RESEARCH ARTICLE

Dietary and Lifestyle Factors and Risk of Non-Hodgkin's Lymphoma in Oman

Amanat Ali[1]*, Buthaina S Al-Belushi[1], Mostafa I Waly[1], Mansour Al-Moundhri[2], Ikram A Burney[2]

Abstract

Background: The incidence of various types of cancers including the non-Hodgkin's lymphoma (NHL) has increased during the recent years. Diet and lifestyle factors have been reported to play an important role in the etiology of NHL. However, no such data are available from the Middle Eastern countries, including Oman. Materials and Methods: Forty-three histologically confirmed cases of non-Hodgkin's lymphoma (NHL) diagnosed at the Sultan Qaboos University Hospital (SQUH) and the Royal Hospital (RH), Muscat, Oman and forty-three age and gender matched controls were the subjects of this study. Frequency matching was used to select the control population. Information on social and demographic data as well as the dietary intake was collected by personal interviews, using a 117-items semi-quantitative food frequency questionnaire. Results: A non-significant increased risk of NHL was observed with higher body mass index (BMI) (OR=1.20, 95%CI: 0.45, 2.93), whereas a significantly decreased risk of NHL was associated with a higher educational level (OR=0.12, 95%CI: 0.03, 0.53). A significantly increased risk was observed for higher intake of energy (OR=2.67, 95%CI: 0.94, 7.57), protein (OR=1.49, 95%CI: 0.54, 4.10) and carbohydrates (OR=5.32, 95%CI: 1.78, 15.86). Higher consumption of daily servings from cereals (OR=3.25, 95%CI: 0.87, 12.09) and meat groups (OR=1.55, 95%CI: 0.58, 4.15) were also found to be associated with risk of NHL, whereas a significantly reduced risk was associated with higher consumption of vegetables (OR=0.24, 95%CI: 0.07, 0.82). The consumption of fruits, milk and dairy products however showed no significant association with the risk of developing NHL. Conclusion: The results suggest that obesity, high caloric intake, higher consumption of carbohydrate and protein are associated with increased risk of NHL, whereas a significantly reduced risk was observed with higher intake of vegetables.

Keywords: Dietary and lifestyle factors - non-Hodgkin's lymphoma - Oman - case-control study

Asian Pacific J Cancer Prev, **14 (2)**, 841-848

Introduction

The incidence of various types of cancers including the non-Hodgkin's lymphoma (NHL) has increased during the recent years. In some countries the incidence of NHL has risen faster than the incidence of all other types of cancers (Chiu and Weisenburger, 2003; Zheng et al., 2004; Kabat et al., 2012). NHL is the 3rd most common cancer in the Gulf Cooperation Council (GCC) states and its rate is higher in men than in women (Khoja and Zahrani, 2010; Salim et al., 2011; Tadmouri and Nair, 2012). Although the awareness on the biology and treatment of NHL has increased, however still little is known about its etiology. The increase in the incidence has been attributed to immunodeficiency, various infections, familial aggregation, blood transfusion, genetic susceptibility, chemical exposure to pesticides and solvents, hair-dyeing agents, nitrates in drinking water, as well as the dietary and lifestyle factors (Chiu and Weisenburger, 2003; Willet et al., 2008; Sangrajgrang et al., 2011; Hosnijeh et al., 2012). There are however, conflicting reports regarding the use of alcohol and smoking (Matsuo et al., 2001; Tramacere et al., 2012). Obesity, energy homeostasis, physical inactivity and early life influences the growth and immune function and therefore may also influence the risk of NHL later in life (Pischon et al., 2008; Reynolds et al., 2011; Kabat et al., 2012).

Food is the largest single antigenic challenge to the human immune system and operates on a regular and perpetual basis. Although it is not possible to exactly quantify the overall risks, it has been estimated that about 35 percent of all cancer deaths may be related to dietary factors (Doll and Peto, 1981; Anand et al., 2008). Culturally specific dietary patterns and a healthy lifestyle are likely to play a major role in determining cancer risk. There is compelling evidence that dietary patterns, food,

*[1]Department of Food Science and Nutrition, College of Agricultural and Marine Sciences, [2]Department of Medicine, College of Medicine and Health Sciences, Sultan Qaboos University, Sultanate of Oman *For correspondence: e-mail amanat@squ.edu.om*

nutrients, and other dietary constituents may be closely associated with the risk for several types of cancers (Davis, 1992; Donaldson, 2004; Ananad et al., 2008). Some studies observed positive associations between the intake of protein, fried red meat, dairy products, total fat, saturated fat and trans-saturated fat and NHL risk whereas the others reported no significant association (Donaldson, 2004; Daniel et al., 2012). The data on the association between meat and other nutrients intake and risk of NHL however, remains inconsistent. Diet high in protein and fat is considered to increase the risk of NHL as it may alter the immune-competence, which is an important and established risk factor for NHL (Zhang et al., 1999; Zheng et al., 2004; Milner, 2006; Lee et al., 2008; Kabat et al., 2012). On the other hand, a reduced risk has been reported with higher intakes of dietary fiber, whole grain foods and several fruits and vegetables. This has been attributed primarily to the presence of biologically active phytochemicals and antioxidant nutrients, which have the ability to quench free radicals and inhibit nitrosation reactions (Frankenfeld.et al., 2008; Thompson et al., 2010; Holtan et al., 2011; Ollberding et al., 2012).

Sultanate of Oman lies in the Southeastern part of Arabian Peninsula and represents a fine mix of ancient society and modern lifestyle. A steady increase in the per capita income, during the past years has improved the socio-economic status of the people resulting in drastic changes in lifestyle and food consumption patterns replacing the traditional foods with more Western-style ready-made foods (Musaiger et al., 2011; 2012). According to the Ministry of Health of Oman, more than 900 new cancer cases are diagnosed in the Sultanate and NHL is the 3rd most common form of cancers (Ministry of Health, 2012). No information is currently available on the effect of dietary and lifestyle factors on the prevalence of NHL in Oman. The present case-control study was therefore conducted to identify various dietary and lifestyle factors associated with the risk of developing NHL in Omani population.

