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Viral and non-viral risk factors for non-Hodgkin's lymphoma in Egypt: heterogeneity by histological and immunological subtypes

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Abstract

Objective—Non-Hodgkin's lymphomas (NHL) are etiologically heterogeneous malignancies. In Egypt, we previously reported an association of increased NHL risk with chronic hepatitis C virus (HCV) infection. Our present aim is to assess the association between HCV infection and histological subtypes of NHL.

Methods—We conducted a case–control study at the National Cancer Institute of Cairo University. Cases with NHL (n = 486) were matched to controls (n = 786) who were orthopedic patients from the same referral regions. Participants provided a blood sample for HCV markers (anti-HCV, HCV RNA) and answered a questionnaire on possible risk factors. Case–control differences were assessed by odds ratios and 95% confidence intervals from logistic regression analysis.

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Results—Cases with diffuse large B cell lymphoma (n = 146), chronic lymphocytic leukemia (n = 58), marginal zone lymphoma (n = 24), follicular lymphoma (n = 23), and mantle cell lymphoma (n = 16) were recruited. HCV RNA prevalence was 27% in controls and 26%–48% in the NHL subgroups: it was associated (p <0.001) with diffuse large B cell, marginal zone, and follicular lymphomas with odds ratios of 3.2, 4.4, and 3.3, respectively.

Conclusion—HCV is a risk factor for diffuse large B cell, marginal zone, and follicular lymphomas in Egypt.

Keywords

Non-Hodgkin's lymphoma; Hepatitis C virus; Egypt; Epidemiology; Risk factors

Introduction

Hepatitis C virus (HCV) is a worldwide health problem, and the World Health Organization (WHO) estimates that 170 million people are currently infected with the hepatitis C virus. The prevalence of the disease ranges between 1% of the population in Europe to over 5% in Africa [1]. Approximately 8–10 million people in Egypt, or 12–15% of Egyptians, have serological evidence of HCV infection [2, 3] although this proportion is even higher among subgroups such as rural males [4]. This high rate of infection may be secondary to prior large scale treatment of schitosomiasis carried out in several areas of the country between 1920 and 1980. An account of these mass campaigns using parenterally administered antimony salt revealed a high potential for spread of blood borne pathogens [5]. Although the incidence of HCV is lower in the younger population, exposure continues, likely secondary to exposure to improperly screened blood products, invasive medical procedures, and the receipt of injections from "informal" health care providers.

HCV has been suggested as a cause or contributing factor in the etiology of B-cell non-Hodgkin's lymphoma (NHL). HCV is a lymphotrophic virus, capable of replicating within the B cells and of triggering malignant transformation, although the carcinogenic mechanism remains to be fully elucidated [6–8]. Some but not all previous epidemiological studies have reported statistically significant associations between serological markers of HCV and increased risk of NHL as a whole, particularly in regions of moderate to high prevalence of the virus [9]. Few studies have reported risk estimates for HCV in separate subtypes of NHL.

Previously, as part of a larger and ongoing study of the malignant complications of chronic HCV infection in Egypt, where the virus is highly endemic, we reported the association of HCV with increased risk of B-cell NHL as a whole (OR = 2.3, 95% CI 1.5–3.5) [10]. The association was statistically significant and robust to potential confounders such as age, sex, and region of residence, but at that time, the sample size was not large enough to examine the HCV association in histological and immunological subtypes of NHL. Our intent in the current study is to reassess the HCV–NHL association in a larger study population, to assess its association with different subtypes of NHL, since the different subtypes are thought to have distinct etiologies, and to evaluate the associations of NHL risk with additional potential environmental and medical risk factors.

Materials and methods

Case population

Cases with NHL were recruited between October 1999 and March 2004 from patients attending the outpatient clinic at the National Cancer Institute (NCI), a major referral center in Cairo that is affiliated to Cairo University. Patients were eligible to participate if they

were over the age of 17, first diagnosed with cancer ≤6 months prior to interview, no history of prior cancer, and physically and mentally capable of understanding and completing the interview. Their classification as confirmed cases was subject to final diagnoses involving pathology data and medical records review according to the WHO classification system for lymphomas. Subjects whose records were not located, or who were found to have a diagnosis other than NHL, were dropped from the study. There were no exclusions of persons with autoimmune diseases or organ transplantation. Details of recruitment were previously reported [10].

