RESEARCH COMMUNICATION

Prevalence and Risk of Leukemia in the Multi-ethnic Population of North Karnataka

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Abstract

Background: The aim of this study was to analyze the trends in the incidence rates of four major types of leukemia in the population of North Karnataka, which accounts for the 2.5% of the whole population of India. Due to the lack of any nationwide leukemia screening program, the majority of the people are not aware of the disease. Epidemiological study can play a vital role in understanding the occurrence and outcome of the disease. Patients and Methods: Focusing on variables like age, sex, race, blood group and lifestyle habits, detailed reports of 417 males and 230 females (M:F ratio 1.8:1) were collected from different hospitals of North Karnataka and analyzed for their risk of leukemia. Results: Compared to female patients, Hindu males were found to have greater risk of occurrence of leukemia (p=0.0333). The males of scheduled caste (SC) and Lingayat communities showed a high risk than other communities (p=0.000). The occurrence of AML showed a significant relationship with ABO blood groups (p=0.0090). The frequency of leukemia is quite high in Belgaum district when compared to others districts of North Karnataka and totally absent in Bidar district. The reasons need precise molecular and genetical studies of the populaton. Conclusions: The localized communities of Lingayat and SCs needs to be further studied to get a better understanding for the higher risk of occurrence of leukemia in males. Moreover, since the spectrum of cancer epidemiology seen in India is different from that in developed countries more emphasis should be placed on better development of regional and national registries.

Keywords: Leukemia - epidemiology - cancer registration - Lingayat, North Karnataka - India

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Introduction

Leukemia, although a rare disease, exceeds a cause of death from many of the acute communicable diseases because of its fatal character (Meadors, 1956). It is characterized by widespread, rapid and disorderly proliferation of leukocytes and their precursor and by the presence of immature leukocytes in blood often in very large numbers unexceptionally at some time during the course of the disease (Forkner, 1938). Epidemiology has played a vital role in learning about the causes of cancer in the past few decades. This further puts the challenge to take these findings into the population and use them to detect different types of cancers earlier or ideally to prevent them altogether. A fundamental step in caring for the patients is to estimate the current burden of blood cancer in India and to understand how the occurrence and outcome of the disease varies across the whole country. In this context, this study aims to describe the prevalence and risk of Leukemia in the population of North Karnataka comprising 14 districts (Figure 1) which covers 3.5% geographical area of India and 2.52% of the whole population according to the Population Census of India, 2001. It is the first ever attempt to describe the prevalence and risk of leukemia in its varied population by compiling the data of the patients suffering from four main types of Leukemia namely chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), acute lymphocytic leukemia (ALL) and acute myelogenous leukemia (AML) from different hospitals of North Karnataka. According to

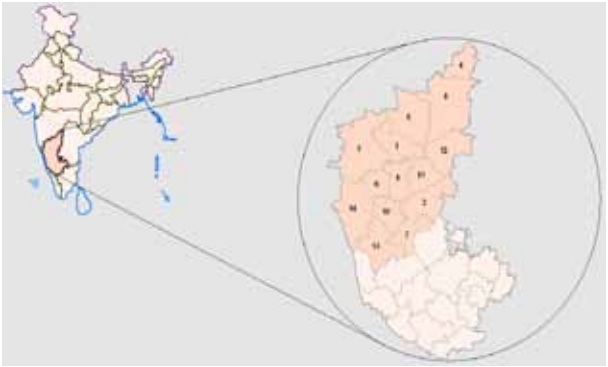

Figure 1. North Karnataka Region. 1, Bagalkot; 2, Bellary; 3, Belgaum; 4, Bidar; 5, Bijapur; 6, Dharwad; 7, Davangere; 8, Gulbarga 9: Gadag; 10, Haveri; 11, Koppal; 12, Raichur; 13, Shimoga; 14, Uttar Kannada

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the Leukemia and Lymphoma society, USA, there were approximately 13,410 new cases of AML, 5,200 new cases of ALL, 4570 cases of CML and 15,110 cases of CLL diagnosed in the year 2007-2008 in USA. Again, this society has reported in the year 2010-11 that blood cancers would account for 9.0 percent of the 1,529,560 new cancer cases diagnosed in the US this year. Leukemia alone comprises 27.5% of cancers affecting the children aged 0 to 19 years in United States. It further states that every 4 minutes, one person in the United States is diagnosed with a blood cancer. The second largest contributor to mortality from childhood cancer in Britain is Leukemia, whereas in India, Leukemia continues to be the largest contributor to cancer related mortality in children (Arora et al, 2009). Due to the lack of any nationwide leukemia screening program, the majority of the population of India is still unaware of this blood disorder. Lack of awareness also plays a role in underlying late presentation and noncompliance with screening guidelines.

