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Multiple myeloma and family history of lymphohaematopoietic cancers: Results from the International Multiple Myeloma Consortium

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Summary

Family clusters of multiple myeloma (MM) suggest disease heritability. Nevertheless, patterns of inheritance and the importance of genetic versus environmental risk factors in MM aetiology remain unclear. We pooled data from eleven case-control studies from the International Multiple Myeloma Consortium to characterize the association of MM risk with having a first-degree relative with a history of a lympho-haematopoietic cancer. Unconditional logistic regression models, adjusted for study, sex, age and education level, were used to estimate associations between MM risk and having a first-degree relative with a history of non-Hodgkin lymphoma, Hodgkin lymphoma, leukaemia or MM. Sex, African American race/ethnicity and age were explored as effect modifiers.

A total of 2,843 cases and 11,470 controls were included. MM risk was elevated in association with having a first-degree relative with any lympho-haematopoietic cancer (Odds Ratio (OR)= 1.29, 95% Confidence Interval (CI): 1.08-1.55). The association was particularly strong for having a first-degree relative with MM (OR= 1.90, 95% CI: 1.26-2.87), especially among men (OR= 4.13, 95% CI: 2.17-7.85) and African Americans (OR= 5.52, 95% CI: 1.87-16.27).

These results support the hypothesis that genetic inheritance plays a role in MM aetiology. Future studies are warranted to characterize interactions of genetic markers with environmental exposures.

Keywords

Multiple myeloma; epidemiology; lympho-haematopoietic malignancies; family history; lymphoma

Introduction

Multiple myeloma (MM) is a rare plasma cell neoplasm with a high mortality rate. Its incidence is highest in Western countries, and lowest in parts of Asia (Ferlay, *et al* 2013). The aetiology of this cancer remains poorly understood. Several case-control studies have reported associations between family history of any cancer (Bourguet, *et al* 1985) or family history of MM (Eriksson and Hallberg 1992) and increased MM risk. In a large, Swedish population-based case-control study, first-degree relatives of MM patients had over twice the

risk of developing MM, compared to first-degree relatives of controls (Kristinsson, *et al* 2009a). Familial aggregation of MM and of MM with the premalignant state, monoclonal gammopathy of undetermined significance (MGUS), has also been documented (Bizzaro and Pasini 1990, Coleman, *et al* 2009, Greenberg, *et al* 2012, Koura and Langston 2013, Ogmundsdottir, *et al* 2005, Shoenfeld, *et al* 1982, Steingrimsdottir, *et al* 2011). In a large, population-based study in Sweden, first-degree relatives of MGUS patients had a nearly 3 times the risk of developing MM compared to first-degree relatives of controls (Risk ratio: 2.9, 95% CI: 1.9-4.3) (Landgren, *et al* 2009).

This familial clustering suggests that the aetiology of MM involves a genetic component. Genome-wide association studies have also demonstrated genetic inheritance (Broderick, *et al* 2012, Chubb, *et al* 2013). Also lending support to hypotheses of genetic inheritance are risk factors for MM, including male sex and African American race (Vangsted, *et al* 2012). Environmental exposures and lifestyle factors, including farming occupation and obesity, are also suspected to be associated with MM (Alexander, *et al* 2007). Familial clustering in close relatives could point to shared non-genetic risk factors, in addition to a genetic predisposition.

It is generally accepted that MM is a complex disease, and that multiple genes and environmental factors contribute to its aetiology. Understanding the configuration of risk in families may help to identify specific modes of inheritance. Further, examination of family history of cancer within subgroups, such as race/ethnicity or sex, may help to identify populations for which genetic inheritance is of particular importance.

With a few exceptions (Kristinsson, *et al* 2009a, Landgren, *et al* 2006), most epidemiological investigations of the association between family history of cancer and MM risk have been based on small samples, leading to low statistical power to detect patterns, especially within population subgroups. To overcome this limitation, we pooled data from 11 case-control study members of the International Multiple Myeloma Consortium to characterize the association of MM risk with family history of non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, leukaemia and MM. The large pooled data set allowed investigation of risk of MM in association with family history of MM and other lymphohaematopoietic (LH) cancer types, in association with LH cancer history in specific familial relations, and these associations within subgroups. We investigated effect modification of the overall associations by sex and age. In addition, this is one of the first analyses to investigate effect modification by race/ethnicity.

Materials and Methods

Data source and case definitions

Data from 11 case-control studies included in the International Multiple Myeloma Consortium (<http://epi.grants.cancer.gov/Consortia/single/immc.html>) (Andreotti, *et al* 2013) that had information on family history of LH cancer (leukaemia, NHL, Hodgkin lymphoma, and MM) were included.

