January 2014

Environmental and occupational factors associated with chronic myeloid leukemia: a case-control study

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J. Afr. Cancer (2014) 6:194-201
DOI 10.1007/s12558-013-0297-2

ORIGINAL ARTICLE / *ARTICLE ORIGINAL*

Environmental and Occupational Factors Associated with Chronic Myeloid Leukemia: a Case-Control Study

Facteurs environnementaux et professionnels associés à la leucémie myéloïde chronique : une étude de cas-témoin

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Received: 22 April 2013; Accepted: 9 September 2013

Abstract *Background*: The relationship between chronic myeloid leukemia (CML) and a broad range of exposures to occupational and environmental factors known to cause leukemia in general is limited. CML is by and large incurable and treatment is just palliative and life prolonging, with high case fatality rate, even in the best centers. Furthermore treatment is very expensive. Identification of leukemogenic factors is therefore important if this can lead to simple public health interventions.
Objective: The objective was to determine key environmental and occupational exposure factors that may be associated with CML.
Methods: This was a case-control study involving CML cases enrolled in Glivec International Patient Assistance Program (GIPAP) clinics at the Nairobi Hospital and Aga Khan University Hospital and two control groups for each case, matched for age and sex: a family- and hospital-based control, was carried out. One hundred and eight cases with age-and-gender-matched family- and hospital-based controls were recruited and a standard questionnaire was administered. Individual data on demographics, occupation, environment, and exposures to benzene and farm organochemical products were obtained. Clinical examination was carried out in control subjects. Statistical analysis was done using bivariate and multivariate analysis to look for associations between exposure factors and CML.
Results: The median age at diagnosis of CML cases was 41.32 years with an age range of 8–81 years and a male to female ratio of 1.7:1. Most of our cases were concentrated in or around Nairobi. There was no significant correlation found for exposure to benzene or pesticides. Long duration of exposure to pesticides in the family control group was significantly associated (t-test, P = 0.017) with risk of CML.
Conclusions: Associations between exposures to organic solvents like pesticides and CML were indicated but were not entirely consistent, although no associations with benzene products were found. Nevertheless, for almost all cases of Ph chromosome-positive CML, other explanations must be sought for.

Keywords Chronic myeloid leukemia · Environmental and occupational factors

Résumé *Contexte* : La relation entre la leucémie myéloïde chronique (LMC) et de nombreuses expositions différentes à des facteurs environnementaux et professionnels connus pour causer une leucémie de manière générale est limitée. Dans l'ensemble, la LMC est incurable et le traitement ne constitue qu'une solution palliative permettant de prolonger la vie, avec un taux de létalité très élevé, même dans les meilleurs centres. En outre, son traitement est extrêmement onéreux. L'identification des facteurs leucémogènes est par conséquent importante si elle permet de recourir à de simples interventions de santé publique.
Objectif : L'objectif était de déterminer les facteurs clés d'exposition environnementale et professionnelle pouvant être associés à la LMC.
Méthodes : Il s'agissait d'une étude de cas-témoins impliquant des cas de LMC déclarés dans des cliniques du

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programme GIPAP à l'hôpital de Nairobi et à l'hôpital universitaire Aga-Khan ainsi que deux groupes témoins pour chaque cas, regroupés en fonction de l'âge et du sexe : une étude de cas-témoins a été réalisée en milieu familial et en milieu hospitalier. Parmi les études en milieu familial et hospitalier regroupées en fonction de l'âge et du sexe, 108 cas ont été recrutés et soumis à un questionnaire standard. Des données individuelles concernant des expositions démographiques, professionnelles et environnementales à du benzène ainsi qu'à des produits chimiques organiques agricoles ont été obtenues. Des examens cliniques ont été réalisés sur les sujets témoins. Une analyse statistique a été effectuée à l'aide d'analyses bivariées et multivariées afin de rechercher des liens entre les facteurs d'exposition et la LMC.

Résultats : L'âge médian lors du diagnostic des cas de LMC était de 41,32 ans sur une amplitude de 8 à 81 ans et un rapport hommes–femmes de 1,7/1. La plupart de nos cas étaient concentrés à Nairobi ou dans ses alentours. Aucune corrélation significative n'a été établie pour les expositions au benzène ou aux pesticides. Une exposition de longue durée à des pesticides dans le groupe témoin en milieu familial était très fortement associée (test de Student, $p = 0{,}017$) au risque de LMC.

