Ecological Study of Dietary and Smoking Links to Lymphoma

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Abstract

The ecological approach is used to investigate dietary and smoking links to lymphoma. International mortality rate data for 1986 and 1994 by gender and age group are compared with national dietary supply values of various food components for up to 10 years prior to the mortality data as well as per capita cigarette consumption rates 5 and 15 years earlier. The non-fat portion of milk, 3-9 years prior to the 1986 mortality data and 4 years prior to the 1994 data, was found to have the highest association with lymphoma, with r as high as 0.89. The results imply that 70 percent of lymphoma mortality may be related to this dietary component. Cigarette smoking in 1980 was found to have a weaker association with 1994 lymphoma mortality rates, being most important for younger men and statistically insignificant for younger women. The non-fat milk result is consistent with both case-control studies and a Norwegian prospective study, and with the often-observed finding that abnormal calcium metabolism, hypercalciuria, and dysregulated calcitriol production are common in normocalcemic patients with non-Hodgkin's lymphoma (NHL). It is hypothesized that excess dietary calcium from milk is a significant risk factor for lymphoma.
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Introduction

A number of environmental, dietary, and lifestyle factors are involved in the etiology of lymphoma. Various chemicals, including herbicides[1,2] and pesticides,[3] have been found to be associated with increased risk. Occupations with significant chemical exposure, such as agricultural work,[4-6] as well as smoking[7,8] have been determined to be risk factors for lymphoma. There are a number of foods which have been associated with an increased risk for lymphoma. Several studies, using either prospective cohort[9] or case-control approaches,[10-12] have found milk to be a risk factor. However, one study found animal fat to be the highest risk factor (risk ratio (RR) = 2.00) in older women, with milk and dairy product consumption not associated with NHL.[13] A study in Uruguay reported that salted meat was a high risk factor (odds ratio (OR) = 5.5).[8] A U.S. study reported that red meat (multivariate relative risk (MRR) = 2.2) and trans unsaturated fat (MRR = 2.4) were risk factors.[14] Finally, a lectin found in raw kidney bean, phytohaemagglutinin (PHA), was found to *reduce* the rate of an NHL tumor in mice.[15]

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Table 1: Data for Lymphoma Mortality for Males and Females Aged 65-74 Years for 1986 and 1994 along with Non-fat Milk Supply for 1977 and 1988.

Country	1986/1994 Mortality Rate		1977/1988 Non-fat Milk
	males	females	
	cases/100,000/year		kcal/day/person
Argentina	25.9/29.2	19.0/19.7	105/116
Australia	56.4/56.6	38.2/44.0	186/206
Austria	33.7/43.9	27.1/30.3	157/166
Belgium	34.5/42.3	26.3/26.7	153/146
Canada	56.8/56.4	37.8/39.0	155/141
Chile	11.2/39.6	13.3/22.6	85/74
Columbia	--/25.5	--/18.1	--/76
Costa Rica	30.5/24.7	32.5/22.5	126/120
Cuba	37.7/35.3	30.0/25.1	154/146
Czechoslovakia	40.1/--	25.0/--	147/--
Denmark	52.4/56.2	37.9/28.4	159/162
Equador	10.6/--	7.1/--	24/--
Finland	51.6/60.7	34.1/33.5	238/202
France	39.7/43.7	23.3/28.2	150/176
Germany	36.2/42.3	22.5/27.7	134/151
Greece	23.6/24.8	14.3/14.4	129/130
Hong Kong	21.4/29.0	16.8/14.3	50/59
Hungary	34.7/42.4	25.7/25.4	99/114
Ireland	39.3/49.9	38.1/39.9	182/253
Italy	36.7/44.7	24.9/31.5	134/113

population was less than two million, if the mortality rates for those aged 75+ years were lower than for those aged 65-74 years, or if the countries were part of the former Soviet Union because these countries do not have medical care systems on par with those in the West. Israel was also omitted because of the large influx of immigrants in recent history. See Figure 1 for 1986 lymphoma mortality rates for males aged 75+ years compared to 1980 non-fat milk consumption. Figure 2 depicts 1994 lymphoma mortality rates for females aged 65-74 years versus 1993 non-fat milk supply.