Details of the studies are given in Table I. The studies were conducted in the United States (US) [Connecticut Study (Purdue, *et al* 2011), Molecular and Genetic Epidemiology (iMAGE) Study of Myeloma (VanValkenburg *et al* 2016), Los Angeles County Case Control Multiple Myeloma Study (LACCMM; Nuyujukian, *et al* 2014), Nebraska Study (Zahm, *et al* 1992), Population Health Study (PopHealth; Baris, *et al* 2004), University of Southern California (USC; Cozen, *et al* 2006), and Utah Study (Camp *et al* 2008)] (,); Canada (Canadian Study; Ghosh, *et al* 2011, McDuffie, *et al* 2009) and Europe [L'Etude des Facteurs environnementaux et génétiques des Lymphomes de l'Adulte (ENGELA; Orsi, *et al* 2009), Epilymph (Casey, *et al* 2006, Perrotta, *et al* 2012), Italian Multicentre (Miligi, *et al* 1999)]. Nearly all of the studies included both men and women, with the exception of the Canadian (Ghosh, *et al* 2011, McDuffie, *et al* 2009) and Connecticut (Purdue, *et al* 2011) studies, which included only men and only women, respectively. Most of the studies used population-based controls. The multi-site Epilymph study from Europe included population-based controls at the German and Italian sites, and hospital-based controls at the Irish, French, Spanish and Czech Republic sites (Casey, *et al* 2006, Perrotta, *et al* 2012). The French study, ENGELA (Orsi, *et al* 2009), enrolled hospital-based controls. The Utah study included spouses of cases as controls, as well as population-based controls. Most studies matched controls to cases based on age, sex, geographic region and/or vital status.

Cases were patients with a primary diagnosis of MM and were identified through cancer registries or hospitals in the individual studies. With the exception of the Utah study, where cases were predominantly prevalent rather than incidental, all studies enrolled incidental MM cases.

Explanatory variables

Data on family history of LH cancers were derived from either in-person or telephone interviews, conducted using structured questionnaires. Participants were either prompted for the type of cancer that affected a first-degree relative using a defined list of cancer types or asked about family history of cancer as an open-ended question (Table I).

Harmonized variables across all studies were created for family history of LH cancer in a first-degree relative. Family history of each of the following were considered as individual explanatory variables: MM, leukaemia, NHL and Hodgkin lymphoma family history of MM excluding cancers of the bone. Family history of leukaemia included acute lymphoblastic leukaemia, acute myeloid leukaemia, acute T-cell, and chronic lymphocytic leukaemia (CLL). In addition to considering associations of MM risk with family history of these individual LH cancer types, a composite variable describing having a first-degree relative with any LH cancer (MM, leukaemia, NHL, Hodgkin lymphoma) was created. Variables available to create the composite family history variable differed across studies, due to differences in questionnaires and reporting. First degree relatives with the following cancers were also included in the composite LH cancer definition: cancers of the blood, bone, bone marrow, corpuscles, lymph glands, neck-side, neck glands, plasmacytoma, Sezary syndrome or spleen. The LH cancer definition excluded sarcoma. In the Epilymph study, a handful of participants reported a family history of MM or Hodgkin lymphoma, but most self-reported

family cancers were coded within the Epilymph study as “hematologic cancer not otherwise specified.” Therefore, individual types of LH cancer were not coded for the Epilymph study.

In analysis, associations of MM risk with a history of LH cancer in a parent, sibling, child, male first-degree relative and female first-degree relative were explored. Having a son and having a daughter with a LH cancer history were also considered as explanatory variables; results from these analyses are not presented because of the small number of such occurrences. Age of the first-degree relative at the time of diagnosis of LH cancer (<55 versus 55+ years) and the number of relatives (1 versus > 1) with any LH cancer were also investigated as explanatory variables. Cut-off points for the latter two variables were based on sample size considerations and hypotheses about associations. In all analyses, the referent category consisted of participants who did not have any first-degree relative with a history of a LH cancer.

Statistical analysis

Unconditional logistic regression models were used to calculate odds ratios (OR) and 95% confidence intervals (CI) as estimates of association of family history of LH cancers with risk of MM. Sex and age were included as covariates in all analytic models. Age was entered into the models using linear and quadratic terms (continuous age + continuous age²). This coding was selected by using likelihood ratio tests to compare the goodness-of-fit of models with different functions of age. Additionally, models were adjusted for education (less than high school graduate versus high school graduate or more), which has been shown to contribute to specificity of self-reported family history of cancer (Chang, *et al* 2006). A term designating study was also included in all models.

Sex, African American race (African American/Black versus European American/White), and age of the MM case at diagnosis (<55 versus 55+ years) were investigated as effect modifiers by including them in interaction terms with the main explanatory variables (e.g. age x family history of MM). Age was investigated as a modifier based on the hypothesis that stronger associations of MM risk with family history of LH cancer among patients diagnosed at younger ages might indicate a detection bias or a genetic component to MM aetiology. Likelihood ratio tests were used to assess effect modification by comparing nested models with and without interaction terms.

Assessment of heterogeneity and sensitivity analyses

Likelihood ratio tests of interaction terms between each explanatory variable and a term for study were also used to assess heterogeneity across studies. We examined the effect of removing each individual study on the overall pooled estimates. The ENGELA and LACCMM studies employed individual matching of controls to cases, which can introduce confounding (Rothman and Greenland 1998). Therefore, we re-ran the individual models for these studies to examine the effect of adjusting for the matching factors used. Race/ethnicity was not included as covariate in the main models, because some studies did not collect this information. We re-ran the pooled analyses, limiting data to studies that had a term for African American race/ethnicity and adjusted for this covariate. In addition, we examined the impact of including only studies that ascertained data on family history of LH cancers

through a prompted list (USC, iMAGE, ENGELA, LACCMM, Utah) versus open-ended questions (Canada, Epilymph, Nebraska, Connecticut, PopHealth, Italy). We also ran the analyses after excluding the two studies that included hospital-based controls (ENGELA and Epilymph).

