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Food of animal origin and risk of non-Hodgkin lymphoma and multiple myeloma: A review of the literature and meta-analysis

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ABSTRACT

Background: Several studies investigated whether the consumption of foods of animal origin affects the risk of haematological malignancies, with conflicting results. To help clarify this issue, we performed a meta-analysis of observational studies published until November 2014 that investigated the association between the consumption of foods of animal origin (red, processed and white meat, fish and seafood, dairy products and eggs) and the risk of non-Hodgkin lymphoma and its major subtypes and multiple myeloma among adults.

Methods: We calculated summary relative risks (SRR) and 95% confidence intervals (95% CI) by using random effect models with maximum likelihood estimation.

Results: Overall, 16,525 non-Hodgkin lymphoma and 3665 multiple myeloma cases from thirty-three independent studies were included. We found an association between consumption of red meat and the risk of non-Hodgkin lymphoma (SRR 1.22, 95% CI 1.03–1.44, $I^2 = 35\%$). The consumption of fish and seafood was inversely associated with the risk of multiple myeloma (SRR 0.71, 95% CI 0.51–1.00, $I^2 = 82\%$), although the between-studies heterogeneity was high. Finally, the consumption of dairy products was positively associated, with borderline significance, with the risk of non-Hodgkin lymphoma (SRR 1.26, 95% CI 0.99–1.60, $I^2 = 49\%$).

Conclusions: Foods of animal origin likely play a role in the aetiology of non-Hodgkin lymphoma and multiple myeloma, with red meat and dairy tending to increase the risk, and fish that tends to decrease

Abbreviations: RR, relative risk; CI, confidence intervals; SRR, summary relative risk.

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it. Our findings reinforce the recommendations to reduce the consumption of red meat by replacing it with vegetables, legumes and fish.

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1. Introduction

Haematological malignancies are a heterogeneous group of diseases that differ considerably among each other in terms of epidemiological characteristics, clinical behaviour and prognosis. In 2012 there were over 900,000 new cases of haematological malignancies and 570,000 deaths worldwide (Ferlay et al., 2015). Non-Hodgkin lymphoma is the most frequent type of haematological malignancy among adults. The most common type of leukaemia among adults, chronic lymphocytic leukaemia, has long been recognized as an equivalent form of small lymphocytic lymphoma, a subtype of B-cell non-Hodgkin lymphoma, from which it differs for the predominant localization of B cells in bone marrow and blood instead of lymph nodes (Campo et al., 2008). Multiple myeloma, a B-cell malignant lymphoid neoplasm derived from plasma cells, is a widespread malignancy as well, responsible of estimated 0.8% of all cancer cases and 1.0% of all cancer deaths worldwide (Ferlay et al., 2015).

The search for risk and protective factors of haematological malignancies has produced only limited evidence to date. Research has identified a few risk factors for non-Hodgkin lymphoma or some of its specific subtypes (Morton et al., 2014), including viruses (like Epstein-Barr virus, hepatitis C virus, and HIV) (Dal Maso and Franceschi, 2006; Parkin, 2011), autoimmune diseases (Zintzaras et al., 2005), some occupational exposures (Merhi et al., 2007; Cocco et al., 2010; Neasham et al., 2011), and tobacco smoking (Nieters et al., 2008; Sergentanis et al., 2013). Overall, however, the proportion of non-Hodgkin lymphoma cases that is attributable to identified exogenous factors is thought to be small (Statistics on preventable cancers, 2015). Likewise, the causes of multiple myeloma remain largely unknown despite some evidence concerning a few occupational exposures (like benzene and ethylene oxide (Cogliano et al., 2011) and ionizing radiation (Schubauer-Berigan et al., 2015) and overweight and obesity (Hofmann et al., 2013).

The hypothesis that foods of animal origin may increase the risk of haematological malignancies originated from the frequent finding of an increased incidence among people who are occupationally exposed to animals and meats, like livestock and poultry farmers, butchers and abattoir workers (Metayer et al., 1998; Moore et al., 2007; t Mannetje et al., 2008; Johnson, 2011; Beane Freeman et al., 2012). Several studies have investigated the possible link between the consumption of foods of animal origin and the risk of non-Hodgkin lymphoma and multiple myeloma in the general (i.e., non-occupationally exposed) population. Overall, this line of research has provided conflicting results, with some claims of causal association (Zhang et al., 1999; Aschebrook-Kilfoy et al., 2012; De Stefani et al., 2013) that were not confirmed in other studies (Cross et al., 2006; Daniel et al., 2012; Saberi Hosnijeh et al., 2014). The latest report of the World Cancer Research Fund/American Institute for Cancer Research (World Cancer Research Fund (W.C.R.F)/American Institute for Cancer Research, 2007) made no judgment regarding the association between diet and cancers of the lympho-haemopoietic system while noting that most published papers reported an increased risk with increasing consumption of meat, milk and dairy products.

To help clarify this issue, we performed a comprehensive review of scientific literature and meta-analysis of the studies that investigated the association between the consumption of foods of animal origin and the risk of non-Hodgkin lymphoma and multiple myeloma.

2. Material and methods

2.1. Definition of outcomes and exposures

Outcomes of interest in the present meta-analysis were non-Hodgkin lymphoma and its major subtypes (diffuse large B-cell lymphoma, follicular lymphoma, chronic lymphocytic leukaemia/small lymphocytic lymphoma) and multiple myeloma.

We considered as exposures of interest the following foods and food groups: red meat, processed meat, white meat, eggs, fish and seafood, dairy products, milk and cheese. The definition of each food group may differ across studies, and is sometimes not stated in a precise manner. For the sake of analysis, the pool of estimates used to calculate the meta-analytical measure of association between red meat and an outcome of interest included all estimates in which the exposure was reported in the original article as "red meat", regardless of whether or not a precise definition of it was given in the text. The same approach was used for the other food groups (i.e. processed meat, white meat, fish and seafood, and dairy). We listed in a supplementary Table (Appendix A) the definition of the food groups given in the papers included in the meta-analysis.

2.2. Literature search and inclusion criteria

The literature search and data analysis were conducted according to the MOOSE guidelines for meta-analysis of observational studies (Stroup et al., 2000). We searched papers that were published until November 30th, 2014, in the following databases: PUBMED, Ovid Medline, EMBASE, Google Scholar, and ISI Web of Knowledge. The literature search was performed by using all possible combinations of an exposure of interest and one of the following MeSH terms indicating an outcome of interest: "lymphoma", "leukaemia", "myeloma", "haematological malignancy/neoplasm", and "site-specific cancer/malignancy/tumour/neoplasm".

We obtained the full copy of all articles that were considered as potentially eligible for the present meta-analysis based on the title and/or the abstract. The reference lists of all retrieved papers (including those that were not eventually included in the meta-analysis) and of previously published reviews and meta-analyses were also searched to find more eligible papers.

We included in the present meta-analysis human observational studies with a cohort, case-control or case-cohort study design that provided sufficient information to estimate a measure of relative risk (RR) (incidence rate ratio, risk ratio, odds ratio, hazard ratio, standardized incidence ratio) and its 95% confidence interval (95%CI) (or another measure of statistical uncertainty, like standard errors, variance, or exact p-value of the significance of the estimates) for the association between a food (or food group) of animal origin and an outcome of interest (as specified above) among adults. We applied no time or language restrictions. We excluded ecological, cross-sectional and case series studies. We also excluded all studies of any design in which the study sample consisted (entirely or predominantly) of people aged 18 years or younger, because paediatric non-Hodgkin lymphoma have different risk factors than

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