CEBP Focus: Update on Lymphoma

Obesity, Diet and Risk of Non-Hodgkin Lymphoma

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Abstract

Non-Hodgkin lymphoma (NHL) represents a group of heterogeneous diseases that significantly vary in their causes, molecular profiles, and natural progression. In 2007, there will be ~59,000 newly diagnosed NHL cases in the United States and over 300,000 cases worldwide. Although new therapeutic regimens are minimizing the number of deaths related to NHL, causes for the majority of lymphomas remain undetermined. Recent studies suggest that dietary factors may contribute to the rising rates of NHL. This review will summarize epidemiologic reports that have studied the relationship between obesity, physical activity, and diet and risk of NHL. Based on a number of case-control and prospective cohort studies, overweight/obesity probably increases the risk of NHL, whereas moderate physical activity may reduce risk. Several studies support an inverse association between intakes of vegetables and NHL risk, particularly for the consumption of cruciferous vegetables. This may relate to the induction of apoptosis and growth arrest in preneoplastic and neoplastic cells, two important actions of isothiocyanates found in cruciferous vegetables. Studies also suggest that fish intake may be inversely associated with risk of NHL, although findings have not been entirely consistent. This may relate to the high organochlorine content in some fish that could override a protective effect. High consumption of fats, meat, and dairy products also may increase lymphoma risk. The accumulated scientific evidence concerning the associations between obesity, diet, and NHL suggests several identified modifiable risk factors that might be recommended to decrease lymphoma risk. (Cancer Epidemiol Biomarkers Prev 2007;16(3):392–5)

Introduction

Worldwide, longer life spans have led to increases in morbidity and mortality as a result of chronic, lifestyle-influenced diseases that may include cancers such as non-Hodgkin lymphoma (NHL). There has been a global rise in NHL over the past several decades, although reasons for this increase are unclear. Factors that enhance proliferation and survival of B cells, such as autoimmune disease and infection, have been associated with lymphoma risk. Recent studies also suggest that obesity and diet may contribute to these rising rates. Obesity results in pathologic states of inflammation and altered immune responses and has been associated with several cancers. Furthermore, diet may influence cancer risk through exposure to dietary carcinogens or through its effects on hormonal and metabolic responses to cell growth and survival. Particularly relevant to lymphoma, the diet imposes substantial antigenic challenges to lymphoid tissue in the gastrointestinal tract that can alter immune-system responses. This review will summarize epidemiologic reports that have studied the relationship between obesity, physical activity, and diet and risk of NHL.

Role of Obesity and Risk of Lymphoma

Several case-control and prospective cohort studies have examined the role of obesity and risk of NHL (Supplementary Table S1) and found fairly consistent evidence that obesity [body mass index (BMI), weight (kg)/height (m^2) ≥30] was associated with elevated risks of NHL, diffuse large B-cell lymphoma (DLCL), follicular lymphoma (FL), and chronic lymphocytic leukemia. Pan et al. also reported that high caloric intakes increased risks for FL, small lymphocytic lymphoma (SLL), and other subtypes, but not for DLCL. Two other large case-control studies found increased risks of DLCL associated with morbid obesity (BMI ≥ 35). However, one large hospital-based cohort study of black and white male veterans in the United States by Samanic et al. found no associations between BMI and NHL, but positive associations were reported for chronic lymphocytic leukemia. Of further note, a large prospective study of >900,000 U.S. adults found that obesity was positively associated with risk of NHL mortality in men (RR, 1.56; 95% CI, 1.29-1.87) and in women (RR, 1.95; 95% CI, 1.39-2.72; ref. 1). In general, these studies support a role for obesity in NHL-related morbidity.

Inconsistencies in NHL-obesity associations among some of the studies may relate to differences in study design, geographic locale, or small numbers. For instance, the hospital-based study by Samanic et al. used a discharge diagnosis of obesity to identify obese individuals, suggesting that the study population could include a disproportionate number of morbidly obese, unhealthy individuals likely to die from conditions other than lymphoma, such as heart attack or stroke. Furthermore, hospital-based populations, in general, do not accurately reflect the general population and, depending on study design, include more smokers, drinkers, and less healthy individuals. Inconsistent risk estimates in studies from different geographic regions also could reflect dietary and other lifestyle differences that may influence disease risk.

Associations have also been reported between NHL and polymorphisms in obesity-related genes such as leptin (*LEP*) and leptin receptor (2, 3), key regulators of energy balance and immune function. Of note, polymorphisms in the *LEP* gene

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(−2548G>A, 19A>G), associated with high circulating leptin levels, were identified as susceptibility loci for NHL in two independent studies (2, 3). Obesity promotes a state of low-grade, chronic inflammation and increased production of proinflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-α, IL-1b, and leptin. These cytokines can deregulate T- and B-cell responses and enhance B-cell proliferation and survival, factors that may provide a milieu that favors lymphomagenesis.

