

Determinants of Non-Hodgkin's Lymphoma at Felegehiwot Specialized Hospital, North West Ethiopia: a case-control study

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Abstract

Background The global burden of cancer continues to increase largely because of the aging and growth of the world population alongside an increasing adoption of cancer-causing behaviors. Hence, the purpose of this study was to identify determinants of Non-Hodgkin lymphoma cancer among individuals who were diagnosed at Felegehiwot specialized hospital, North West Ethiopia, 2019.

Methods An institution-based unmatched case-control study was conducted at Felegehiwot Specialized hospital from December 2018 up to June 2019. The sample size calculated using the two population proportion formula with 1:2 cases to control ratio. Then the final sample size was 486, (162cases and 324 controls). The simple random sampling method was employed to catch up with the estimated samples. The collected data entered into Epi-data 3.1 and analyzed using SPSS version 21. Descriptive statistics were computed. Simple logistic analysis was run (at 95% CI and p-value < 0.05) to identify factors associated with non-Hodgkin's lymphoma.

Result: A total of 486 patients participated. Larger portion of cases (34%) and controls (35.2%) were in the age group of 46-60 years. About 90% of cases and 91% of controls were Orthodox Christian. Having monthly income of < 28 dollar [AOR=2.73; 95% CI (1.8, 4.2)], being male sex [AOR=1.8; 95% CI (1.2, 2.8)], ever had chemical exposure, [AOR=11.9; 95% CI (7.6, 18.8)], had no regular physical exercise [AOR=15.5, 95% CI (5.7, 42.3)] and having hypertension [AOR=0.03; 95% CI (0.005,0.2)], lung disease (COPD) [AOR=0.2; 95% CI (0.06, 0.7)], and other health problems [AOR=0.06; 95% CI (0.01, 0.2)] were the identified root causes for non-Hodgkin's lymphoma.

Conclusions Having low monthly income, being male sex, ever had chemical exposure, not engaged in regular physical exercise and being diabetic patient was at an increased risk for non-Hodgkin's lymphoma.

Background

Despite decades of intensive research, Non-Hodgkin Lymphoma (NHL) remains poorly understood and is largely incurable[1].

Non-Hodgkin's lymphoma(NHL) is a heterogeneous group of malignancies with multiple subtypeswith unique histological and syndromic features[1], But it mainly originates in the blood cells (lymphocytes) and the [lymph node](#) tissues[2]. However, in some cases,the NHL involves the bone marrow and intestine and central nervous system[3].

NHL cancer affects all human beings[2]and can occurat any age[4]. Risk of developing NHL increases as the age advances and of 65 or older years [4].The incidence rates of Non-Hodgkin lymphomavary across the globe, from 3.5 per 10,000 in developing countries to 8.6 per 100,000in more developed countries;which revealed that the risk of NHL is about four-fold higher than that of developed countries[5].

In Africa, approximately 300,000 cases of non-Hodgkin lymphoma (NHL) occur each year and these infections are among the top ten causes of cancer in this continent region[6]. In Ethiopia, studies showed that there are more than 150,000 cancer cases per year[2]. Although, it appears to vary markedly throughout the region and is different among children and adults [6].

Lifestyle-related risk factors such as body weight, physical activity, diet, and tobacco use play a major role in developing NHL[7]. Thus, identifying the risk factors for NHL may improve our understanding of the disease and is of very crucial for policymakers and program implementers at national as well as regional levels to design evidence-based intervention strategies to give emphasis and tackle the risk factors of NHL.

Methods

Study Design

An institution-based unmatched case-control study was conducted from November 2018 up to June 2019 at Felegehiwot specialized referral hospital. The hospital is located in Bahir Dar city, Amhara regional state, which is 564 km apart from Addis Ababa, the capital city of Ethiopia. The hospital is comprised of different service delivery departments. The oncology department is established in 2017. Since then, 169 patients were registered in the logbook.