Selection of controls

Control subjects free from cancer were sampled from the Kasr El Aini Faculty of Medicine Orthopaedic Hospital in Cairo, Egypt. They were frequency-matched to the case group by rural versus urban birthplace, gender, and five-year age category. The rationale for selecting fracture patients was to obtain a representative sample of the source population of the cases by region, since both hospitals draw patients from the same area, and by HCV infection status, since HCV positivity and fracture are likely to be independent [10]. Potential controls had to be ≥18 years old, as well as physically and mentally capable of participating.

Interview procedures

The institutional review boards at each of the participating institutions approved the study protocol. Written or witnessed oral informed consent was obtained from each participant. Trained research assistants administered a standardized Arabic-language questionnaire in a face-to-face interview that lasted 30 min. The questionnaire asked about birthplace, residency and employment histories, alcohol and smoking histories, exposures to pesticides and other industrial or agricultural substances (solvents, dyes, paints, adhesives, pesticides, and herbicides), education, and medical history (diabetes, blood transfusion or donation, bilharzia, tuberculosis, and liver problems). On completion of the interview, a specimen of whole blood was collected.

Laboratory assays

Within 4 h of collection, the blood was separated and the serum was divided into aliquots and stored at −80°C. Samples were later thawed and tested for anti-HCV antibody by Abbott HCV enzyme-linked immunoassay (EIA) 3.0 (Abbott Park, IL, USA) according to the manufacturer's instructions. Samples were initially tested for HCV RNA by direct nested reverse transcription-polymerase chain reaction (RT-PCR) as described previously [11]. Samples that tested negative by RT-PCR and positive by EIA were retested by conventional RT-PCR, which included an RNA purification step.

In all cases where formalin-fixed tissue from NHL cases was available at the NCI (365 cases, 75% of all cases), immunophenotyping for B- and T-cell markers was performed in the Department of Pathology, using pan-B (CD-20) and pan-T (CD-45) monoclonal antibodies with the DAKO EnVision System (Code No. K4006, DAKO, Carpinteria, CA, USA). The extraction results did yield different results in 51 subjects (changed from positive to negative). There were 17 samples that were negative for anti-HCV and positive for HCV RNA.

Statistical analyses

Characteristics of cases and controls were compared either by Pearson's χ^2 test (for categorical variables) or by a *t*-test (for continuous variables). Odds ratios (OR) and 95% confidence interval (CI) were calculated for each subtype separately, using unconditional logistic regression models with adjustment for matching on age, birthplace, and gender. All

tests were two-tailed, and the statistical analyses were performed using SAS, version 9.1 (Cary, NC).

Results

From 1,567 contacted subjects with provisional diagnoses of NHL, 1,094 were eligible and 966 agreed to participate (88.3%). From these participants, 486 were confirmed as NHL at the time of the statistical analysis. A total of 1,022 control subjects were recruited; the participation rate in the controls was 76.9%.

Table 1 shows the frequency of each NHL subtype. The majority were of diffuse large cell type (54.9%), of which 146 (30.0%) were confirmed to be of B cell lineage by immunohistochemistry (IHC). Other common subtypes were chronic lymphocytic leukemia (11.9%), follicular lymphoma (6.3%), and mantle cell lymphoma (3.3%). We combined the T cell lymphoma subgroups—precursor T cell, peripheral T cell, and not otherwise specified T cell—into one group, T cell lymphoma ($n = 23$, 6.6%). We also combined mucosa associated lymphoid tissue lymphoma with nodal marginal zone lymphoma into one group ($n = 24$, 6.6%) according to the World Health Organization classification system. The remaining subgroups had very few cases to be included in statistical analysis. The unclassified lymphoma subgroup and the cutaneous lymphoma not otherwise specified subgroup was excluded from further analysis.

