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Region Variation of Hematological Malignancies and Solid Tumors in Children in East Java

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ABSTRACT

Introduction: The prevalence of childhood cancer in East Java is unevenly associated with differences in exposure to carcinogens in urban-industrial areas, agricultural chemicals, industrial waste along the river, and socio-culture. However, there are no data on regional variations in childhood cancer in East Java. We describe the regional variation of hematological malignancies and solid tumors in East Java.

Material and Methods: The study was conducted by cross-sectional on children with cancer aged <18 years in dr. Soetomo General Academic Hospital in 2014-2015. The data evaluated were gender, age, and cancer type (hematological malignancy and solid tumor). They came from Mataraman, Madura Island, industrial-urban areas (Surabaya-Sidoarjo-Gresik), and Tapal Kuda. We used the Chi-square test and Logistic Regression for data analysis ($p<0.05$ for two-tailed test).

Results: During the study period, there were 353 children with cancer, consisting of 56.9% hematological malignancies and 43.1% solid tumors: 60.9% boys, and 82.4% aged <10 years. Hematological malignancies in industries-urban areas are more numerous than in Mataraman, Madura Island, and Tapal Kuda; 67.8%, 52.8%, 47.2%, and 50.9%, respectively ($p=0.031$). Hematologic malignancies were also more common in aged <10 years (60.5% vs 40.3%; $p=0.004$ OR=2.265; 95% CI=1.295-3.362) and Javanese race ($p=0.025$; OR=3.257; 95% CI=1.121-5.263). Children in industrial-urban areas had more hematological malignancies than Mataraman ($p=0.027$; OR=2.353; 95% CI=1.101-5.030) also Tapal Kuda ($p=0.015$; OR=1.881; 95% CI=1.132-3.124) and Madura Island ($p=0.032$; OR=2.033; 95% CI=1.064-3.882).

Conclusion: Hematological malignancies in industry and urban areas are more numerous than Mataraman, Madura Island, and Tapal Kuda area. Solid tumors were mostly found on Madura Island.

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INTRODUCTION

Accurate knowledge of cancer epidemiology can provide information about possible causes and trends in the population. This is useful in prevention strategies, early detection, and treatment. The utilization of cancer epidemiology can also develop efficient policies for prevention, screening, and diagnosis [1]. Race, ethnicity, gender, age group, socioeconomic status, and geographic location are common indicators of childhood cancer disparity [2–4]. The incidence of some cancers is associated with increased detection and access to treatment, which can vary by geographic location [5–7]. Geographical variations may be influenced by age, economic status, or rural or urban classification [3,5,8–10].

The most common cancers in children younger than 14 years are leukemia (37%), cancers of the brain and nervous system (16%), and lymphoma (13%). In the age range of 15-49 years, breast cancer (13%) was the most common malignancy, followed by liver cancer (12%) and lung (9%) [11]. Boys and girls have the same proportion of hematological malignancies or solid tumors in all regions. Based on cancer registry data from

14 cancer service centers in Indonesia, the most cases of childhood cancer were boys (57%) from 4156 cases in 2008-2012. Cancer in males was also higher for epithelial malignancies (22.4% and 17.2%) and leukemia (19.3% and 14.3%) [12]. One-third of solid tumors in industrialized countries during adolescence are lymphomas, followed by CNS tumors in a quarter of cases [13]. This study reported that most cancers were leukemia, lymphoma, bone tumor, and retinoblastoma. Cancer incidence in children in industrialized countries is quite high [13].

Industrial and urban areas will increase the risk of cancer in children due to exposure to carcinogens and chemicals, but geographic variability also affects the incidence of childhood cancer. Variations in cancer incidence are influenced by differences in exposure to carcinogenic chemicals such as air pollution, cigarettes, food, and other chemicals [3,7,14]. Genetic predisposition also influences the incidence of cancer in children [7]. The prevalence of childhood cancer in East Java is unevenly associated with differences in exposure to carcinogens in urban-industrial areas, agricultural chemicals, industrial waste along the river, and socio-culture. However, there are no data on regional variations in childhood cancer in East Java. This study aimed to describe the regionalization of childhood cancer in East Java, which was differentiated into hematological malignancies and solid tumors.