All analyses were conducted using SAS 9.3 (SAS Institute, Cary, NC, USA)

Results

The pooled data consisted of 2,843 cases and 11,470 controls (Table II). A higher proportion of cases and controls were men (56.3% and 57.4%, respectively). The mean ages of cases and controls were 62.5 and 59.5 years, respectively. Cases and controls had similar education levels.

Figure 1 shows study-specific estimates of association between having a first-degree relative with a history of any LH cancer and MM risk, along with the pooled OR. Overall, having a family member with any LH cancer was associated with a higher risk of MM. In the pooled analysis, risk of MM was positively associated with having a first-degree relative with any LH cancer (OR=1.29, 95% CI: 1.08-1.55).

Figure 2 shows study-specific associations of MM risk with family history of each of the LH cancer types (NHL, leukaemia, Hodgkin lymphoma and MM), along with the pooled ORs. All study-specific OR estimates for associations with having a first-degree relative with a history of MM were 1.4 or greater, with the exception of the OR estimate from the Utah Study. Study-specific ORs could not be estimated for two studies; ENGELA had no exposed cases and the Italian study had no exposed controls. In the pooled analysis, MM risk was positively associated with having a first-degree relative with MM (OR=1.90, 95% CI: 1.27-2.88). MM risk was also elevated in those cases that had a first-degree relative with a history of NHL (OR=1.35, 95% CI: 0.91-1.99) or leukaemia (OR=1.21, 95% CI: 0.92-1.59).

Having more than one relative with a history of LH cancer was associated with a higher relative risk of MM (OR=1.67, 95% CI: 0.95-2.94, Table III) than having only one relative with a history of LH cancer (OR=1.26, 95% CI: 1.01-1.58). Having a sibling with a history of LH cancer was associated with an increased risk of MM (OR=1.56, 95% CI: 1.18-2.07). Having a female first-degree relative with a LH cancer history was more strongly associated with MM risk compared to having a male relative with a LH cancer history. This was particularly evident for relationships with sibling type; MM risk was more strongly associated with having a sister (OR=1.81, 95% CI: 1.18-2.78) than a brother (OR=1.35, 95% CI: 0.92-1.98) with a LH cancer. Risk of MM was not associated with having a parent or a child with a LH cancer history. However, having a mother with a history of LH cancer was associated with an elevated relative risk of MM (OR=1.43, 95% CI: 0.97-2.11). Age of the first-degree relative with a LH cancer history was not associated with MM.

When sex was investigated as an effect modifier, associations were generally stronger among men (Table III). Men had a strong, positive risk of MM in association with family history of MM, whereas the association for women was close to the null (men: OR=4.13, 95% CI: 2.17-7.85 versus women: OR=1.09, 95% CI: 0.62-1.90, p-value for likelihood ratio test of

interaction term: <0.01). Likewise, family history of any LH cancer was associated with an elevated risk of MM for men but not women (men: OR=1.58, 95% CI: 1.24-2.00 versus women: OR=1.01, 95% CI: 0.77-1.33, p-value for likelihood ratio test of interaction term: 0.02). Similarly, the effects of having a female relative, particularly a mother, with a history of LH cancer was restricted to men (men: OR=1.63, 95% CI: 1.13-2.35 versus women: OR=1.09, 95% CI: 0.91-1.68; p-value for likelihood ratio test of interaction term: 0.16 for female relative; men: OR=1.93, 95% CI: 1.16-3.22 versus women: OR=0.99, 95% CI: 0.55-1.79; p-value for likelihood ratio test of interaction term: 0.10 for mother).

When the pooled analyses were restricted to data from studies with African American participants, and adjusted for race/ethnicity in addition to sex, age, education and study, results were similar to those from analyses of the full data set that were unadjusted for race/ethnicity (Table IV). The association between MM risk and having a first-degree relative with a history of MM was stronger among African Americans/Blacks than European Americans/Whites (African Americans: OR=5.52, 95% CI: 1.87-16.28 versus European Americans/whites: OR=1.26, 95% CI: 0.75-2.10; p-value for likelihood ratio test of interaction term: 0.01). Also, the association between MM risk and having a female relative, particularly a mother, with a LH cancer history was stronger for African Americans than European Americans (African Americans: OR=2.71, 95% CI: 1.25-5.87 versus European Americans/whites: OR=1.23, 95% CI: 0.86-1.77, p-value for likelihood ratio test of interaction term: 0.07 for female relative; African Americans: OR=4.24, 95% CI: 1.49-12.02 versus European Americans/whites: OR=1.32, 95% CI: 0.80-2.17, p-value for likelihood ratio test of interaction term: 0.05 for mother).

Many of the associations were slightly stronger among MM cases diagnosed at younger ages (Supplementary Table 1). However, most of the differences across categories of age of diagnosis or enrolment were not substantially different.