Conclusions : Des liens entre les expositions à des solvants organiques tels que des pesticides et la LMC ont été indiqués mais n'étaient pas totalement cohérents, bien qu'aucune association avec des produits au benzène n'ait été trouvée. Néanmoins, pour presque tous les cas de Ph+LMC, il est nécessaire de rechercher d'autres explications.

Mots clés Leucémie myéloïde chronique · Facteurs envionnementaux et professionnels

Introduction

Chronic myeloid leukemia (CML) runs a stable course for several years before assuming a rapid downhill progression. It results from neoplastic proliferation of a multipotential hematopoetic stem cell. More than 90% of the cases of CML have Philadelphia (Ph) chromosome-positive leukemic cells replacing marrow cells [1]. This chromosome is an abnormally short chromosome 22, which results from reciprocal translocations between chromosomes 9 and 22. One break occurs at band q34 near the long end of chromosome 9 and another in the upper half of chromosome 22 in the long end at band q11. The translocation breakpoint at chromosome 9 occurs near the 5' end of the Abelson (ABL, c-abl) oncogene, and ABL is, through these events, translocated from its normal location on chromosome 9 to chromosome 22. The gene located at the breakpoint of chromosome 22 is termed breakpoint cluster region (BCR) and measures 130 kilobases (kb). A segment of BCR in which the break occurs is referred to as bcr (small breakpoint cluster region). The t(9:22)(q34:q11) gene fusion leads to formation of a chimeric (hybrid) gene, resulting in production of chimeric mRNA which leads to production of a chimeric ABL protein product which is larger (210 kb) than normal (145 kb). The mechanism by which this chimeric gene promotes the transition from benign state to fully malignant involves the resultant increased tyrosine kinase activity, leading to abnormal proliferation of myeloid cells [2]. This is usually related to chronic stable phase. After variable periods, other molecular changes occur, leading to disease progression to accelerated and blastic phases [1].

Carcinogens bring about neoplastic transformation through various mechanisms. In the case of CML, they are responsible for bringing about the mitotic error that leads to the breaks and aberrant fusions involving chromosomes 9 and 22.

Various chemicals have been implicated in the process of carcinogenesis. Benzene is one such product. It is used mainly as a starting material in the synthesis of numerous chemicals. The main public health issue concerning benzene in the United States and other developed countries is its use as a component of gasoline and the fact that the shift to unleaded gasoline has tended to increase its benzene content [3–6].

Occupational exposure to chemicals, especially solvents containing benzene, has been associated with leukemia [7]. Workers exposed to benzene with exposures greater than 200 ppm/year have more than 20 times greater risk of developing acute myeloid leukemia (AML) than the general population [8]. The ability of benzene to cause AML was first fully established in the 1970s following epidemiological studies in Italy and Turkey [9–11].

The Ph chromosome was observed by classical cytogenetics in a case of preleukemia (leucopenia) resulting from chronic exposure to benzene for 4 years without the signs of leukemia. After further 4 years without exposure, the aberration disappeared [12].

For the data on organic solvents, an effect was found for moderate or high intensity of exposure (odds ratio (OR) = 3.4, and for long duration (15–20 years) of exposure OR = 2.1) [13].

Pesticides and farm chemicals also contain many carcinogenic compounds. Aromatic organochlorides include chlorophenoxy pesticides, combustion by-products, such as polychlorinated dibenzo-P-dioxins (PCDDs) and dibenzofurans (PCDFs), and industrial products, such as polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs). These compounds are chemically stable over many decades; they are passed along food chains, accumulate in fatty tissue, and are eliminated slowly from the body. Animal studies have shown that PCBs and DDT are carcinogens at high doses [14].

Two reviews have reached similar conclusions regarding role of pesticides in childhood leukemias. Zalm and Ward from National Cancer Institute (NCI) concluded in their review of 17 case-controlled studies and one cohort study that the literature supports a possible role for pesticides in development of childhood leukemias [15]. After reviewing the same literature, Daniels and colleagues in University of North Carolina concluded that leukemia association was more consistent among children whose parents had occupational pesticide exposures than among parents with residential pesticide exposure [16]. We decided to carry out a survey to determine the exposure to benzene compounds and farm chemicals in patients with CML. Our main objective was to determine key environmental and occupational factors that may be associated with this disease.

