Risk factors of hematological malignancies in Upper Egypt: a case-control study

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Background

The definite etiologies of hematological malignancies (HMs) are still unknown. **Objective**

The aim of our study was to identify the distribution of HMs and its subtypes as well as to determine their risk factors in Assiut Governorate, Upper Egypt.

Patients and methods

This case–control study included 1137 patients diagnosed with different HMs (leukemia, lymphoma, myelodysplastic syndromes, and multiple myeloma) and normal healthy controls from January 2014 to December 2017. Data were collected using interviewed administered questionnaire, and clinical and biochemical assessment. Logistic regression analysis was conducted to identify the predictors of HMs and their subtypes.

Results

Leukemia was the most common presented HM (75%), nearly half of leukemic cases were acute myeloid leukemia, while non-Hodgkin's represented the majority of patients with lymphoma. Increasing age and diabetes mellitus were significantly associated with all HMs. Except for multiple myeloma, hepatitis C virus and obesity had significantly higher odds ratio for HMs and their subtypes. Exposure to agricultural chemicals was a risk factor for lymphoma and myelodysplastic syndromes while exposure to electromagnetic field was a significant risk factor for leukemia.

Conclusion and recommendations

This is the first study evaluating the different risk factors and distribution of HMs in Upper Egypt. Studies with a more detailed evaluation of the role of the possible risk factors in the occurrence of blood cancers in Egypt are recommended.

Keywords:

distribution, hematological malignancies, leukemia, lymphoma, risk factors

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Introduction

Hematological malignancies (HMs) are a heterogenous group of diseases characterized by uncontrolled malignant proliferation of hematopoietic cells. During the past 10 years, the frequency of HMs has increased with complete difference between the developing and developed countries [1]. The exact causes of HMs are still unknown although multiple epidemiological studies have reported an association between the development of HMs and several risk factors [2]. Some factors are well documented to increase the risk of some types of leukemia such as benzene exposure and ionizing radiation [3]. However, many other factors were observed to have an association with HMs such as age, gender [4], tobacco smoking [5], obesity [6], hepatitis C virus (HCV) infection [7], family history [8], and environmental exposure to pesticides [9] but with no clear evidence.

In Egypt, a nationally representative study based on data from three governorates, one governorate represented each of the Egyptian geographic strata (upper, middle, and lower), reported Non Hodgkin's Lymphoma (NHL) among the most frequent cancers in Egypt [10]. Another study in the Gharbiah Governorate conducted during 1999–2005 in Lower Egypt showed that NHL had the highest incidence among all hematological cancers [11].

Aim

As there is deficiency of epidemiological studies on HMs in Upper Egypt, the aim of the current study is to achieve a better understanding of the problem of HMs in upper Egypt.

Objectives

(1) To identify the distribution of HMs and its subtypes.

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(2) To determine their risk factors in Assiut Governorate, Upper Egypt.

Patients and methods

This is a case-control study conducted in Assiut Governorate. Assiut is a large governorate which is located in the Middle Upper Egypt region and has a large university hospital and cancer institute which serves the population of the governorate and whole Upper Egypt. The studied population included all patients diagnosed with HMs (1137 cases) including leukemia, lymphoma, myelodysplastic syndromes and multiple myeloma (MM) and 1137 healthy controls. HMs cases were recruited from those presented to the Hematology Unit, Internal Medicine Clinical Department, Assiut University Hospital and South Egypt Cancer Institute, from January 2014 to December 2017. Diagnosis of HM patients was done according to the WHO 2008 guidelines. All patients were subjected to history taking and clinical examination, with careful assessment of clinical signs such as lymphadenopathy and/or organomegaly. Complete blood picture, liver function tests, renal function tests, bone marrow aspirate, bone marrow biopsy, and immunophenotyping were done to cases. Excisional lymph node biopsy along with immunohistochemistry also were done for the diagnosis of lymphoma. Serum and urine protein electrophoresis with immunofixation, serum calcium, lactate dehydrogenase and $\beta 2$ microglobulin, and complete skeletal survey were performed for the diagnosis of MM.