Materials and Methods

In a case-control study approach, we evaluated the multiple potential causes of NHL. The study was conducted at the out-patient departments of Oncology Clinic, Sultan Qaboos University Hospital (SQUH) and Royal Hospital (RH), Muscat, Oman. Histologically confirmed cases of NHL classified according to the International Classification of Diseases, (WHO, 1977), diagnosed at SQUH and RH, Muscat were recruited for this study. Population based controls were recruited by random access method from the Muscat area and frequency matching was done to achieve a similar age and sex distribution to that of all cancer cases. Cases and control were frequency matched by age in 5-years intervals by adjusting the number of controls randomly selected in each age stratum. Forty-three cases and 43 age and gender matched controls were included in this study. The cases and controls were asked to complete a comprehensive questionnaire that included both demographic information and 117-items food frequency questionaire, in personal interviews. The study questionnaire was tested for validitiy, reliability and reproducibility before conducting the study. All study subjects were recruited on voluntary basis and a written informed consent was obtained. The study was approved by the Medical Research Ethics Committee of Sultan Qaboos University, Muscat, Oman.

Demographic and anthropometric data

The variables related to demographic, anthropometric and social characteristics such as gender, age, marital status, occupation, educational level, smoking, tobacco chewing, main sources of drinking water and intake of mineral and vitamin supplements, were included in the questionnaire. The anthropometric measurements included, weight, height and body mass index.

Semi-quantitative food frequency questionnaire (FFQ)

A comprehensive 117-items semi-quantitative food frequency questionnaire (FFQ) was designed to collect dietary information about the amount and frequency of consumption for various food items commonly consumed in Oman (Table 1). The FFQ was developed based on the already developed and validated food frequency questionnaires according to Block et al. (1990) and Willet (1998) keeping in view the Omani food consumption patterns. For each food item, a portion size was specified using the common household serving units/utensils (table spoon, tea spoon, cup 180mL, cup 240mL), which were shown to the volunteers to comprehend their intake of foods. Each subject was personally interviewed to complete the questionnaire characterizing his/her usual diet intake stating how often, on the average, they consumed the specific amount of each food during a period of one year prior to being interviewed with the understanding that this is highly correlated with more distant past. There were nine possible responses, including never, a few times per year, 1-2 times/month, 1-2 times/week, 3-4 times/week, 5-6 times/week, 1-3 times /day, 4-5 times/day, and more than or equal to (≥6) times/day. The data was collected on the consumption frequency and usual portion sizes for 117 food items in one year (before the diagnosis of NHL). The different food groups included in the questionnaire were: breads, vegetables, fruits, meat and meat products, milk and milk products, desserts, beverages, sandwiches, and traditional Omani dishes. These food items were included based on their contribution to the total intake of energy by the population groups and account for over 90% of total Omani population's intake. Each question had several choices and the interviewing researcher marked the best appropriate choice according to the reply of the subject.

Estimation of nutrient intake

The information from the food frequency questionnaire was summarized into several nutrients and food groups. Estimates of total daily intake of energy, protein, carbohydrate and fat were calculated from the nutrient estimates assigned to each dietary item using a computer based Nutrient Analysis Program (NutriBase 6.0). The chemical composition of traditional Omani dishes was determined from either our own laboratory data on the composition of food or from the already published