MATERIAL AND METHODS

The study was conducted cross-sectionally on children with cancer, who were less than 18 years old, both boys and girls. The children with cancer were registered in the Division of Hematology-Oncology, Department of Child Health, Dr. Soetomo General Academic Hospital between 2014 and 2015. All the data were taken primarily by the researcher from the data registration. This study only evaluated children from East Java Province. Children with cancer living outside East Java were excluded. The basic data evaluated were gender, age, and type of cancer. The age of children was grouped into two, namely childhood and adolescence. The criteria for childhood were children aged less than 10 years old, and adolescence were children aged 11-18 years old when the cancer diagnosis was made.

Research ethics were obtained from the Health Research Ethics Committee, Dr. Soetomo General Academic Hospital Surabaya.

Cancer in children was grouped into two, namely hematological malignancies and solid tumors. The diagnosis of hematological malignancy was made on the basis of bone marrow aspiration. Bone marrow aspiration examination was carried out by a Pediatrician, Consultant Hematology Oncology at the Department of Child Health, Dr. Soetomo General Academic Hospital. The types of cancer in this group are acute lymphoblastic leukemia (ALL), acute myeloblastic leukemia (AML) and chronic myelocytic leukemia (CML). Solid tumors were confirmed by histopathological examination by a specialist in anatomical pathology at Dr. Soetomo General Academic Hospital Surabaya or radiological examinations such as computed tomography scan (CT Scan) and magnetic resonance imaging (MRI). Types of cancer that are categorized as solid tumors include retinoblastoma, osteosarcoma, nephroblastoma, germ cell tumors, lymphoma, and rhabdomyosarcoma. Tumors originating in the central nervous system (CNS tumors) were not included in this study. CNS tumors were treated in the Department of Neurosurgery and not in the Department of Child Health. The clinical signs and symptoms of cancer were not assessed. The results of supporting examinations and outcomes were also not assessed in this study.

Regionalization of residence was defined as the child's domicile in the last 2 years based on medical record information. The place of residence does not refer to the address according to the parent's identity card but the location in the last 2 years where the child lives. Children who come from outside the East Java region and seek treatment at Dr. Soetomo General Academic Hospital were excluded. Children with addresses from East Java but living outside East Java were also excluded from this study. The regionalization was divided based on ethnicity, use of language, and natural phenomenon that exist in the area, such as areas with dominance of rice fields or rivers, industrial buildings, and mountainous areas.

The subject's place of residence was divided into Mataraman (western part of East Java, the main language is Java), Madura Island, urban-industrial area (Surabaya, Sidoarjo, Gresik) and Tapal Kuda or The Eastern Salient of Java area (eastern part of East Java and the main language is Madura). The Mataraman area consists of Ngawi, Madiun, Magetan, Pacitan, Ponorogo, Kediri, Blitar, Nganjuk, Trenggalek, Tulungagung, Bojonegoro, Tuban, Lamongan, Jombang and Malang. The Madura Island area consists of Bangkalan, Sampang, Pamekasan and Sumenep. The urban industrial area consists of Gresik, Surabaya and Sidoarjo. The Tapal Kuda area consists of Pasuruan, Lumajang, Probolinggo, Jember and Banyuwangi. One area may be an insertion of two regions, for example Malang Regency, which is partly Mataraman and part of the Tapal Kuda area, but in this study the main classification was chosen.