Table 2 shows the distributions of age, sex, marital status, and rural birthplace for the largest NHL subgroups. Cases with mantle cell lymphoma, chronic lymphocytic leukemia, or diffuse large B cell lymphoma had mean ages that were similar to those of controls (within five years). T cell lymphoma cases were notable for having a mean age nearly 15 years younger than controls (35.5 vs. 50.3 years, respectively). Cases and controls did not differ by percentage of males, except for the T cell lymphoma group, which had the lowest proportion of males (37.5% vs. 66.4% in controls, $p = 0.012$). This case group, along with mantle cell lymphoma, also differed from controls in marital status. Higher proportions of cases with rural birthplace compared to controls were characteristic of diffuse large B cell and chronic lymphocytic leukemia.

The prevalence of viral hepatitis markers among the NHL subtypes is described in Table 3. Both anti-HCV and HCV-RNA measures are dichotomous variables. Statistically significant associations with past and current HCV infections were observed for diffuse large B cell (OR = 2.6, 95% CI 1.8–3.9, and OR = 3.2, 95% CI 2.1–4.7, respectively) and marginal zone lymphomas (OR = 3.4, 95% CI 1.4–8.5, and OR = 4.4, 95% CI 1.8–10.6, respectively). All models were adjusted for sex, age, and birthplace. In addition, current HCV infection was associated with a significantly elevated risk of follicular lymphoma (OR = 3.3, 95% CI 1.3–8.0). Among all the analyzed subtypes, there was no group for which only anti-HCV and not HCV RNA positivity was associated with NHL risk. For all cases combined, the OR was 1.9 (95% CI 1.4–2.6) and 2.4 (95% CI 1.8–3.2) for past and current HCV infections, respectively. Odds ratios for blood transfusion were as follows: diffused $B = 0.6$ (0.3–1.0), leukemia = 1.4 (0.7–2.7), T-cell = 0.3 (0.1–1.5), Mucosa-Associated Lymphatic Tissue Lymphomas = 1.9 (0.8–4.8), follicular = 0.2 (0.02–1.4), and Mantle = 2.0 (0.7–5.9). Since no association between NHL subtype and blood transfusion was significant, we did not include these results in the paper.

When the polytomous analysis was performed to analyze the heterogeneity by NHL subtypes, the odds ratios for HCV infection remained elevated for diffused large B cell (OR = 2.0 95% CI 1.4–2.9 for anti HCV, and OR = 2.6, 95% CI 1.8–3.7 for HCV RNA). The marginal zone lymphoma odds ratios for anti HCV stayed elevated as well at 2.3 (95% CI

1.1–5.4), but HCV RNA became insignificant (OR = 3.2 95% CI 0.2–2.6). The results for follicular lymphoma were no longer significant in the polytomous regression (OR = 0.8 95% CI 0.3–2.2 for anti HCV).

We also examined the possible associations between the major NHL subgroups and behavioral, occupational, environmental, and medical characteristics where the exposed group consisted of at least 10 subjects. Smoking, treatment of shistosomiasis, diabetes, exposures to pesticides, or other chemicals were not significantly associated with any case subtypes nor were any of these odds ratios >1.5. Shoveling grains, which was included in the questionnaire as a possible marker of aflatoxin exposure, was associated with elevated risk of follicular lymphoma (OR = 2.2, 95% CI 1.2–4.3). Even after adjustment for sex, age, and urban vs rural birthplace, positive association with growing rice was seen for diffuse large B cell lymphoma (OR = 5.1, 95% CI 2.3–11.2). Dog ownership was associated with increased risk for mantle cell lymphoma (OR = 7.5, 95% CI 1.7–32.4, *p*-value 0.0069), while cat owners had increased risk of chronic lymphocytic leukemia (OR = 3.5, 95% CI 1.1–11.3).

Discussion

The present study is among the largest investigations of HCV and NHL and its subtypes to date. Our results suggest that past and present HCV infections are associated with diffuse large B cell, marginal zone, and follicular B-cell lymphomas (Table 4). Birthplace in rural areas and rice cultivation (possible markers for past exposure to HCV) were associated with diffuse large B cell lymphoma. Certain environmental factors, such as shoveling grains (a possible marker for mycotoxins) and pet ownership, were associated with follicular and mantle cell lymphomas.