Table 1. Dietary Items Included

	Portion/ Serving size		Portion/ Serving size		Portion/ Serving size
Vegetables		40). Chicken Soup	1/2 cup	80). Chicken	2 oz
1). Broccoli	1/2 cup	41). Chickpeas (hummus)	1/2 cup	81). Cheddar	2 oz
2). Cabbage	1/2 cup	42). Harees chicken	1/2 cup	82). Cream cheese	2 oz
3). Carrot	1/2 cup	43). Harees meat	1/2 cup	83). sliced cheese	2 oz
4). Cauliflower	1/2 cup	44). Kidney beans	1/2 cup	84). Milk (whole milk)	1 cup
5). Chilli	1/2 cup	45). Lentils	1/2 cup	85). Milk w chocolate	1 cup
6). Cucumber	1/2 cup	46). Macaroni	1/2 cup	86). Milk w fruits	1 cup
7). Eggplant	1/2 cup	47). Makboos chicken	1/2 cup	87). yogurt (plain)	1 cup
8). Garlic	Yes/ No	48). Makboos fish	1/2 cup	88). yogurt w frui	1 cup
9). Green onion	1/2cup	49). Makboos meat	1/2 cup	89). Egg (scrambled, boiled, omelet)	1 egg
10). Green pepper	1/2cup	50). Meat Soup	1/2 cup	**Beverages and drinks**	
11). Lady finger	1/2cup	51). Pizza	1 pce	90). Coffee (Omani) (brewed)	1 cup
12). Lettuce	1 cup	52). Qabooli chicken	1/2 cup	91). Instant coffee (Nescafe)	1 cup
13). Mixed vegetables, raw, cooked	1/2 cup	53). Qabooli fish	1/2 cup	92). Tea w milk	1 cup
14). Onions (raw or cooked)	1/2 cup	54). Qabooli meat	1/2 cup	93). Tea w/o milk	1 cup
15). Potato*	1/2 cup	55). Saloona chicken	1/2 cup	94). Soft Drinks	1 cup
16). Spinach	1 cup	56). Saloona fish	1/2 cup	95). bottled or canned fuit juice	1 cup
17). Sweet potatoes	1/2 cup	57). Saloona meat	1/2 cup	**Sandwiches**	
18). Olive (green-Black)	1/2 cup	58). Samosa	2 small/1 big pce	96). Egg sandwich	1 sandwich
19). Tomatoes	1/2 cup	59). Thareed chicken	1/2 cup	97). Cheese sandwich	1 sandwich
Fruits		60). Thareed meat	1/2 cup	98). Chicken sandwich	1 sandwich
20). Apple	1/2 cup	61). White Rice (boiled or cooked w fat)	1/2 cup	99). Falafel sandwich	1 sandwich
21). Banana	1/2 cup	**Breads**		100). Cheese burger	1 sandwich
22). Dates (Ratab/tamar)	1/4 cup	62). Brown Toast bread	1 pc/25g	101). Chicken fillet	1 sandwich
23). Grapes	1/2 cup	63). Burger bread	1/2 bun	102). Fish fillet	1 sandwich
24). Guava	1/2 cup	64). Chapati bread	1slice	**Desserts**	
25). Kiwi	1/2 cup	65). Lebnani bread -brown	1slice	103). Apple pie	2 oz
26). Mango	1/2 cup	66). Lebnani bread-white	1slice	104). Biscuit	15 g (piece)
27). Melon	1/2 cup	67). Parata	1/2 slice	105). Cake (sponge)	2 oz
28). Orange	1/2 cup	68). Rekhal	1 slice	106). Cheese cake	80 g
29). papaya	1/2 cup	69). Salalah bread	1 slice	107). Croissant	1croissant
30). Peach	1/2 cup	70). Tanoor Bread	1/2 slice	108). Custard	150 g
31). Pears	1/2 cup	71). Unspecified bread	1 slice	109). Date pie	80 g
32). Pomegranate	1/2 cup	72). White Toast bread	1 slice	110). Donuts	2 oz
33). Watermelon	1 pce/3-4 cm	**Meats, Milk, Dairy products, Nuts**		111). Luqaimat	2 oz
Traditional Omani dishes		73). Almonds	1/2 oz	112). Omani Halwa	1 oz
34). Arsiya chicken	1/2 cup	74). Cashew	1/2 oz	113). Pancake	40 g
35). Arsiya meat	1/2 cup	75). Peanuts	1/2 oz	114). Potato chips	30 g
36). Beans	1/2 cup	76). Pistachio	1/2 oz	115). Pudding	150 g
37). Beriani chicken	1/2 cup	77). Fish (cooked)	2 oz	116). Sweets/ chocolate/candy	46 g
38). Beriani fish	1/2 cup	78). Tuna (canned)	2 oz	**Fast Food**	
39). Beriani meat	1/2 cup	79). Meat (lamb) (Mutton)	2 oz	117) KFC/ Pizza Hut/McDonald's	1 sandwich

*mashed, boiled or baked french fries

literature (Musaiger et al., 1998; Ministry of Health, 2006). In order to calculate the intake of nutrients (protein, carbohydrates, and fat) in grams, all the frequencies were converted into daily basis. The nutrients were calculated by multiplying the portion sizes (in grams) by the nutrient content per 100 grams of that food by the frequency intake per day. Finally the total daily intake of each nutrient was calculated by summing the nutrient values across all foods which contained that specific nutrient. All the respondents were subsequently grouped according to their intake level of each nutrient based on the frequency of consumption among both cases and controls.

In addition to this, the number of daily servings of food groups according to the food guide pyramid (Cereals, Vegetables, Fruits, Milk and Meat) was estimated. Serving sizes were defined either in usual natural units (e.g. teaspoon, tablespoon or cup) or as an average serving in grams. This was achieved by estimating the number of servings provided by each food item in FFQ. Some questionnaire items were allocated to two or more food groups; according to their nutrient contents (e.g. pizza was apportioned into both bread and cheese for one half serving each) and then the daily servings for each food group were calculated by multiplying the portion size by the number of serving of that food by the frequency intake per day. Finally the total daily intake of each nutrient was calculated by summing up the serving values across all food items which contributed any servings to that food group. Subsequently, all the respondents were grouped according to their intake level for each food group based on frequency of consumption among cases and controls. There is often an interest in how much of one's caloric intake comes from a particular nutrient. We therefore computed the percentage contribution of total calories the respondents consumed from that particular nutrient (protein, carbohydrate or fat). Both the cases and controls were categorized according to their nutrient densities from each macronutrient.

Statistical analysis of the data

A number of variables were created from the original data sets, which were defined and categorized into 3 quartiles in order to facilitate the interpretation of results and to assess the disease risk. The consumption of nutrients was examined in terms of absolute quantitative terms (in grams) and the percentage of total calories consumed by respondents was calculated based on macronutrients intake. The total daily intake of number of servings per day for each food group (cereals, vegetables, fruits, milk and milk products and meat and meat substitutes) were estimated according to food guide pyramid and were also categorized into 3 quartiles of consumption. The lowest

quartile of intake served as the reference group for all comparisons.

The statistical analysis of data was done using the Statistical Analysis Software Package (SPSS) version 16. The statistical model suggested by Willet and Stamfer (1986) was used to assess the effect of calories and nutrient intake. The adjustments for confounding variables were also considered in the final model. Multivariate analysis was used to assess the independent contribution of each nutrient of interest to disease status. The association between the food groups and risk of NHL was estimated using the odds ratios (OR) and 95% confidence intervals (95%CI) calculated from the maximum likelihood estimates using binary logistic regressions. The OR and 95%CI relating to non-dietary components and NHL were calculated using binary logistic regressions.