Heterogeneity

For the most part, formal statistical tests of heterogeneity of effects across studies, which were assessed using likelihood ratio tests of interaction terms between study and the explanatory variables, indicated homogeneity; the p-values for the test of homogeneity were 0.23 or greater (a small p-value would be suggestive of heterogeneity). There was evidence of some heterogeneity in the association of MM risk with family history of MM (p-value for likelihood ratio test: 0.07). However, excluding data from the Utah study removed the suggestion of heterogeneity (p for likelihood ratio test of interaction term after removing Utah study: 0.49).

Sensitivity analyses

When models were re-run for the ENGELA and LACCM studies with adjustment for the individual level matching variables in each, the results were nearly identical to those in which models were adjusted for age, sex and education (data not shown).

For the most part, exclusion of individual studies did not substantially impact the pooled OR estimates. However, when data from the Utah study were excluded, associations with having

a family history of MM became stronger, moving from an OR=1.90, 95% CI: 1.26-2.87 to an OR of 2.71, 95% CI: 1.69-4.36.

When pooled analyses were restricted to data from studies that used an open-ended question to ascertain information about first-degree relatives' cancer type (Canada, Epilymph, Nebraska, Connecticut, PopHealth, Italy), the OR estimate of association between MM risk and family history of MM became stronger, moving from OR=1.90 (95% CI: 1.26-2.87) to OR=3.40 (95% CI: 1.88-6.14). By comparison, when analyses were restricted to include only data from studies that ascertained family history of LH cancer using a prompted list, the estimate of association between MM risk and family history of MM decreased towards the null, to OR=1.32 (95% CI: 0.75-2.30). Removing data from the two studies that enrolled hospital based controls did not cause any substantial changes in results.

Discussion

We pooled data from studies conducted in the US, Canada and several European countries to investigate associations between history of LH cancer in first-degree relatives and MM risk. Elevated risk of MM was associated with having a first-degree relative with a history of any LH cancer, and especially with a history of MM. Higher risk of MM was associated with having a female first-degree relative, a sibling, and especially a sister, with a history of a LH cancer. Most associations were stronger among men. The association between MM and having a first degree relative with a history of MM was stronger in African Americans; this is the largest analysis to show familial aggregation patterns among African Americans.

The finding of a higher risk of MM associated with a family history of LH cancer, and especially MM, is consistent with previous reports (Eriksson and Hallberg 1992, Bourguet, *et al* 1985). Associations of MM with family history of NHL, Hodgkin lymphoma and leukaemia were less substantial than with family history of MM, suggesting that the associations between MM risk and family history of any LH cancer were driven by family history of MM. This is consistent with previous research (Kristinsson, *et al* 2009a, Kristinsson, *et al* 2009b). Most associations were stronger among men, including having a family member with a history of LH cancer or a history of MM, and having a mother with a history of LH cancer. These sex-related results are somewhat in conflict with previous studies, which have found higher risk of MM in daughters of mothers with MM, and in sons of fathers with a history of MM (Lynch, *et al* 2005).

It is not clear why most associations were stronger among men. It is possible that these results reflect a sex-related reporting bias, especially among controls. A higher proportion of female than male controls reported having a family history of a LH cancer. Past validation studies have shown that females report a family history of cancer with higher sensitivity but lower specificity than men (Chang, *et al* 2006). If, in the data used in this pooled analysis, female controls reported family history with greater sensitivity and lower specificity than male controls, this could partially explain the results.

This is one of the first analyses to show that familial aggregation of MM is stronger among African Americans. Higher risk of MM in association with having a relative with a history

of LH cancer, and with a history of MM, has been observed previously in Blacks versus Whites (Brown, *et al* 1999). Rates of MM have been shown to be higher among African Americans than in European Americans/Whites. In 2011 in the US, the age-adjusted rate of MM in African Americans was more than twice the rate among European Americans/Whites (Howlander, *et al* 2015). The stronger association among African Americans could suggest genetic susceptibility to MM.

Our results are supported by evidence of genetic components to MM disease aetiology. Carriage of the hyperphosphorylated form of the paratarg-7 protein (pP-7), which is a single target protein whose function remains unknown, is a molecularly defined autosomal dominantly inherited risk factor for MGUS and MM (Grass, *et al* 2009). A higher prevalence of pP-7 carriage has been observed among African American MM patients compared to other ethnic groups, although the pP-7 carrier state is also a strong risk factor in European MM cases (Zwick, *et al* 2014). Hyperphosphorylation of other autoantigenic paraprotein targets, including paratargs 2,5,6,8,9,10 and 11, have been identified in MM patients (Koura and Langston 2013). Human leucocyte antigen (HLA) types, including HLA-Cw2 and HLA-B18, have been investigated as potentially associated with MM (Koura and Langston 2013). Additionally, genome wide association studies (GWAS) have identified regions on chromosomes 3p22, 7p15.3 and 2p23.3 as potentially associated with MM (Broderick, *et al* 2012, Koura and Langston 2013). The SNP rs2456449 polymorphism on chromosome 8q24, associated with CLL (Crowther-Swanepoel, *et al* 2010), has also been associated with MM (Campa, *et al* 2012). This could indicate common susceptibility between MM and CLL. CLL is a subtype of NHL. We observed an elevated risk of MM in association with having a first-degree relative with NHL. However, due to sample size considerations and a lack of information on NHL subtypes from all of the contributing studies, we did not evaluate the association between family history of CLL, specifically, and MM risk.