It should also be noted that neither childhood leukemia nor lymphoma have strong dietary links but seem to be linked to infections.[16-18]

Methods

Lymphoma mortality data used in this study were obtained for 38 countries for 1986 and 33 countries for 1994 (+1/-2 years) from the World Health Organization's *World Health Statistics Annual*.[19] The countries used in the analysis along with the 1986 and 1994 mortality rates for those aged 65-74 years are given in Table 1. Countries were excluded if the

National dietary supply data for this study were obtained from the Food and Agriculture Organization (FAO) *Food Balance Sheets*.[20] Such data are often used in international ecologic studies. It has been shown that in the United States 75 percent of the consumer food supply is actually consumed by people.[22] It is assumed that similar factors apply to other countries. FAO dietary fat data appear to be consistent with studies from various European countries.[23] To further examine the usefulness of the FAO dietary supply values for this study,

Figure 1: 1986 Lymphoma Mortality Rates, Males (aged 75+ years), vs. 1980 Non-fat Milk Supply.
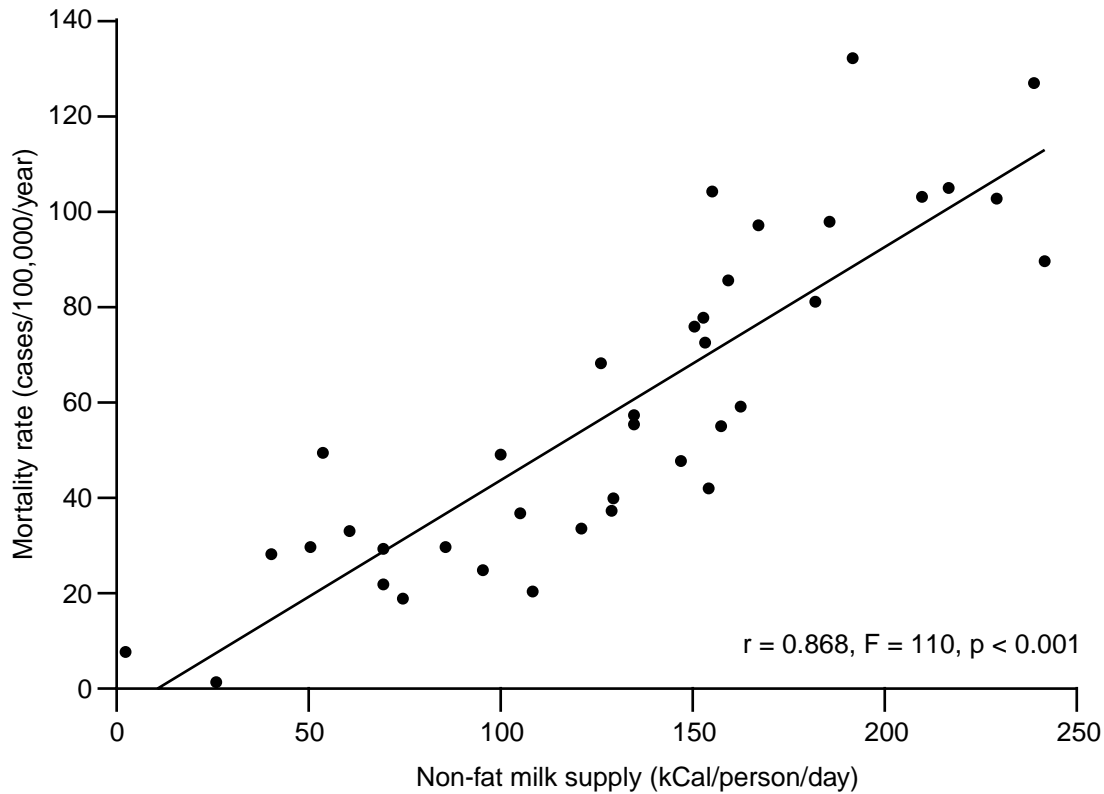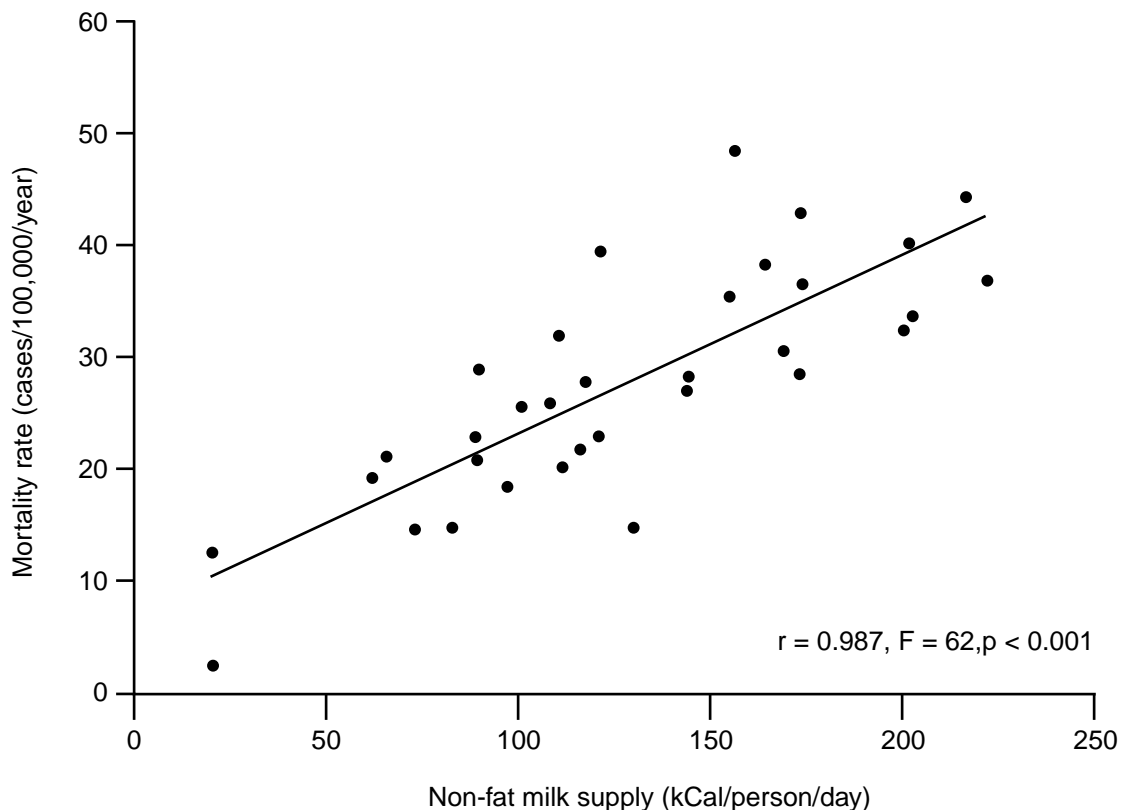

those values are compared with recent surveys of food intakes in ten Western European countries.[24] Aside from alcohol, the energy values in the studies compared to the FAO data for carbohydrates, total energy, fat, and protein lie in the range from 0.62 to 0.88. The value of 0.62 for fat when the Mediterranean countries are included could be due to widespread use of olive oil in cooking not reflected in intake. The study values are also affected by underreporting[25] and, in the case of alcohol, whether the study was conducted during the week or weekend.[26] Nonetheless, the standard deviation (SD) of the values in terms of energy, omitting alcohol, lie in the 0.12-0.20 range. The SDs for the primary categories as fractions of total energy lie in the range 0.04-0.12. The statistical results for dietary components and disease values are similar whether absolute or energy-normalized dietary values

are used. These SD values are much lower than the variations of the FAO data between countries. Thus, it appears appropriate to assume the FAO data can be used in such ecological studies.