De Re et al. [12] concluded that specific B clone cells proliferate as a consequence of a chronic antigen stimulation exerted by HCV-associated antigens, and thus, HCV infected lymphomas appear to provide a plausible example of lymphoma initiation by chronic antigen stimulation. This association between HCV and NHL has been reported by several studies [5, 13–15]. Gisbert et al. [13] observed that HCV prevalence in NHL patients is approximately 15% higher than in the general population. Although few studies have looked at the association between HCV and various NHL subgroups, a link between lymphomas of B cell lineage and HCV has been suggested [16, 17]. While our finding of a significant association between active HCV infection and diffuse large B cell lymphomas is consistent with the results of several European and American studies, it is contradicted by others. These differences seem to be largely geographical-based: studies conducted in Romania, Hungary, Italy, and California report the mean incidence of HCV infection in patients with NHL to be between 19 and 22%, much higher than that in the general population [18–21]. However, studies conducted in Germany, France, Spain, Turkey, Switzerland, and Canada reported a low prevalence of HCV infection in patients with B cell NHL [16, 17, 22–26]. Subtypes of NHL were examined separately in only a few reports, but our results are consistent with the recent pooled analysis of seven studies reported by de Sanjose et al. [27]; our study and theirs reported associations between HCV and diffuse large B-cell and marginal zone lymphomas. Also, a report from a low HCV prevalence region (Sweden and Denmark) found a positive association between HCV and B-cell NHL [28]. Seve et al. [29] observed a significantly high prevalence of HCV antibodies in MALT lymphoma patients (odds ratio 9.87; 95% CI 2.59–37.69). In our study, a comparable association was observed in Egypt with a somewhat lower OR of 4.0 (95% CI 1.3–11.9).

Among other possible medical risk factors for NHL are adult-onset diabetes [30], a history of blood transfusions [31], and certain medications, e.g., antibiotics in general [32],

sulfonamides and cimetidine [33], while factors associated with a lower risk of NHL include certain vaccines, non-steroidal anti-inflammatory drugs, and allergies to plants and animals [33]. A previous study of the association of NHL with blood transfusions (a possible marker for transfusion-acquired HCV) was much stronger in follicular and small lymphocytic subtypes than with diffuse large cell NHL [31]. In contrast, we did not observe any significant associations with self-reported medical history factors.

Regarding the possible association of cigarette smoking history with the NHL subtypes, we found no statistically significant case–control differences. On the other hand, Besson et al. [34] concluded that an association is observed between smoking and NHL among women only, although in the total population a relationship was suggested between smoking and follicular NHL. Stagnaro et al. [35] similarly observed associations between increased risks for follicular lymphoma among smokers of blond (OR = 2.1, 95% CI 1.4–3.2) and mixed (OR = 1.8, 95% CI 1.1–3.0) types of tobacco.

Associations of pesticides and increased NHL prevalence have been reported in several studies from diverse regions [32, 36, 37]. However, none of these studies examined the association between the individual NHL subgroups. We found no such associations in our study population, although it is possible that the association we report between rice cultivation and large B cell lymphoma is a marker for chemical exposures.

While this study has a relatively large sample size, we recognize its limitations. Most of the NHL subtypes were rare in this population, with exception of diffuse large B-cell NHL. Although we confirmed HCV status by serological testing, all other variables were self-reported. It is possible that some subjects with low viral load were mis-classified as HCV RNA negative due to the low sensitivity of RT PCR in such instances. This would tend to reduce the magnitude of the odds ratios we reported; therefore, it is possible that we underestimated the true association of HCV and NHL. We confirmed each individual diagnosis by an expert pathology review that included immunohistochemical testing in the majority cases (75%). Our questionnaire was extensive and covered medical and environmental exposures. Finally, it is possible that HCV, rather than a causal factor itself, may be a marker for immunosuppression or immune deficiency that could underlie both the chronic infection and the malignancy.

In conclusion, this study demonstrated an association between potential risk factors and certain subtypes of NHL. Diffuse large B cell, marginal zone, and follicular lymphomas were strongly associated with HCV infection. Several of the examined environmental exposures also demonstrated positive relationships among the NHL subgroups.

