RESEARCH ARTICLE

Lifestyle Factors Including Diet and Leukemia Development: a Case-Control Study from Mumbai, India

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Abstract

In India, among males, leukemia rates vary across the country. The present unmatched hospital-based case-control study conducted at Tata Memorial Hospital included subjects registered between the years 1997-99. There were 246 leukemia cases and 1,383 normal controls. Data on demographics, lifestyle, diet and occupation history were recorded. Cigarette (OR=2.1) and bidi smoking (OR=3.4) showed excess risk for leukemia. Odds ratios were 3.9 for fish-eaters, 0.40 for chilli eaters, 1.5 for milk drinkers and 0.60 for coffee drinkers, compared to non-drinkers/eaters. However, neither exposure to use of pesticides nor cotton dust showed any excess risk for leukemia.

Keywords: Leukemia - risk factors - case - control study - smoking, - alcohol - coffee - fish - diet - India

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Introduction

Globally, it is estimated that there are approximately 13 million new cancer cases and 8 million cancer deaths (Ferlay, 2008). The estimated number of new leukemia cases are about 0.35 million and deaths are 0.26 million in the world. In more developed countries, the incidence rates are 7.3 per 100,000 while in less developed countries, the rates was 4.0 per 100,000. In India, though the incidence rates are low (M=3.5, F=2.6), compared those in other parts of the world, there are approximately 33,000 new leukemia cases reported each year (Ferlay, 2008). The incidence rates of leukemia are very low and vary across India as well (NCRP, 2009). Among males, it varies between 1.8 in Mumbai to 2.4 in Bangalore, while among females it varies between 1.7 in Bangalore to 1.9 in Chennai (NCRP, 2009). There are many studies reporting on the risk factors for leukemia from different countries (Xiaomei, 2009).

The present study was carried out to study the risk factors for leukemia with regard to life-style habits, diet and occupational history. This study was partially funded by International Agency for Research in Cancer (IARC Monographs, 2004) and was carried out between the years 1997-99. A statistically significant increased risk for acute myeloid leukemia (AML) associated with active smoking was reported in one of the earlier studies (Kasim, 2005) other factors reported in the literature are the body mass index (Kasim, 2005), meat intake (Xiaomei, 2009) etc have been shown to be associated with leukemia. A significant relationship was observed between acute leukemia and high or medium exposure to benzene, as well as over 10 years high or medium exposure to exhaust gas. In addition a significant relationship was observed with exposure to pesticides (Richardson, 1992). The Indian population is known to be less obese than the western population, basically attributed to the life-style. The body mass index is quite low for Indians. As per the recent survey in India, the mean BMI for Indian men (15-54 years) is 20.3 and for women (15-49 years) it is 20.5 (NFHS, 2007). The Indian diet includes a major portion of vegetables and fruits. Non-vegetarian diet is rarely consumed on a daily basis, unlike in western countries. The present study thus attempts to determine the various factors associated with leukemia, such as tobacco, alcohol drinking, dietary items and occupational exposure history.

Materials and Methods

The present study, a hospital-based case-control study, was conducted at the Tata Memorial Hospital (TMH), Mumbai, India. The period of data collection was 1997-99 that included subjects who visited TMH for diagnosis and treatment. Patients were interviewed at the Out-patient department of TMH. The information was recorded in a pre-designed questionnaire, which was pre-tested at the hospital; this included demographic characteristics (age, sex, religion etc), life-style (habits such as smoking, chewing, alcohol drinking etc), dietary habits and occupational exposure. The hospital being a comprehensive cancer centre for diagnosis and treatment attracts patients from all parts of India. In general, in a year, 30-40% of patients of total registrations are diagnosed as free of cancer. These cancer-free patients were considered

