Multiple myeloma and work in agriculture: results of a case-control study in Forlì, Italy

Oriana Nanni, Fabio Falcini, Eva Buiatti, Lauro Bucchi, Monica Naldoni, Patrizia Serra, Emanuela Scarpi, Luca Saragoni, and Dino Amadori

(Received 14 October 1997; accepted in revised form 20 January 1998)

Objectives: To evaluate the relation between the exposure to specific pesticides in agricultural work and the risk of multiple myeloma (MM).

Methods: A case-control study was conducted in the province of Forlì, Italy. Forty-six cases of MM (20 females, 26 males; mean age 64 years, range 40 to 74) identified through the Romagna Cancer Registry in the years 1987-90, and 230 age- and gender-matched controls from the general population were interviewed in-person using a structured questionnaire focused on exposure to pesticides and other occupational and nonoccupational variables.

Results: Among nonoccupational factors, the education level and the altitude of the place of residence were related inversely to MM risk. First-degree familiarity for hematolymphopoietic neoplasias and previous herpes zoster diagnosis were associated positively with the disease. A nonsignificant increase in MM risk was observed among workers in agriculture as a whole (odds ratio [OR] = 1.31, 95 percent confidence interval [CI] = 0.62-2.74). An increased risk was associated specifically with the cultivation of apples and pears (OR = 1.75, CI = 1.05-2.91). As regards pesticide exposure, only the chlorinated insecticides were related to an increase in the risk of MM.

Conclusions: This study suggests that agricultural work and exposure to pesticides have a role in the etiology of MM. Cancer Causes and Control 1998, 9, 277-283

Key words: Agriculture, altitude, Italy, multiple myeloma, pesticides.

Introduction

It is generally agreed that the current knowledge of the etiology of multiple myeloma (MM) is poor.1 Genetic factors are likely to influence the susceptibility to potentially transforming events. Major risk factors1,2 can be grouped into occupational exposures (agriculture, benzene, metals, rubber manufacturing), radiation exposures, and pre-existing medical conditions responsible for chronic antigenic stimulation. Although most occupational associations with MM have been observed in agriculture, the specific etiologic role of the pesticides is not clear. Ecologic studies as well as case-control and cohort studies have provided contradictory evidence.3 An increased risk has been observed in case-control studies9 and cohort studies.10-11 Other investigations

Dr. Nanni, Serra, and Scarpi are with the Istituto Oncologico Romagnolo, Forlì, Italy. Drs. Falcini and Amadori are with the Medical Oncology Department, Luigi Pierantoni Hospital, Forlì, Italy. Dr. Buiatti is with the Epidemiology Unit, Center for Study and Prevention of Cancer, Florence, Italy. Dr. Bucchi is with the Romagna Cancer Registry, Forlì, Italy. Dr. Saragoni is with the Pathology Department, Luigi Pierantoni Hospital, Forlì, Italy. Address correspondence to Dr. Nanni, Medical Oncology Department, Luigi Pierantoni Hospital, 47100 Forlì, Italy. This study was funded by the following institutions: Provincia di Forlì, Forlì; Regione Emilia Romagna, Bologna; Istituto Oncologico Romagnolo, Forlì; Lega Italiana per la Lotta contro i Tumori, Milan; Associazione Italiana per la Ricerca sul Cancro, Milan; and Ministero del Lavoro, Direzione Generale della Previdenza ed Assistenza Sociale, Rome, Italy.
based on general occupational data failed to confirm the role of pesticides in the epidemiology of the disease. The major limitation of these studies was the poor definition of exposure due to difficulties in classifying the use of specific pesticides in the agricultural work. A few researchers have provided information on specific exposures. An increase in the risk of MM has been documented in farmers exposed to dichlorodiphenyltrichloroethane (DDT) and other organochlorine insecticides. However, no association has been observed in any of the many other studies of this type. Similarly, only inconclusive observations have been reported from studies addressing the relationship between exposure to agricultural pesticides and the risk of non-Hodgkin's lymphoma, leukemia, Hodgkin's lymphoma, soft tissue sarcoma and some epithelial malignancies.

In the province of Forlì, Italy, the impact of exposure to specific pesticides in the agricultural work on the risk of hemolymphopoietic neoplasias has been evaluated in a registry-based case-control study. The area is characterized by high levels of employment in agriculture and a widespread utilization of chemical pesticides. The risk of non-Hodgkin's lymphoma and chronic lymphocytic leukemia has been the subject of previous publications. The present paper evaluates risk for MM and selected agricultural and non-agricultural exposures in this population.

Materials and methods

Population and area

Incident cases of MM for this study were identified through the population-based cancer registry that covers the Romagna region of northern Italy (Romagna Cancer Registry). The study was restricted to the Province of Forlì (population 351,000). The surface area is 2,390 square kilometers (72 percent hills and mountains, 28 percent plains). The main crops are: cereals, grapes, and fodder (in the hills and mountains); fruit, green vegetables, legumes, and sugar beets (in the plains). The proportion of the active population employed in agriculture decreased from 53 percent in 1951 to less than 10 percent in the most recent years. In the 1980s, the annual use of pesticides was as high as 280 kilograms per square kilometer.

Cases and controls

Case eligibility criteria were: (i) year of registration in 1987-92; (ii) age 15 to 74 years; (iii) no previous diagnosis of cancer or AIDS; (iv) availability of bone marrow-aspiration cytology specimens; and (v) confirmation of MM diagnosis on cytologic review. There were 46 such cases (20 females, 26 males; mean age of 64 years, standard deviation 8.3, range 40 to 74).

As described in detail elsewhere, 977 controls were randomly abstracted from the files of the local offices for registration of residents. For each of those who refused to be interviewed (118 or 12 percent), the next subject of the same gender and age (± 2.5 years) in the list of residents was enrolled. This large pool of controls has been used for previous analyses addressing the risk of non-Hodgkin's lymphoma and chronic lymphocytic leukemia. For the purposes of the present study, five gender- and age-matched (± 2.5 years) controls were available for each case (exact matching) and thus were included in the analysis (total number of 230).

Interview

Both cases and controls were interviewed in-person by trained personnel using a structured questionnaire. This is described in detail elsewhere. Briefly, the items of information addressed the demographic characteristics; residential history; community life; dietary habits; smoking habits; alcohol consumption; family history of cancer (including tumors of the hematolymphopoietic system); medical history (focused on allergic disorders and infections); drug use; vaccination; exposure to radiation; and occupational history. All jobs ever held (with an experience of at least one year) were recorded. As the working categories were not mutually exclusive, subjects could be classified into more than one category. For all study subjects who reported having been employed in agriculture (even as a second job or after retirement), the crops cultivated as well as the exposure to pesticides were recorded. The latter was assessed by means of a priori exposure matrices as applied to the questionnaire. The matrices consider the items of information reported (crops, surface area, infestations, time period) as circumstantial predictors of the type of pesticide used, with a decreased frequency of missing data and a greater accuracy in exposure classification.

Analysis

The association between the recorded exposures and case-control status was assessed by the maximum likelihood estimate of the odds ratio (OR) as an estimate of the risk ratio. For each OR, the 95 percent confidence interval (CI) was calculated. Nonoccupational variables were examined first, according to a matched pair analysis using age and gender as matching variables. Those shown to be associated significantly with the risk of MM were entered together with occupational variables into conditional logistic regression models with the case-control status being used as a response variable. The analysis was carried out using the SAS statistical package.