Methods

This was a case-control study in which cases were matched by age with gender, familial, and hospital control population. The study sites were Glivec International Patients Assistance Programme (GIPAP) clinics which run at the Nairobi Hospital and Aga Khan University Hospitals. This is an assistance program which provides Ph chromosome-positive patients with imatinib mesylate (marketed as Gleevec® or Glivec®) at no cost. The cases and familial controls were recruited at these clinics.

The hospital controls were recruited from the Kenyatta National Hospital (KNH) medical outpatient and specialized clinics.

Patients were considered to suffer from CML if they presented with suggestive history, usually with features of massive splenomegaly. Peripheral blood film features of profuse neutrophil leukocytosis coexisting with increased basophils, eosinophils, and monocytes with display of full maturation spectrum of myeloid series (promyelocytes, myelocytes, metamyelocytes, band forms, and mature elements), confirmed by hyper cellular bone marrow with myeloid hyperplasia, were the requisite hematologic findings. All patients were cytogenetically confirmed as Ph chromosome-positive, which was determined by fluorescent in situ hybridization (FISH) method. This information was obtained from the patients' clinical records.

Hospital controls were patients with a non-malignant, non-hematological disease with physical examination not suggestive of any malignancy or hematological disorder and a normal hemogram parameter (WBC $< 11 \times 10^9$/L) and normal morphology of WBC on PBF. They were patients from medical outpatient clinics in KNH, with any other medical condition. A familial control was defined as a family member of the case, being a 1st, 2nd, or 3rd degree relative.

All CML patients on follow up in GIPAP program were included and family members who were 1st, 2nd, or 3rd degree relative of the patient were included as familial controls.

Those who declined to consent for interview, and controls suffering from any other malignancy or with abnormal hemogram were excluded.

A detailed standard questionnaire was administered to each recruited subject. A lifelong occupational history was obtained, focusing on all jobs held for at least 1 year, including work task, department, and duration of employment. Evidence for specific exposures was enquired about exposure to benzene and organic solvents by working in petrochemical, paint, plastic, or motor repair industries, or application of pesticides by working as a gardener, horticulturist, farmer, or farmhand. The information was recorded in the questionnaire.

All patients attending GIPAP clinics had the details of the study explained to them, and if they consented, they were recruited and administered the questionnaire. The systematic recruitment continued until the desired sample size was achieved. If the patient was accompanied by an appropriate familial control subject, he/she was also recruited in the same fashion; otherwise the patient was requested to bring an appropriate family member on the next visit.

Each week, a similar number of age and gender matched hospital controls were also picked from medical outpatient and specialized clinics, and a search was carried out through the patients' files to select appropriate age and gender matched individuals. Once a control subject was identified, the study was explained to him/her, and if consent was obtained, the questionnaire was administered. If no consent was given, another control was identified in the same way and the procedure repeated.

Physical examination was performed on all recruited control subjects to rule out any definite hematological or oncological disorder, with special emphasis on weight loss, lymphadenopathy or splenomegaly.

After the interview, 2 ml of venous blood was drawn from cubital veins of the controls for hemogram and peripheral blood film. This was put in EDTA tubes and analyzed within 8 h in the hematology unit using the Cell Dyne 1300® model of automated cell counts.

The result of the blood analysis was communicated to the subject by phone. Subjects with abnormal result were guided to receive appropriate medical attention and subsequently excluded from the study.

Data Management and Analysis

Data was entered into MS Access, cleaned and verified. Statistical analysis of data was undertaken using Statistical Package for Social Sciences (SPSS) version 11.5. Data was

presented in the form of tables, graphs, and pie charts. Descriptive statistics, such as mean, median, and standard deviation, were determined where applicable. Duration of exposure, age, and BMI were calculated as continuous variables. For purposes of diagrammatic presentation, the number of persons per district and age were used as categorical variables. Exposure variables were categorized in a binary format as ever or never exposed. To assess the significance of differences in continuous data, the t-test was used and for categorical data, chi-square was used. Comparison of results using OR with 95% confidence interval was done. Multivariate risk analysis was done using logistic regression. P values of <0.05 were considered significant. P values in the OR tables were obtained from chi square tests computed for 2 × 2 tables with appropriate statistical correction where necessary. Data was analyzed and both sets of analysis were presented separately for each control group to avoid non-differential bias [17].

