



Risk of lymphoma subtypes and dietary habits in a Mediterranean area



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ABSTRACT

Background: Previous studies have suggested that diet might affect risk of lymphoma subtypes. We investigated risk of lymphoma and its major subtypes associated with diet in the Mediterranean island of Sardinia, Italy.

Methods: In 1998–2004, 322 incident lymphoma cases and 446 randomly selected population controls participated in a case-control study on lymphoma etiology in central-southern Sardinia. Questionnaire interviews included frequency of intake of 112 food items. Risk associated with individual dietary items and groups thereof was explored by unconditional and polytomous logistic regression analysis, adjusting by age, gender and education.

Results: We observed an upward trend in risk of lymphoma (all subtypes combined) and B-cell lymphoma with frequency of intake of well done grilled/roasted chicken (p for trend=0.01), and pizza (p for trend=0.047). Neither adherence to Mediterranean diet nor a frequent intake of its individual components conveyed protection. We detected heterogeneity in risk associated with several food items and groups thereof by lymphoma subtypes although we could not rule out chance as responsible for the observed direct or inverse associations.

Conclusions: Adherence to a Mediterranean diet does not seem to convey protection against the development of lymphoma. The association with specific food items might vary by lymphoma subtype.

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Abbreviations: BMI, body mass index; Cas, cases; CLL, chronic lymphocytic leukaemia; ctrl, controls; DLBCL, diffuse large B-cell lymphoma; EPIC, European prospective investigation of diet and cancer; FL, follicular lymphoma; HCAs, heterocyclic amines; HL, Hodgkin lymphoma; MM, multiple myeloma; NHL, non Hodgkin lymphoma; OR, odds ratio; 95% CI, 95% confidence intervals; PAHs, polycyclic aromatic hydrocarbons; Q1–Q5, quantiles, approximate; WHO, World Health Organization.

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1. Introduction

Diet might intervene in the development of lymphoma through antigenic stimulation of lymphoid tissue in the gastrointestinal tract due to the effect of specific nutrients, resulting in changes in the immune system response [1]. However, in spite of a few reports of an increasing risk [2,3], overall, results on red meat are not convincing of its involvement in NHL risk, irrespective of cooking method and grade of doneness, including those typically leading to the formation of heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) [4–8]. Likewise, intake of dairy products has been reported as a risk factor in some studies [8,9], but not in a large prospective trial conducted in Europe [7]. On the other hand, subjects reporting a high fat fish intake run a lower risk of NHL as well as all the other lymphatic cancer in a Canadian study [10], while fresh fruits and vegetables might convey protection [2,3,11,12].

Because of its balanced supply of nutrients, the Mediterranean diet is considered to prevent against chronic degenerative diseases, including cardiovascular diseases and cancer [13]. However, in an Italian case-control study, typical Mediterranean diet items, such as pasta and rice, showed an association with NHL risk, while fruits and vegetables showed an inverse association [14].

The Mediterranean island of Sardinia, Italy is home for the highest rate of male centenarians in the world, and diet, together with genes and physical activity, is thought to have contributed [15]. We used the epidemiological data collected in a case-control study conducted in central-southern Sardinia (Italy) in 1998–2004 to explore whether food items typical of a Mediterranean diet might affect risk of lymphoma and its most prevalent subtypes.

