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Nutritional Factors and the Development of Non-Hodgkin's Lymphoma: A Review of the Evidence[1]

Scott Davis

Program in Epidemiology, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center and Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, Washington 98104

Abstract

Lymphomas of the non-Hodgkin's type represent a heterogeneous group of tumors, probably comprised of groups of related diseases each with a distinct etiology. The epidemiology of non-Hodgkin's lymphoma is poorly characterized, and little is known about factors which increase a person's risk of developing one of these tumors. Available epidemiological evidence suggests the influence of a number of environmental factors. Although diet is potentially one of the most significant environmental factors that could be related to disease etiology, very little has been done to investigate the role of diet in the development of non-Hodgkin's lymphoma. In this paper, the existing epidemiological findings are reviewed, and the plausibility of an etiological association between dietary factors and non-Hodgkin's lymphoma is considered in the context of relevant animal research.

Introduction

Non-Hodgkin's lymphomas are a heterogeneous group of tumors which account for approximately 3% of all cancer diagnosed in the United States (1). Tumors classified as non-Hodgkin's lymphoma represent a number of distinct morphological and histological entities, exhibit varying clinical patterns, and respond differently to treatment. In short, lymphomas of the non-Hodgkin's type are most likely comprised of several distinct groups of similar and related diseases, each perhaps with a distinct etiology.

Such heterogeneity makes it difficult to study non-Hodgkin's lymphoma. To date, most epidemiological studies have grouped all tumor types together and have generally failed to distinguish major subtypes of non-Hodgkin's lymphoma. Consequently, the epidemiology of these diseases is poorly characterized, and relatively little is known regarding the etiology of non-Hodgkin's lymphomas as a group or the major component subgroups thereof. Few factors have been identified that increase a person's risk of developing one of these tumors.

Descriptive characterizations of non-Hodgkin's lymphoma have for the most part utilized mortality data, although more recent descriptions, particularly in the United States, have included incidence data as well. A striking feature of these diseases is marked international variation in both mortality (2, 3) and incidence (4, 5), as well as increases in mortality and incidence over time (6–10). There is also limited evidence that mortality from non-Hodgkin's lymphoma among persons who migrate, and subsequent generations as well, more closely resembles that in the host country than that in the country of origin (11, 12). Although methodological problems of accurately describing the occurrence of non-Hodgkin's lymphoma in different populations are substantial, the degree of variation in occurrence that has been reported, both geographically and over time, focuses attention on environmental influences to explain these patterns. Indeed, a number of environmental factors have been reported to increase the risk of non-Hodgkin's lymphoma, including exposure to chemical (13–21) and immunosuppressive agents (22–24), ionizing radiation (25), and working in farming occupations (26–34).

Potentially, one of the most significant environmental and/or behavioral factors that might be considered in searching for etiological clues is diet or nutritional status. Indeed, food and drink constitute some of the most complex mixtures of substances to which humans are exposed. Exposures to specific dietary constituents may occur frequently and/or on a regular basis over prolonged periods of time, can vary substantially from place to place, and can change over time. Thus, it is natural to consider the possible influence of diet on a disease that appears to exhibit a pattern of occurrence that also varies from place to place and that has changed (increased) over time. Furthermore, there is increasing evidence to suggest that selected components of the diet (*e.g.*, fats) may be associated with the development of specific forms of cancer, most notably of the breast (35–38) and large bowel (39).

A number of mechanisms have been proposed to account for ways that diet could influence human carcinogenesis, ranging from the direct presence of carcinogens or their precursors in the diet to the alteration of natural DNA repair mechanisms (40). Probably of most relevance with regard to a possible role of diet in the etiology of non-Hodgkin's lymphoma are mechanisms which affect one or more aspects of the immune response and those which alter membrane composition or structure. There is limited evidence from animal studies that specific dietary constituents can have both types of effects. The purpose of this review is to consider the existing epidemiological findings regarding diet and non-Hodgkin's lymphoma and to comment on the plausibility of an etiological association between dietary factors and this group of diseases.