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as 'controls' by scrutinizing their medical history and diagnosis. Cases were microscopically proven cancer cases of leukemia. Controls were classified as those that were diagnosed by microscope as 'free of cancer' and not having any ailments and thus diagnosed as 'no evidence of disease'. Only male subjects and above the age of 24 years are included in the study. In all there were 246 Cases and 1383 Controls enrolled into the study. The questionnaire contained socio-demographic information, life-style habits like chewing, smoking, alcohol consumption and dietary items. The questionnaire on food items were based on recollection of consumption of routine food items prior to one-year of the date of interview. Information on food frequency per week was also collected. The dietary items were classified as vegetarian diet and non-vegetarian diet. The non-vegetarian diet included items as fish, chicken and red-meat. Red-meat included mutton, liver, pork, brain etc. Consumption of vegetables, fruits, chilly was recorded. Intake of beverages as tea, coffee, milk was also recorded. Although frequency of consumption was recorded, it was not taken into account for analysis because of incompleteness. Unconditional logistic regression model was applied for obtaining the risk estimates (odds ratio) and its 95%confidence limits using SPSS Version 15.0 software. In the analysis, independent variables were categorized into binary form and entered into the model. The results were considered for statistical significance at 5%.

Results

Demographic characteristics of Cases and Controls are shown in Table 1. It is seen that the ratio of cases to controls is approximately 1:5. The average age for cases and controls was 39.4 years and 46.5 years respectively. 93.3% of Controls and 89.4% of cases were literates, and only 1.2% of cases had a family history of hematopoetic cancer. History of working in pesticides industry was only 2.4% among the cases, while it was 0.8% of cases who had worked in cotton dust industry.

Table 2 shows the crude odds ratio (OR) for lifestyle habits, dietary habits and occupational factors. The categories considered were 'never' vs 'everexposed'. In the univariate analysis, it is seen that the excess risk was 2.1 and 2.3 for cigarette smokers and bidi smokers respectively, compared to the non-smokers. The crude OR for those who chewed pan with tobacco was 0.6 and likewise 0.6 for tobacco-lime chewers, 0.4 for pan-parag chewers and 0.4 for betelnut chewers compared to non-chewers. Alcohol drinkers had a 2-fold (OR=1.9), significant risk, compared to non-drinkers. Among dietary items, it was observed that fish-eaters (OR=2.8), chicken (OR=2.4), mutton (OR=2.3) and egg (OR=2.6) eaters all had excess significant risk compared to non-eaters. Those who consumed vegetable, fruits or chilly showed a 80%, 50% and 80% reduction in risk respectively. Consumption of milk showed 3.2-fold excess risk while tea and coffee consumption showed 90% and 70% reduction in risk respectively; history of hematopoetic malignancies in the family didn't show any difference between the cases and controls. Likewise exposure to pesticides or didn't show any excess risk for leukemia, while cotton dust showed a reduction in risk, probably due to small number of cases.

Table-3 elucidates the adjusted-odds ratio, adjusted for age and literacy status, and their 95% confidence limits, for different factors under study. It is observed that after

Table 1. Demographic Characteristics of Cases and Controls : Leukemia Case-Control Study

Factor	Characteristics	Cases (%)	Controls (%)
Total		246	1383
Age	<40 years	146 (59.3)	517 (37.4)
	≥40 years	100 (40.7)	866 (62.6)
Average Age (in years)		39.4	46.5
Education	Literate	220 (89.4)	1290 (93.3)
	Illiterate	26 (10.6)	93 (6.7)
History of Hemato-poetic Cancer	Yes	3 (1.2)	14 (1.0)
	No	243 (98.8)	1369 (99.0)
Occupational history			
Pesticide worker	Yes	6 (2.4)	18 (1.3)
	No	240 (97.6)	1365 (98.7)
Cotton-dust worker	Yes	2 (0.8)	67 (4.8)
	No	244 (99.2)	1316 (95.2)