A number of dietary components were used in the analysis, including animal fat, cereals, dairy fat, fruit, milk, total fat, total energy, and vegetable products. The years used in the analysis for dietary components extended from 1977-1983 for the 1986 mortality data, and 1988-1993 for the 1994 mortality data, since it cannot be determined *a priori* which years are most important in the etiology. Linear and multiple linear regression analyses were performed on the various data sets. The F-value was used to rank the results and evaluate the multiple linear regression results. Smoking data were obtained[27] and reported as number of cigarettes smoked per

Figure 2: 1994 Lymphoma Mortality Rates, Females (aged 65-74 years), vs. 1993 Non-fat Milk Supply.

r = 0.987, F = 62, p < 0.001

Mortality rate (cases/100,000/year) (y-axis)

Non-fat milk supply (kCal/person/day) (x-axis)

person per year for 1980-1982 and 1990-1992.

Results

The highest statistical association between dietary factors and lymphoma was found for the non-fat portion of milk (Tables 2 and 3). The non-fat portion of milk is calculated from total energy derived from milk minus four times the milk protein weight (grams) and nine times the milk fat weight (grams). The statistical results passed all tests applied, including normality, constant variance, and test with alpha.

Cigarette smoking per capita for 1980 also showed a positive association with lymphoma mortality rates, being highest for males aged 55-64 years, and lowest for females aged 55-64 years (Table 4). However, the inclusion of cigarette smoking in the multiple linear regression reduced, rather than increased, the F (t^2, student-t test) value, indicating that smoking as measured in that manner had a weak association with lymphoma mortality. While other dietary components had positive or inverse associations with lymphoma mortality, none increased the F value in a multiple linear regression, and none did as well as cigarette smoking, although cereals came close. Therefore, the ecological approach cannot determine whether they are risk or risk-reduction factors or merely confounding factors, so these results are not reported here.

Table 2: Statistical Results of Lymphoma Using 1986 Mortality Data and the Non-fat Portion of Milk for Various Years for 38 Countries.

Gender, Age	Year of dietary data		
Years	1977	1980	1983
	r, F	r, F	r, F
MALE, 55-64	0.820, 74	0.796, 62	0.815, 71
FEMALE, 55-64	0.786, 56	0.763, 49	0.767, 50
MALE, 65-74	0.817, 72	0.807, 67	0.831, 81
FEMALE, 65-74	0.840, 86	0.817, 72	0.816, 77
MALE, 75+	0.875, 117	0.868, 110	0.867, 109
FEMALE, 75+	0.885, 130	0.880, 124	0.881, 125

Table 3: Statistical Results for Lymphoma Using 1994 Mortality Data and the Non-fat Portion of Milk from Various Years for 33 Countries.

Gender, Age	Year of dietary data		
Years	1988	1990	1993
	r, F	r, F	r, F
MALE, 55-64	0.688, 28	0.691, 28	0.654, 23
MALE, 65-74	0.811, 60	0.827, 67	0.782, 49
MALE, 75+	0.853, 83	0.863, 91	0.833, 70
FEMALE, 55-64	0.752, 40	0.736, 37	0.637, 21
FEMALE, 65-74	0.870, 97	0.863, 90	0.870, 97
FEMALE, 75+	0.830, 69	0.847, 79	0.816, 62

Discussion

The statistical results for adult lymphoma reported here are consistent with several prior studies in which milk was found to be associated with mortality from the disease. In a prospective cohort study in Norway,[9] cancer of the lymphatic organs was the cancer found to have the highest association with milk consumption (OR for >2 glasses/day vs <1 glass/day was 3.36, 95% CI = 1.4-8.2). In a case-control study of dietary factors and NHL,[10] milk had the highest statistical association. However, one study found an insignificantly elevated risk of NHL among men with high milk consumption.[11] A case-control study[12] reported an OR for milk for the highest tertile of 1.8 for NHL. They also reported an OR for whole-grain foods of 0.4. It is not clear why other reports have failed to find a connection between milk consumption and NHL in women.[13] However, their analysis did not consider the non-fat portion of milk separately, nor the amount of cereals in the diet. They did find reduced RRs for carbohydrates and dietary fiber.