Sample size determination

To determine the sample size, Epi-Info version 7 software were used by considering 95% CI, 80% Power with 1:2 case to control ratio. Then, the final sample size was 486. (Table 1)

Table1: sample size determination from various determinants, 2019.

Variable	AOR	exposed cases	Exposed controls	Required sample		Total Samples	Reference
				Case	Control		
Cigarette Smoking	2.4	50	29.4	65	129	194	[3]
History of cancer	2.6	34.1	16.6	67	134	201	[8]
Exposure of pesticides	3.7	10.3	3	115	229	334	[9]
Coffee drinking	2.9	94.1	84.6	141	281	422	[3]
Lifestyle	2.797	94.5	86	162	324	486	[10]

Sampling procedure

Cases: All 169 NHL patients who are on follow-up in the oncology department were scrutinized for cancer histopathological confirmation; and then, 162 NHL cases were confirmed.

Controls: Chronically ill medical patients who were on follow-up and had non-cancerous pathology result attached to their charts in the medical department were the controls. Two unmatched controls for each case were taken by systematic sampling technique from the list of the service delivery logbook.

Exclusion criteria

Cases: the nine histo-pathologically non-confirmed patients and not on follow up in the oncology department of the hospital were excluded.

Control: non-cancerous, chronically ill medical patients, who had not pathology result attached to their charts and who were not on follow-up in the medical department of the hospital were excluded.

Data collection and analysis

A pre-tested and structured questionnaire was used to collect data adopted from a variety of literature. Patients sociodemographic characteristics, nutritional status, and exposure to carcinogenic chemical exposure relating characteristics were collected from patient service delivery record book. Two clinical nurses and one supervisor were involved in the data collection process. Two days of rigorous training was given on how to select study participants and review medical documents. The collected data were edited, coded and entered into Epi-Data version 3.1 and export to SPSS version 20 software for further data management and analysis. Summary measures like percentage mean and the standard deviation were computed and presented in tables. A simple logistic regression model was fitted to identify factors associated with non-Hodgkin's lymphoma. Crude and adjusted odds ratios (OR) with a 95% CI were computed to assess the strength of association between the independent and outcome variables. Variables with a p-value of less than 0.05 were considered as statistically significant predictors of non-Hodgkin's lymphoma.

Ethical Consideration

Ethical approval was obtained from the research Ethical Review Board of Bahir Dar University with reference number. After receiving a permission letter from the regional health bureau. Before the beginning of data collection, permission letter was obtained from Amhara National Regional Institute of Public Health and from each concerned body prior to the data collection period. Written consent was received from the study participants only. However, for fewer than 16 years old, written consent was taken from parents/guardians and assent from study members were secured. Names of the respondents did

not use to ensure anonymity and confidentiality. All information obtained from the respondents was kept confidential.

Results

Descriptive Statistics for socio-demographic characteristics

A total of 486 (162 cases 324 and controls) study participants at follow up in Felegehiwot specialized Hospital were interviewed and yielded a response rate of 100%.

A larger portion of cases (34%) and controls (35.2 %) were in the age group of 46-60 years. About ninety percent of cases and controls were Orthodox Christian. Majority of the cases (84 %) and controls (84.3 %) were from the Amhara ethnic group. About two-thirds of cases and controls were unable to read and write. The majority of the cases and controls were married. More than three-fourths of the respondents come from a rural area, and more than one-fourth of the respondents were farmers (**Table 2**).