In sensitivity analyses, exclusion of data from the Utah study caused the pooled OR to increase. Also, the test of heterogeneity suggested that the Utah study contributed to heterogeneity in the estimate of association between family history of MM and MM risk. This difference in association might be due to the Utah study having included predominantly prevalent rather than incidental cases. The inclusion of predominantly prevalent cases might have caused a selection bias; by including prevalent cases, the Utah study might have included MM cases with a better prognosis and, in association with this superior prognosis, weaker inheritance patterns. There is genetic evidence that could support this theory. A GWAS study identified SNPs at chromosome 16p13 that were associated with mortality among MM patients (Ziv, *et al* 2015), suggesting that poorer prognosis might be associated with inheritance.

In support of our finding of an association between having a sibling with a LH cancer history and MM risk, several reports have shown a strong clustering of MM among siblings (Jain, *et al* 2009, Shoenfeld, *et al* 1982). However, in a population-based study in Sweden (Altieri, *et al* 2006), having parents rather than siblings with a history of MM was associated with a higher risk of MM, although the estimates of association among siblings were based on small numbers. Strong sibling risk is consistent with an aetiology that includes recessive genetic components. Other models could also be suggested, such as gene-environment

interactions with early life exposures. Thus far, such models have not been well studied for MM.

This analysis had several strengths. The large data set accommodated investigation of associations with MM within strata of sex, age, and race/ethnicity. Because this analysis was restricted to history of cancer among first-degree relatives of MM cases and controls, the participant's recall of relative's cancer history should have been fairly good, leading to less misclassification. Indeed, probands with breast, ovarian, and colorectal cancers have been shown to better recall the cancer history of first-degree versus second-degree relatives (Ziogas and Anton-Culver 2003).

Limitations in this analysis include the potential for recall bias. Cases may have more accurately recalled family history than controls and, among controls, women may have had better recall than men. We were unable to validate self-reports of family history of cancer. In an investigation of self-reports of cancer among case and population-based control participants of a study of incident malignant lymphoma in Denmark and Sweden, the sensitivity of self-reports for any cancer, and more specifically for history of haematopoietic cancer, was higher for cases than controls, but the specificity was marginally higher for controls than cases (Ahmed, *et al* 2006). If a similar phenomenon occurred in the current report, it would have inflated our effect estimates. Although our sensitivity analysis that restricted analyses to data from studies that ascertained family history of cancer type using an open-ended question suggested that the risk estimate of association with family history of MM was inflated, this could be partially a result of removing the data from the Utah Study.

Although unlikely due to the rarity of MM, it is possible that cases may have been diagnosed earlier and more frequently because of a family history of the disease. However, when age at diagnosis/enrolment was investigated as an effect modifier, the differences in associations were not substantially different for younger versus older participants. To some extent, this indicates that diagnosis bias is unlikely to explain the results. Restricting analyses to family history of MM in first-degree relatives makes it difficult to separate shared genetics from shared environmental exposures. Family history of MM in more distant relatives might be more indicative of genetic associations; however, those data are difficult to acquire outside of genealogical studies. Because most of the contributing studies did not have information on family size, we could not adjust for this variable, which could have confounded the association of family history of LH cancer with risk of MM. Finally, MGUS has been shown to be more prevalent in relatives of MM patients than in the general population (Vachon, *et al* 2009). However, we were unable to evaluate associations of MM risk with a family history of MGUS due to lack of data.

Results from this pooled analysis provide compelling evidence to support hypotheses that genetic inheritance plays a role in the aetiology of MM. Future studies should investigate the interaction of genetic markers with shared environmental exposures or lifestyle factors within families, such as pesticide use in the home environment and obesity. These results also suggest the need for further study of genetic inheritance among African Americans and identification of genetic markers that may account for associations of MM risk with family history of specific types of LH cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Forest plot showing study-specific and pooled odds ratio (OR, diamond) estimates (95% confidence interval, CI, indicated by the horizontal line) of association between multiple myeloma risk and having a first-degree relative with a history of a lymphohaematopoietic cancer. All models were adjusted for sex, age (coded using a linear and quadratic terms) and education (< high school versus high school or more). The pooled OR estimates were also adjusted for study. Abbreviations: iMAGE, Molecular and Genetic Epidemiology Study of Myeloma; LACCMM, Los Angeles County Case Control Multiple Myeloma Study; USC, University of Southern California.

A. Multiple Myeloma

B. NHL

C. Leukaemia

D. Hodgkin Lymphoma

Figure 2.

Forest plots showing study-specific and pooled odds ratio (OR, diamond) estimates (95% confidence interval, CI, indicated by the horizontal line) of association between multiple myeloma and having a first-degree relative with a history of: A) multiple myeloma, B) NHL, C) leukaemia and D) Hodgkin lymphoma. All models were adjusted for sex, age (coded using a linear and quadratic terms) and education (< high school versus high school or more). The pooled OR estimates were also adjusted for study.

Abbreviations: NHL, non Hodgkin lymphoma; NE, Not estimable; iMAGE, Molecular and Genetic Epidemiology Study of Myeloma; LACCMM, Los Angeles County Case Control Multiple Myeloma Study; USC, University of Southern California.