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Abbreviations

NHL	Non-Hodgkin’s lymphoma
HCV	Hepatitis C virus
CLL	Chronic lymphocytic leukemia

WHO	World Health Organization
OR	Odds ratio
CI	Confidence interval
NCI	National Cancer Institute
EIA	Enzyme-linked immunoassay
RT-PCR	Reverse transcription-polymerase chain reaction

References

1. World Health Organization. Hepatitis C Infection. 2000. Report Number 164
2. Abdel-Aziz F, Habib M, Mohamed MK, et al. Hepatitis C virus (HCV) infection in a community in the Nile Delta: population description and HCV prevalence. Hepatology. 2000; 32:111–115.10.1053/jhep.2000.8438 [PubMed: 10869297]
3. Darwish MA, Faris R, Clemens JD, Rao MR, Edelman R. High seroprevalence of hepatitis A, B, C, and E viruses in residents in an Egyptian village in The Nile Delta: a pilot study. Am J Trop Med Hyg. 1996; 54:554–558. [PubMed: 8686770]
4. Ezzat S, Abdel-Hamid M, Eissa SA, et al. Associations of pesticides, HCV, HBV, and hepatocellular carcinoma in Egypt. Int J Hyg Environ Health. 2005; 208:329–339.10.1016/j.ijheh.2005. 04.003 [PubMed: 16217918]
5. Frank C, Mohamed MK, Strickland GT, et al. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. Lancet. 2000; 355:887–891.10.1016/S0140-6736 (99)06527-7 [PubMed: 10752705]
6. Quinn ER, Chan CH, Hadlock KG, Foung SK, Flint M, Levy S. The B-cell receptor of a hepatitis C virus (HCV)-associated non-Hodgkin lymphoma binds the viral E2 envelope protein, implicating HCV in lymphomagenesis. Blood. 2001; 98:3745–3749.10.1182/blood.V98.13.3745 [PubMed: 11739181]
7. Suarez F, Lortholary O, Hermine O, Lecuit M. Infection-associated lymphomas derived from marginal zone B cells: a model of antigen-driven lymphoproliferation. Blood. 2006; 107:3034–3044.10.1182/blood-2005-09-3679 [PubMed: 16397126]
8. Turner NC, Dusheiko G, Jones A. Hepatitis C and B-cell lymphoma. Ann Oncol. 2003; 14:1341–1345.10.1093/annonc/ mdg363 [PubMed: 12954572]
9. Dal Maso L, Franceschi S. Hepatitis C virus and risk of lymphoma and other lymphoid neoplasms: a meta-analysis of epidemiologic studies. Cancer Epidemiol Biomarkers Prev. 2006; 15: 2078–2085.10.1158/1055-9965.EPI-06-0308 [PubMed: 17119031]
10. Cowgill KD, Loffredo CA, Eissa SA, et al. Case–control study of non-Hodgkin's lymphoma and hepatitis C virus infection in Egypt. Int J Epidemiol. 2004; 33:1034–1039.10.1093/ije/dyh183 [PubMed: 15155696]
11. Abdel-Hamid M, Edelman DC, Highsmith WE, Constantine NT. Optimization, assessment, and proposed use of a direct nested reverse transcription-polymerase chain reaction protocol for the detection of hepatitis C virus. J Hum Virol. 1997; 1:58–65. [PubMed: 10195232]
12. De Re V, De Vita S, Marzotto A, et al. Sequence analysis of the immunoglobulin antigen receptor of hepatitis C virus-associated non-Hodgkin lymphomas suggests that the malignant cells are derived from the rheumatoid factor-producing cells that occur mainly in type II cryoglobulinemia. Blood. 2000; 96:3578–3584. [PubMed: 11071657]
13. Gisbert JP, Garcia-Buey L, Pajares JM, Moreno-Otero R. Prevalence of hepatitis C virus infection in B-cell non-Hodgkin's lymphoma: systematic review and meta-analysis. Gastroenterology. 2003; 125:1723–1732.10.1053/j.gastro.2003.09.025 [PubMed: 14724825]
14. Shapira MY, Muszkat M, Braunstein I, Gotsman I. Co-occurrence of hepatocellular carcinoma and lymphoma in patients with hepatitis C virus cirrhosis. J Clin Gastroenterol. 2001; 32:368–369.10.1097/00004836-200104000-00023 [PubMed: 11276290]