Table 1. Basic Characteristics of Research Subjects

Characteristics	Hematological Malignancies n = 201	Solid Tumor n = 152	Total n = 353	*p*
Age				
Mean (SD), years	5.7 (3.7)	6.2 (4.41)	5.9 (4.04)	0.668[a]
Median (range), years	5 (1-17)	5 (1-16)	5 (1-17)	
Age category				
< 1 years	16 (8.0)	15 (9.9)	31 (8.8)	0.005[b]
1-5 years	99 (49.43)	73 (48.0)	172 (48.7)	
6-10 years	61 (30.3)	27 (17.9)	88 (24.9)	
>10 years	25 (12.4)	37 (24.3)	33 (15.9%)	
Gender				
Boys	120 (59.7)	95 (62.5)	215 (60.9)	0.594[b]
Girls	81 (40.3)	57 (37.5)	138 (39.1)	
Area of origin				
Surabaya	40 (19.9)	26 (17.1)	66 (18.7)	0.505[b]
Outside Surabaya	161 (80.1)	126 (82.9)	287 (81.3)	

Description= p[a] analyzed by Mann-Whitney U test, p[b] analyzed by Chi-Square Tests

All data were recorded in a data collection sheet and then coded, sorted, and typed into a worksheet on a computer using the SPSS 18 program. The data was displayed in the form of tables and frequencies. The difference in the proportions between hematological malignancies and solid tumors based on age and sex classification was evaluated by the Chi-square test. Differences in the proportion of cancer types and regionalization in East Java were analyzed using the Kolmogorov-Smirnov test and logistic regression. The amount of risk is expressed in the odd ratio (OR) with a 95% confidence interval (95% CI). All tests were performed at =0.05 for the two-tailed test with a significance level of p<0.05.

RESULTS

During the study period, 414 children were diagnosed with cancer in our hospital. A total of 24 children were excluded because they live outside the East Java region consisting of Central Java (2), Kalimantan (15), Papua (1), Nusa Tenggara (5), and Sumatra (1). A total of 37 children were excluded because the examination data were incomplete. The number of children included in the analysis was 353 children (85.3%). During the study period, the number of children with a diagnosis of hematological malignancy was 201 (56.9%) and 152 children (43.1%). The data can be seen in Table 1.

The proportion of age in the type of cancer showed a significant difference (p=0.005). Hematologic malignancies and solid tumors are more common in children less than 5 years old. In older children (aged 6-10 years), the proportion of hematological malignancies was higher than that of solid tumors at 30.3% compared to 24.3%. Solid tumors are more common in children aged over 10 years, namely 24.3%. The number of boys is more than girls for both hematological malignancies and solid tumors. Most of the children came from outside Surabaya (81.3%).

Table 2. Types of Cancer in Children

Hematological Malignancies		Solid Tumor	
Type	**Frequency (Percentage)**	**Type**	**Frequency (Percentage)**
Acute lymphoblastic leukemia	184 (91.5)	Limfoma (Non-Hodgkin, Hodgkin dan Burkitt)	33 (21.7)
Acute myeloblastic leukemia	9 (4.5)	Retinoblastoma	28 (18.4)
Chronic myelocytic leukemia	8 (4.0)	Bone tumor (Osteosarcoma, Ewing Sarcoma dan PNET)	17 (11.3)
		Germ Cell tumor	15 (9.9)
		Squamous cell carcinoma	9 (5.9)
		Hepatoblastoma	7 (4.6)
		Histiocytosis	7 (4.6)
		Rhabdomyosarcoma	5 (3.3)
		Nasopharyngeal cancer	5 (3.3)
		Others	15 (9.9)

Table 3. Risk Factors for Cancer Incidence based on The Characteristics of Age, Gender and Domicile Regionalization in East Java

Characteristics	Hematological Malignancies n = 201	Solid Tumor n = 152	*p*	OR	95% CI
Age category					
< 10 years	176 (87.6)	115 (75.7)	0.004[a]	2.265	1.295 to 3.962
≥10 years	25 (12.4)	37 (24.3)			
Gender					
Boys	120 (59.7)	95 (62.5)	0.594[a]	0.889	0.577 to 1.370
Girls	81 (40.3)	57 (37.5)			
Area of origin					
Surabaya	40 (19.9)	26 (17.1)	0.505[a]	1.204	0.697 to 2.079
Outside Surabaya	161 (80.1)	126 (82.9)			
Main ethnic group classification					
Javanese	155 (77.1)	105 (69.1)	0.025[a]	3.257	1.121-5.263
Madurese	46 (22.9)	47 (30.9)			
Region classification					
Mataraman[c]	75 (37.3)	67 (44.1)	0.031[a]		
Tapal Kuda area	29 (14.4)	28 (18.4)	0.015[b]	1.881	1.132 to 3.124
Madura Island	17 (8.5)	19 (12.5)	0.032[b]	2.033	1.064 to 3.882
Industrial and urban	80 (39.8)	38 (25.0)	0.027[b]	2.353	1.101 to 5.030