Table 2. Odds-Ratio (Crude) and 95% Confidence Interval for Life-Style Factors

Factor	Characteristics	Cases	Controls	Crude Odds Ratio & 95% CI (Lower,Upper)
Cigarette Smoking	Smokers	117	412	2.1 (1.6,2.8)*
	Non - Smokers	129	971	1
Bidi Smoking	Smokers	52	145	2.3 (1.6,3.3)*
	Non - Smokers	194	1238	1
Pan Tobacco Chewing	Chewers	32	297	0.6 (0.4,0.8)*
	Non-Chewers	214	1086	1
Tobacco Lime Chewing	Chewers	4	38	0.6 (0.2,1.7)
	Non-Chewers	242	1345	1
Pan Parag Chewing	Chewers	3	43	0.4 (0.1,1.3)
	Non-Chewers	243	1340	1
Betel Nut Chewing	Chewers	5	63	0.4 (0.2,1.1)
	Non-Chewers	241	1320	1
Alcohol Drinking	Drinkers	20	63	1.9 (1.1,3.1)*
	Non Drinker	226	1320	1
Fish eater	Yes	205	884	2.8 (2.0,4.0)*
	No	41	499	1
Chicken eater	Yes	197	862	2.4 (1.8,3.4)*
	No	49	521	1
Mutton eater	Yes	190	820	2.3 (1.7,3.2)*
	No	56	562	1
Egg eater	Yes	203	895	2.6 (1.8,3.6)*
	No	43	488	1
Vegetable eater	No	6	8	0.2 (0.9,0.7)*
	Yes	240	1375	1
Fruit eater	No	5	13	0.5 (0.2,1.3)
	Yes	241	1370	1
Chilli eater	Yes	87	966	0.2 (0.2,0.3)*
	No	157	410	1
Milk drinker	Yes	162	523	3.2 (2.4,4.3)*
	No	82	855	1
Tea drinker	Yes	237	1372	0.1 (0.04,0.4)*
	No	7	6	1
Coffee drinker	Yes	143	1166	0.3 (0.2,0.3)*
	No	101	212	1
History of Hemato-poetic Cancer	Yes	3	14	1.2 (0.3,4.2)
	No	243	1369	1
Occupation history				
Pesticides worker	Yes	6	18	0.5 (0.2,1.3)
	No	240	1365	1
Cotton dust worker	Yes	2	67	0.2 (0.1,0.6)*
	No	244	1316	1

Table 3. Odds-Ratio (Adjusted) and 95% Confidence Interval for Life-Style Factors

Factor	Characteristics	Cases	Controls	Adj. OR **	95% C.I (Lower, Upper)
Cigarette Smoking	Smokers	117	412	2.0 *	1.6, 2.7
	Non-Smokers	129	971	1	
Bidi Smoking	Smokers	52	145	2.3*	1.6, 3.3
	Non-Smokers	194	1238	1	
Pan Tobacco Chewing	Chewers	32	214	0.6	0.4, 1.3
	Non-Chewers	297	1086	1	
Alcohol Drinking	Drinkers	20	63	1.7*	1.1, 3.2
	Non Drinker	226	1320	1	
Fish eater	Yes	205	884	2.7 *	1.9, 3.8
	No	41	499	1	
Chicken eater	Yes	197	862	2.2 *	1.6, 3.2
	No	49	521	1	
Mutton eater	Yes	190	820	2.2 *	1.6, 3.0
	No	56	562	1	
Eggs eater	Yes	203	895	2.4 *	1.7, 3.5
	No	43	488	1	
Vegetable eater	No	6	8	0.2*	0.1, 0.7
	Yes	240	1375	1	
Chilly eater	Yes	87	966	0.2 *	0.2, 0.3
	No	157	410	1	
Milk consumption	Yes	162	523	3.3 *	2.5, 4.4
	No	82	855	1	
Tea drinker	Yes	237	1372	0.16 *	0.1, 0.5
	No	7	6	1	
Coffee drinker	Yes	143	1166	0.27 *	0.2, 0.4
	No	101	212	1	
Cotton dust	Yes	2	67	0.2	0.3, 1.7
	No	244	1316	1	