Ethical approval to carry out this study was obtained from Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UON ERC) and patients were enrolled for study only after giving informed written consent. All information obtained from the study had been handled in confidence and used only for intended purpose.

The only invasive procedure was collection of blood for full hemogram in the control population. The results of blood test were communicated to the subjects. In case of abnormal results in the hemogram of control population, they were guided for the appropriate clinical interventions. No extra financial cost was borne by the patients or controls as they were interviewed when they came for their routine clinic. The familial controls requested to accompany the patients were reimbursed their transport costs. Questionnaire was in simple English which could easily be translated into Kiswahili or local languages.

Results

A total of 120 cases, 108 familial controls, and 112 hospital controls were recruited between August 2008 and January 2009.

Twelve cases were excluded for various reasons: two did not give consent and ten failed to bring appropriate familial control subjects. Four hospital controls were excluded: two had a history of suffering from previous malignancy; one from breast cancer and other one from Kaposi's sarcoma and two had elevated WBC counts. One hundred and eight cases with two controls for each were analyzed. Full hemogram and peripheral blood film was done for all controls (Fig. 1).

Demographic Characteristics

Patients' ages ranged from 8 to 81 years with the median age of 40.5 and mean age of 41.31 ± 15.33. The mean age in males was 40.35 ± 15.74 while in females was 42.97 ± 14.69. The mean age in familial and hospital control groups was 41.07 ± 15.21 and 41.2 ± 14.83 with medians of 41.0 and 40.0, respectively.

Sixty-eight (63%) males and 40 (37%) females were enrolled into the study, with a male to female ratio of 1.7:1, which is comparable with previous literature [18].

The most prevalent age group for the cases was in the age bracket of 35–40 years, which was also the most prevalent age group in males, while in females it was 25–30 years. Cases with extremes of age, the youngest and oldest patients were also males (Fig. 2).

The results of the demographic characteristics and body mass index (BMI) for the three study groups are summarized in the Table 1.