Description = pa analyzed by Chi-Square Tests, pb analyzed by binary logistic, r reference group

Acute lymphoblastic leukemia (ALL) occupies the highest proportion of hematological malignancies, namely 91.5%. ALL also ranks first of all malignancies, namely 184/353 (52.1%). Acute myeloblastic leukemia and chronic myelocytic leukemia have a small proportion of only 4%. Lymphoma was ranked first for solid tumors in children, namely 21.7% consisting of Hodgkin's lymphoma, non-Hodgkin's lymphoma, and Burkitt's lymphoma. The second most common solid tumor was retinoblastoma (18.4) followed by bone tumor (11.3%) consisting of osteosarcoma, Ewing sarcoma, and PNET. The data can be seen in Table 2.

Hematological malignancies are more common in children aged less than 10 years (childhood) than children aged over 10 years (adolescence). The risk of developing hematological malignancies in childhood was OR=2.265 (p=0.004; 95% CI 1.295 to 3.962). The proportion of hematological malignancies and solid tumors did not differ between boys and girls (p=0.594). The proportion of hematological malignancies and solid tumors also did not differ based on the origin of Surabaya and outside Surabaya as the provincial capital (p=0.505). Hematological malignancies are also more common in areas where the main language of instruction is Javanese or Javanese compared to Madura (p=0.025; OR=3.257; 95%CI 1.121-5.263).

Hematological malignancies were the most common type of cancer in Mataraman and industrial-urban areas, namely 75/142 (52.8%) and 80/118 (67.8%). Solid tumors were mostly found on Madura Island, namely 19/36 (52.8%). The proportion of hematological malignancies and solid tumors in the Tapal Kuda area is almost the same, namely 50%. The proportion of cancer incidence between hematological malignancies and solid tumors based on regionalization in East Java showed a significant difference with p=0.031. The data can be seen in table 3. Children in industrial-urban areas more experienced hematological malignancies than Mataraman (p=0.027; OR=2.353; 95%CI 1.101-5.030) also in Tapal Kuda (p=0.015; OR=1.881; 95%). CI=1.132-3.124) and Madura Island (p=0.032; OR=2.033; 95%CI=1.064-3.882).

DISCUSSION

Regionalization of cancer in an area will provide different treatment strategies. This study shows that the distribution of cancer in East Java is very different in terms of age variations, variations in cancer types, and regionalization of the most common cancer types. Cancer in East Java is more common in children aged less than 10 years, especially those who live in industrial and urban areas. Certain age groups tend to develop certain types of cancer. Leukemia in this study was more commonly found at the age of less than 5 years, while solid tumors were more commonly found at the age of over 10 years. The proportion of hematological malignancies found was 56.9% of 353 children under 18 years of age. The most common cancers in children younger than 14 years are leukemia (37%), cancers of the brain and nervous system (16%), and lymphoma (13%). In the age range of 15-49 years, breast cancer (13%) was the most common malignancy, followed by liver cancer (12%) and lung (9%) [11]. Boys and girls have the same proportion of hematological malignancies or solid tumors in all regions.

Based on cancer registry data from 14 cancer service centers in Indonesia, the most cases of childhood cancer were boys (57%) from 4156 cases in 2008-2012. Cancer in males was also higher for epithelial malignancies (22.4% and 17.2%) and leukemia (19.3% and 14.3%) [12]. One-third of solid tumors in industrialized countries during adolescence are lymphomas, followed by CNS tumors with a quarter of cases [13]. This study reported that most cancers were leukemia, lymphoma, bone tumor, and retinoblastoma.