Table 4. Odds Ratio (OR) and 95% CI for Factors by Regression Method: Leukemia Case-control Study

Factor	Characteristics	Adj. OR**	95% C.I (Lower, Upper)
Cigarette	Smoking	2.1 *	1.5, 2.9
	Non - Smoker	1	
Bidi Smoking	Smoker	3.4 *	2.2, 5.2
	Non - Smoker	1	
Alcohol Drinker	Drinker	1.1	0.6, 2.0
	Non - Drinker	1	
Milk Drinker	Yes	1.5 *	1
	No	1	
Tea Drinker	Yes	0.4	0.1, 1.5
	No	1	
Coffee Drinker	Yes	0.6 *	0.4, 0.8
	No	1	
Chicken eater	Yes	0.7	0.3, 1.5
	No	1	
Mutton eater	Yes	0.8	0.4, 1.8
	No	1	
Eggs eater	Yes	0.7	0.2, 1.8
	No	1	
Fish eater	Yes	3.9 *	1.3, 11.7
	No	1	
Chilli eater	Yes	0.4 *	0.3, 0.6
	No	1	

adjustment, cigarette smokers (OR=2.0) and bidi smokers (OR=2.3), continued to show enhanced risk compared to non-smokers, and alcohol drinkers (OR=1.7) too had increased risk for leukemia compared to non-drinkers; however pan-tobacco chewers did not show significant risk. After adjusting for age and literacy, those that continue to show excess significant risk were those who ate fish (OR=2.7), chicken (OR=2.2) , mutton (OR=2.2) and egg (OR=2.4) eaters all had excess significant risk compared to non-eaters. Those who consumed vegetable or chilly continued to show a 80% reduction in risk each. Milk-drinkers showed 3.3-fold excess risk while tea and coffee consumption continued to show 80% and 70% reduction in risk respectively. Exposure to cotton dust didn't show any excess risk for leukemia after adjusting for age and literacy.

Table 4 shows odds ratio and confidence limits obtained by applying regression method in which factors are adjusted for each other. Cigarette smokers showed a 2.1-fold risk and bidi-smokers 3.4-fold significant enhanced risk for leukemia, compared to non-smokers, while alcohol-drinkers didn't show any statistically excess risk. Milk drinkers had an 1.5-fold excess risk compared to the non-drinkers, while Coffee drinkers showed a 40% reduction in risk. Among the dietary items, only fish-eaters showed a near 4-fold excess risk while chilly-eaters showed a 60% reduction in risk, compared to non-eaters.

Discussion

The incidence rates for leukemia are as low as 4.0 per 100,000 in less developed countries compared to 7. 3 per 100,000 in more developed countries (Ferlay, 2008). The risk factors include tobacco smoking, alcohol abuse, diet, body mass index, occupational exposure etc. The present study is an hospital-based case-control study on association of life-style factors, occupational exposure, dietary items, and beverages, on leukemia. In the present study, a total of 246 leukemia cases and 1383 normal controls were analyzed. Due to unforeseen circumstances, the study results could not be reported earlier. The authors wish to accept that due to the delay, there is possibility that some additional information on risk factors might have been reported in the literature; nonetheless the study is of importance since it addresses the possible association of tobacco, dietary habits and occupational exposure to leukemia, in the Indian setting.