Data were collected from the studied population through personal interview. The questionnaire included data about: age, gender, residence, self-reported smoking status (yes, no), exposure to electromagnetic fields (cellular telephone, living near powerlines, use of electric appliances), exposure to agricultural chemicals pesticides, and presence of autoimmune disease (systemic lupus erythromatosus, rheumatoid arthritis, and use of immunosuppressive therapy). The participants were considered diabetic according to the diagnostic criteria of American Diabetes Association [12]. Confirmation of positive HCV infection by anti-HCV antibodies (Abs) detection was done by enzyme-linked immunosorbant assay (ELISA) and PCR. Weight and height were measured following a standard methodology. BMI was calculated as weight in kilograms divided by height in meters squared and the participants were categorized as obese or not according to the WHO Global Database on BMI $\geq 30 \text{ kg/m}^2$ [13]. The study was approved by the Medical Ethics Committee of Assiut University. Ethical principles

were followed with the study participants including explaining the aim of the study, ensuring voluntary participation and that refusal would have no negative effect on the provided medical services. Informed consent was obtained from all study participants. Confidentiality was assured and maintained by removing the participant's names from the data entry file. Only numbers were kept for identification.

Statistical analysis

Data analysis was conducted using the SPSS software version 20 (statistical package for the social sciences, version 20; IBM, Armonk, New York, USA). Continuous data were expressed in the form of mean±SD while qualitative data were expressed in the form of frequencies and percentages. analysis Multivariate logistic regression was performed to identify the significant predictors of HMs such as overall, leukemia and its subtypes, lymphoma, multiple myeloma, and myelodysplastic syndromes as dependent variables. The explanatory variables in the models were age as continuous variable, gender (male, female), residence either urban or rural, being smoker or not, absence or presence of obesity, diabetes, autoimmune disease, HCV infection, and exposure to electrical field and agricultural chemicals. Odds ratios (OR) were reported with their corresponding 95% confidence intervals (95%CI). Statistical significance was considered at the P less than 0.05 level.

Results

This case–control study included 1137 patients with different HMs and 1137 healthy controls. The median age of HM cases was 50 years with a range of 19–90 and that of control was 35 years with a range of 20–76 years. Men have slightly higher proportion (52.8%) compared with women (47.2%) among HM cases. About two-thirds of the studied cases were rural residents (63.7%) as shown in Table 1. Leukemia was the most common presented HM, it represented about three quarters of the studied population (75%), followed by lymphoma (11.4%), multiple myeloma, and myelodysplastic syndromes as shown in Table 2. About half of the diagnosed leukemic patients were acute myeloid leukemia (49.7%) while NHL predominated in patients with lymphoma (81.34%).

Increasing age was significantly associated with all types of HMs. Female gender, smoking, and rural residence were significant predictors for developing HMs as total and its subtypes except lymphoma. Those with autoimmune disease have significantly

 Table 1 The characteristic of the studied population

 (hematological malignancies patients and healthy controls)

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	Cases [n (%)]	Control [n (%)]
Gender		
Male	619 (52.8)	535 (45.6)
Female	554 (47.2)	638 (54.4)
Residence		
Urban	426 (36.3)	840 (71.6)
Rural	747 (63.7)	333 (28.4)

Table 2 Distribution of hematological malignancies, adult greater than or equal to 19 years, Assiut Governorate (2014–2017)

	Cases [n (%)]
Leukemia	879 (75)
AML	437 (37.3)
ALL	125(10.7)
CML	184 (15.7)
CLL	133 (11.3)
Lymphoma	134 (11.4)
HL	25 (2.1)
NHL	109 (9.3)
MDS	66 (5.6)
MM	94 (8.0)
Total	1137

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndromes.

