Familial occurrence of hematologic malignancies and other diseases in multiple myeloma: a case-control study

Mikael Eriksson and Bengt Hällberg

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In a population-based case-control study in Sweden on multiple myeloma, the occurrence of different diseases in relatives, particularly hematologic malignancies and different types of cancer, was investigated. Through a questionnaire mailed to all living subjects, i.e. cases and controls, and to the next-of-kin for deceased subjects, information was obtained on malignant and certain other diseases among relatives. All malignant diseases reported among first-degree relatives were verified, if possible, through parochial authorities and the Swedish Cancer Register. In total, data from 239 cases with myeloma and 220 controls were analyzed. An increased risk was found for persons with first-degree relatives with hematologic malignancies (relative risk \( RR = 2.36 \), 90 percent confidence interval \( CI = 0.90-6.15 \)), and also with multiple myeloma specifically (\( RR = 5.64 \), \( CI = 1.16-27.51 \)). An increased risk also was seen if the close relatives had experienced another tumor disease (\( RR = 1.21 \), \( CI = 0.86-1.71 \)). Particularly, occurrence of prostatic cancer (\( RR = 3.11 \), \( CI = 1.25-7.71 \)) or brain tumor (\( RR = 6.61 \), \( CI = 1.42-30.67 \)) in relatives increased the risk for multiple myeloma.

Key words: Case-control study, familial occurrence, multiple myeloma, Sweden.

Introduction

Although familial multiple myeloma (MM) was mentioned briefly by the 1920s, the first detailed case history, dealing with two sisters with MM, was published in 1954. Subsequent reports have been reviewed by Shoenfeld et al., who found 36 families with at least two members affected by MM in the literature; furthermore, they added a case history of their own. Twenty-seven of these 37 families involved siblings.

Since this report, 11 additional case reports of familial MM have been published. These reports, included a review of families with three affected siblings and two descriptions of monozygotic twins with MM. Moreover, two earlier publications of cases of MM and another type of lymphoproliferative disease in the same family have been followed by a report including three similar relations.

In a hospital-based case-control study in the United States, a family history of cancer of any type, as well as of hematologic malignancy, resulted in statistically significant increased relative risks (RR) for MM of 1.4 and 2.4, respectively. Furthermore, two US studies found increased risks for MM when first-degree relatives had degenerative or demyelinating central nervous system disorders, e.g. Parkinson's disease and multiple sclerosis, or rheumatoid arthritis, respectively.

This report presents data on family history of dif-
ferent diseases from a population-based case-control study on MM in northern Sweden. Malignant diseases as well as autoimmune and certain other diseases have been considered. The phrase 'hematologic malignancies' is used here to denote all cases of malignant lymphoma, multiple myeloma, leukemia, polycythemia vera, and myelofibrosis (i.e., ICD8 codes 200-209). 'Lymphoproliferative diseases' contains MM, malignant lymphoma, and chronic lymphatic leukemia.

Materials and methods

Cases

All cases of MM in the four northernmost counties of Sweden who were reported to the Swedish Cancer Register between 1 July 1982 and 30 June 1986 were included, regardless of age, sex, or vital status. The medical records of these cases were scrutinized to confirm that they fulfilled widely-accepted diagnostic criteria proposed for use in therapeutic trials on MM. Eighteen out of 293 did not, and were excluded, leaving 275 eligible cases. At the time of the study, 156 (57 percent) were living, whereas 119 (43 percent) were deceased; 141 were men and 134 women.

Controls

For each of the 275 cases, a single control was selected through a matching procedure taking into consideration age, gender, and county. For living cases, live controls were drawn from the Swedish National Population Register. To obtain similar recall conditions between responders for cases and controls, deceased cases were matched with deceased controls, drawn from the National Register for Causes of Death (excluding any suicides). The deceased controls also were matched on year of death.

Assessment of exposure

A questionnaire was mailed to all living cases and controls, and to the next-of-kin (in the order of: wife or husband, child, parent, sibling, or other) for the deceased subjects. The questionnaire inquired about different exposures, disease experience, etc. In an attached letter, general information about the investigation was provided, but the specific aim of the research was not disclosed, and it was not mentioned that any particular disease was under study. All non-respondents were sent reminder letters, with no difference in the effort to obtain data from cases or controls.

This report discusses data on family history of different diseases, especially malignant disorders. Diseases of interest were listed in the following order: ‘heart disease,’ ‘diabetes,’ ‘rheumatic disease,’ ‘tumor,’ ‘blood disease,’ ‘asthma,’ and ‘other serious disease.’ For any diseases reported in a family member, subjects were asked to give information on family relationship, and also were asked to specify the type of any 'other disease.'

Since the main hypothesis to be tested was that MM and other hematologic malignancies, as defined above, and cancer were more frequent in the families of persons suffering from MM, a further extensive investigation was performed in order to verify such information in the questionnaires. Thus, for all subjects who reported 'blood disease' or 'tumor' in a first-degree relative (i.e. sibling, parent, or child), this information was checked through the parochial authorities, where death certificates are available for persons who had died in that parish. If many instances, several parishes were searched, because the traced persons had moved, sometimes several times. In a subject reported 'tumor' or 'blood disease' in a sibling, attempts were made to trace all siblings.

If no information on type of relation was given in the questionnaire all first-degree relatives were traced; but if, for example, cousin or uncle were mentioned, no further investigation ensued. Furthermore, if the traced persons were alive, the Swedish Cancer Register was checked to ascertain if there were any hematologic malignancies or tumors registered and, if so, which type. A similar search was made through the Cancer Register if the person had died after 1958 (when this Register started) and if the death certificate did not reveal any malignant disease. Some reported family members who had died before 1958, and without a malignant disease noted on their death certificate, had to be considered as 'non-verified.'

Most of the information given in the questionnaires regarding first-degree relatives could be verified by the methods mentioned. In some instances, however, particularly regarding the general phrase 'blood disease,' obvious misinterpretations existed (whereby, e.g., thromboembolic or ischemic condition existed but no malignancy).

Statistical methods

To simplify the analyses, RRs were calculated with dissolved matching. However, since the study was matched, the factors with increased risks and 90 percent confidence intervals (CI) not including 1.0 were tested also with sustained matching, based on principles stipulated by Miettinen. Missing information from some controls matched to exposed cases, led to a certain decrease in the RRs, which will be presented in this article. The 90 percent CIs of the RRs were calculated with a test-based approximative method.\textsuperscript{19}