Table 1

Individual studies contributing to the pooled analysis

Study (reference)	Location	Year	Family history ascertainment	Cases			Controls			Matching criteria	
				N	Age at diagnosis, years: mean (SD)	Female N (%)	N	Age at enrolment, years: mean (SD)	Female N (%)		Source
Canadian Ghosh <i>et al</i> (2011); McDuffie <i>et al</i> (2009)	Canada	1991-1994	Self-administered postal questionnaire; Open-ended responses for cancer.	342	64.7 (11.1)	0	1506	54.1 (16.4)	0	P	Frequency matched to the age distribution of the entire case group of HL, MM, NHL and STS cases within each province
Connecticut Study Purdue <i>et al</i> (2011)	New Haven, CT, USA	1996-2000	In person interviews Open ended responses for cancer.	183	66.4 (11.5)	183 (100)	716	61.4 (14.3)	716 (100)	P	Frequency matched to NHL cases for a parallel study
L'Etude des Facteurs environnementaux et génétique des Lymphomes de l'Adulte (ENGELA) Orsi <i>et al</i> (2009)	France	2000-2004	Self-administered standardized questionnaires Prompted for HL, lymphoma, MM, lymphoid leukaemia, myeloid leukaemia, or leukaemia.	108	59.6 (9.1)	52 (48.2)	478	58.8 (9.0)	165 (34.5)	H	Individually matched on centre, sex, age
Epilymph Casey <i>et al</i> (2006); Perrotta, <i>et al</i> (2012)	Italy, Spain, Germany, France, Ireland, Czech Republic	1998-2004	Questionnaire administered by a locally trained interviewer Open ended responses for cancer.	278	62.4 (12.1)	120 (43.2)	2465	56.1 (16.0)	1143 (46.4)	P in Germany and Italy; H in Ireland, France, Spain, and the Czech Republic	Frequency matched by sex, age intervals, residence area
Molecular and Genetic Epidemiology (iMAGE) Study of Myeloma Van Valkenburg <i>et al</i> (2016)	University of Alabama at Birmingham, AL	2009-2013	Prompted for leukaemia, HL, NHL, MGUS, MDS and select solid tumours; open-ended responses for other cancers	259	59.9 (9.3)	117 (45.2)	461	62.5 (11.3)	252 (54.7)	P	Frequency matched on sex, race, age (± 5 years), geography
Italian Multicentre Miligi <i>et al</i> (1999)	Italy	1991-1993	In-person interviews using structured questionnaires Open-ended responses cancer.	270	62.5 (8.5)	137 (50.7)	1161	54.4 (14.1)	566 (48.8)	P	Random sample of general population, stratified by sex and 5-year age groups

	Cases				Controls			
	278	61.2 (9.0)	126 (45.3)		278	61.2 (9.0)	126 (45.3)	P (Neighbourhood)
Los Angeles County Case Control Multiple Myeloma Study (LACCMIM) Nuyujukian <i>et al</i> (2014)				Prompted for MM, leukaemia, Hodgkin disease or lymphoma				Individually matched by sex, race, date of birth within 5 years, neighbourhood of residence at case's diagnosis
Nebraska Zahm <i>et al</i> (1992)	72	68.9 (9.6)	32 (44.4)	Telephone interviews Open-ended question for cancer.	1427	67.1 (16.1)	724 (50.7)	P
Population Health Study (PopHealth) Baris <i>et al</i> (2004)	573	64.2 (10.1)	289 (50.4)	In-person interviews Open-ended responses for cancer.	2146	61.6 (11.0)	782 (36.4)	P
University of Southern California (USC) Cozen <i>et al</i> (2006)	150	58.9 (10.1)	59 (39.3)	Questionnaires administered during in-person interviews (except 65 telephone interviews conducted with relatives of cases living outside LA County) Cases prompted for family history of HL, leukaemia and myeloma. Also open-ended for other types of cancers. Controls prompted for family history of NHL, HL, leukaemia, and MM.	252	58.8 (10.5)	112 (44.4)	P
Utah Camp <i>et al</i> (2008)	330	59.7 (10.8)	128 (39.8)	Prompted for family history of NHL, MM, HL and leukaemia	580	66.2 (10.3)	296 (51.0)	Population and spouses matched by birth cohort and sex

Abbreviations: P, Population; H, Hospital; NHL, non Hodgkin lymphoma; HL, Hodgkin lymphoma; MM, multiple myeloma; MGUS, monoclonal gammopathy of undetermined significance; MDS, myelodysplastic syndrome; CLL, chronic lymphocytic leukaemia; STS, soft tissue sarcoma; USA, United States of America; SD, standard deviation.