We have chosen the region of North Karnataka for our study because of its multiethnic nature of population and its exposure to different environmental and cultural conditions. Because of its rigid endogamous marriage system, the genes are conserved in the same community since thousands of years. This inbreeding has maintained the gene pool of different communities intact which can be helpful for genetical analysis with respect to particular disease as well as the incidence pattern in different communities. But, due to the lack of proper epidemiological survey, these approaches are still far off from clinical research. In this study, the research on incidence rates of Leukemia in different endogamous communities of North Karnataka has been conducted.

Trends in the risk of leukemia over a period of time are an important factor to study changes in Leukemia (Murthy et al,. 2004). Consolidated data pertaining to sufficient duration enabling study of time trends are available only from Mumbai registry as the Population Based Cancer Registry (PBCR) has been operating since 1964. This trend analysis of cancer incidence data show that cancers related to lymphoma are increasing. A detailed analysis of our data reveal the fact that, regionally the number of lymphoma patients is insignificant and static (data unpublished). For detailed and precise study on leukemia, a subunit of PBCR needs to be started regionally in lines with Pune and Nagpur which would help the researchers and clinicians to get a better understanding of the trends of incidence rates of Leukemia in this region.

Materials and Methods

The medical records of all cases of Leukemia diagnosed at different hospitals and clinics of Dharwad and a major hospital- Karnataka Cancer Treatment and Research Institute (KCTRI), from 2001-2010 were traced through the computer and personal database. Care was taken to see that the records of patients are not repeated in case they have visited more than one hospital. From a clinical viewpoint it is desirable to know such factors as the age, sex, blood group, habits and race of patients, because of the influence that these attributes might have upon the care and outcome of the individual case. Information acquired from summation of hospital series is generally adequate for this purpose. From the epidemiologic standpoint, however, these attributes are desired for characterization of the kinds of people who acquire or escape the disease; that is, to measure their influence on risk of acquiring the disease (Alexander et al., 1953).

The variables calculated were for example patient's age, sex, blood group, addiction habits and their residence addresses. Controls have been chosen by keeping the patients' detail in consideration. All statistical analysis was carried out by using SPSS 16.0 version. Odds ratios with 95% confidence intervals were calculated to determine the strength of the associations.

Results

The data obtained during the present investigation are presented in Tables 1 and 2. Out of 659 eligible cases, data of only 647 patients comprising 417 male and 230 female (overall M:F ratio 1.8:1) have been collected as reports were untraceable for 12 patients. The data have been first divided religion wise i.e. Hindu and others. The data show that in Hindus, the male patients have more chances of occurrence of leukemia as compared to female patients. But, in the patients of other religions, it was found that the female patients have more chances of occurrence of leukemia than male patients. Significant risk values were observed in Hindu males (p=0.033) and females of other religions (p=0.043). Subsequently, the data of Hindu patients were split community wise, namely Lingayat, other backward castes (OBCs). Schedule castes

Table 1. Male and Female Leukemia Patients by Religion and Community Group

		Male		Female		Total		Odds Ratio	95% CI	p-value
		Patients	Controls	Patients	Controls	Patients	Controls			
Religion	Hindu	366	627	194	419	560	1,046	1.2607	1.0130-1.5708	0.0333*
	Others	51	112	36	45	87	157	0.5692	0.3173-1.0251	0.0433*
Community of Hindus	Lingayat	140	145	83	168	223	313	2.5941	1.8155-3.7106	0.0000*
	OBCs	52	125	29	74	81	199	1.0615	0.6012-1.8928	0.8277
	SC	95	154	45	99	140	253	2.7280	1.7731-4.2216	0.0000*
	Brahmin	37	99	29	50	66	149	0.6444	0.3419-1.2211	0.1453
	Maratha	42	104	8	28	50	132	1.4135	0.5672-3.8803	0.4307
Total		366	627	194	419	560	1046	1.2607	1.0130-1.5708	0.0333*

*p<0.05; OBCs, other backward castes; SC, scheduled castes

Table 2. Comparison of Male and Female Patients with Different Types of Leukemia during 2001-2010