Results

Demographic and social characteristics

The characteristics of patients with NHL and controls are shown in Table 2. All the reported associations are relative to the lowest quartile. There was no significant difference in the age between the cases and controls. The educational level of controls was significantly better than that of cases. Although no consistent increase or decrease was observed, there was a significant decreasing trend in the risk of NHL with increasing level of education (OR=1.00, 0.21, 0.27, 0.12). Our results are in line with the findings of Hermann et al. (2010), who also could not confirm an overall consistent association between educational level and risk of Hodgkin's lymphoma (HL) and NHL. Although the risk of the NHL was equal among single and married respondents in both the groups (OR=1.00), a non-significant increased risk of NHL was observed with higher BMI level (OR=1.00, 1.84, 1.20). Significant differences were also observed in the smoking status (P=0.02). There were more smokers (21%) among cases (NHL patients) as compared to controls (5%). No significant difference was observed in tobacco chewing (P=0.31). The source of drinking water as well as the intake of vitamins and minerals supplement also did not show any significant differences (Table 3). Overall the results revealed a significantly increased risk of NHL with increasing BMI. However, the risk of NHL decreased significantly with increasing level of education. No significant differences were observed for gender, marital status, tobacco chewing, vitamins and minerals supplement intake and source of drinking water.

Conflicting results have been reported in the literature on the relationship of obesity to NHL risk. The increased risk of NHL associated with overweight and obesity observed in our study is consistent with the reports, which indicated that obese men and women (BMI ≥30 Kg/m^2) had a significantly increased risk of NHL (Pan et al., 2005; Skibola, 2007; Reynolds et al., 2011; Kabat et al., 2012). People with lower BMI were found to have consistently lower risk of NHL (Kelemen et al., 2006). The mechanism for the link between NHL risk and obesity is not clear. One proposed hypothesis is that early life influences on

Table 2. Characteristics of NHL Cancer Cases and Controls

		Cases		Controls		OR	95% (CI)
		No	%	No	%		
Age	<25	6	14	6	14	1	Reference
	25-40	9	20.9	8	18.6	1.05	(0.29-3.84)
	40-55	8	18.6	10	23.3	0.94	(0.30-2.93)
	≥55	20	46.5	19	44.2	1.32	(0.43-4.04)
Sex	Male	23	53.5	23	53.5	1	Reference
	Female	20	46.5	20	46.5	1	(0.43-2.33)
Education							
	Never Attended School	20	46.5	16	37.2	1	Reference
	Elementary	6	14	6	14	0.21	(0.06-0.77)
	High School	13	30.2	6	14	0.27	(0.06-1.30)
	University	4	9.3	15	34.9	0.12	(0.03-0.53)
BMI	<21	5	11.6	8	18.6	1	Reference
	21-25	15	34.9	15	34.9	1.84	(0.52-6.54)
	≥25	23	53.5	20	46.5	1.2	(0.45-2.93)
Marital Status							
	Married	36	83.7	36	83.7	1	Reference
	Single	7	16.3	7	16.3	1	(0.32-3.14)

Table 3. Comparison of Other Risk Factors of NHL among Cases and Controls

			Cases		Controls		p value
			No	%	No	%	
Smoking		Yes	9	20.9	2	4.7	0.02
		No	34	79.1	41	95.3	
Tobacco Chewing		Yes	1	2.3	0	0	0.31
		No	42	97.7	43	100	
Vitamin & Mineral Suppl.		Yes	0	0	3	7	0.08
		No	43	100	40	93	
Drinking water	Well Water		17	39.5	24	55.8	0.3
	City+Bottled Water		5	11.6	3	7	
	City+well Water		2	4.7	0	0	
	Well+Bottled Water		4	9.3	2	4.7	
	City Water		10	23.3	6	14	
	Bottled Water		5	11.6	8	18.6	

Table 4. The Association of NHL with Energy Intake (kilocalories/day)

	Cases		Control		OR	95% (CI)
	No.	%	No.	%		
Intake of energy (Kcal/day)						
<1800	8	18.6	16	37.2	1	Reference
1800-2500	15	34.9	18	41.9	4.44	(1.40-14.14)
≥2500	20	46.5	9	20.9	2.67	(0.94-7.57)

Table 5. Association of Protein Consumption and Percent of Calories from Protein with NHL

	Cases		Control		OR	95% (CI)
	No	%	No	%		
Total protein consumption (g/day)						
<65	6	14	12	27.9	1	Reference
65-90	11	25.6	12	27.9	2.74	(0.87-8.60)
≥90	26	60.5	19	44.2	1.49	(0.54-4.10)
% of calories from protein						
<15%	9	20.9	6	14	1	Reference
15-19	28	65.1	31	72.1	0.67	(0.14-3.09)
≥19	6	14	6	14	1.11	(0.32-3.83)

growth and immune function and obesity may impair the immune function and therefore may increase the risk of NHL later in life (Lee et al., 2008; Kabat et al., 2012). Another possible mechanism is that obesity can cause changes in the metabolism of endogenous hormones, including sex steroids, insulin and insulin-like growth factors, which could distort the normal balance between cell proliferation, differentiation, and apoptosis (Bianchini et al., 2002). Leptin also plays an important role in the regulation of food intake, energy expenditure, and the control of body weight (Pan et al., 2005). Based on the data from case-control and prospective cohort studies there is increasing evidence that obesity may increase the risk of NHL. Our results are consistent with these findings.

Total energy intake and risk of NHL

Significant differences were observed in the total energy intake between the cases and controls (Table 4). Although there was no specific trend between an increase in energy intake and risk of NHL, the higher intake of energy was found to be associated with an increased risk of NHL. The quartiles of caloric intake suggested an increased risk of NHL in the second quartile followed by a decrease in OR in the 3rd quartile as shown in Table 4. The percentage of energy (kcal/day) contribution from various macronutrients is shown in Figure 1. No significant differences were observed in the percentages of daily energy intake from protein and fat between the cases and the controls (p=0.69, 0.86, 0.07 for protein, fat and carbohydrate respectively). A positive effect of total caloric intake on disease has been suggested previously (Purdue et al., 2004; Pan et al., 2005). A population-based case-control study from eight Canadian provinces found that high total energy intake showed a relatively strong association with risk of NHL (Purdue et al., 2004). However, some other studies did not observe such association (Chang et al., 2006; Talamini et al., 2006). Obesity, energy homeostasis and physical inactivity have been reported to influence the immune function and therefore may influence the risk of NHL (Pischon et al., 2008; Kobat et al., 2012). The results of our study showed a relatively positive association between the total energy intake and risk of NHL and are in line with these findings.