A statistically significant increased risk (OR=1.5) for acute myeloid leukemia associated with active smoking (Kasim, 2005). A similar outcome was reported by an US cohort study and the risk enhanced for heavy smokers (Xiaomei, 2009). The present study reiterated that the cigarette smokers had an elevated risk of 2-fold compared to non-smokers and bidi (Indian cigarette) smokers also a 3-fold risk for leukemia, compared to non-smokers. This is in agreement with the above studies as well as other such studies reported in the literature. Although an association of cigarette smoking and AML has not been a universal finding in the studies on this topic, the majority of studies in the last 20 years have reported a statistically significant, moderate relationship (Thomas,2004, Brownson,1993). In 2004, the International Agency on Research in Cancer of the World Health Organization (IARC Monographs, 2004) concluded, based on the data available, that cigarette smoking caused AML. The frequency of smoking was recorded but was not analyzed due to incompleteness. In the present study, tobacco- chewing did not show any excess risk for leukemia.

Reports on association of alcohol drinking and

leukemia have not been consistent and there has been conflicting findings. A population-based case-control study in 11 Italian areas found a a non-significantly inverse association for moderate levels of total alcohol and wine intake, but increased risks at high levels (Gorini, 2007). In another study (Brown, 1992) a Population-based case-control interview studies from Iowa and Minnesota reported that although drinkers had non-significantly elevated risks for specific subtypes of leukemia (acute lymphocytic leukemia (OR=3.0), myelodysplasia (OR=1.6), and other leukemia (OR=1.5) and multiple myeloma (OR=1.3), there were no statistically significant findings and no dose-response gradients with amount of alcohol consumed and thus they concluded that alcohol was not an important contributor to the etiology of lymphatic and hematopoietic tumors. In the present study, though the risk for alcohol drinkers was slightly higher, but was not significant.

Study on diet has always been difficult for various reasons. There are few studies reported from India on association of diet with cancer. The dietary items in the present study has been classified as vegetarians and non-vegetarians; non-vegetarian diet included red- meat (mutton, pork), chicken, fish; vegetarian diet such as vegetables (both raw and cooked), fruits (citrus and fresh-fruit) and consumption of chilly.

A large study, examined the association between meat and fish intake and the risk of various cancers from 19,732 incident, histologically confirmed cases of various cancers which also included leukemia (Hu, 2008). Total meat and processed meat were directly related to the risk of leukemia among other cancers as stomach, colon etc. Higher meat intake was associated with an increased risk of acute myeloid leukemia (hazard ratio=1.45, 95% confidence interval: 1.02, 2.07 for the fifth vs. first quintile; p for trend=0.06) (Xiaomei, 2009); in the sub-cohort for whom they had meat-cooking information, there were no clear effects of cooking method or doneness level. This large prospective study identified meat intake as risk factors for acute myeloid leukemia. Risk of leukemia was associated with intake of meat and processed meat, but no results were presented specifically for AML (Hu, 2008). In the present study, neither chicken nor mutton showed any excess significant risk while fish intake showed an 4-fold excess risk for leukemia. This could be due to the fact that the type of fish consumed was not classified as 'dry fish', 'salted fish' or 'fresh fish' and thus there might be a possibility that this might have masked the real effect. Dry fish stored with preservatives as well as salted fish are known to enhance the risk for cancer and there are reports showing the reduction in risk for fish eaters (Fritschi, 2004); the present study concluded that the fish consumed might be more of dry fish or salted fish rather than fresh-fish.

Capsaicin (trans-8-methyl-N-vanillyl-6-nonenamide) is the principal pungent component in hot peppers, including red chili peppers, jalapeños, and habaneros. Consumed worldwide, capsaicin has a long and convoluted history of controversy about whether its consumption or topical application is entirely safe. Conflicting epidemiologic data and basic research study results suggest that capsaicin can act as a carcinogen or as a cancer preventive agent (Bode, 2011). There are few studies reporting on the role of chilli eating and risk of cancer. In our study, chilly eating showed a 60% reduction in risk for leukemia after adjustment for other background factors. In a recent study, researchers found that red chili pepper appear to be effective inhibitors of the cancer process. They looked at the chemotherapeutic potential of capsaicin, the "hot" ingredient in red chili pepper that is often associated with antioxidative and anti-inflammatory activities.