Leukemia	Gender	Mean	SD	t-value	p-value
CLL	Male	44,000	25,000	3.036	0.0071*
	Female	18,000	10,300		
CML	Male	121,000	22,800	5.016	0.0001*
	Female	68,000	24,400		
ALL	Male	130,000	31,300	4.423	0.0003*
	Female	66,000	33,400		
AML	Male	122,000	28,600	3.644	0.0019*
	Female	78,000	25,300		
Total	Male	417,000	4.14	8.615	0.0000*
Female		230,000	5.48		0.0000*

*by t-test

(SCs), Brahmin and Maratha (Table 1). The data reveal that in Lingayat and SC communities male patients have approximately 3 times more risk than other communities (p=0.000).

No association with smoking habit was noted for any of the types of leukemia. For identifying an association between blood groups and leukemia, the patients with negative Rh status have been excluded as their number is not significant (only 9). So, the total no. of cases considered is 638 only. A significant relationship between various blood groups in occurrence of AML in males and females is observed. But, other leukemias are not significantly associated with blood group. The highest number of leukemia cases have been found in B+ve blood group.

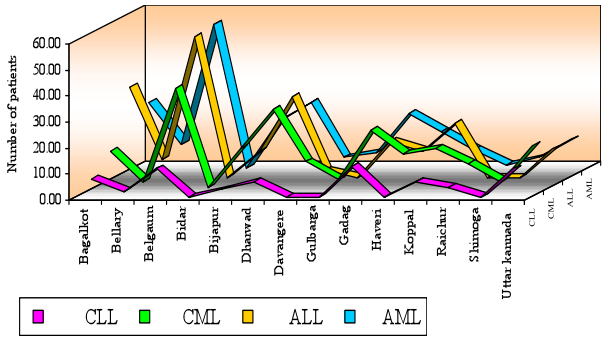

Figure 2. Distribution of Various Leukemia Patients According to Different Districts

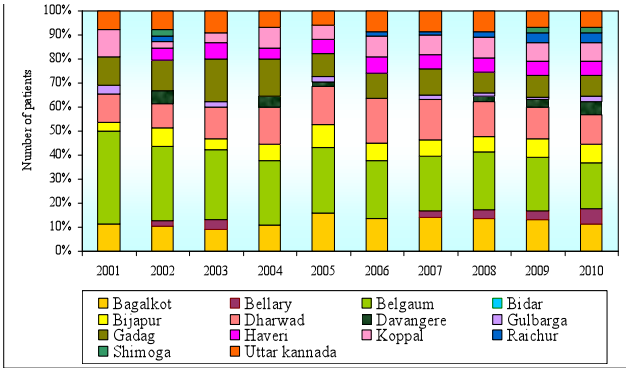

Figure 3. Distribution of Patients According to the Districts and Years

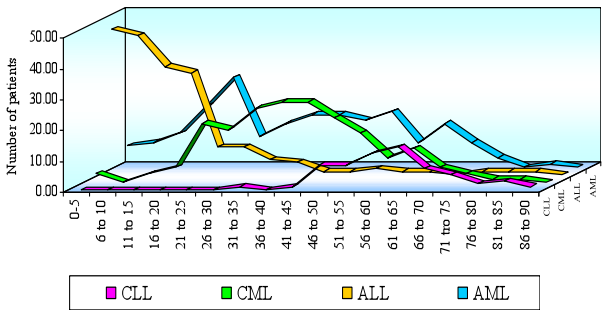

Figure 4. Distribution of Patients According to Age groups and Leukemia Type

Figure 2 represents that more number of CLL cases have been observed in Belgaum, Gadag and Uttar Kannada districts. The number of CML cases are highest in Belgaum followed by Dharwad and Gadag. ALL cases have been reported mostly from Bagalkot followed by Dharwad and Koppal. The number of AML cases are equal in Bagalkot and Dharwad preceeded by Belgaum. In all four major types of leukemia, male numbers were higher than females (see Table 2).

Figure 3 depicts that there is no report of Leukemia case in Bidar district through out the study. Belgaum has higher number of incidence followed by Bagalkot. The gradual increase in the no. of leukemia patients advocates the need of more research and detailed study about the reasons for leukemia in various districts of North Karnataka. ALL has been found to be the most common form of leukemia during childhood (Greaves, 1997). The same result has been obtained in our study (Figure 4). CML is higher in the age group of 36-45 whereas risk of AML is higher in age group of 21-25.