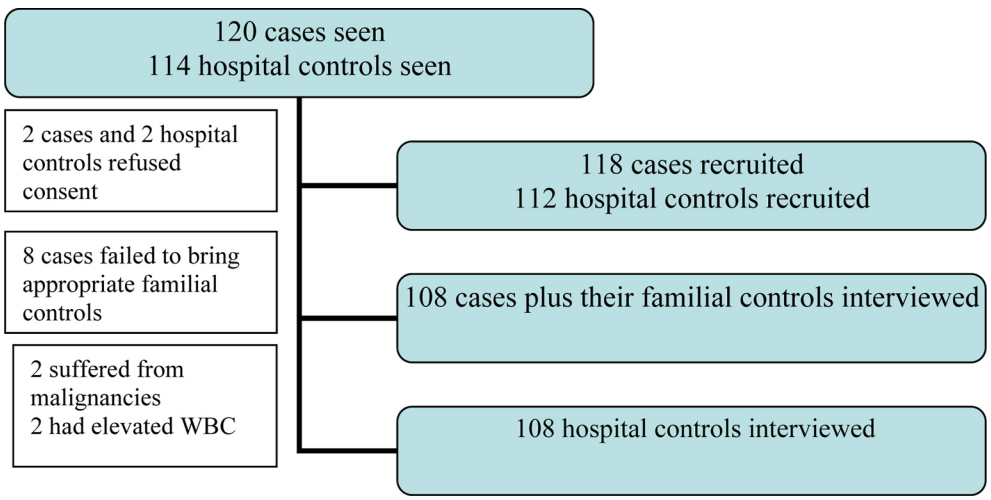

Fig. 1 Patient flow chart

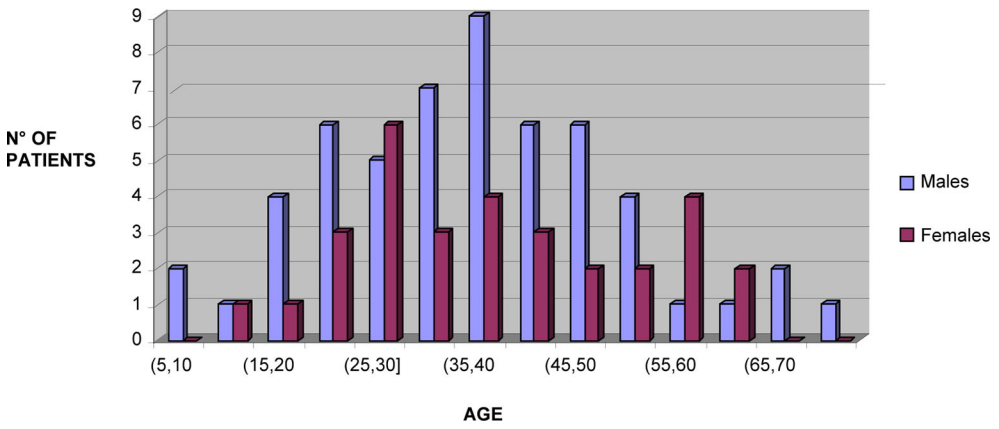

Fig. 2 Case distribution by age and gender

Table 1 Demographic characteristics of study subjects.

	Cases	Familial control	P value	Hospital control	P value
Age in years					
Mean	41.32 ± 15.34	41.07 ± 15.21	0.90	41.2 ± 15.09	0.95
Median	40.5	41.0		40.0	
Occupation					
Indoor	63.3%	73.5%	0.11	56.3%	0.33
Outdoor	36.7%	26.5%		43.7%	
BMI					
Mean	25.26 ± 6.25	25.04 ± 5.69	0.70	23.16 ± 4.41	0.08
Median	23.93	23.84		22.42	

Cases and control groups were more involved in indoor occupations rather than outdoor, although the hospital control group was more equally distributed (indoor = 56.3% and outdoor = 43.7%). The familial control group had more indoor occupations, at 73.5% of the whole group than the rest (Table 1).

Majority of patients seen came from the vicinity of Nairobi city, which was the study site, and its immediate environs. There were also a high number of patients from Mombasa, which is the second largest city in Kenya. Overall, the cases were mainly from the southern, more populated part of Kenya except two patients who came from the North Eastern province. Nine patients had lived out of Kenya at some points in their life (Fig. 3).

Exposure to Benzene

Thirteen cases were exposed to benzene in terms of working in petroleum, plastic, and motor repair industries as compared to 21 individuals in familial control group and 15 patients in hospital control group. There were 4 (3.7%) cases and 4 controls in each group exposed to petroleum, giving an OR of unity. Two cases (1.9%) and two familial controls, with no hospital control, were exposed to plastic industry, with OR at unity again. Exposure to paints yielded 6 (5.6%) cases, 13(12.0%) familial controls and 7 (5.6%) hospital controls, giving an OR of 0.43 (95% CI = 0.16 − 1.18, P = 0.093) and OR of 0.85 (95% CI = 0.28 − 2.61, P = 0.76) respectively. Exposure to solvents in motor vehicle repairs had 3 (2.8%) cases, 2 (1.9%) familial and 4 (3.7%) hospital controls, giving an OR of 1.51 (95% CI = 0.24 − 9.25, P = 0.65) and OR of 0.74 (95% CI = 0.16 − 3.40, P = 0.70), respectively.

Exposure to Pesticides

There were 46 (43.0%) cases exposed to pesticides in terms of working on farms, gardens or as horticulturalists, either as an occupation or as a hobby, compared to 36 (33.3%) in familial control group and 46 (42.6%) patients in hospital control group. This was found to be non-significant with OR of 1.51 (95% CI = 0.87 − 2.62, P = 0.15) in comparison to familial controls and OR 1.02 (95% CI = 0.59 − 1.75, P = 0.95) in comparison to hospital control group (Tables 2, 3).

The cases had a mean of 11.38±9.65 years (95%CI = 6.23 − 16.52) for exposure to benzene, compared to 7.95 ± 8.97 years (95% CI = 3.63 − 12.27, P = 0.288) in familial control group