2. Materials and methods

Details on the study design can be found elsewhere [16]. Briefly, incident cases were enrolled in two referral centres for diagnosis and treatment of haematological malignancies in the region. Histological diagnosis and slides were available for review for 70.1% of cases. A panel of pathologists (coordinated by MR) reviewed the slides of 25% of the cases with available slides, to apply the 2008 WHO classification of lymphomas. Overall, the study population comprised 322 lymphoma cases (all subtypes combined), including 186 B-cell lymphoma cases, 12 T-cell lymphoma cases, 30 Hodgkin lymphoma cases, and 94 cases of not otherwise specified NHL. For the latter cases, only the diagnosis from the clinical records, and a first pathology report about the morphological features, but not immunohistochemistry, was available, because of dropout from the diagnostic work up. We included these cases in the analysis of all lymphoma subtypes combined. Controls were randomly selected within the same time frame of case recruitment among the census population of the study area, frequency matched to cases by gender, 5-year age-groups, and area (local health unit) of residence. The study protocol was approved by the Ethical Committee of the University Hospital of Cagliari, and by the Ethical Committee of the Local Health Unit N. 3, Nuoro. All study participants signed an informed consent form according to the Helsinki declaration. Participation rate was 88% among the eligible cases, and to 69.2% among the eligible controls. Trained interviewers used a semi-structured questionnaire eliciting information on the frequency of intake of 112 dietary items, categorized as never, occasional (up to once a month), 1–4 times a month, 2–6 times a week, or daily. For eight type of fresh meat items, preferred cooking method and degree of doneness, classified as rare, medium, well done, and very well done (burned on surface), were also asked. Beef, pork, horse meat and lamb were analyzed separately, and combined within the commodity definition of red meat. We selected for analysis the most frequently reported vegetable items, and we grouped separately leafy and cruciferous vegetables. Onions and garlic were the most popular condiments, and we analyzed them individually. A question on olive oil was included in the dietary questionnaire when the study was in the field, and the information was therefore available only for a subset of the study population (42 cases and 112 controls). We nevertheless mention this result, because of its a priori interest as a typical component of the Mediterranean diet. We grouped together citrus fruits, including oranges, tangerines, lemons and grapefruits, and summer fruits, including cherries, nectarines, plums, prunes, apricots, and strawberries. Nerve stimulant beverages, such as coffee, tea, and cola beverages, were analyzed individually.

Following Buckland et al. [17], we constructed a score of adherence to a Mediterranean diet by summing up the frequency score for each fresh fruit, vegetable, legume, fresh fish, shell fish and crustacean (crabs, shrimps, crayfish, lobster and similar) in our

list of dietary items, along with pasta, rice, and bread. As a variation in respect to the Buckland et al. score, we excluded white meat (poultry and rabbit) from the calculation, and used the sum of scores of the individual red meat items as a denominator, rather than a subtrahend. Besides, we did not consider dairy food items because of inconsistent opinions in the literature about these items being components of the Mediterranean diet [17,18], and because being historically an important part of the local diet and the local economy. As it concerns alcohol, only a moderate daily intake of wine, but not other alcoholic beverages, was considered to add to the Mediterranean diet score, while abstinence from wine or a more than moderate total alcohol intake did not add to the score. Olive oil was also not included as pertinent information was collected only in a fraction of the study population, and among those who provided the information 81% were daily consumer, with none having a less than weekly intake.

2.1. Statistical methods

We used unconditional logistic regression analysis to calculate the odds ratio (OR) for lymphoma (all subtypes combined), B-cell lymphoma overall, its most represented subtypes, including DLBCL, CLL, FL, and MM, and HL, associated with frequency of intake of selected food items and groups thereof, as well as the cooking method and grade of doneness of meat items. To categorize the intake of food groups, such as red meat, cruciferous vegetables, leafy vegetables and citrus fruits, we summed up the frequency score of each item in that group; then, we categorized the sum into quartiles or quintiles based on its distribution among the controls. For a few food groups, due to the concentration of study subjects in a limited set of values of such sum of scores, when a cut point between quantiles fell within one of such values, moving to one quantile all the study subjects with the same score generated a non homogeneous distribution of study subjects across the quantile categories.

To account for changes in the age, gender and socio-economic status balance between cases and controls, due to possibly differential participation refusal rates, we adjusted the ORs by age, as a continuous variables, gender and education (categorized as primary school, middle school, high school or higher education). Including other covariates, such as body mass index (BMI), alcohol intake, or smoking in the regression models resulted in only marginal changes in the risk estimates. We conducted polytomous regression analysis and used the Cochran Q test to assess heterogeneity in risk by gender and by histological subtype. We also calculated two-tail 95% confidence intervals (95% CI) of the ORs using Wald's algorithm ($e^{\beta \pm (z_{\alpha/2} \times se_{\beta})}$), and we used the Wald's test for trend to calculate the probability associated with a linear increase or decrease in the ORs, as the ratio between the regression coefficient associated with the continuous covariate of interest and its standard error. We used the 5% (two-tail) threshold value to reject chance.

The procedures followed in our study were in accordance with the ethical standards of the responsible institutional and national committee on human experimentation, and with the Helsinki Declaration of 1975, as revised in 2000 and 2008.

3. Results

Table 1 summarizes the demographics of our study populations. Obese and overweight subjects and more than moderate alcohol drinkers were more prevalent among the controls, and current smokers were slightly more prevalent among the cases. Most individual food items did not show an association with risk of lymphoma (all subtypes combined). One exception was well done

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