Table 2: Socio-demographic characteristics of the respondents, 2019 (n=486)

Variable	Category	Cases	Controls	Total
		N (%)	N (%)	N (%)
Age (in a year)	<15 years	10(6.2)	4(1.2)	14(2.9)
	15-30 years	21(13.0)	59(18.2)	80(16.5)
	31-45 years	33(20.4)	84(25.9)	117(24.1)
	46-60 years	55(34.0)	114(35.2)	169(34.8)
	61 -75 years	36(22.2)	46(14.2)	82(16.9)
	>75 years	7(4.3)	17(5.2)	24(4.9)
Religion	Orthodox	146(90.1)	295(91.0)	441(90.7)
	Protestant	5(3.1)	3(0.9)	8(1.6)
	Muslim	11(6.8)	26(8.0)	37(7.6)
Ethnicity	Amhara	136(84.0)	273(84.3)	409(84.2)
	Non-Amhara	26(16.0)	51(15.7)	77(15.8)
Educational status	Unable to read and write	106(65.4)	216(66.7)	322(66.3)
	Elementary	41(25.3)	67(20.7)	108(22.2)
	Secondary	9(5.6)	23(7.1)	32(6.6)
	Diploma and above	6(3.7)	18(5.6)	24(4.9)
Marital Status	Married	107(66.0)	197(60.8)	304(62.6)
	Unmarried	55(34.0)	127(39.2)	182(37.4)
Residence	Urban	16(9.9)	79(24.4)	95(19.5)
	Rural	146(90.1)	245(75.6)	391(80.5)
Monthly Income (in American Dollar)	≤28dollar	112(69.1)	141(43.5)	253(52.1)
	>28dollar	50(30.9)	183(56.5)	233(47.9)
Sex	Male	106(65.4)	177(54.6)	283(58.2)
	Female	56(34.6)	147(45.4)	203(41.8)
Occupation	Farmer	70(43.2)	100(30.9)	170(35.0)
	Housewife	43(26.5)	91(28.1)	134(27.6)
	Government employee	6(3.7)	27(8.3)	33(6.8)
	Military	3(1.9)	3(0.9)	6(1.2)

Factory worker	12(7.4)	25(7.7)	37(7.6)
Daily laborer	28(17.3)	78(24.1)	106(21.8)

Chemical exposure-related characteristics

About seventy-eight percent of the cases and twenty-two percent of the controls had previous exposure to carcinogenic chemicals. From these, more than one-third of the respondents were exposed to Herbicides. Half of the respondents exposed for more than fifteen years. About eight percent of the cases and five percent of the controls were cigarette smokers; of which, fifty-four percent of cases and sixty-two percent of controls smoked for more than ten years, respectively. Eighty-six percent of cases and sixty-seven percent of controls had drunken alcohol. Eighty-eight percent of cases and eighty-three percent of controls had drunken cultural alcohol. Eighty-six percent of cases and seventy-four percent of controls were coffee drinker. Of which, three-fourth of the respondents drunk coffee for more than thirty years. **(Table 3)**

Table 3: Chemical exposure-related characteristics of the respondents, 2019 (n=486)

Variable	Category	Cases	Control	Total
		N (%)	N (%)	N (%)
Ever had chemical exposure	No	36(22.2)	250(77.4)	286(59.0)
	Yes	126(77.8)	73(22.6)	199(41.0)
Smoking Cigarette	No	149(92.0)	309(95.4)	458(94.2)
	Yes	13(8.0)	15(4.6)	28(5.8)
Years of smoked	≤10 years	6(46.2)	5(33.3)	11(39.3)
	>10 years	7(53.8)	10(66.7)	17(60.7)
Alcohol drink	No	22(13.6)	116(35.8)	138(28.4)
	Yes	140(86.4)	208(64.2)	348(71.6)
Types of alcohol taken	Beer	16(11.4)	36(17.3)	52(14.9)
	Cultural alcohol	124(88.6)	172(82.7)	296(85.1)
Coffee drink	No	22(13.6)	83(25.6)	105(21.6)
	Yes	140(86.4)	241(74.4)	381(78.4)
Years of drink coffee	<20 years	14(10.0)	32(13.3)	46(12.1)
	≥20 years	126(90.0)	209(86.7)	335(87.9)

Behavioral and nutrition-related characteristics

More than two-thirds of the respondents had regular physical exercise, and more than half of the cases had a history of chronic illness. More than one-third of the cases (40%) and one-fourth of controls (26%) had lung disease (COPD). Two-third of the cases and about sixty percent of controls didn't know their HIV status. More than one-fourth of the cases and controls have started treatment on time. **(Table 4)**