Discussion

The largest contributors to mortality from childhood cancer in Britain are CNS tumors, reflecting the relatively poor survival in this group, followed by Leukemia and Neuroblastomas. In contrast, in India, Leukemia continues to be the largest contributor to cancer-related mortality in children followed by Lymphoma and CNS tumors, which have similar mortality rates. This pattern is a result of the lower survival of all cancers, including Leukemia in India (Arora et al., 2009).

Multiple inter-related factors are responsible for the poorer outlook of blood cancer in India. Expensive treatment, treatment related death, treatment refusal or abandonment by patients, relapse of diseases is frequent unwanted outcome (Arora et al., 2007). Educational and planned programs, which foster interactions between public hospitals in developing countries and established cancer treatment center elsewhere, have been seen to reduce abandonment and improve survival elsewhere in the world (Quaddoumi et al., 2008). These types of approaches are still lacking in this region. With centralization of treatment and enrollment in clinical trials, tremendous progress has been made in caring for patients in the developing countries and overall survival of all blood cancers combined is increasing gradually.

The incidence of leukemia varies with gender and ethnicity. Indian populations being multicultural and multiethnic have conserved their gene pool because of the caste system and intra caste marriage requirement. Hindus

(including Sikhs, Buddhists, Jains) constitute 85% of the population and 15% religious minorities are comprised of Muslims and Christians. The records of leukemia comprise 86.5% of Hindus and rest for other religions which are in accordance with their population.

Epidemiological studies have recently begun to consider that some risk factors may be specific to AML subtypes. One interesting development regarding the AML-smoking hypothesis is the possibility that increased risk may be limited to one or more French-American – British subtypes of the disease (Pogoda et al, 2001). But, the population of this region did not show any such type of inclination. Nevertheless, the smokers are at 2-3 times higher risks of leukemia but there are limitations that must be considered in the interpretation of our findings because of relatively very small sample size of smokers. Although any specific mechanism has not been identified yet, smoking seems biologically plausible as a cause for Leukemia. Tobacco smoke contains two occupational leukemogens, benzene and ionizing radiation. It has been found that in the urine of smokers, the concentration of benzene is significantly higher than in that of non-smokers. Ionizing radiation is present in tobacco smoke in the forms of lead-210 and polonium-210. Animal's studies suggest that polonium-210 interacts with benzene in tobacco smoke to promote carcinogenesis. Our analysis of duration since exposure suggests that distant exposure results in higher risk of leukemia than exposure that occurs closer to Leukemia diagnosis. The similar pattern has been observed in the case study of exposure result and AML risk (Pogoda et al., 2001).

The number of Rhesus -ve patients are insignificant (only 9) as the percentage population of Rh-ve people in India is just 2-5%, so only the blood groups with +ve Rh status have been considered for this study. Acute Myeloid leukemia (AML) is the most common of all the adult-onset leukemias and is a leading cause of leukemia mortality (Pogoda et al, 2001). The significant presence of AML has been observed in all types of blood groups and it is statistically significant (p=0.0090) which gives the impression of its preponderance among all types of leukemia in the region whereas other types of leukemias did not show statistically significant relationship with blood groups. Significant results have been obtained on the association of ABO blood groups and different cancers like duodenal ulcer (Clarke 1961), gastric cancers (Roberts, 1957) etc. But, several other diseases have been investigated for such association with statistically insignificant results (Roberts, 1957).

The distribution by the blood groups of the two leukemia series and of the systematic comparison of sample by Macmohan & Foulsiak (1958) shows the tendency of leukemia to occur less frequently in persons of group O than in persons of group B and AB but our study nullifies the concept of tendency of any particular blood group toward leukemia. Although confirmation of these results must await further research, the data here should be of interest to those doing work on blood groups and diseases.

Sex disparities in cancer have often been acknowledged but have rarely been the focus of interest in the epidemiological literature (Cook et al., 2009). As observed in the result of this study, all different forms of leukemia show higher risk value in male, representing the overall ratio of 1:8.1. There is no obvious explanation for this unexpected observation that females appear to be relatively protected against leukemia cases (Jackson et al., 1999). In contrast, according to the present study, the female patients of other religions (other than Hindus) show higher risk value for the occurrence of leukemia.