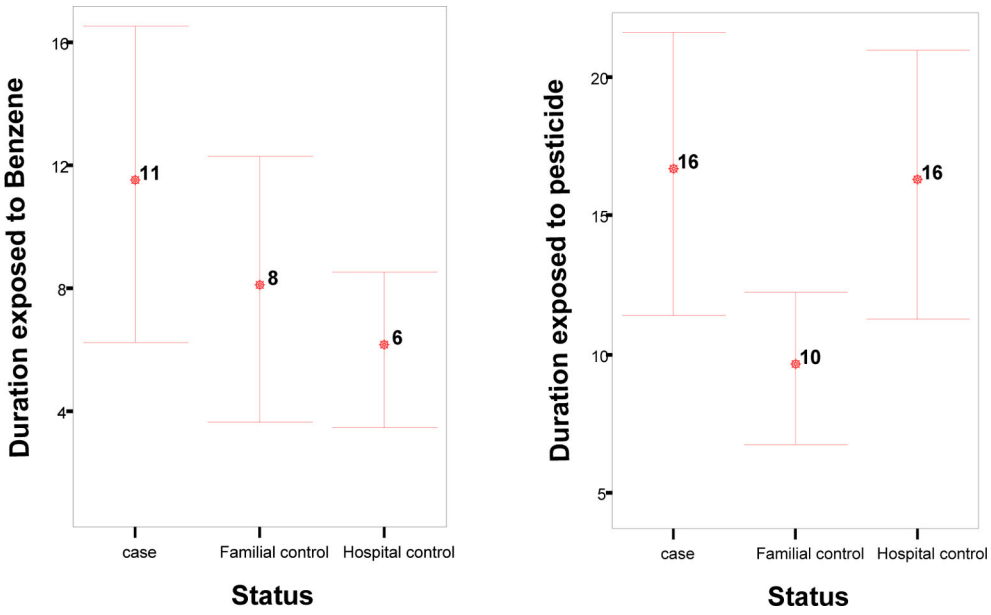

Fig. 3 Duration of exposure to benzene and pesticides against status

Table 2 Odds ratios for exposure to benzene and pesticides.

Exposure factor		Cases	Familial control	OR with 95% CI	P value
Petroleum	Yes	4 (3.7%)	4 (3.7%)	1 (0.24–4.11)	1.00
	No	104 (96.3%)	104 (96.3%)		
Plastic	Yes	2 (1.9%)	2 (1.9%)	1.0 (0.14–1.18)	1.00
	No	106 (98.1%)	106 (98.1%)		
Paints	Yes	6 (5.6%)	13 (12.0%)	0.43 (0.16–1.18)	0.093
	No	102 (94.4%)	95 (88%)		
Motor repair	Yes	3 (2.8%)	2 (1.9%)	1.51 (0.24–9.25)	0.65
	No	105 (97.2%)	106 (98.1%)		
Pesticides	Yes	46 (43.0%)	36 (33.3%)	1.51 (0.87–2.62)	0.15
	No	62 (57.0%)	72 (66.7%)		

Table 3 Odds ratios for exposure to benzene and pesticides.

Exposure Factor		Cases	Hospital control	OR with 95% CI	P value
Petroleum	Yes	4 (3.7%)	4 (3.7%)	1 (0.24–4.11)	1.00
	No	104 (96.3%)	104 (96.3%)		
Plastic	Yes	2 (1.9%)	0 (0.0%)		0.15
	No	106 (98.1%)	108 (100.0%)		
Paints	Yes	6 (5.6%)	7 (6.5%)	0.85 (0.28–2.61)	0.76
	No	102 (94.4%)	101 (93.5%)		
Motor repair	Yes	3 (2.8%)	4 (3.7%)	0.74 (0.16–3.40)	0.70
	No	105 (97.2%)	104 (96.3%)		
Pesticides	Yes	46 (43.0%)	46 (42.6%)	1.02 (0.59–1.75)	0.95
	No	62 (57.0%)	62 (57.4%)		

and 6.00 ± 4.35 years (95% CI = 3.49 − 8.51, P = 0.058) in hospital control group. None of these reached statistically significant levels.

Duration of exposure to pesticides in the cases had a mean of 16.49 ± 17.31 years (95% CI = 11.41 − 21.57) compared to the hospital-control mean duration of 16.09 ± 16.06 years (95% CI = 11.26 − 20.91), but a statistically significant difference with P = 0.017 with familial control mean duration of 9.50 ± 8.54 years (95% CI = 6.77 − 12.23) was observed (Fig. 3) (Table 4).

Discussion

The median age for patients in this study is 41.32 with an age range of 8–81 years. Othieno-Abinya et al found a similar age range of 10–72 years in KNH in 2000 [18]. They found a median age of 35 years at diagnosis whereas Bjork in Sweden found a median age of occurrence of CML at 51 years, almost 10 years younger than our population [13]. Our male to female ratio was 1.7:1, which is comparable to what Othieno-Abinya and colleagues [18] found at 1.1:1 and Bjork et al at 1.23:1 [13], which is in keeping with the general observations.