Physical Activity and Risk of Lymphoma

Few studies have examined the role of exercise relative to lymphoma risk. In a cohort study of women in the United States, low physical activity was associated with an increased risk for FL (OR, 1.8; 95% CI, 0.9-3.6), consistent with two large case-control studies based in the United States and Canada. The U.S. study found that vigorous leisure-time physical activity was associated with a reduced risk of NHL (OR, 0.79; 95% CI, 0.60-1.04), particularly DLCL (OR, 0.60; 95% CI, 0.40-0.88; ref. 4). In the Canadian study, moderate physical activity was associated with reduced risk of NHL, with a stronger inverse association with FL and SLL than with DLCL (5). Overall, these studies suggest that low physical activity increases the risk of NHL, and that moderate exercise may reduce risk.

Diet and Risk of Lymphoma

Dairy. International correlation studies show a positive association between consumption of the nonfat portion of milk and NHL mortality, consistent with reports of increased lymphoma risk associated with milk consumption in studies from Norway, the United States, and Italy (6-9). Positive associations also have been reported between NHL and intakes of butter or margarine, cream soups, ice cream or milkshakes (9), cheese (10, 11), and dairy products (12). However, the Canadian, Swedish, and another U.S. study (13) found no association with milk consumption.

Mechanisms remain to be resolved for the link between dairy consumption and NHL. One potential mechanism could involve inhibition of $1,25(OH)_2D$ production (the biologically active form of vitamin D) by the calcium in dairy products. $1,25(OH)_2D$ is considered an anticarcinogen because it promotes differentiation and apoptosis and inhibits cell growth in preneoplastic and neoplastic cells. Inverse associations between vitamin D intake (14) and UV sunlight exposure (15) and NHL risk lend further credence to the hypothesis that vitamin D might protect against NHL, although more evidence is needed to establish a causal role of vitamin D deficiency.

Dairy fat contains significant levels of organochlorines such as dioxins and polychlorinated biphenyls, known human carcinogens and immunotoxins that can alter normal B-cell responses. Positive associations between organochlorines and NHL suggest a role of dairy fat in lymphomagenesis. Finally, bovine leukemia virus associated with lymphosarcoma in cattle may be transmitted through milk to humans, although there is no clear evidence of human infection. Further studies are warranted that include examination of calcium and dairy fat intakes and the potential relevance of bovine leukemia virus infection in risk of NHL.

Meat. Several studies reported associations with red meat or meat protein consumption in risk of NHL (reviewed in ref. 16). More recently, the Nurses' Health Study (17) and several case-control studies reported positive associations between red meat (18), processed meat (11), fried red meat (12), and animal protein (9) intake and NHL risk. Three case-control studies, two from the United States (8, 19) and one from Japan (18), found no associations with red meat intake and NHL, although Cross et al. found a marginally elevated risk for NHL associated with broiled meat (OR, 1.32; 95% CI, 0.99-1.77). Furthermore, they reported that animal protein was inversely associated with NHL (OR, 0.39; 95% CI, 0.22-0.70). Although a suggestive link exists between meat consumption and risk of NHL, more data are needed to clarify this association.

Fish. Reports of fish consumption and risk of lymphoma have varied. A number of studies (13, 20, 21) found statistically nonsignificant decreased risks for NHL associated with high fish consumption. Furthermore, Fritschi et al. found that those in the highest versus lowest quartile of proportion of fat from fresh fish and those that had worked in the fishing industry had significant reductions in NHL, leukemia, and multiple myeloma. A Japanese study reported an inverse association between fish intake and NHL in women (OR, 0.6; 95% CI, 0.46-0.99; ref. 18), consistent with findings from a U.S.-based case-control study (9). However, two large case-control studies did not support associations between fish consumption and risk for NHL, although odds ratios were not reported by sex or for high versus low percent fat intake from fish (11, 12). Furthermore, the Nurses' Health Study found no association between fish ω-3 fatty acid intake and risk of NHL, although the number of cases in quintiles was small (17). Overall, the evidence is inconclusive but suggests that an inverse association between fish consumption and NHL exists. Possible reasons for discrepancies across studies may reflect varying levels of organochlorine pesticides and polychlorinated biphenyls compounds that have been associated with NHL. Thus, adverse health effects related to their high content in some fish may diminish the otherwise protective effects conferred by fish consumption.