Epidemiological Findings

There is exceedingly little epidemiological evidence to suggest an etiological link between dietary factors and non-Hodgkin's lymphoma. Most of the work in this area to date has been descriptive and provides only indirect clues. There is some indication, for example, that people in upper socioeconomic groups are at an increased risk of developing non-Hodgkin's lymphoma (8, 41–43). Some such people tend to be "overnourished" in the sense of consuming excess amounts of fat and total calories. Indeed, consumption of animal protein is higher in several groups that have been shown to have higher mortality rates from lymphoma and Hodgkin's disease: populations in northern Europe, North America, and the northern United States; higher socioeconomic groups; males; farm residents; small families; and Caucasians. In contrast, poor nutrition, which is often a consequence of underprivilege, may adversely affect the development of an effective immune response (44) and thus conceivably could influence the risk of lymphoma as well.

To date there have been only two epidemiological studies conducted that were specifically designed to investigate the relationship between diet and non-Hodgkin's lymphoma. The

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first was an international correlational study (2). Age-standardized death rates for the period 1963–1965 for non-Hodgkin's lymphoma, Hodgkin's disease, and all cancer combined were correlated with per capita protein consumption data for 15 developed countries. A significant positive correlation was found between deaths from lymphoma and per capita consumption of animal protein. Protein from nine sources (food groups) was considered in these analyses, as well as total protein. The correlation was strongest for bovine sources of protein and remained significant even when the outlying country with lowest protein consumption (Japan) was excluded from the analysis. Similar correlations were not observed for other foods or for cancer in general.

The second study was a hospital-based case-control study of non-Hodgkin's lymphoma conducted in northeastern Italy (45). It was designed to investigate the role of life-style and, in particular, dietary habits. Prediagnostic dietary histories were obtained from 208 cases of histologically confirmed non-Hodgkin's lymphoma and approximately twice that number of control subjects. The frequency of consumption per week of 14 selected food items was ascertained, along with information regarding the consumption of alcoholic and other types of beverages and smoking status. A significant increase in risk was associated with a high consumption of liver, milk, butter, and oil (chiefly polyunsaturated). These results were not substantially changed after adjustment for age, sex, education, weight, and smoking status. A significant reduction in the risk of non-Hodgkin's lymphoma was associated with the consumption of whole-grain bread and pasta. The consumption of cured meats, salami, sausages, and margarine was associated with a modest increase in risk, whereas a high consumption of green vegetables and carrots showed a slight reduction in risk.

A recent cohort study (46) derived from 11.5 years of follow-up of 15,914 individuals in Norway reports a similar association with milk consumption. A strong and significant positive association was observed between milk consumption (two or more glasses/day) and cancer of the lymphatic system (odds ratio, 3.4; 95% confidence interval, 1.4–8.2). This increase in risk was strongest among those cases classified as lymphosarcoma (as opposed to reticulum cell sarcoma or other unspecified types). This relationship was restricted primarily to nonsmokers and was stronger among subjects born in urban areas.

Biological Plausibility

There is some evidence from laboratory studies to suggest that dietary components can affect the development of lymphoma. In fact, the correlational study reported by Cunningham (2) appears to have been motivated largely by some intriguing results in rats reported more than a decade earlier. Ross and Bras (47) attempted to evaluate lifelong tumor incidence patterns in a large closed population of Charles River rats in which nonfood substances or known carcinogens were purposefully avoided in the diet and environment. They constructed five lifelong, uniform dietary regimens that varied only in the levels of proteins, calories, and sucrose. Of 934 rats, 644 were observed until their natural death. The remaining 290, chosen at random, were sacrificed at seven different age periods between 100 and 995 days. Age-specific incidence rates and rate ratios were calculated by tumor type to assess nutritional effects.

Within each of the five feeding regimens, rats of heavier weight had higher tumor incidence. Malignant lymphomas were predominant in rats with high protein intake. In two groups with identical caloric intake, the risk for all tumor types was similar, but the group with higher protein intake had a higher risk of lymphoma.

A number of other potential clues can be gleaned from additional laboratory studies since that time. Immune resistance in the mouse can be either increased or decreased, depending upon the timing and severity of nutritional deprivation (48). This is particularly evident with regard to dietary protein. In experiments in which cellular immunity was measured, limiting a single essential amino acid in the diet resulted in profound depression of immune responses (48). Such changes have been shown to affect the immune resistance of the host animal to tumor growth.