Our peak age of occurrence of CML is 10 years younger than in the West. The peak for females is even at a younger age of 25–30 years, but the number is too small to make a firm statement. Similar median age of 40 years for CML was found in Nigeria [19], reflecting generally younger age of occurrence of CML in Africa.

Other cancers in Africans have also been found to be occurring at a younger age group, for example, median age of occurrence of non-Hodgkin's lymphoma in Kenya is only 32 years against the mean age of 50 years internationally [1]. It is not clear why we have an earlier age of occurrence of CML and further studies are required to probe into the etiologic possibilities of this significant difference. The important contributing factors could be genetic, environmental, and socioeconomic.

Majority of the patients came from environs of Nairobi and 44.5% of our patients came from or had at one time lived in Nairobi at least for a year. The patient population was concentrated proximal to health facility, particularly Nairobi, where expertise, health personnel, and diagnostic facilities are available, and also ease of communication. Clinicians and physicians outside Nairobi may not be aware of the GIPAP program and may not be referring patients to the program. The only far away pocket was seven patients coming from Mombasa district on the Coast of Kenya. This is the second largest city in Kenya with a high population density and good infrastructure and links to Nairobi. The pocket of patients from North Eastern Kenya could be explained by links of people from the province with Nairobi, particularly in the Eastleigh area. Some areas in Southern Kenya yielded no cases and that could possibly be explained by the healthcare-seeking behavior of the communities living in those regions and possible belief in traditional and herbal modes of treatment. Othieno-Abinya and co-workers also had more than 35% of cases being from Kikuyu tribe, and they thought it was possibly due to proximity to Nairobi [18]. This is reflected in other chronic disease outpatient clinics in KNH and is thought to be due to the patient catchment area.

We found the OR for benzene exposure from petrochemicals plastic and rubber industries and exposure to paint were close to unity in CML patients. Failure to stratify by intensity or duration may have failed to show association of CML with benzene. Longer duration of exposure, as found in the cases, may probably be contributing to risk of developing CML. The findings by Bjork and colleagues in Sweden were similar [13].

This also agrees well with a combined cohort study of petroleum workers in China, who were exposed to petrochemicals such as benzene at low concentrations and gasoline [20]. At higher concentration exposures, non-significant effects of occupational exposure to benzene on leukemias other than AML have, however, been reported. [21]

Yu and co-workers suggested a possible link between living in an area with high exposure to airborne petrochemicals (derivatives of petroleum or natural gas) and risk of developing leukemia in a study in Taiwan [22]. We only had one case in our study residing in close proximity to an oil refinery.

The association between farming and leukemia in general, which has been studied in numerous epidemiological settings, is likely to be weak, if present at all [23]. Our data did not indicate risk of CML associated with agricultural life, manifested by OR estimates almost at unity for typical agricultural exposures such as farming occupations and pesticides. The OR was just above unity when compared with familial controls. Duration of exposure to pesticides was similar with hospital control but significantly lower in familial group. We

Table 4 Duration of exposure to benzene and pesticides.

Exposure	Cases (Mean years)	Familial control (Mean years)	t-Test significance	Hospital control (Mean years)	t-Test significance
Benzene	11.38	7.95	0.288	6	0.058
Pesticides	16.49	9.5	0.017	16.09	0.909

think this may be due to the general nature of agricultural lifestyle in the hospital control group, who had a homogenous distribution in the country.

A meta analysis by Belgian researchers to determine if occupational exposure to pesticides was associated with a higher risk of CML. Overall, the case-control studies indicated a relative risk of 1.38 (95% CI = 1.06 − 1.79) of developing CML among farmers and agricultural workers exposed to pesticides [24]. However, Bjork found the OR for exposure to pesticides for Ph chromosome-positive CML patients in Sweden to be 0.75 (95% CI = 0.42 − 1.3) [13].

Conclusion

Associations between exposures to organic solvents like pesticides, creosote as used in timber preservation, water treatment by chlorinated chemicals and Ph chromosome-positive CML were indicated but were not entirely consistent.

Acknowledgements This abstract was presented in poster version at the 2011 AORTIC meeting in Cairo, Egypt.

Conflict of interest: R. Kasmani, N.A. Othieno-Abinya, M.t. Singh Riyat, G.W. Kiarie and P. Wanzala have no conflict of interest to declare.

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