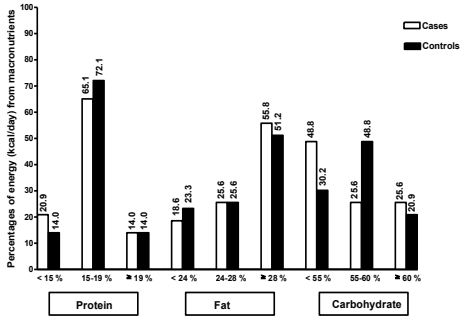

Figure 1. Percentages of Energy (kcal/day) from Macronutrients

Consumption of protein, fat, carbohydrate and risk of NHL

The mean daily consumption of protein, fat and carbohydrate for cases and controls is presented in Tables 5, 6 and 7 respectively. No significant differences (P=0.21) were observed in the protein intake. Although the risk estimate for the highest quartile of protein intake (≥90 g/day) was 1.49, only significantly elevated OR of 2.74 was observed for the second quartile of protein consumption (65-90 g/day). However, when the total protein intake was examined in quartiles as the percentage energy contribution from protein, no association was observed with risk of NHL (1.00, 0.67, and 1.11). The increased NHL risk associated with higher protein intake observed in this study is consistent with the data reported in some previous studies, which suggested that high intake of protein can influence the metabolic pathways of immune system and may increase the risk of NHL (Talamini et al., 2006, Mozaheb et al., 2012). Although the evidence from animal studies supports an etiologic role of high protein consumption, the results from epidemiological studies are inconsistent. A population based case-control study conducted by Ward et al. (1994) found that animal protein was not significantly associated with the risk of NHL, whereas Chiu et al. (1996) found an elevated risk associated with higher consumption of animal protein. The increased risk associated with higher protein intake appeared to be mainly related to animal protein sources and not with vegetable protein consumption (Zheng et al., 2004). Other studies however found no association between animal or vegetable protein intake and NHL risk (Ward et al., 1994, Zhang et al., 1999). Diets high in animal protein may lead to prolonged (chronic) antigenic stimulation which could induce a state of immune unresponsiveness or oral tolerance and possibly may elevate the lymphoma risk. On the other hand, a population-based case-control study conducted in eight Canadian provinces found no association between the protein intake and risk of NHL (Purdue et al., 2004). A similar study from Sweden also reported similar results

Table 6. Association of Fat Consumption and Percent of Calories from Fat with NHL

	Cases No	%	Control No	%	OR	95% (CI)
Total fat consumption (g/day)						
<65	13	30.2	26	60.5	1	Reference
65-80	12	27.9	5	11.6	3	(1.12-8.06)
>80	18	41.9	12	27.9	0.63	(0.18-2.23)
Percentage of calories from fat						
<24	8	18.6	10	23.3	1	Reference
24-28	11	25.6	11	25.6	1.36	(0.46-4.08)
≥28	24	55.8	22	51.2	1.09	(0.40-3.02)

Table 7. The Association of NHL with Carbohydrate Consumption /day

	Cases No	%	Control No	%	OR	95% (CI)
Total carbohydrate consumption (g/day)						
100-250	8	18.6	14	32.6	1.00	Reference
250-350	13	30.2	22	51.2	5.50	(1.63-18.55)
>350	22	51.2	7	16.3	5.32	(1.78-15.86)
% of calories from carbohydrate						
<55	21	48.8	13	30.2	1.00	Reference
55-60	11	25.6	21	48.8	0.76	(0.25-2.32)
≥60	11	25.6	9	20.9	2.33	(0.74-7.32)

Table 8. The Association of NHL with Food Group Servings Per Day

Food group (serving/day)		Case No	Case %	Control No	Control %	OR	95% (CI)
Cereal	<8	10	23.3	28	65.1	1	Reference
	8-10	7	16.3	7	16.3	9.1	(3.12-26.58)
	≥10	26	60.5	8	18.6	3.25	(0.87-12.09)
Vegetable	<4.5	25	58.1	9	20.9	1	Reference
	4.5-6	13	30.2	13	30.2	0.09	(0.03-0.30)
	≥6	5	11.6	21	48.8	0.24	(0.07-0.82)
Fruit	<2	13	30.2	9	20.9	1	Reference
	2-4	19	44.2	26	60.5	0.95	(0.27-3.31)
	>4	11	25.6	8	18.6	1.88	(0.64-5.57)
Milk	<0.5	12	27.9	8	18.6	1	Reference
	0.5-1.5	21	48.8	22	51.2	0.51	(0.15-1.73)
	≥1.5	10	23.3	13	30.2	0.81	(0.29-2.23)
Meat	<2.5	8	18.6	13	30.2	1	Reference
	2.5-5.0	16	37.2	17	39.5	2.38	(0.77-7.34)
	≥5.0	19	44.2	13	30.2	1.55	(0.58-4.15)

(Chang et al., 2006).

The mean daily fat intake between the cases (80.4 g/day) and controls (62.2 g/day) differed significantly (p=0.02). However, the mean daily fat intake did not show a consistent association with NHL risk. An increase in NHL risk (OR=3.00) was observed in the second quartile for daily fat intake, followed by a decrease in risk in the third quartile (OR=0.63), which was much lower than that in first quartile (Table 6). Similarly, the percentage energy contribution from fat in different quartiles did not show a consistent increase or decrease in risk estimates (OR=1.00, 1.36, 1.09) (Table 7). No apparent association could therefore be established between the amount of fat intake and percentage of calories contributed from fat with NHL risk. Our results however do not support the data that higher consumption of total fat, saturated fat and trans-saturated fat is associated with higher NHL risk (Purdue et al., 2004). The discrepancy in the results may be because of a smaller sample size.