Hematologic malignancies or leukemia are more commonly found in younger children (childhood) than in adolescence. The magnitude of the risk of developing hematological malignancies in childhood is 2.3 times greater. Until now, leukemia is still the largest part of malignancy in children [13]. The proportion of hematologic malignancies and solid tumors did not differ between boys and girls. The proportion of hematological malignancies and solid tumors also did not differ based on the origin of Surabaya and outside Surabaya as the provincial capital. Race, ethnicity, gender, age group, socioeconomic status, and geographic location are common indicators of childhood cancer disparities [2,3]. Different races and ethnicities will affect the prevalence of different cancers and also the type of cancer. Hematologic malignancies are more often found in areas with Javanese ethnicity compared to Madura, with a 3.2 times greater risk. Racial disparities are particularly evident in ALL with a higher incidence in whites [3,4].

Hematological malignancies were the most common type of cancer in Mataraman and industrial-urban areas, namely 75/142 (52.8%) and 80/118 (67.8%). Solid tumors were mostly found in Madura Island, namely 19/36 (52.8%). The incidence of cancer in children and adolescents in industrialized countries is less than 2%, but the mortality rate is quite high [13]. Children living in industrial and urban areas are prone to various carcinogens and exposure to chemicals. The proportion of hematological malignancies and solid tumors in the Tapal Kuda area is almost the same, namely 50%. Geographic variations in the incidence of childhood cancer can be caused by many factors. Variations in cancer incidence are associated with differences in exposure to carcinogenic chemicals such as air pollution, cigarettes, and contaminated food and beverages [3,7,14]. Genetic predisposition also influences the incidence of cancer in children [7]. This is what causes the difference in the prevalence of cancer in children in East Java. Children in East Java are divided into two main ethnic groups, namely the Javanese and the Madurese. Some areas may be evenly mixed so that the basic characteristics of the tribe become invisible. The incidence of cancer can differ depending on race; for example, Hispanic children are more likely to develop acute lymphoblastic leukemia [3,7]. Most cancers are not solely caused by genetic factors. Exposure to radiation and cancer-causing chemicals in food, water, air, and consumer products early in life can cause cancer later in life. Prevention of early-life exposure to carcinogens is critical [14].

The incidence of some types of cancer may be associated with increased detection and access to treatment, which can vary by geographic location [5–7]. Therefore, the incidence of cancer in industrial and urban areas, namely Gresik, Sidoarjo, and Surabaya became quite a lot of cases (33.3%). In addition, geographic variation may be influenced by age, economic status, or rural or urban classification [3,5,8–10]. Children in urban industries such as Surabaya, Gresik, and Sidoarjo are more likely to experience hematological malignancies than in Mataraman areas with 2.3 times greater risk. Epidemiological data link parental occupations related to hydrocarbons, such as repair shop workers, motor vehicle mechanics, machinists, woodcutters, painters, dyers, and cleaners with childhood cancer [3,15]. Father's occupations, particularly gas station attendants, car or truck repair, and aircraft maintenance, have been linked to infant leukemia, and maternal occupations, particularly laundry/dry cleaning, have been linked to Wilm's tumor. Parental work, especially work related to hydrocarbons, metals, and radiation, has been linked to the development of childhood cancers, especially Wilms tumor, acute non-lymphocytic leukemia, and hepatocellular carcinoma [2,3,16].

Cancer in the Mataraman area is higher at 40% but the area is under more than 15 districts/cities in East Java. The Mataraman area is more dominant in agriculture and also the coast and river flow. Pesticide exposure in the father, during pregnancy, and postpartum is associated with childhood cancer. A geographical location dominated by rice fields and agriculture is associated with the potential for pesticide use and external exposure to clothing that increases the incidence of childhood cancer [2,15,17].