Changes in dietary fat have been shown to alter membrane phospholipid fatty acid composition in a variety of cellular and subcellular membranes, resulting in altered membrane function (49–51). In lymphocytes, such alterations could lead to impaired immune function and, perhaps, impaired immune surveillance.

ω-6 polyunsaturated fatty acids have been reported to increase the incidence and growth of experimental tumors (52). In contrast, recent studies in which fish oils were used as sources of ω-3 fatty acids have suggested that these fatty acids either have no enhancing effect or inhibit the development of carcinogen-induced tumors. Yam and colleagues (52) recently confirmed this finding regarding ω-3 fatty acids in relation to EL4-lymphoma in mice.

Finally, there is considerable evidence that polyunsaturated fatty acids have an immunosuppressive effect. Diets rich in polyunsaturated fatty acids are more effective than diets rich in saturated fat in enhancing tumorigenesis in animals (53–54). The immune system appears to be sensitive to both the quantity of fat in the diet and the degree of saturation.

If diet is indeed related to the development of non-Hodgkin's lymphoma in humans, do these results from animal studies suggest a plausible biological mechanism? It has long been thought that prolonged stimulation of the immune system may be causally related to the development of lymphoma (55). Food is the largest single antigenic challenge facing the human immune system and is operative on a regular and prolonged basis. There is evidence that intact macromolecules, sufficient in size to be antigenic, pass through the epithelium of the gastrointestinal tract, interact with the mucosal immune system, and gain access to the circulation (56). Antigenic proteins that pass through the mucosal endothelium elicit an immune response, resulting in active secretion of specific antibodies into the gut (mostly of the IgA type). Abnormalities, *e.g.*, excessive animal protein in the diet, perhaps could lead in this way to increased, chronic antigenic stimulation.

Cunningham (2) has proposed that such forms of chronic antigenic stimulation through absorption of food antigens might be directly related to the development of lymphoma. He has further suggested that bovine proteins may be especially potent lymphoid stimulants, a fact perhaps of particular relevance given the recent case-control (45) and cohort (46) findings regarding milk. Alternatively, it has been suggested that chronic lymphoid stimulation of this type may serve as a cofactor, or act in concert with other factors such as oncogenic viruses or genetic susceptibility, to increase the risk of non-Hodgkin's lymphoma.

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Concluding Thoughts

In summary, there is some intriguing evidence from studies in rats and mice that changes in diet, particularly regarding animal protein and fats, can affect immune response and even growth and development of lymphomas. Reasonable biological mechanisms have been proposed to account for such effects. To date, little epidemiological evidence exists to either corroborate or refute these findings. Descriptive studies of non-Hodgkin's lymphoma suggest that there is considerable variation in occurrence worldwide and that there has been a substantial increase in these diseases in recent years. Such patterns would be consistent with etiological factors that covary in a similar manner and have led to the investigation of a number of environmental influences, including diet. Evidence is now beginning to emerge that suggests that specific components of the diet, perhaps protein in particular, may be associated with an increased risk of non-Hodgkin's lymphoma.

Dietary factors may be a logical point of focus in attempting to explain large geographical differences in the occurrence of lymphomas or changes in lymphoma incidence over time. If specific constituents of the diet do affect lymphoma risk, variations in the basic composition of the diet in different populations, or systematic changes in dietary composition over time, might result in some of the patterns currently being observed. At present, however, one can only speculate on the degree to which dietary factors are related to the development of lymphoma and, therefore, the degree to which such factors might account for the increasing incidence of non-Hodgkin's lymphoma over time. Nevertheless, there is probably sufficient suggestive evidence to warrant additional investigation in this area. Of particular interest may be the influence of nutritional factors working in combination with other factors (*e.g.*, viruses), perhaps to increase susceptibility to the development of non-Hodgkin's lymphoma. In addition, future studies must be designed to investigate specific histological subtypes of lymphoma or groupings of related types, for it may be that dietary influences are somewhat specific in their actions.

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