The non-fat milk supply values for 1977[20] and 1988[21] are given in Table 1. For the 17 countries for which non-fat milk increased, lymphoma mortality rates increased for males and/or females aged 65-74 years in 14 countries. There are six countries for which Table 1 shows a decrease in non-fat milk supply while another source[21] showed either no change or a slight increase. Excluding these countries leaves eight for which the non-fat milk supply clearly decreased. For these countries, lymphoma mortality rates for males aged 65-74 years decreased in four of the countries, while they decreased for females aged 65-74 years in three countries. Some of the

Table 4: Statistical Results for Lymphoma Mortality for 32 Countries in 1994 Including Non-fat Milk for 1990 and Cigarettes per capita for 1980 (risk factors) and Cereals (risk reduction factor).

Gender	Age	r, F	p(non-fat milk)	p(cigarettes)	p(cereals)
Male	55-64	0.774, 22	<0.001	0.005	
	65-74	0.849, 38	<0.001	0.060	
	75+	0.889, 55	<0.001	0.060	
Female	55-64	0.738, 17	<0.001	0.303	
	65-74	0.877, 48	<0.001	0.068	
	75+	0.869, 45	<0.001	0.049	
Male	55-64	0.774, 14	0.004	0.006	0.900
	65-74	0.856, 26	<0.001	0.072	0.289
	75+	0.892, 36	<0.001	0.071	0.470
Female	55-64	0.742, 11	0.005	0.333	0.525
	65-74	0.879, 32	<0.001	0.079	0.560
	75+	0.886, 34	<0.001	0.057	0.058

Table 5: Ratio of Male Lymphoma Mortality Rates Divided by that for Females.

Age range (years)	55-64	65-74	75+
1986 mean values	1.52	1.55	1.58
1986 median values	1.52	1.49	1.50
1994 mean values	1.47	1.52	1.48
1994 median values	1.51	1.45	1.43

countries, such as Chile, may be seeing an increase in lymphoma mortality rates due to increased use of agricultural chemicals.

The ratios of lymphoid mortality rates for males to females for three age groups are listed in Table 5. There is no statistically significant gender difference. This suggests that gender-specific hormones are not involved, since for other diseases such as acute myocardial infarction, female hormones seem to play a role, resulting in rapid ratio changes above 55 years of age.[28]

Since adult lymphoma is highly associated with the non-fat portion of milk and inversely associated with whole grain cereals,[29] it is likely that calcium is involved in the etiology. It is not likely to be either lactose, which is implicated in ischemic heart disease,[28] or milk protein, which is implicated in osteoporosis,[30] both of which have lower associations with adult lymphoma than the non-fat portion of milk. Phytate in whole grains reduces calcium absorption,[31] and whole grains also have other protective compounds.[29] Whole grain food intake has been found to be inversely related to lymphoma (OR = 0.5),[32] while other researchers have found

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refined-cereal intake to be positively associated with a number of cancers.[33] The ecological results presented in Table 4 did not find a statistically significant risk-reduction factor for whole and refined cereals combined. However, if whole grains alone could be studied using the ecological approach, a protective effect might well be found.