higher OR for HMs (OR=2.04, 95% CI: 1.21-3.46), leukemia (OR=2.27, 95% CI: 1.27-4.06), and MM (OR=6.38, 95% CI: 2.62–15.51) while it was not a risk in lymphoma (OR=0.92, 95% CI: 0.26-3.23) and myelodysplastic syndromes (MDS) (OR=0.78, 95% CI: 0.19–3.16). Being a diabetic patient significantly increased the risk for developing HMs as overall and all its subtypes. Except in MM, those positive for HCV infection and obese patients had significantly higher OR for HMs and its subtypes compared with negative HCV infection and nonobese participants. Exposure to agricultural chemicals was not a significant predictor in developing HM as overall (OR=1.10, 95% CI: 0.71 - 1.71),leukemia (OR=1.24, 95% CI: 0.79–1.95), or MM (OR=0.83, 95% CI: 0.31–2.22) while it was a risk factor in lymphoma (OR=3.01, 95%) CI: 1.45-6.05) and in myelodysplastic syndromes (OR=7.88, 95% CI: 3.04–20.43). Exposure to electrical field was a significant predictor in HMs overall (OR=4.73, 95% CI: 2.96-7.55) and leukemia (OR=5.12, 95% CI: 3.16-8.28) as shown in Table 3.

Regarding leukemia subtypes, increasing age was a significant predictor in all types of leukemia. Women and obese participants have significantly higher OR for occurrence of all leukemia types compared with males and nonobese individuals .

Those residing in rural areas are more likely to develop all types of leukemia except acute lymphocytic leukemia (ALL) compared with those residing in urban areas. Smoking was a risk factor for ALL (OR=9.41, 95% CI: 5.31-16.69), chronic myelogenous leukemia (CML) (OR=11.19, 95% CI: 6.54–19.13), and chronic lymphocytic leukemia (CLL) patients (OR=13.21, 95% CI: 6.44-27.13); however, it was not in acute myeloid leukemia (AML) patients (OR=0.76, 95% CI: 0.50-1.15). Existence of autoimmune disease increased the risk for developing ALL (OR=7.58, 95% CI: 3.17-18.15) while it was not a significant predictor for other leukemia types. Being HCV positive the patients increased the risk for getting ALL and CLL but not the myeloid leukemia subtypes. Those exposed to electrical field had higher OR for developing all types of leukemia except CLL (OR=0.31, 95% CI: 0.07-1.34). Exposure to chemical substance was a significant predictor for developing CLL only (OR=12.15, 95% CI: 5.69-25.95). Diabetes mellitus was a risk factor in AML (OR=3.31, 95% CI: and ALL (OR=10.09, 95% CI: 1.72 - 6.374.66–21.84); however, not in the chronic subtypes as shown in Table 4.

Discussion

The distribution of HMs in developing countries is different from their distribution in developed countries [1], with a lack of studies which determine the distribution and the risk factors for HMs in the developing countries. This study is considered the earliest study that aims to evaluate the distribution and risk factors for HMs in Assiut, Upper Egypt.

Our results have shown that leukemia was the most common presented HM in Assiut, Upper Egypt (75%), followed by lymphoma (11.4%). AML was the most frequent subtype of leukemia (49.7%) while NHL predominates in patients with lymphoma (81.34%).

Regarding developing countries, our results were supported by the results of Egyptian National Cancer Registry Program in Aswan Governorate which reported that leukemia was the most common HM followed by lymphoma [10]. Also, in Sudan, the maximum number of cases were seen in the age group of 45–64 years and in both gender, leukemia had a higher frequency than lymphoma among the reported common cancer sites [14]. In Bangladesh, leukemia patients were over three times higher compared with the NHL patients [15]. A different pattern was observed, where lymphoma specially NHL was the