15. Talamini R, Montella M, Crovatto M, et al. Non-Hodgkin's lymphoma and hepatitis C virus: a case–control study from northern and southern Italy. Int J Cancer. 2004; 110:380–385.10.1002/ijc.20137 [PubMed: 15095303]
16. Arican A, Sengezer T, Bozdayi M, et al. Prevalence of hepatitis-G virus and hepatitis-C virus infection in patients with non-Hodgkin's lymphoma. Med Oncol. 2000; 17:123–126.10.1007/BF02796207 [PubMed: 10871818]
17. Shariff S, Yoshida EM, Gascoyne RD, et al. Hepatitis C infection and B-cell non-Hodgkin's lymphoma in British Columbia: a cross-sectional analysis. Ann Oncol. 1999; 10:961–964.10.1023/A:1008361311409 [PubMed: 10509159]
18. Cucuianu A, Patiu M, Duma M, et al. Hepatitis B and C virus infection in Romanian non-Hodgkin's lymphoma patients. Br J Haematol. 1999; 107:353–356.10.1046/j.1365-2141.1999.01692.x [PubMed: 10583224]
19. Gasztonyi B, Par A, Szomor A, et al. Hepatitis C virus infection associated with B-cell non-Hodgkin's lymphoma in Hungarian patients. Br J Haematol. 2000; 110:497–498. [PubMed: 11023295]
20. Silvestri F, Baccarani M. Hepatitis C virus-related lymphomas. Br J Haematol. 1997; 99:475–480.10.1046/j.1365-2141. 1997.4023216.x [PubMed: 9401053]
21. Zuckerman E, Zuckerman T, Levine AM, et al. Hepatitis C virus infection in patients with B-cell non-Hodgkin lymphoma. Ann Intern Med. 1997; 127:423–428. [PubMed: 9312998]
22. Collier JD, Zanke B, Moore M, et al. No association between hepatitis C and B-cell lymphoma. Hepatology. 1999; 29:1259–1261.10.1002/hep.510290422 [PubMed: 10094973]
23. Ellenrieder V, Weidenbach H, Frickhofen N, et al. HCV and HGV in B-cell non-Hodgkin's lymphoma. J Hepatol. 1998; 28:34–39.10.1016/S0168-8278(98)80199-2 [PubMed: 9537861]
24. Hausfater P, Cacoub P, Rosenthal E, et al. Hepatitis C virus infection and lymphoproliferative diseases in France: a national study. The GERMIVIC Group. Am J Hematol. 2000; 64:107–111.10.1002/(SICI)1096-8652(200006)64:<107::AID-AJH6> 3.0.CO;2-C [PubMed: 10814989]
25. Sanchez Ruiz AC, Yebra BM, Portero F, Provencio PM, Miralles FC, Espana SP. Prevalence of hepatitis C virus infection in patients with non-Hodgkin's lymphoma. Med Clin (Barc). 2001; 116:333–334. [PubMed: 11333763]
26. Zucca E, Bertoni F, Roggero E, Cavalli F. The gastric marginal zone B-cell lymphoma of MALT type. Blood. 2000; 96:410–419. [PubMed: 10887100]
27. de Sanjose S, Benavente Y, Vajdic CM, et al. Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium. Clin Gastroenterol Hepatol. 2008; 6:451–458.10.1016/j. cgh.2008.02.011 [PubMed: 18387498]
28. Schollkopf C, Smedby KE, Hjalgrim H, et al. Hepatitis C infection and risk of malignant lymphoma. Int J Cancer. 2008; 122: 1885–1890.10.1002/ijc.23416 [PubMed: 18271005]
29. Seve P, Renaudier P, Sasco AJ, et al. Hepatitis C virus infection and B-cell non-Hodgkin's lymphoma: a cross-sectional study in Lyon, France. Eur J Gastroenterol Hepatol. 2004; 16:1361–1365.10.1097/00042737-200412000-00021 [PubMed: 15618846]
30. Cerhan JR, Wallace RB, Folsom AR, et al. Medical history risk factors for non-Hodgkin's lymphoma in older women. J Natl Cancer Inst. 1997; 89:314–318. [PubMed: 9048836]
31. Cerhan JR, Wallace RB, Dick F, et al. Blood transfusions and risk of non-Hodgkin's lymphoma subtypes and chronic lymphocytic leukemia. Cancer Epidemiol Biomarkers Prev. 2001; 10:361–368. [PubMed: 11319177]
32. Kato I, Koenig KL, Baptiste MS, et al. History of antibiotic use and risk of non-Hodgkin's lymphoma (NHL). Int J Cancer. 2003; 107:99–105.10.1002/ijc.11356 [PubMed: 12925963]
33. Holly EA, Bracci PM. Population-based study of non-Hodgkin lymphoma, histology, and medical history among human immunodeficiency virus-negative participants in San Francisco. Am J Epidemiol. 2003; 158:316–327.10.1093/aje/kwg145 [PubMed: 12915497]
34. Besson H, Renaudier P, Merrill RM, et al. Smoking and non-Hodgkin's lymphoma: a case–control study in the Rhone-Alpes region of France. Cancer Causes Control. 2003; 14:381–389.10.1023/A:1023978730962 [PubMed: 12846371]
35. Stagnaro E, Tumino R, Parodi S, et al. Non-Hodgkin's lymphoma and type of tobacco smoke. Cancer Epidemiol Biomarkers Prev. 2004; 13:431–437. [PubMed: 15006920]