A number of studies have investigated the roles of vitamin D metabolism and hypercalcemia in relation to Hodgkin's lymphoma (HL). In one case, a patient with HL experienced abnormal vitamin D metabolism that resulted in hypercalcemia when he was exposed to ultraviolet radiation.[34] It was hypothesized that HL caused abnormal vitamin D metabolism. A number of such cases have been reviewed.[35] Calcitriol has been implicated as a hematolymphoid regulatory hormone.[36] It has been reported that deregulated synthesis of a $1,25(OH)_2$-D-like metabolite is a common cause of hypercalcemia and hypercalciuria in patients with lymphoma.[37] Abnormal calcium metabolism, hypercalciuria, and dysregulated calcitriol production are common findings in normocalcemic patients with NHL.[38] Adult T-cell leukemia-lymphoma patients with elevated serum calcium levels were found to have lower survival rates than those with normal serum calcium.[39] Researchers report that calcitriol-mediated A-to-B calcium transport in Caco-2 cells is a specific, transcellular process that requires transcriptional events normally mediated through the vitamin D receptor, with $1,25(OH)_2$-D3 being the regulator.[40] Cats with neoplasia, the most common of which were lymphoma and squamous cell carcinoma, had higher serum calcium levels than those with renal failure.[41] Hepatic and serum levels of iron, zinc, and calcium were highly elevated 15 days after transplantation of Dalton's lymphoma in male Swiss albino mice.[42] From monitoring gamma-glutamyl transferase levels in the liver as well, it was concluded that the metals studied may have a role in initiating and controlling cellular proliferation.

While these papers support the hypothesis that HL gives rise to vitamin D metabolism abnormalities followed by hypercalcemia, that may not be the complete story since excess dietary calcium seems to be linked to lymphoma mortality rates. It could be that the excess calcium from milk, with or without a disruption of vitamin D metabolism, is involved in the etiology of lymphoma among adults. The role of cereals may either be to displace milk from the diet or to reduce the absorption of calcium, perhaps through phytates found in whole grains, as discussed above.

The statistical results for the non-fat portion of milk given in Tables 2 and 3 can be used to estimate the fraction of lymphoma mortality due to diet. For the 1994 data, the mortality rate increased by a factor of 2.3 from age 55-64 years to age 65-74 years, and a factor of 1.8 from 65-74 years to 75+ years. Suitably averaging the r^2 values for the three age groups gives 0.69 for males and 0.71 for females. Thus, diet seems to explain approximately 70 percent of the lymphoma mortality rates on a global basis. On the other hand, the annual incidence of NHL has risen in the United States from 5.9 per 100,000 in 1950 to 13.7 in 1989, which may be consistent with chemical exposure increases during this period. Milk consumption was relatively unchanged during that period, with the per capita supply staying in the range 342-376 kCal/day from 1962 to 1993. However, cancers generally have several risk and risk-reduction factors, so the increase in incidence rates for NHL does not necessarily argue against the results of this study.

In another study,[43] the roles of solar UV-B exposure and vitamin D as risk reduction factors for various forms of cancer were studied. NHL and prostate cancer were found to have similar fractions of U.S. mortality from 1970-1994 related to insufficient solar UV-B radiation, 3-5 percent or 7-9 percent, respectively, depending on the UV-B data used, which was lower than for most other cancers

studied. This finding is consistent with a common etiology, dietary calcium in this case. Many of the other cancer types have dietary fat as the high risk factor.

Note that the dietary links to lymphoma differ from those for leukemia. Using the ecological approach, age-adjusted mortality data[44-45] found total dietary fat to have the highest association with leukemia. However, using age-adjusted incidence data for those aged 35-64 years, it was found that total caloric supply gave the best results.[46] Using the 1986 leukemia mortality data[19] it can be shown that leukemia mortality is most highly associated with total energy supply of adults under the age of 64 years, after which dietary fat has the highest association. This point is made here to demonstrate that leukemia and lymphoma have different dietary links, hence, different etiologies, and to suggest that the ecological approach is not just selecting out non-fat milk as a general risk for cancer mortality.

Whether disruptions in calcium metabolism are a cause or an effect of lymphoma (or both) still remains to be seen. It is hoped that the results presented here will lead to more case-control, clinical, and cohort studies to evaluate and extend these findings and result in guidelines for reducing the risk of adult lymphoma.

Acknowledgements

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