	HM		Leukemia		Lymphoma		MDS		MM	
	OR (95% Cl)	P value	OR (95% Cl)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% Cl)	P value
Age	1.06 (1.05–1.07)	0.000	1.06 (1.05–1.07)	0.000	1.062 (1.04–1.09)	0.000	1.05 (1.02–1.08)	0.001	1.10 (1.08–1.13)	0.000
Gender (female)	1.66 (1.31–2.098)		1.73 (1.34–2.23)	0.000	1.75 (0.99–3.09)	0.055	7.88 (3.16–19.62)		4.58 (2.46–8.50)	0.000
Residence (rural)	3.17 (2.53–3.98)	0.000	3.12 (2.44–3.97)	0.000	1.24 (0.71–2.16)	0.451	3.80 (1.67–8.65)			0.000
Smoking (yes)	3.14 (2.40–4.11)	0.000		0.000	1.51 (0.81–2.82)	0.199	8.84 (3.91–20.04)			0.003
	4.73 (2.96–7.55)	0.000		0.000	2.14 (0.79–5.79)	0.135	1.57 (0.53–4.64)			0.852
Pesticides (yes)	1.10 (0.71–1.71)	0.663	1.24 (0.79–1.95)	0.346	(, , , , , , , , , , , , , , , , , , ,	0.002	/ · · - ·	0.000	0.83 (0.31–2.22)	0.705
Obesity (yes)	8.02 (5.00–12.87)	0.000	6.41 (3.93–10.45)	0.000		0.000	14.71 (6.35–34.07)	0.000	2.30 (0.90–5.88)	0.083
Autoimmune disease (yes)		0.008	2.27 (1.27–4.06)	0.006	0.92 (0.26–3.23)	0.893	0.78 (0.19–3.16)	0.729	6.38 (2.62–15.51)	0.000
HCV infection (yes)	3.90 (2.33–6.53)		2.10 (1.19–3.70)		34.21 (16.63–70.38)		4.14 (1.08–15.78)		1.64 (0.42–6.49)	0.478
Diabetes mellitus (yes)	3.93 (2.36–6.53)	0.000			2.99 (1.25–7.15)		12.00 (4.19–34.12)			0.000

Table 3 Risk factors of hematological malignancies, leukemia, lymphoma, myelodysplastic syndrome, and multiple myeloma; adult cases greater than or equal to 19 years in Assiut Governorate (2014–2017)

Adjusted logistic regression models; Reference groups in categorical variables were: gender (male), smoking (no), presence of autoimmune disease (no), HCV infection (no), exposure to electrical field (no), chemical substance exposure (no), obesity (no), diabetes mellitus (no), and residence (urban). CI, confidence interval; HCV, hepatitis C virus; MDS, myelodysplastic syndromes; OR, odds ratio.

Table 4 Risk factors of acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, and chronic lymphoid
leukemia; adult cases greater than or equal to 19 years in Assiut Governorate (2014–2017)

	AML		ALL		CML		CLL	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Age	1.07 (1.06–1.08)	0.000	1.05 (1.03–1.07)	0.000	1.06 (1.04–1.08)	0.000	1.09 (1.07–1.12)	0.000
Gender (female)	1.70 (1.25–2.30)	0.001	2.37 (1.34–4.20)	0.003	4.02 (2.38–6.80)	0.000	3.25 (1.61–6.53)	0.001
Residence (rural)	3.14 (2.34–4.212)	0.000	1.43 (0.84–2.43)	0.183	3.46 (2.12-5.65)	0.000	2.14 (1.13–4.06)	0.019
Smoking (yes)	0.76 (0.50–1.15)	0.191	9.41 (5.31–16.69)	0.000	11.19 (6.54–19.13)	0.000	13.21 (6.44–27.13)	0.000
Electrical field (yes)	3.06 (1.76–5.32)	0.000	11.88 (5.49–25.72)	0.000	10.49 (4.80–22.94)	0.000	0.31 (0.07–1.34)	0.117
Pesticides (yes)	1.59 (0.95–2.67)	0.078	0.97 (0.41–2.27)	0.941	1.27 (0.57–2.84)	0.563	12.15 (5.69–25.95)	0.000
Obesity (yes)	8.16 (4.68–14.20)	0.000	2.87 (1.14–7.24)	0.025	8.08 (3.94–16.57)	0.000	28.36 (13.50–59.58)	0.000
Autoimmune disease (yes)	1.54 (0.76–3.16)	0.234	7.58 (3.17–18.15)	0.000	1.88 (0.78–4.50)	0.157	0.80 (0.24–2.64)	0.712
HCV infection (yes)	1.30 (0.60–2.81)	0.502	4.47 (1.94–10.30)	0.000	2.38 (0.98–5.78)	0.056	4.46 (1.7–12.02)	0.003
Diabetes mellitus (yes)	3.31 (1.72–6.37)	0.000	10.09 (4.66–21.84)	0.000	0. 83 (0.31–2.23)	0.718	0.72 (0.21–2.53)	0.608