36. McDuffie HH, Pahwa P, Spinelli JJ, et al. Canadian male farm residents, pesticide safety handling practices, exposure to animals and non-Hodgkin's lymphoma (NHL). Am J Ind Med Suppl. 2002; 2:54–61.10.1002/ajim.10041

37. Miligi L, Costantini AS, Bolejack V, et al. Non-Hodgkin's lymphoma, leukemia, and exposures in agriculture: results from the Italian multicenter case–control study. Am J Ind Med. 2003; 44:627–636.10.1002/ajim.10289 [PubMed: 14635239]

Table 1

Prevalence of NHL subtypes among the NHL patients, Egypt 1999–2004

NHL subtype	*n*	%
Diffuse large cell—histopathology diagnosis only	121	24.90
Diffuse large B cell—proven by IHC	146	30.04
Chronic lymphocytic leukemia	58	11.93
Unclassified lymphoma	53	10.91
Follicular lymphoma	23	4.73
MALT[a] lymphoma	19	3.91
Mantle cell lymphoma	16	3.29
Peripheral T cell	11	2.26
Anaplastic large cell	9	1.85
T cell, not otherwise specified (NOS)	8	1.65
Nodal marginal zone lymphoma	5	1.03
Precursor T lymphoblastic lymphoma	4	0.82
Cutaneous lymphoma NOS	6	1.23
Lymphoplasmacytoid lymphoma	3	0.62
Burkitt's lymphoma	1	0.21
Plasma cell myeloma	2	0.41
Precursor B lymphoblastic leukemia	1	0.21
Total	486	

[a] *MALT* Mucosa associated lymphoid tissue lymphoma

Table 2

Social and demographic characteristics of major NHL subtypes, Egypt 1999–2004

	n	Average age	Male		Rural birthplace	
			n (%)	*p*	*n* (%)	*p*
Diffuse large B cell	146	46.7	90 (61.6)	0.249	73 (50.3)	0.2824
Chronic lymphocytic leukemia	58	54.6	34 (58.6)	0.217	31 (53.5)	0.7975
T cell lymphoma	24	35.5	9 (37.5)	0.012	13 (59.1)	0.7164
Marginal zone lymphoma	24	44.2	15 (62.5)	0.677	13 (54.2)	0.9212
Follicular lymphoma	23	44.6	11 (52.2)	0.150	12 (52.2)	0.7747
Mantle cell lymphoma	16	49.7	8 (50.0)	0.165	10 (62.5)	0.5602
Controls	786	50.3	522 (66.4)		308 (39.2)	