Significant differences were observed in carbohydrate intake between the cases (354.7 g/day) and controls (286.1 g/day). Carbohydrate intakes in the second and third quartiles were both associated with significantly elevated OR of 5.50 and 5.32 respectively. Overall the total carbohydrate consumption in terms of absolute intake showed an elevated NHL risk (Table 7). The ORs for the percentage energy contribution from carbohydrate in three different categories of consumptions were 1.00, 0.76 and 2.33 respectively. The data from various epidemiologic studies presents an inconsistent picture of the association between carbohydrate intake and overall risk of NHL, ranging from significantly increased risk (Zheng et al., 2004) to no association (Chang et al., 2006). Our results however suggest that high intake of carbohydrates, in particular from refined grains; can increase the risk of NHL.

Intake of number of servings from various food groups and risk of NHL

Significant differences were observed in the daily intake of number of servings from the cereals and vegetables groups between the cases and controls. No significant differences were however observed in the daily intake of number of servings from fruits, milk and milk products and meat and meat substitute groups (Table 8) The OR describing the association between the individual food groups and risk of NHL are presented in Table 8. There was a dramatic increase in NHL risk associated with second quartile of cereal consumption, which decreased in the third quartile (OR=1.00, 9.10, 3.25). Overall, higher intake of number of daily serving from cereals, in particular from refined grains, was found to be positively associated with risk of NHL. Likewise, no consistent increase or decrease was found to be associated in all three quartiles of consumption of meat and vegetables groups. However, higher total meat consumption was generally found to be associated with a significantly higher risk of NHL (OR=1.00, 2.38, 1.55), whereas a decreased risk of NHL was associated with higher daily intake of number of servings from vegetables group (OR=1.00, 0.09, 0.24). No apparent association was observed between the quartiles for the daily intake of number of servings from fruits and milk and milk products with NHL risk (OR=1.00, 0.95, 1.88 for fruit and OR=1.00, 0.51, 0.81 for milk and milk products). Our results support the hypothesis that higher consumption of cereals, in particular the refined grains, is associated with increased risk of NHL (Talamini et al., 2006). Our results are also consistent with the data from other case-control studies, which showed that the consumption of breads and cereal products was positively associated with NHL risk (Ward et al., 1994; Zheng et al., 2004). The results from some other studies however did not report any such association (Purdue et al., 2004; Chang et al., 2006).

Our results indicated that higher total meat consumption was found to be associated with significantly higher risk of NHL. These results are in line with the previously reported data (Chiu et al., 1996; Zheng et al., 2004; Chang et al., 2006). Association with NHL risk was however inconsistently observed across different types of meat (De-Stefani et al., 1998). The consumption of cured meat, salami, and sausages was associated with a modest increase in NHL risk (Davis, 1992). A positive association has also been reported between the high intake of beef, pork, lamb meat and liver with increased NHL risk (Francheschi et al., 1989; Zhang et al., 1999). The results of the present study are consistent with these findings. Some other studies however, found no associations with red meat intake and NHL risk (Talamini et al., 2006; Skibola, 2007; Daniel et al., 2012). Such inconsistencies in the results may be attributed to differences in study design, geographic location, or smaller sample size. The results from the studies on fish consumption and reduced risk of NHL are also inconsistent and have reported only a weak but non-significant inverse association between the fish consumption (≥4 servings of fish per week) and risk of NHL (Matsuo et al., 2001; Purdue et al., 2004; Skibola, 2007). Other studies however did not support an association between fish consumption and reduced risk of NHL (Ward et al., 1994). Overall, the evidence is inconclusive but suggests that an inverse association exits between the fish consumption and NHL risk.

The results of the present study showed an inverse

association between the vegetable consumption and risk of NHL. Our results are consistent with the reported data suggesting that a higher intake of vegetables, in particular the dark green leafy vegetables, may reduce the risk of NHL (Ward et al., 1994; Talamini et al., 2006; Chang et al., 2006; Kelemen et al., 2006; Skibola, 2007; Chiu et al., 2011; Chen et al., 2012). Vegetables are considered as a rich source of carotenoids, vitamins C, E, folate and dietary fiber, as well as numerous other phytochemicals that may inhibit the carcinogenesis by neutralizing the reactive oxygen species generated endogenously or supplied exogenously. Thus, they may reduce the oxidative DNA damage and mutations, and enhance immune responses (Zhang et al., 2000; Hemsdorff et al., 2012; Lee et al., 2012). The increase in the magnitude of cancer over the last 33 years in Kuwait has been attributed to changes in lifestyle such as dietary habits, physical activity and obesity (Elbasmi et al., 2010). It has been suggested that the primary focus in the prevention of cancer should be given to reduce the obesity (Willet, 2010) and increased consumption of fruits and vegetable will not only help in reducing the rate of obesity but will also help in reducing the risk of many cancers (Aune et al., 2012; Reiss et al., 2012). Our results are consistent with these findings and showed that higher daily intake of vegetables was associated with a decreased risk of NHL.

Study limitations

There are however some limitations of the study, for example the methodological issues such as the use of a semi-quantitative FFQ, which is not a perfect tool for measuring the dietary intakes. However, it is the most practical and well-validated method available for such type of studies. Secondly, the study did not examine the heterogeneity across the NHL subtypes with respect to dietary associations. Thirdly, the small sample size (n=86, 43 cases and 43 controls) limited the statistical power of the analysis to detect some weak associations. The findings for individual dietary factors should therefore be interpreted with caution.

Discussion

In conclusions, Overall, this study revealed a number of risk factors among which obesity, high caloric and protein intakes were found to be associated with elevated risk of NHL Higher consumption of cereals, in particular the refined grains and meat were also found to be associated with increased risk of NHL, whereas a significantly reduced risk was observed with higher consumption of vegetables. This is the first study to report about an association between diet and NHL risk in Omani population. The results add valuable information on the subject and also lead to a better understanding of dietary consumption patterns in Omani population and their implications in overall health and disease. Considering how little is known about the etiology of NHL in Oman, further well-designed randomized control trials with larger cohorts should be conducted to validate these preliminary results and to quantify the effects of various nutritional and metabolic biomarkers in the context of entire diet and its possible association to NHL and other types of cancers.