Adjusted logistic regression models; reference groups in categorical variables were: gender (male), smoking (no), presence of autoimmune disease (no), HCV infection (no), exposure to electrical field (no), chemical substance exposure (no), obesity (no), diabetes mellitus (no), and residence (urban). ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; CI, confidence interval; CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; HCV, hepatitis C virus; OR, odds ratio.

most frequently presented HM as reported by the US Cancer Fact and Figures 2016 [16]. Also, in South Africa (2000–2006) [17], Nigeria (1999–2005) [18], and even in Lower Egypt, NHL was the most common

HM [11]. In Lower Egypt (Gharbiah Governorate) Study CLL was reported as the most common subtype of leukemia. The difference in the distribution of HMs between upper and lower Egypt could be attributed to the variation in risk factors that needed to be investigated in future studies and to the high prevalence of HCV infection in Lower Egypt.

Regarding the detected significant predictors of HMs as overall and its subtypes in this study, increasing age was a significant risk factor for all HMs with all its subtypes. There is evidence of association between aging and cancer particularly HMs. This could be attributed to demographic shift, prolonged exposure to carcinogens and chronic antigenic stimulation and age-accompanied changes in genetics and immunity. The resulting genetic damage changes do not exclude hematopoietic stem cells [19].

Gender is an important contributing factor that impacts the risk factors for diseases. Generally, there is observed preponderance for men in malignant hemopathies. In acute leukemia, hypothesis of male risk remains an unexplained fact [20]. In lymphoma, gravidity had a protective role against NHL occurrence [21]. In MDS patients, being male is among the common risk factors. In contrast, the present study showed that women compared with men had a significantly higher risk for developing HMs as overall and all its subtypes except lymphoma.

Regarding residence, our results reported significant association between rural residence and all HMs except lymphoma and ALL. Similarly, a cohort study of health in older women detected positive association of farm or rural residence with acute myeloid leukemia [22]. However, a different situation was observed in Lower Egypt, where a higher urban incidence for all HMs was observed [11].

In developed countries, about 25-30% of deaths caused by all cancers are related to tobacco smoking [23]. Multiple studies have evaluated the role of smoking in HMs. The International Agency for Research on Cancer (IARC) had previously reported a relation between smoking and AML [24]. In the present study, smoking increased the risk for leukemia combined with ALL, CLL, and CML, but there was no significant association detected with AML. These results are supported by a Japanese study done in 2017 reporting no significant relationship between cigarette smoking and risk of AML even with an increasing dose [25]. Another study had reported an increased risk for AML and CML with increasing intensity of smoking in both men and women and that the risk is markedly decreased in long-term quitters where it becomes comparable to never smokers [26]. Also a Canadian study reported that smoking was not a statistically significant risk factor for all leukemia combined, ALL and CLL but a statistically significant risk factor for AML [27]. On the other side, a Thai study observed no association between smoking and all types of leukemias [28]. Cigarette smoking has been linked to malignancy development by exposing the smokers to a large number of chemical agents such as benzene, arsenic, formaldehyde, and others [29].

There is a growing concern that exposure to electromagnetic fields increases the incidence of hematological cancers. This was first described by Milham et al. in electrical workers [30]. In the present study, a defined exposure to electromagnetic field had a significant higher OR for aggregated HMs and leukemia, AML, ALL, and CML. A previous case-control study in New Zealand reported a significant risk of acute leukemia in electric field workers in general and specifically in some occupations as welders/flame cutters and telephone line workers [31]. These results were contradicted by another study who found no association between acute leukemia and exposure to electromagnetic fields in general but they reported a significant increase in ALL specific in women with electromagnetic exposure at work compared with never exposed women [32]. Also, a Thai study reported that working with or near powerlines was significantly associated with AML [28].

In our study, pesticide exposure increased the risk for lymphoma, MDS, and CLL. Multiple previous studies have suggested an association between farmers and risk for leukemia [33]. Hematopoeitic cancers in rodents were linked to exposure to several pesticides such as dichlorodiphenyltrichloroethane, atrazine, and dichlorvos [34]. It is still unclear how the risk of CLL can be increased by exposure to chemicals. Several reports had linked the exposure to pesticides and solvents to immune system impairment and induction of chromosomal rearrangements, which may be a central factor for the development of CLL in these cases [35]. However, on the other side, an Indian case-control study did not show any association between exposure to pesticides and increased risk for leukemia [36]. Our results were supported by Merhi [37], who observed that exposure to pesticides was not a statistically significant risk factor for leukemia and MM.