Table 3

Prevalence and odds ratios of serum anti-HCV in major NHL subtypes, Egypt 1999–2004

		Anti-HCV[a]					
		n	**%**	**OR[b]**	**95% CI**		***p*-value**
Controls	*n* = 786	283	37.4	1.0	ref.		
Diffuse large B cell	*n* = 146	79	54.9	**2.6**	**1.8**	**3.9**	**<0.0001**
Chronic lymphocytic leukemia	*n* = 58	24	41.38	1.1	0.6	2.0	0.6829
T cell lymphoma	*n* = 24	8	34.8	1.7	0.6	4.7	0.3173
Marginal zone lymphoma	*n* = 24	14	58.3	**3.4**	**1.4**	**8.5**	**0.0076**
Follicular lymphoma	*n* = 23	9	40.9	1.5	0.6	3.8	0.3928
Mantle cell lymphoma	*n* = 16	5	31.3	0.8	0.2	2.3	0.6186
NHL cases listed	*n* = 296	139	47.0	**1.9**	**1.4**	**2.6**	**<0.0001**

		HCV RNA[c]					
		n	**%**	**OR[b]**	**95% CI**		***p*-value**
Controls	*n* = 786	180	23.8	1.0	ref.		
Diffuse large B cell	*n* = 146	65	44.5	**3.2**	**2.1**	**4.7**	**<0.0001**
Chronic lymphocytic leukemia	*n* = 58	19	32.8	1.5	0.9	2.8	0.1552
T cell lymphoma	*n* = 24	6	26.1	1.7	0.6	5.0	0.3605
Marginal zone lymphoma	*n* = 24	12	50.0	**4.4**	**1.8**	**10.6**	**0.0010**
Follicular lymphoma	*n* = 23	10	43.5	**3.3**	**1.3**	**8.0**	**0.0096**
Mantle cell lymphoma	*n* = 16	3	18.8	0.7	0.2	2.6	0.6171
NHL cases listed	*n* = 296	115	38.9	**2.4**	**1.8**	**3.2**	**<0.0001**

[a] Anti-HCV antibody is considered a measure of past HCV infection

[b] Adjusted for age, gender, and rural birthplace

[c] HCV-RNA is a measure of current HCV infection

Table 4

Odds ratios of agriculture exposures in major NHL subtypes, Egypt 1999–2004

	Growing rice				Shoveling grains			
	OR[a]	**95% CI**		***p***	**OR[a]**	**95% CI**		***p***
Controls	1	ref.			1	ref.		
Diffused large B cell	**5.1**	**2.3**	**11.2**	**<.0001**	0.9	0.6	1.3	0.4487
Chronic lymphocytic leukemia	3.1	1.0	9.9	0.0529	1.0	1.0	1.8	0.9754
T cell	3.2	0.2	48.8	0.3974	1.6	0.7	3.7	0.2332
Marginal zone	1.7	0.3	10.0	0.6	1.3	1.3	2.8	0.5504
Follicular	2.2	0.5	9.6	0.3050	**2.2**	**1.2**	**4.3**	**0.0166**
Mantle cell	0.8	0.1	7.5	0.8535	0.9	0.3	0.3	0.8434

	Owning cats				Owning dogs			
	OR[a]	**95% CI**		***p***	**OR[a]**	**95% CI**		***p***
Controls	1	ref.			1	ref.		
Diffused large B cell	**2.5**	**1.0**	**6.2**	**0.0471**	1.3	0.5	3.4	0.5650
Chronic lymphocytic leukemia	**3.5**	**1.1**	**11.3**	**0.0407**	1.8	0.5	6.5	0.3698
T cell	4.1	0.8	20.7	0.0836	3.0	0.6	14.7	0.1750
Marginal zone	1.9	0.2	15.6	0.5577	–	–	–	–
Follicular	4.6	0.9	23.3	0.0652	–	–	–	–
Mantle cell	2.6	0.3	22.2	0.3851	**7.5**	**1.7**	**32.4**	**0.0069**

[a]Unadjusted