The analyzed data suggest that there is a lesser incidence of blood cancer in some areas of North Karnataka or as is more likely, there is under ascertainment of cases. Belgaum has been observed to show the highest frequency of CLL, CML and AML cases. The reason for the non reporting of Leukemia cases from Bidar may be attributed to the fact that, the patients may have access to treatment of Leukemia in the hospitals of bordering states. The facts behind these results emphasize the need for elaborate and precise molecular and genetical studies of the population.

It has been proposed that T-cell ALL predominates in economically disadvantaged areas, but with urbanization, industrialization and increasing affluence , common ALL, which peaks in incidence between the age of 2 and 5 years, increases (Ramot et al., 1982). In our study, due to insufficient medical records, it was not possible to observe the abundance of the subtypes of ALL over each other. The cases of ALL are much greater in number than AML which is consistent with previous studies. In country like India where there are geographic disparities in treatment facilities, the existing treatment facilities for cancer control in-terms of radiotherapy and financial allocation are woefully inadequate to take care of even the present load (Murthy et al., 2004). Thus spectrum of cancer epidemiology seen in India is different than that seen in any developed country (Editorial, IJMP). It should be stressed that cancer registry data in the region are scanty, especially for the country like India with a large population, so that emphasis should be placed on better development of regional and national registries. There may be too much reliance on pathology reports and luekemias, for example AML are likely to be under-reported (Salim et al., 2009).

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References

Alexander GG (1953). Age, sex, and race selection at death from leukemia and the lymphomas. *Blood*, **8**, 693-702.

Arora R S, Eden T, Pizer B (2007). The problem of treatment abandonment in children from developing countries with cancer. *Paediatric Blood Cancer*, **49**, 941-6.

Arora RS, Eden TOB, Kapoor G (2009). Epidemiology of childhood cancer in India. *Indian J Cancer*, **46**, 264-73.

Ashok S. Cancer epidemiology. Health Administrator Vol: XVII, Number, pp 14-15.

Brian M, John C. Folusiak (1958). Leukemia and ABO Blood Group. Downstate Medical Center, pp 287-293.

Clarke CA, Edwards JW, Haddock DRW, et al (1956). ABO blood groups and secretion character in duodenal ulcer. Population and sibship studies. *BMJ*, **2,** 725-31.

Cohen B L (1993). Relationship between exposure to radon and various types of cancer. Health Phys;65: 529–37.

Editorial (2004). Cancer epidemiology of India. *Indian J Med Paediatric Oncol*, **25**, 3.

Forkner, CE (1938) Leukemia and allied disorders. New York, Macmillan Co., , pp 333.

Leukemia and Lymphoma Society. USA (2010). Facts 2010-2011, pp1-25.

Meadors GF (1956). Epidemiology of Leukemia. PHR Review, Vol 71.2

Greaves MF (1997). Aetiology of acute leukaemia. Lancet, 349, 344-9.

Jackson N, Menon B.S., Zarina W, et al (1999). Why is acute leukemia more common in males? A possible sex-determined risk linked to the ABO blood group genes. *Ann Hematol*, **78**, 233-6.

Murthy NS, Aleyamma M (2004). Cancer epidemiology, prevention and control. *Current Sci*, **86**, 518-27.

Ong C N, Lee B L, Shi C Y, et al (1994). Elevated levels of benzene- related compounds in the urine of cigarette smokers. *Int J Cancer*, **59**, 177-80.

Pogoda JM, Susan P.M., Nichols PW, et al (2002). Smoking and risk of acute myeloid leukemia: results from a Los Angeles County case-control study. *Am J Epidemiol*, **155**, 546-53.

Quaddoumi I, Musharbash A, Elayyan M et al (2008). Closing the survival gap: Implementation of medulloblastoma protocols in a low-income country through a twinning program. *Int J Cancer*, **122**, 1203-6.

Ramot B, Bracha I (1982). Hypothesis: he environment is a major determinant of the immunological sub-type of lymphoma and acute lymphoblastic leukaemia in children. *Br J Haematol*, **50**, 183-9.

Roberts JAF.(1957). Blood groups and susceptibility to disease. *Br J Prev Social Med*, **11**, 107-25.

Salim EI, Moore MA, Al-Lawati JA, et al (2009). Cancer epidemiology in the Arab Region. *Asian Pac J Cancer Prev*, **10**, 3-16.

Tso TC, Harley N, Alexander LT (1966). Source of lead-210 and polonium- 210 in tobacco. *Science*, **153**, 880-2.