Consumption of vegetables has been shown to be protective for many cancers, but the present study, did not show any association with leukemia. Studies on dietary factors and AML are scarce and usually include a small number of cases. A large case-control study, did not observe any association between intake of fruits and vegetables and the risk of adult leukemia overall (1,068 cases) or AML in particular (307 cases) (Kasim, 2005; Xiaomei, 2009). No association was observed with intake of fruits, vegetables (Xiaomei, 2009).

Although tea drinking is more common in India, it did not show any additional or excess risk for leukemia in the present study which is in agreement with an earlier study who found no association between green tea consumption and the risk of AML (Zhang, 2008; Xiaomei, 2009). In our study, though there was a reduction in risk but it was not statistically significant.

Another beverage not so common as tea drinking in India, Coffee drinking, showed reduction in risk in our study, compared to non-drinkers. Individuals who did not drink coffee appeared to have a higher risk of acute myeloid leukemia than those who drank various quantities of coffee (Xiaomei, 2009); however, the small number of non-coffee drinkers, the lack of a dose-response relation, and the fact that no other studies are known to have reported such an association suggested that this finding should be interpreted with caution. In the present study, coffee drinkers showed a 50% reduction in risk compared to non-drinkers which is in agreement with most of the studies in literature.

Few epidemiological studies have considered relationships between dairy products and adult leukemia. An ecologic study of international data showed some positive correlations between energy intake and leukemia incidence, particularly with lymphoblastic leukemia, but no analytic study has examined this association (Hursting, 1993). Kwiatkowski (1993), in a case-control study of 119 adult patients with acute leukemia (91 AML and 28 ALL), reported possible increased risk with consumption of milk, poultry, and soft water.

A baseline survey conducted for 11,349 residents in 12 communities in Japan, which included collection of demographic data and a self-administered food-frequency questionnaire inquiring about three dairy products: milk, butter and yogurt reported causes of death for these cancers using death certificates, showed that the frequencies of butter consumption, and probably that of milk, were correlated with death from hematopoietic neoplasm, particularly from non-lymphomas (Matsumoto, 2007). The Iowa Women's Health Study is a prospective

cohort study of 55-69 year old women, concluded that consumption of unpasteurized milk does not increase risk of cancer (Sellers, 2008). In the present study, milk consumption increased the risk by 50% showing it to be risk factor leukemia. It might be worthwhile to investigate the type of milk consumed was pasteurized or otherwise. In the present study, occupational exposure to pesticide, asbestos, cotton-dust, exhaust gas etc didn't show any significant risk, though there are studies which report significant relationship with leukemia (Richardson, 1992).

In summary, in the present study, smoking emerged as high risk factor for leukemia, while alcohol drinking didn't show any excess risk. Among the dietary items, fish intake increased the risk four-fold while chicken and mutton didn't show any excess risk for leukemia. Coffee drinking showed a 50% reduction in risk for leukemia. Consumption of milk increased the risk by 50% compared to non-drinkers; though unpasteurized milk has not been shown to be a risk factor for leukemia; this could be further investigated on the type of milk consumed in a larger study. None of the occupational history showed any excess risk for leukemia in our study. Epidemiologic studies have suggested that coffee intake may decrease the risk of cancer. Coffee may help protect against cancer through the activity of its anticarcinogenic constituents (Daglia, 2000; Cavin, 2002; Hashimoto, 2004; Rogers, 2007) or polyphenolic compounds (Manach, 2004), which inhibit carcinogenesis through antioxidant, antihormonal, and anti-inflammatory mechanisms (Scalbert, 2005). Cafestol and kahweal, 2 coffee-specific diterpenes, can reduce the genotoxicity of multiple carcinogens (Cavin, 2002).

Based on these findings, it may be concluded that prevention of tobacco use, limited use of certain dietary items, dairy products could prove to be beneficial in prevention of leukemia.

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