Table 4: Behavioral and nutrition-related characteristics of the respondents 2019 (n=486)

Variable	Category	Cases	Control	Total
		N (%)	N (%)	N (%)
Regular physical exercise	No	35(21.6)	120(37.0)	155(31.9)
	Yes	127(78.4)	204(63.0)	331(68.1)
Had chronic diseases other than cancer	No	75(46.3)	–	75(15.4)
	Yes	87(53.7)	324 (100)	411(84.6)
Type of the diseases	Diabetes Mellitus	25(28.7)	73(22.5)	98(20.2)
	Liver disease	4(4.6)	32(9.9)	36(7.4)
	Hypertension related	3(3.4)	53(16.4)	56(11.5)
	Lung disease(COPD)	35(40.2)	82(25.3)	117(24.1)
	Other [€]	20(23.0)	84(25.9)	104(21.4)
HIV status	No	109(67.3)	189(58.3)	298(61.3)
	Yes	26(16.0)	30(9.3)	56(11.5)
	Unknown	27(16.7)	105(32.4)	132(27.2)
previous Nutritional/ feeding/ practice	Meat	17(10.5)	36(11.1)	53(10.9)
	Vegetation	9(5.6)	15(4.6)	24(4.9)
	Non- vegetation	2(1.2)	12(3.7)	14(2.9)
	Milk	7(4.3)	28(8.6)	35(7.2)
	Other ^{€€}	127(78.4)	233(71.9)	360(74.1)
Have you got any treatment	No	19(11.7)	32(9.9)	51(10.5)
	Yes	143(88.3)	292(90.1)	435(89.5)
Outcome if the patient was treated	Progressed	112(78.3)	203(79.5)	315(72.4)
	Deteriorated	8(5.6)	20(6.8)	29(6.7)
	Same	22(15.4)	66(22.5)	88(20.2)
	Not mentioned	1(0.6)	3(1.0)	4(0.9)
BMI of the patient	<18.5 kg/h ²	49(30.2)	227(70.1)	276(56.8)
	18.5-24.9 kg/h ²	113(69.8)	96(29.6)	209(43.0)
		0(0.0)	1(0.3)	1(0.2)

25-29.9 kg/h²

Where treated during starting the disease	Cultural medicine	26(16.0)	32(9.9)	58(11.9)
	Modern medicine	78(48.1)	180(55.6)	258(53.1)
	Holly water	58(35.8)	112(34.6)	170(35.0)

Other[€]: chronic kidney disease, peptic ulcer disease, and cardiac failure; other^{€€}: nutritional intake of 'Injjera with watt' or Bread

Factors Associated with Non-Hodgkin's Lymphoma

Variables having a p-value less than 0.2 were taken into multiple logistic regressions as significant. Hence, it was found out that some socio-demographic determinants like residence, monthly income, sex (male), chemical exposure-related determinants like Ever had Chemical exposure and drinking alcohol; Behavioral and nutrition-related determinants; Physical exercise/sport and type of chronic disease were eligible to enter to multiple regressions before. However, residence, occupation and drink alcohol were not statistically associated with the outcome variable (Table 5).

Socio-demographic determinants of NHL

After adjusting the potential confounders (chemical exposure and behavioral and nutrition) monthly income and sex were found to be determinants for non-Hodgkin's lymphoma.

Respondents whose monthly income of less than or equal to 28 dollars were about three times more likely at risk for non-Hodgkin's lymphoma [AOR=2.73, 95% CI(1.8, 4.2)] as compared to greater than 28 dollars. Similarly, male respondents were about two times more likely at risk to have NHL compared to female respondents [AOR=1.83, 95% CI (1.21, 2.76)] (Table 5).

Chemical exposure determinant factors of NHL

Ever had a history of exposure for chemicals were found to be the root cause for NHL.