Obesity and its association with several cancers have been established by multiple studies [6]. In this study, obesity significantly increased the risk of all studied hematological diseases (combined HMs, aggregated leukemia and its subtypes, lymphoma and MDS) except MM. These results were supported by two previous meta-analyses. One meta-analysis included 26 studies and proved that increased incidence of AML was associated with obesity [38]. The other meta-analysis included four studies which proved a significant increased risk of all leukemia subtypes with obesity. The underlying biological mechanism is unclear. This may be due to the promotion of tumorogenesis through insulin resistance and increased pancreatic insulin secretion. Also, chronic inflammation and impaired immune function may play a role in this process [39].

Hematologic abnormalities are common presentations of connective tissue diseases. Besides, they are prognostic indicators of inflammatory activity. There is an observed increase of hematologic malignancies, especially lymphoproliferative diseases with autoimmune diseases [40]. However, in the present study, autoimmune diseases were not a significant predictor for lymphoma and CLL. They were risk factors for overall HMs, leukemia (combined), ALL and MM. In agreement with our results, autoimmune disease was found to be a risk factor for HM combined [41] and multiple myeloma [42], and not risky for myeloid leukemia [43] and CML [44]. Contradictory to our observation, autoimmune conditions were significantly associated with AML and MDS. This association between HMs and autoimmune disorders may be explained by the use of medications such as azathioprine in the treatment of these conditions, direct infiltration of bone marrow, or shared genetic predisposition [44].

HCV infection in Egypt is considered a major health problem. The prevalence of HCV in the age group of 15–59 years was 10% in 2015 [45]. Chronic hepatitis C has a well-documented association with hepatic malignancies [46]. Our results support the evidence of HCV infection with lymphoma and detect a significant association with MDS and leukemias except myeloid subtypes. The strongest evidence for the relationship between HCV and malignancy is for B-NHL. Different mechanisms explaining the HCV-induced malignant transformation have been postulated and this includes cryoglobulinemia, viral-induced cell damage, and lymphocyte proliferation caused by viral antigen stimulation. Previous studies have found a weak association between HCV and other HMs [47]. The high prevalence of HCV in Egypt may explain the association with other HMs in our study. In 2017, 425 million people have diabetes mellitus worldwide with 8222 million cases in Egypt. In our study, diabetes mellitus significantly increased the risk for all studied HMs except chronic leukemia (CML and CLL). This is supported by the results of meta-analysis of 26 observational studies which showed that diabetic patients had a higher OR for developing non-Hodgkin's lymphoma (OR=1.22, 95% CI=1.07-1.39), leukemia 95% CI=1.03-1.44), and myeloma (OR=1.22, CI=0.98-1.53). The odds of (OR=1.22, 95% leukemia were increased in men more than women and increased in Asians and Americans. However, when evaluating lymphoid and myeloid leukemia separately no clear association was found mostly due to the low number of studies evaluating leukemia included in the meta-analysis [48]. Different pathophysiological mechanisms may explain the role of diabetes in the promotion of carcinogenesis. The American Diabetes Association and the American Cancer Society have previously published a joint consensus report on the association of diabetes and postulating different possible links cancer as hyperglycemia, hyperinsulinemia, insulin growth overproduction, factor and oversecretion of inflammatory cytokines. These phenomena were observed in patients with DM may not only favor malignant transformation but may also lead to tumor progression [48].

Conclusion

This is the first study evaluating the different risk factors and distribution of HMs in Upper Egypt. Leukemia was the most common presented HM (75%), nearly half of leukemic cases were acute myeloid leukemia. Increasing age and diabetes mellitus were significantly associated with all HMs.

Recommendations

It is recommended to conduct further nationally representative studies to portray the distribution of HMs in different Egyptian geographical areas and a more detailed evaluation of the role of the possible risk factors in the occurrence of blood cancers in Egypt.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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