Fat. Positive associations between saturated fat consumption and NHL were reported in two large case-control studies (9, 11) and two cohort studies (13, 17), whereas another case-control study found positive associations between NHL and oil, mainly polyunsaturated (6). Studies that stratified by subtype found that this association was particularly evident for DLCL but not FL (9, 11). Trans-unsaturated fats (17) and animal fat (13, 19) also were associated with increased risks. Furthermore, two studies found positive associations with monounsaturated fats (11, 13), although two studies found protective effects for NHL and DLCL for high consumption of polyunsaturated fats (9, 14). These studies provide fairly strong evidence of an association between high fat intake and NHL risk, although questions remain as to whether effects of fat differ by level and form of saturation. Saturated fats can modulate immune function by enhancing nuclear factor-κB activation and antiapoptotic behavior in T cells, and increasing expression of proinflammatory agents such as IL-6, cyclooxygenase-2, and inducible nitric oxide synthase. On the other hand, ω-3 fats, such as from fish oil, inhibit production of proinflammatory arachidonate-derived agents and up-regulate apoptosis in T lymphocytes.

Fruits and Vegetables. There is increasing evidence to suggest that high vegetable intakes may reduce the risk of NHL. Specifically, NHL risk was inversely associated with vegetable intake, particularly of green leafy and cruciferous vegetables in a U.S. case-control study (22). Consistent with these findings, the U.S. Nurses' Health Study found that vegetables, particularly cruciferous vegetables, were associated with reduced NHL risk (17), and an Italian group (10)

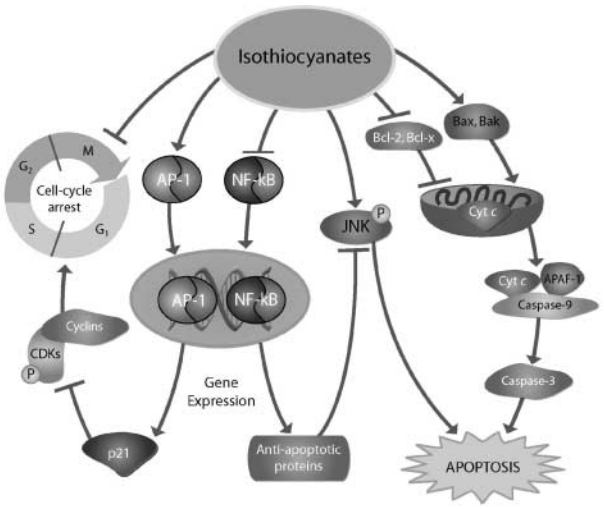

Figure 1. Mechanisms of apoptosis and growth arrest by isothiocyanates. Isothiocyanates induce apoptosis and growth arrest involving a number of mechanisms, which may be particularly relevant in preventing lymphomagenesis and other neoplasms. Some potential mechanisms may involve their ability to inhibit the antiapoptotic proteins, Bcl-2 and Bcl-x, and up-regulate the proapoptotic molecules, Bax and Bak, initiating apoptotic cell death through cytochrome *c* release and the subsequent activation of caspases. Isothiocyanates also can promote apoptotic cell death through the up-regulation of c-Jun N-terminal kinase (*JNK*) and down-regulation of nuclear factor-κB (*NF-kB*) signaling pathways. These compounds also may induce cell cycle arrest by the induction of activator protein 1 (*AP-1*) resulting in up-regulation of the cyclin-dependent kinase (*CDK*) inhibitor, p21, and subsequent G_2-M arrest.

reported inverse associations for vegetable (OR, 0.49; 95% CI, 0.28-0.87) and fruit intakes (OR, 0.51; 95% CI, 0.30-0.85). In a U.S. case-control study of women (9), high intakes of tomatoes, cruciferous vegetables, lettuce, and fiber were associated with significant reductions in NHL risk. Furthermore, two Swedish and Japanese case-control studies found a variety of vegetables including cruciferous vegetables inversely associated with NHL risk although this was limited to women (12, 18). In contrast, a U.S. case-control study found that green vegetables, carrots, and citrus fruit intakes were inversely associated with NHL risk in men (8).

Overall, intakes of vegetables, particularly of cruciferous vegetables, were inversely associated with lymphoma risk. Green leafy vegetables contain high levels of lutein, a potent antioxidant that may protect cells from free radical damage. They are also rich in vitamins, particularly folate, which provides one-carbon units for normal DNA synthesis, repair, and methylation processes. Folate deficiency has been associated with chromosomal damage and increased cancer risk. Cruciferous vegetables contain indole-3-carbinol and isothiocyanates, compounds that have multiple anticarcinogenic properties (Fig. 1). Furthermore, indole-3-carbinol ameliorates the effects of estrogen in estrogen-dependent tissues, a factor that may be related to the observed sex-specific differences in disease risk in some studies.