Acknowledgements

We are thankful to the study volunteers, staff of Sultan Qaboos University Hospital and Royal Hospital for their help and cooperation. Thanks are also due to Dr. Shyam Ganguly and Dr. Mohammed Saleh Ahmed for their help and assistance in the statistical analysis of the data. The financial assistance provided by Sultan Qaboos University under an internal research grant (IG/AGR/FOOD/07/01) is greatly acknowledged. "We are also thankful to Prof. Venket Rao and Prof. Nancy Krieger from University of Toronto, Canada, for their help and cooperation in the development of food frequency questionnaire".

References

Anand P, Kunnumakara AB, Sundaram C, et al (2008). Cancer is preventable disease that requires major lifestyle changes. *Pharmaceutical Res*, **25**, 2097-116.

Aune D, Chan DS, Vieira AR, et al (2012) Fruits, vegetables and breast cancer risk: a systematic review and meta-analysis of prospective studies. *Breast CancerRes Treat*, **134**, 479-93.

Bianchini F, Kaaks R, Vainio H (2002). Overweight, obesity and cancer risk. *Lancet Oncology*, **3**, 565-74.

Block G, Hartman AM, Naughton D (1990). A reduced dietary questionnaire development and validation. *Epidemiol,* **1**, 58-64.

Chang ET, Balter KM, Torrang A, et al (2006). Nutrient intakes and risk of non-Hodgkin's lymphoma. *Am J Epidemiol*, **164**, 1222-32.

Chen GC, Da-Bing LV, Pang Z, et al (2012) Fruits and vegetables consumption and risk of non-Hodgkin's lymphoma: a meta-analysis of observational studies. *Int J Cancer*, **10**, 27992.

Chiu BCH, Cerhan JR, Folsom AR, et al (1996) Diet and risk of non-Hodgkin's lymphoma in older women. *JAMA*, **276**, 1315-21.

Chiu, BC, Weisenburger, DD (2003). An update of epidemiology of non-Hodgkin's lymphoma. *Clin Lymphoma*, **4**, 161-8.

Chiu BC, Kwon S, Evens AM, et al (2011). Dietary intake of fruit and vegetables and risk of non-hodgkin lymphoma. *Cancer Causes Control*, **22**, 1183-95.

Daniel CR, Sinha R, Park Y, et al (2012). Meat intake is not associated with risk of non-Hodgkin's lymphoma in a large prospective cohort of U.S. men and women. *J Nutr*, **142**, 1074-80.

Davis, S (1992). Nutritional factors and the development of non-Hodgkin's lymphoma: A review of the evidence. *Cancer Res*, **52**, 5492-5.

De-Stefani E, Fierro L, Barrios E, et al (1998). Tobacco, alcohol, diet and risk of non-hodgkin's lymphoma: a case-control study in Uruguay. *Leuk Res*, **22**, 445-52.

Donadlson MS (2004). Nutrition and cancer; a review of the evidence for an anti-cancer diet. *Nutrition J*, **3**, 19.

Doll R, Peto R (1981). The causes of cancer: quantitative estimates of avoidable risk of cancer in The United States today. *J Natl Cancer Inst*, **66**, 1192-308.

Elbasmi A, Al-Asfour A, Al-Nesf Y, et al (2010). Cancer in kuwait: magnitude of the problem. *Gulf J Oncolog*, **1**, 7-14.

Frankenfeld CL, Cerhan JR, Cozen W, et al (2008). Dietary flavonoid intake and non-Hodgkin lymphoma risk. *Am J Clin Nutr*, **87**, 1439-45.

Franceschi S, Serraino D, Carbone A, et al (1989). Dietary factors and non-Hodgkin's lymphoma: a case control study