Respondents whoever had previous history chemical exposure were 12 times more likely at risk to have NHL [AOR=11.98, 95% CI (7.62-18.85)] compare to who had not exposed in the past (Table 5).

Behavioral and nutrition-related determinants of NHL

Not having regular physical exercise and the type of chronic illness they had were the identified root causes for NHL. Those respondents who had not regular physical exercise were about 15 times more likely at risk for NHL as compared to who had [AOR=15.5, 95% CI(5.7, 42.3)]. Respondents who had history of chronic

disease of hypertension-related, COPD and others(CKD, PUD and Cardiac failure) were less likely at risk as compared to those who had diabetes mellitus [AOR=0.03,95%CI(0.005,0.18)], [AOR=0.21295%CI(0.06,0.70)], [AOR=0.05,95% CI(0.01,0.21)],respectively(**Table 5**).

Table 5: Simple logistic regression on determinants of NHL among patients, 2019 (n=486)

Variable	NHL		COR (95 % CI)	AOR (95 % CI)	P-value
	Case	Control			
Residence					
Urban	16	79	0.340(0.2,0.6)	0.55(0.3, 1.1)	0.061
Rural	146	245	1.00	1.00	
Monthly income					
≤28Dollar	112	141	2.9(1.9, 4.3)	2.73(1.8, 4.2)	0.0001***
> 28Dollar	50	183	1.00	1.00	
Sex					
Male	106	177	1.6(1.1, 2.3)	1.8(1.2, 2.8)	0.004**
Female	56	147	1.00	1.00	
Occupation					
Farmer	70	100	1.00	1.00	
House-wife	43	91	0.7(0.4, 1.1)	2.3(0.6, 3.0)	0.161
governmental employee	6	27	0.3(0.1,0.8)	0.928(0.3, 2.7)	0.891
Military	3	3	1.4(0.3, 7.3)	1.690(0.3, 9.7)	0.556
Factory workers	12	25	0.7(0.3, 1.4)	1.1(0.5, 2.6)	0.769
Others [€]	28	78	0.5(0.3, 0.9)	0.6(0.3, 1.1)	0.131
Ever had chemical exposure					
No	36	251	1.00	1.00	
Yes	126	73	11.986(7.62,18.85)	11.9(7.6,18.8)	0.0001***
Alcohol drank					
No	22	116	1.00	1.00	
Yes	140	208	3.5(2.1, 5.8)		0.198
Coffee drank					
No	22	83	1.00	1.00	
Yes	140	241	2.2(1.3,3.6)		0.316
Had a regular physical exercise					

Yes	35	120	1.00	1.00	
No	127	204	2.1(1.3, 3.3)	15.5(5.7,42.3)	0.0001***
Type of chronic disease					
Diabetes Mellitus	25	73	1.00	1.00	
Liver disease	4	32	1.1(0.3, 4.7)	0.3(0.02,3.8)	0.365
Hypertension	3	53	0.2(0.1,0.6)	0.03(0.005,0.2)	0.0001***
COPD	35	82	1.1(0.5,2.01)	0.2(0.06, 0.7)	0.011*
Others [#]	20	84	0.4(0.2,0.8)	0.06(0.01,0.2)	0.0001***
HIV status					
No	109	189	2.2(1.4,3.6)	1.6(0.5,4.8)	0.399
Yes	26	30	3.4(1.7,6.6)	1.2(0.3,5.004)	0.812
Unknown	27	105	1.00	1.00	

* P-value<0.05; **<0.01;***<0.001; COPD: chronic obstructive pulmonary disease

Others[#]:chronic kidney disease, chronic liver disease,and cardiac failure

Discussion

Monthly income

This study investigated different exploratory variables and identified the root causes of non-Hodgkin's lymphoma. It was recognized that monthly income was one of the crucial determinants for the root causes of non-Hodgkin's lymphoma. Respondents who had monthly income of less than or equal to 28 dollars were about three-fold more at risk to NHL compared to who had greater than 28 dollars. This finding is supported by a study done at Glostrup University Hospital, Denmark [11]. This might be as having little income and deprived living status could be the risk factor for non-Hodgkin's lymphoma. As a result, it may down the chance of study participants to gain awareness in non-Hodgkin's lymphoma. It is also could be justified, even if the study participants had health-seeking behavior, they become tied to not gaining it due to the inability to cover the cost of the service. That might also increase the risk of non-Hodgkin's lymphoma.