Demographic characteristics of cases and controls included in the pooled analysis of family history of lymphohaematopoietic cancer and risk of multiple myeloma

Table II

	Cases, n (%)	Controls, n (%)
Total	2,843 (19.9)	11,470 (80.1)
Sex		
Men	1,600 (56.3)	6,588 (57.4)
Women	1,243 (43.7)	4,882 (42.6)
Age, mean ± standard deviation	62.5 ± 10.5	59.5 ± 14.7
Education		
Less than high school graduate	983 (35.0)	4,108 (36.6)
High school graduate or more	1,822 (65.0)	7,126 (63.4)

Table III

Associations between family history of lymphohaematopoietic cancer and multiple myeloma, overall and stratified by sex¹

	Males (N=8,188)				Females (N=6,125)				Total		Likelihood ratio test of the interaction term	
	Cases	Controls	OR, 95% CI	Cases	Controls	OR, 95% CI	OR, 95% CI	OR, 95% CI	OR, 95% CI	OR, 95% CI	Chi square	(p-value)
Multiple myeloma ²	25 (1.9)	20 (0.4)	4.13, 2.17-7.85	20 (1.9)	40 (1.1)	1.09, 0.62-1.90	1.90, 1.26-2.87	9.76 (<0.01)				
NHL ³	27 (2.2)	51 (1.0)	1.65, 1.00-2.73	15 (1.6)	48 (1.40)	1.02, 0.55-1.88	1.35, 0.91-1.99	1.46 (0.23)				
Leukaemia ²	49 (3.2)	117 (1.8)	1.45, 1.02-2.07	36 (3.0)	103 (2.2)	0.97, 0.64-1.46	1.21, 0.92-1.59	2.15 (0.14)				
Hodgkin lymphoma ³	9 (0.8)	36 (0.7)	0.95, 0.44-2.05	6 (0.6)	21 (0.6)	1.00, 0.39-2.60	0.97, 0.53-1.76	0.01 (0.94)				
Any LH cancer	119 (7.5)	268 (4.1)	1.58, 1.24-2.00	81 (6.5)	261 (5.4)	1.01, 0.77-1.33	1.29, 1.08-1.55	5.90 (0.02)				
1 relative ⁴	74 (5.7)	212 (3.4)	1.60, 1.20-2.12	43 (4.1)	200 (4.5)	0.92, 0.65-1.31	1.26, 1.01-1.58	5.75 (0.06)				
> 1 relative	12 (0.9)	17 (0.3)	1.66, 0.73-3.80	15 (1.4)	16 (0.4)	1.66, 0.77-3.60	1.67, 0.95-2.94					
Male relative ⁵	55 (4.7)	139 (2.5)	1.47, 1.05-2.06	34 (3.8)	138 (3.5)	0.89, 0.60-1.34	1.18, 0.91-1.53	3.52 (0.06)				
Female relative ⁵	46 (3.9)	118 (2.1)	1.63, 1.13-2.35	30 (3.4)	99 (2.5)	1.09, 0.71-1.68	1.37, 1.04-1.81	1.94 (0.16)				
Sibling ⁶	45 (3.5)	98 (1.6)	1.78, 1.22-2.60	36 (3.5)	103 (2.3)	1.35, 0.90-2.04	1.56, 1.18-2.07	0.93 (0.34)				
Sister ⁷	19 (1.7)	41 (0.8)	1.70, 0.95-3.04	16 (1.9)	36 (1.0)	1.96, 1.04-3.68	1.81, 1.18-2.78	0.10 (0.75)				
Brother ⁷	23 (2.1)	56 (1.1)	1.59, 0.94-2.67	18 (2.2)	59 (1.6)	1.12, 0.63-1.98	1.35, 0.92-1.98	0.80 (0.37)				
Parent ⁶	49 (3.8)	128 (2.1)	1.52, 1.07-2.18	27 (2.7)	117 (2.6)	0.80, 0.51-1.24	1.16, 0.88-1.53	5.14 (0.02)				
Mother ⁸	23 (1.9)	58 (1.0)	1.93, 1.16-3.22	16 (1.7)	53 (1.2)	0.99, 0.55-1.79	1.43, 0.97-2.11	2.74 (0.10)				
Father ⁸	26 (2.1)	66 (1.1)	1.29, 0.79-2.10	9 (1.0)	60 (1.4)	0.51, 0.24-1.05	0.91, 0.61-1.37	4.68 (0.03)				
Child ⁶	11 (0.9)	40 (0.7)	0.98, 0.49-1.96	7 (0.7)	33 (0.7)	0.73, 0.31-1.69	0.86, 0.50-1.47	0.28 (0.60)				
First-degree relative aged <55 years ⁹	16 (3.3)	25 (1.0)	2.22, 1.12-4.38	16 (2.6)	70 (2.5)	0.81, 0.46-1.42	1.17, 0.77-1.79	5.08 (0.08)				
First-degree relative aged ≥ 55 years	8 (1.6)	31 (1.3)	0.91, 0.40-2.06	13 (2.2)	51 (1.8)	1.00, 0.53-1.89	0.97, 0.59-1.60					

Abbreviations: MM, multiple myeloma; NHL, non Hodgkin lymphoma; LH, lymphohaematopoietic; OR, Odds ratio; CI, confidence interval

¹ All models were adjusted for study, sex, age (entered as a linear and quadratic term) and education (< high school versus high school or more). The referent categories consisted of those without any relative with any history of lymphohaematopoietic cancers among the entire cohort for the unstratified model or among women in the model with an interaction term between sex and family history variables.