Vitamins. Epidemiologic data relating vitamin intake to NHL risk are limited and somewhat inconsistent (8, 9, 14, 17, 21-23). This may be attributed to differences in study design or measurement error as, in some studies, vitamin intakes were based on food intake estimates. However, reported associations between NHL and genetic polymorphisms in folate-metabolizing genes such as 5,10-methylenetetrahydrofolate reductase, thymidylate synthase, and methionine synthase (24, 25) suggest etiologic involvement of one-carbon metabolism and its related dietary exposures (Fig. 2). Although genetic studies suggest that folate influences risk of lymphoma, recent evidence suggests that the influence of gene variants on disease risk may be modified by folate status. Thus, studies are needed that consider interactions between folate status and relevant genetic polymorphisms to establish the role of folate in lymphomagenesis.

Conclusions

In summary, there is increasing evidence, based on case-control and prospective cohort studies, that obesity increases NHL incidence and that moderate physical activity may reduce NHL risk. Epidemiologic studies suggest that common dietary exposures are likely to influence lymphoma risk. Cruciferous vegetable and fish intakes may reduce risk for NHL, which seems to be more evident in women than in men. However, fish with high organochlorine content could obviate

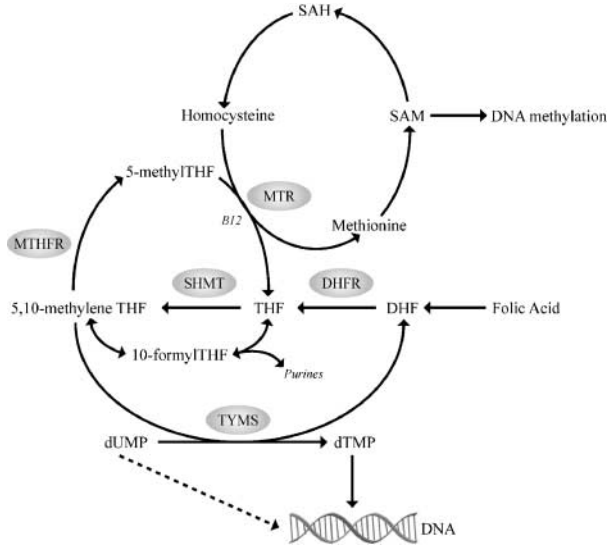

Figure 2. Overview of the folate metabolic pathway. Abnormal one-carbon metabolism, either through folate deficiency or through polymorphisms in folate metabolizing genes, may promote lymphomagenesis through mechanisms involving aberrant DNA synthesis, repair, and methylation (hypomethylation of proto-oncogenes or hypermethylation of tumor suppressor genes). A 677C>T (222Ala>Val) polymorphism in the *MTHFR* gene, associated with reduced 5,10-methylenetetrahydrofolate reductase (*MTHFR*) enzyme activity, may cause DNA hypomethylation, whereas increasing the flux of one-carbon units available for purine and DNA synthesis and repair. Reduced TYMS enzyme activity may increase uracil incorporated in DNA and result in chromosome damage and fragile site induction. A 28-bp double repeat in the promoter region and a 6-bp deletion in the 3′-untranslated region of the *TYMS* gene alter *TYMS* gene expression and mRNA stability that can influence the rate of DNA double-strand breaks and chromosomal translocations. *SAM, S*-adenosylmethionine; *SAH, S*-adenosylhomocysteine; *THF,* tetrahydrofolate; *SHMT,* serine hydroxymethyltransferase; *5,10-methylene THF,* 5,10-methylenetetrahydrofolate; *5-methyl THF,* 5-methyltetrahydrofolate; *MTR,* methionine synthase; and *TYMS,* thymidylate synthase.

a protective effect. There is some evidence that dairy and red meat consumption are positively associated with NHL, but these associations will need further investigation.

Based on epidemiologic reports, there is growing evidence that diet plays a role in lymphomagenesis. Pooled analyses through consortia will be needed to more thoroughly investigate associations between lymphoma and dietary, lifestyle, and relevant genetic factors and to provide sufficient power to examine gene-environment interactions. Mechanistic studies also will be needed to shed light on how these factors may modulate initiation and progression. Results of these studies should substantially advance our current understanding of the relationship of diet and lymphoma risk that can be translated into prevention and treatment programs aimed at reducing the public health burden of NHL worldwide.

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