Sex

The odds of having NHL in males were 2 times compared to females. This is supported by a study done in Yale University, USA [1]. The reason for this risk difference between the two sexes could be males in our country are highly exposed to out-door work. And the majority of the respondents in our study were

farmers, which their work is mainly confined to farm work. As a result, they may be more exposed to carcinogenic chemicals like herbicides and pesticides.

Ever had chemical exposure

It was found out in this study that, respondents who had chemical exposure were 12 times more likely at risk for NHL than their counterparts. This is supported by a study done in the Yale University, USA[1], a meta-analysis [12], and Sweden [8]. However, a study finding in the USA showed that respondents who exposed to chemicals were protected from [13].

This is because the majority of chemicals are carcinogenic by their nature and the current study showed four times risk factors compare to the developed country was conducted. This may be the result of our country population might have poor knowledge and understanding about the dangerous chemicals and how to use than Indian and Sweden population.

Regular physical exercise

The odds of being caught by NHL from non-regular physical exercising respondents were about five times more likely at risk than those who did in the past. This finding is supported by a case-control study conducted in California[14] and a study in Canada, Ottawa[15]. There is big risk difference between the current study and the latter two studies. This might be as a result of a regular physical exercise in our country is not as habitual as compared to California and Canada population.

Type of chronic disease

The current study revealed that the likelihood of risk for NHL among various chronic ill patients was different. Respondents who had a chronic disease like hypertension-related, lung disease and others (CKD, PUD and Cardiac failure) 97%, 78.8% and 95% less at risk for NHL compared to those who had diabetes mellitus respectively. This study finding supported by a meta-analysis study[16] as DM patients were at high risk for NHL. However, the underlying mechanism is unclear. The possible justification might be Diabetes Mellitus; especially type two is an autoimmune disease which as a result may aggravate the likelihood for the NHL occurrence. Future studies should focus on elucidating potential pathophysiologic links between diabetes and NHL.

Strength of the study

Since the study design was a case-control study, it gave more strong evidence on the determinants of NHL compared to cross-sectional and other descriptive studies.

Limitation of the study

The possibility of recall bias. When participants report about their NHL, previous chemical exposure and related factors might not be recalling exactly.

Another limitation of this study was measurement error; though training on measurements and standard procedures were given, it could not be 100% perfect on measurement weight and height.

Conclusions

This study identified the root causes of the NHL. Having low monthly income, being male sex, ever had chemical exposure, not engaged in regular physical exercise and being diabetic patient was at an increased risk for non-Hodgkin's lymphoma.

Declarations

Abbreviations

BMI: Body Mass Index; HIV: Human Immunodeficiency Virus; NHL:non-Hodgkin lymphoma

Ethical approval and consent to participate

Ethical approval was obtained from the research Ethical Review Board of Bahir Dar University with reference number. After receiving a permission letter from the regional health bureau. Before the beginning of data collection, permission letter was obtained from Amhara National Regional Institute of Public Health and from each concerned body prior to the data collection period. Written consent was received from the study participants only. However, for fewer than 16 years old, written consent was taken from parents/guardians and assent from study members were secured. Names of the respondents did not use to ensure anonymity and confidentiality. All information obtained from the respondents was kept confidential.

Consent for publication

Not applicable as there is no image or other confidentiality related issues.

Availability of data and materials

The datasets could be provided from the corresponding author on reasonable request.

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Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DC, MB, YM, and GMB conceived the study, involved in the study design, data collection, and data analysis, drafted the manuscript and critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

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