The Mataraman area and Tapal Kuda area are two areas that are geographically categorized as rural and far from cancer centers. Although many parents work in agricultural areas in the Mataraman area, the amount of exposure experienced may vary. Carcinogens and mutagens that stick to clothes and are brought into the home may also be different. Many different chemicals, but farmers can be exposed to pesticides, chemical fertilizers, solvents and other chemicals, fuel, and engine exhaust, organic and inorganic dust, welding fumes, mycotoxins and zoonotic viruses, heat, noise, and vibration [18]. The geographic distribution of the incidence rates of all pediatric cancers varies and is at least 10% higher incidence in rural areas more than 1 hour from urban healthcare centers [10]. Previous studies investigating the geographic burden of care in

pediatric cancer revealed that driving distances of two hours or more from a treatment center could have financial and social impacts on patients and their families [10,19].

The leading exogenous causes of cancer in children are ionizing radiation, ultraviolet radiation from sunlight, and certain viruses. As many as 10% of children and adolescents with cancer may have germline mutations in cancer-predisposing genes and the remainder is more towards environmental exposure [13]. The rate of the type of cancer that mostly affects adults also vary according to rural and urban status. Cancer in adults may be associated with obesity or smoking, which may not explain the rural and urban variation in childhood cancer [3,9]. Exposure to carcinogens in children in rural and urban areas is different, as well as children in industrial and agricultural areas as well as children along rivers and coastal monitoring areas are also different. Carcinogens do not immediately cause cancer but require a long induction period [3,20]. The presence of carcinogens may require high cumulative doses that are only present in certain areas, but this study does not have data on types of environmental carcinogens.

The area of East Java stretches from the west end of Pacitan and reaches Banyuwangi at the east end on the southern coast of Java Island. The northern area stretches from Tuban to Gresik and Surabaya at the eastern end as well as Madura Island. The north side of Mataraman area is the watershed of the Solo River and the Berantas River. The two major rivers carry various pollutants, especially agricultural pollutants and household industrial pollutants along their streams. Therefore, the incidence of cancer is common in the areas of Tuban, Bojonegoro, Lamongan, and Gresik for cases of childhood leukemia. Many carcinogenic chemicals have become an integral part of our food and water supply and are present in the air and the general environment that follows along streams [14]. The incidence of cancer is also increased in individuals living in the area of food crops, especially for leukemia, lymphoma, neuroblastoma, Wilms tumor, and other tumors except for retinoblastoma [17].

East Java has a large area consisting of rural areas, especially in the Mataraman and Tapal Kuda areas. Both areas come from two different ethnicities, namely Javanese and Madurese, but the main livelihood is agriculture and they live in rural areas. Cancer incidence rates are generally higher in urban than rural populations (10.2% vs. 4.8%) to studies in the United States [9]. Communities in rural areas also have barriers to access to health care, a lack of cancer service facilities and a lack of understanding and distance from cancer service centers. Rural residents have lower rates of cancer screening and experience lower-quality cancer care [9,21,22].

This study successfully showed regional variations in East Java with the incidence of hematological malignancies and solid tumors in children. However, this research also has limitations. The size of the overall child population varies from year to year. This is associated with a population that only comes from one cancer center in East Java. Some cancer centers in East Java are Dr. Soetomo General Academic Hospital and Syaiful Anwar Hospital in Malang. In addition, some children who live in the western part of East Java also seek treatment in Solo, Jogja and Semarang. This causes the prevalence of cancer in the Mataraman area to decrease even though it is estimated that the area is large which oversees 15 districts/cities. The study also did not report on cancers treated outside the Department of Child Health. Cancers of the eye, kidney and CNS cancers were also missed in this study.

CONCLUSION

Childhood cancer in East Java is more often found at the age of less than 10 years who live in industrial-urban areas and from the Javanese compared to Madura. Hematological malignancies in industry and urban areas are more numerous than Mataraman, Madura Island, and Tapal Kuda area. Solid tumors were mostly found on Madura Island.

By knowing the epidemiological pattern of cancer in children, we can find out the distribution pattern associated with the risk factors in that area. We can identify the possible carcinogens or mutagens that exist, so we can prevent cancer in children by avoiding or minimizing these exposures. Unfortunately, this study did not evaluate what types of pollutants, carcinogens or mutagens that may affect cancer occurrence. To find out the causal relationship between the type of chemical and the type of cancer further research is needed.

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CONFLICT OF INTEREST

The authors declare there is no potential conflict of interest.

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