in the Northeastern part of Italy. *Nutr Cancer*, **12**, 333-41.
Hermsdorff HH, Barbosa KB, Volp AC, et al (2012). Vitamin C and fibre consumption from fruits and vegetables improves oxidative stress markers in healthy young adults. *Br J Nutr*, **107**, 1119-27.
Holtan SG, O'Connor HM, Fredericksen ZS, et al (2012). Food-frequency questionnaire-based estimates of total antioxidant capacity and risk of non-hodgkin lymphoma. *Int J Cancer*, **131**, 1158-68.
Hermann S, Rohrmann S, Linseisen J, et al (2010). Level of education and the risk of lymphoma in the European prospective investigation into cancer and nutrition. *J Cancer Res Clin Oncol*, **136**, 71-7.
Hosnijeh FS, Heederik D, Vermeulen R (2012). A review of the role of lymphoma markers and occupational and environmental exposures. *Vet Q*, **32**, 61-73.
Kabat GC, Kim MY, Wactawski-Wende J, et al (2012). Anthropometric factors, physical activity and risk of Non-hodgkin's lymphoma in the women's health initiative. *Cancer Epidemiology*, **36**, 52-59.
Kelemen LE, Cerhan JR, Lim U, et al (2006). Vegetables, fruits, and antioxidant- related nutrients and risk of non-Hodgkin's lymphoma; a national cancer institute- surveillance, epidemiololgy, and end results population-based case-control study. *Am J Clinical Nutrition*, **83**, 1401-10.
Khoja T, Zahrani A (2010). Epidemiology of cancer in the Gulf region. *Pan Arab J Oncology*, **3**, 9.
Lee JE, Spiegelman D, Hunter DJ, et al (2008). Fat protein and meat consumption and renal cell cancer risk: A pooled analysis of 13 prospective studies. *J Natl Cancer Inst*, **100**, 1695-706.
Lee JH, Khor TO, Shu L, et al (2012). Dietary phytochemicals and cancer prevention: Nrf2 signaling, epigenetics, and cell death mechanisms in blocking cancer initiation and progression. *Pharmacol Ther*, **10**, 163-7258.
Matsuo K, Hamajima N, Hirose K, et al (2001). Alcohol, smoking, and dietary status and susceptibility to malignant lymphoma in Japan: results of a hospital-based case-control study at Aichi Cancer centre. *Jap J Cancer Res*, **92**, 1011-7.
Milner, JA, (2006). Diet and cancer: facts and controversies. *Nutrition and Cancer*, **56**, 216-24.
Ministry of Health (MOH). 2006. Chemical composition and recipes of common Omani foods, 2006. Ministry of Health, Muscat, Oman.
Ministry of Health (2012) Cancer Incidence in Oman: Annual Report of 2010, Department of non-Communicable Diseases Surveillance and control, Directorate General of Health Affairs, Ministry of Health, Muscat, Oman. http://www.moh.gov.om/en/reports/. Accessed on Aug 27, 2012.
Mozaheb Z, Aledavood A, Farzad F (2012). Diet and non-Hodgkin's lymphoma risk. *Pan Afr Med J*, **12**, 53.
Musaiger AO, Hassan AS, Obeid O (2011). The paradox of nutrition-related disease in the arab countries: the need for action. *Int J Environ Res Public Hlth*, **8**, 3637-71.
Musaiger AO, Takruri HR, Hassan AS, et al (2012). Food-based dietary guidelines for the Arab Gulf countries. *J Nutrition and Metabolism*, **10**, 905303.
Musaiger AO, Ahmed AM, Rao MV (1998). Chemical composition of some traditional dishes of Oman. *Food Chemistry*, **61**, 17-22.
Ollberding NJ, Maskarinec G, Conroy SM, et al (2012). Prediagnostic circulating carotenoid levels and the risk of non-Hodgkin lymphoma: the Multiethnic Cohort. *Blood*, **119**, 5817-23.
Pan SY, Mao Y, Ugnat A (2005). Physical activity, obesity, energy intake, and the risk of non-Hodgkin's lymphoma: a population-based case control study. *Am J Epidemiol*, **162**, 1162-73.
Pischon L, Nothlings U, Boeing H (2008). Obesity and cancer. *Proc Nutr Soc*, **67**, 128-145.
Purdue MP, Bassani DG, Klar NS, et al (2004). Dietary factors and risk of non-Hodgkin's lymphoma by histologic sub-type: A case control analysis. Cancer Epidemiology, *Biomarker and Prevention*, **13**, 1665-76.
Reiss R, Johnston J, Tucker K, et al (2012) Estimation of cancer risks and benefits associated with a potential increased consumption of fruits and vegetables. *Food Chem Toxicol*, **50**, 4421-27.
Reynold JV, Donohoe CL, Doyle SL (2011). Diet, obesity and cancer. *Ir J Med Sci*, **180**, 521-7.
Salim EI, Jazieh AR, Moore MA (2011). Lung cancer incidence in the Arab league countries; risk factors and control. *Asian Pac J Cancer Prev*, **12**, 17-34.
Sangrajrang S, Renard H, Kuhaprema T, et al (2011). Personal use of hair dyes--increased risk of non-hodgkin's lymphoma in Thailand. *Asian Pac J Cancer Prev*, **12**, 2393-6.
Skibola CF (2007). Obesity, diet and risk of non-Hodgkin's lymphoma. *Cancer Epidemiol, Biomarkers and Prev*, **16**, 392-95.
Tadmouri GO, Nair P (2012). Cancers in Arab populations, concise notes. *Hamdan Med J*, **5**, 79-82.
Talamini R, Polesel J, Montella M, et al (2006) Food groups and risk of non-Hodgkin's lymphoma: A multicenter case-control study in Italy. *Int J Cancer*, **118**, 2871-6.
Thompson CA, Habermann TM, Wang AH, et al (2010). Antioxidant intake from fruits, vegetables and other sources and risk of non-hodgkin's lymphoma: the iowa women's health study. *Int J Cancer*, **126**, 992-1003.
Tramacere I, Pelucchi C, Bonifazi M, et al (2012). Alcohol drinking and non-Hodgkin's lymphoma risk: a systematic review and a meta-analysis. *Ann Oncol*, **23**, 2791-8.
Ward HM, Zahm SH, Weisenburger DD, et al (1994). Dietary factors and non-hodgkin's lymphoma in Nebraska (United States). *Cancer Causes and Control*, **5**, 422-32.
Willet WC (1998). Nutritional Epidemiology. Oxford University Press, New York.
Willet WC (2010). Fruits, vegetables and cancer prevention: Turmoil in the produce section. *J National Cancer Institute*, **102**, 510-11.
Willet WC, Stampfer MJ (1986). Total energy intake: implications for epidemiologic analysis. *Am J Epidemiol*, **124**, 17-27.
Willett EV, Morten LM, Hartge P, et al (2008). Non-hodgkin's lymphoma and obesity: a pooled analysis from the InterLink consortium. *Inter J Cancer*, **122**, 2062-70.
World Health Organization, WHO (1977) Manual of international classification of diseases, injuries and causes of death. 9th revision, Geneva, WHO.
Zhang S, Hunter DJ, Rosoner BA, et al (1999). Dietary fat and protein in relation to risk of non-hodgkin's lymphoma among women. *J National Cancer Institute*, **91**, 1751-8.
Zhang SM, Hunter DJ, Rosner BA, et al (2000). Intakes of Fruits, vegetables and the risk of non-hodgkin's lymphoma among women. *Cancer Epidemiol, Biomarkers and Prev,* **9**, 477-85.
Zheng, T, Holford, TR, Leaderer B, et al (2004). Diet and nutrient intakes and risk of non-hodgkin's lymphoma in connecticut women. *Am J Epidemiol*, **159**, 454-66.