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- ²Epilymph not included
- ³Epilymph and LACCCMM not included
- ⁴USC and Utah not included
- ⁵USC, Italy and LACCCMM not included
- ⁶USC and LACCCMM not included
- ⁷USC, ENGELA, Italian multicentre and LACCCMM not included
- ⁸USC, ENGELA and LACCCMM not included
- ⁹USC and Utah not included

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Table IV

Associations between family history of lympho-haematopoietic (LH) cancer and multiple myeloma, overall and stratified by African American race/ethnicity, in the subset of studies with race data¹

	African American (N=1,754)				White/European (N=5,764)				Total	Likelihood ratio test for interaction term
	Cases N (%)	Controls N (%)	OR, 95% CI	Cases N (%)	Controls N (%)	OR, 95% CI	OR, 95% CI	OR, 95% CI	Chi square (p-value)	
Multiple myeloma	12 (2.9)	5 (0.4)	5.52, 1.87-16.27	24 (2.0)	47 (1.1)	1.26, 0.75-2.10	1.69, 1.08-2.64	6.39 (0.01)		
NHL ²	1 (0.3)	6 (0.5)	0.48, 0.06-4.10	33 (3.1)	69 (1.7)	1.43, 0.91-2.24	1.34, 0.87-2.08	1.16 (0.28)		
Leukaemia	11 (2.6)	26 (2.0)	1.30, 0.63-2.70	49 (3.9)	124 (2.9)	1.20, 0.83-1.73	1.22, 0.88-1.70	0.04 (0.84)		
Hodgkin lymphoma ²	3 (0.9)	2 (0.2)	3.13, 0.52-18.90	10 (1.0)	39 (1.0)	1.11, 0.53-2.32	1.29, 0.66-2.51	1.12 (0.29)		
Any LH cancer	26 (6.0)	47 (3.6)	1.57, 0.95-2.60	121 (9.2)	310 (7.0)	1.23, 0.97-1.56	1.28, 1.03-1.59	0.75 (0.39)		
1 relative ³	17 (4.3)	37 (3.0)	1.44, 0.79-2.63	56 (6.0)	212 (5.7)	1.19, 0.86-1.64	1.24, 0.93-1.65	1.33 (0.51)		
>1 relative	6 (1.5)	5 (0.4)	2.68, 0.77-9.31	16 (1.7)	22 (0.6)	1.27, 0.61-2.63	1.53, 0.81-2.89			
Male relative ⁴	9 (2.8)	26 (2.2)	1.05, 0.48-2.29	52 (5.2)	167 (4.2)	1.07, 0.76-1.51	1.07, 0.78-1.46	0.00 (0.96)		
Female relative ⁴	12 (3.6)	16 (1.4)	2.71, 1.25-5.87	46 (4.6)	135 (3.4)	1.23, 0.86-1.77	1.41, 1.01-1.95	3.14 (0.07)		
Sibling ⁴	9 (2.8)	16 (1.4)	1.83, 0.79-4.26	42 (4.2)	119 (3.0)	1.38, 0.93-2.04	1.45, 1.02-2.06	0.35 (0.55)		
Sister ⁴	5 (1.6)	7 (0.6)	2.53, 0.77-8.26	19 (2.0)	53 (1.4)	1.45, 0.82-2.55	1.60, 0.96-2.66	0.68 (0.41)		
Brother ⁴	5 (1.6)	10 (0.9)	1.49, 0.50-4.49	23 (2.4)	72 (1.9)	1.20, 0.71-2.02	1.25, 0.78-2.00	0.12 (0.73)		
Parent ⁴	11 (3.3)	21 (1.8)	1.66, 0.78-3.54	46 (4.6)	140 (3.6)	1.07, 0.74-1.53	1.15, 0.83-1.60	1.06 (0.30)		
Mother ⁴	8 (2.5)	7 (0.6)	4.24, 1.49-12.02	24 (2.5)	64 (1.7)	1.32, 0.80-2.17	1.62, 1.04-2.53	3.89 (0.05)		
Father ⁴	3 (0.9)	14 (1.2)	0.59, 0.17-2.10	24 (2.5)	78 (2.0)	0.91, 0.56-1.49	0.85, 0.54-1.35	0.42 (0.52)		
Child ⁴	2 (0.6)	6 (0.5)	1.20, 0.24-6.06	10 (1.0)	44 (1.1)	0.76, 0.37-1.55	0.81, 0.42-1.56	0.24 (0.62)		
First-degree relative aged <55 years ⁹	5 (4.0)	6 (2.7)	1.39, 0.41-4.69	15 (4.9)	45 (4.9)	0.87, 0.47-1.61	0.96, 0.56-1.65	0.57 (0.75)		
First-degree relative aged ≥55 years	3 (2.4)	4 (1.8)	1.19, 0.26-5.49	9 (2.9)	28 (3.0)	0.85, 0.39-1.85	0.91, 0.45-1.82			

Abbreviations: NHL, non Hodgkin lymphoma; LH, lymphohaematopoietic; OR, Odds ratio; CI, confidence interval

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¹Data from Epilymph, Canada, Italian multicentre and ENGELA were not included because of lack of information on race. All models were adjusted for study, sex, age at diagnosis (entered as a linear and quadratic term), race and education (< high school versus high school or more). The referent category for the models consisted of those without any relative with any history of lymphohaematopoietic cancers among the entire cohort for the unstratified model or among whites in the stratified model.

²LACMMM not included

³USC and Utah not included

⁴USC and LACMMM not included