in the 20-50 year age category at 67.3% (72 samples)
Zhang et al., (2023)	experimental study	20 samples with diagnosis of osteosarcoma	less than 25 years and more than 45 years	Methylmalonic acid (MMA) levels in elderly patients were significantly higher than in young patients. Then from MNNG/HOS cells showing the level of proliferation and migration of osteosarcoma cells were found in human serum of 10% of four young patients and four elderly patients.

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The influence of residential proximity to industrial areas on the malignancy rate of bone tumours

Based on Table 4 shows characteristics the influence proximity of the residence to the industrial area of less than 2.5 km on the malignancy rate of bone tumours, the Chi-square p-value of 0.121 is obtained, indicating an insignificant effect. Respondents with benign bone tumours were more (88.7%) compared to respondents with malignant bone tumours (77.3%). The results of this study are in accordance with research conducted by Edwards et al. (2021) in the United States. The study stated that there was no significant effect that assessed exposure to phenoxy and chlorophenol herbicides and the incidence of sarcoma with a p-value = 1.00. This study involved the criteria of respondents aged over 18 years with exposure to chemicals including herbicides, pesticides, dioxins, vinyl chloride monomers and others. (Edwards et al., 2021).

These findings contradict research conducted by Garcia-Perez et al. (2019) in Spain. This study stated that there was a statistically significant difference between bone tumours and industrial distances of less than or equal to 2.5 km found in environments with facilities that release substances included in all groups of the International Agency for Research on Cancer (IARC) (Garcia-Perez et al, 2019). IARC is divided into three groups, group 1, namely human carcinogens including arsenic, cadmium, chromium, nickel, lindane and so on with an odds ratio value = 2.02. Group 2A, namely possibly carcinogenic to humans, includes lead, dichloromethane, tetrachloroethylene, DDT and hexabromobiphenyl with an odds ratio value = 2.13. Group 2B, which is possibly carcinogenic to humans with a lower level of confidence, includes chlordane, 1,2-dichloroethane, dichloromethane, heptachlor ethyl benzene and so on with an odds ratio value = 2.26. This study involved respondents aged 0-14 years, gender and place of residence regarding the proximity of settlements to environmental pollution (García-Pérez et al., 2016).

Another study by Garcia-Pérez et al., (2017) in Spain at the age of less than 15 years mentioned bone tumours in children around industrial areas with a distance of less than 3 km obtained an OR value = 2.33. This is associated with bone tumours in children in urban areas with a distance of less than 3 km obtained an OR value = 4.43. The study involved respondents with criteria for proximity to industrial areas, industrial installations, urban distance to the respondent's residence. (García-Pérez et al., 2017).

A meta-analytic study by Soria & Buckberry (2022) in the United Kindom, analyzing samples with malignant bone neoplasms in two periods, medieval and industrial revolution, showed significant differences. This research proved that the prevalence of malignant neoplasms progressed from medieval (0.06%) to industrial revolution (0.36%) with a p value <0.001. This supports the hypothesis that the malignancy of bone tumours increased with the rapid expansion of industrialization. This study involved respondents with criteria of gender, age, and socio-economic status. The development of malignant bone disease is known to increase due to exposure to carcinogens and pollution during the industrial revolution (Soria & Buckberry, 2022).

The "near vs far" analysis by industry group category (≤2.5 km) was differentiated by metal production and processing, metal and plastic surface treatment, cement and lime, organic chemical industry, pharmaceutical products and municipal wastewater management plants. The energy sector (combustion plants) releases carcinogens into the environment (metals, dioxins, polyaromatic hydrocarbons (PAHs) and benzene) and this industry group is the largest polluter of aromatic pollutant complexes (PACs) and persistent organic pollutants (POPs) in the air and sea. In addition, emissions from coal-fired plants contain radioactive elements mainly thorium and uranium as well as by-products such as radon, radium, cyanotopes, bismuth and lead. These findings are associated with an excess risk of bone cancer near such facilities.

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Industrial areas emit hazardous materials especially those of carcinogenic nature, significantly contributing to the pathogenesis of bone tumours. These substances affect body systems such as the cardiovascular, respiratory and nervous systems potentially leading to the development of bone tumours as an ingredient of the tumourigenesis process. Carcinogens from industrial emissions can access the intranuclear compartment of cells, causing DNA nucleobase damage and characteristic activating genomic events in tumour formation (Bignold, 2015).

This study focused on 106 respondents with 53 osteosarcoma case variables and 53 GCT control variables. The classification of industrial areas in this study used the distance categories <2.5 km and ≥2.5 km. The table below is a summary of previous research related to risk factors of the residence to the industrial area on the malignancy rate of bone tumours.

Table 6. Summary of previous research of the residence to the industrial area on the malignancy rate of bone tumours

Research	Research Methods	Sample	Country	Results
Edwards et al. (2021)	systematic literature review	adults aged more than 18 years with exposure to various chemicals	Sweden, Italy, Canada, New Zealand and the United States	Significant association between occupational exposure to phenoxy and chlorophenol herbicides and sarcoma incidence. Mortality associated with sarcoma in the cohort study also showed a significant association, with a Standardized Mortality Ratio (SMR) of 40.93 (95% CI 2.19, 765.90), P = 0.013.
Garcia-Pérez et al., (2017)	cross sectional	114 cases (children diagnosed with bone tumours) and 684 controls (children without bone tumours)	Spain with focus on Catalonia and Madrid	The results were significant for distances of 3 km (OR = 2.33, 95% CI = 1.17–4.63) and distances of 2.5 km (OR = 2.19, 95% CI = 1.10–4.39)
Soria & Buckberry, 2022	meta-analytic	respondents from the two century : medieval and industrial revolution periods with a total of 13,721 cases of malignant neoplastic disease of bone	England	There was a significant increase in bone malignancy from the medieval period (0.06%) to the industrial period (0.36%). The difference was statistically significant ($p < 0.001$).

Conclusion

This study shows that age and proximity to industrial areas do not affect the level of bone tumour malignancy. Based on the results of the study, further exploratory research is needed on the risk factors for bone tumour malignancy.

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