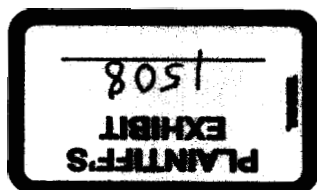


Neoplastic Diseases of the Blood

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EPIDEMIOLOGY OF MULTIPLE MYELOMA

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Multiple myeloma is the prototype of a group of conditions known as monoclonal gammopathies. A common presenting complaint is bone pain or pathologic fracture associated with radiographic evidence of punched-out bony destruction. As a result of this clinical characteristic, myeloma has traditionally been considered a bone tumor, for purposes of disease classification. It was not until 1950 that multiple myeloma was assigned its own code number, 203, under the category of "neoplasms of lymphatic and hemopoietic tissues" in the *Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death*.¹

DEMOGRAPHIC FEATURES AND GEOGRAPHIC VARIATION

U.S. Incidence

According to the most recent U.S. incidence data, 1982 to 1986, from the Surveillance, Epidemiology, and End Results (SEER) Program, multiple myeloma accounts for 1.0 percent of all malignancies in whites and 2.2 percent in blacks.² The average annual age-adjusted (1970 U.S. standard) incidence rates per 100,000 for whites are 4.6 in males and 3.1 in females, while for blacks, the rates are nearly double, at 10.8 in males and 7.2 in females.² Figure 23-1 presents the distribution of the histologic subtypes of lymphoreticular neoplasms. Among blacks, multiple myeloma accounts for 33 percent of lymphoreticular neoplasms, compared with 13 percent among whites, while all leukemia occurs equally in blacks and whites (30 percent and 32 percent, respectively). A distinctive feature of myeloma is its late age of onset. In the United States from 1982 to 1986, the median age

U.S. Incidence Trends

The incidence of multiple myeloma in the United States appears to be increasing. However, it is not clear whether this increase is real or attributable to improved diagnostic practices. The percentage increase in myeloma incidence rates from the Second National Cancer Survey (1947 to 1948) and the Third National Cancer Survey (TNCS) (1969 to 1971) was greater than for any other form of cancer for both whites and nonwhites.³ The upward trend was greater among nonwhites than whites, especially at older ages. Comparison of the TNCS age-adjusted incidence rates⁴ with more recent 1982 to 1986 calculations from the SEER program² reveals a 33.3 percent increase in the rates of myeloma in black males and appreciably smaller percentage increases in black females, white males, and white females (10.8 percent, 15.0 percent, and 14.8 percent, respectively). Some evidence suggests that the increase may be partly due to improvement in diagnosis. Linos and colleagues⁵ reviewed the time trends in incidence of myeloma in Olmsted County, Minnesota, over 1945 to 1977. Case ascertainment was based on a thorough search of laboratory and medical records and death certificates. Average annual incidence rates of multiple myeloma did not increase during the three decades (rates of 2.9, 3.0, and 2.7 per 100,000 respectively). In an in-depth evaluation of cancer trends among whites, using U.S. data from 1947 to 1984, Devesa

at diagnosis was 68.0 for males and 71.0 for females.² The average annual age-specific incidence curves for the United States increase sharply with age, regardless of race or gender, and blacks have higher rates than whites at virtually all ages² (Fig. 23-2). A male predominance is seen in both races, although black females have higher rates than do white males.

Fig. 23-1. Incidence rate per 100,000 person-years (age-adjusted, U.S. 1970 standard) and relative proportion (%) of lymphoreticular malignancies in U.S. whites and blacks, 1982 to 1986.² AGL, acute granulocytic leukemia; ALL, acute lymphocytic leukemia; CGL, chronic granulocytic leukemia; CLL, chronic lymphocytic leukemia; HD, Hodgkin's disease; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma.

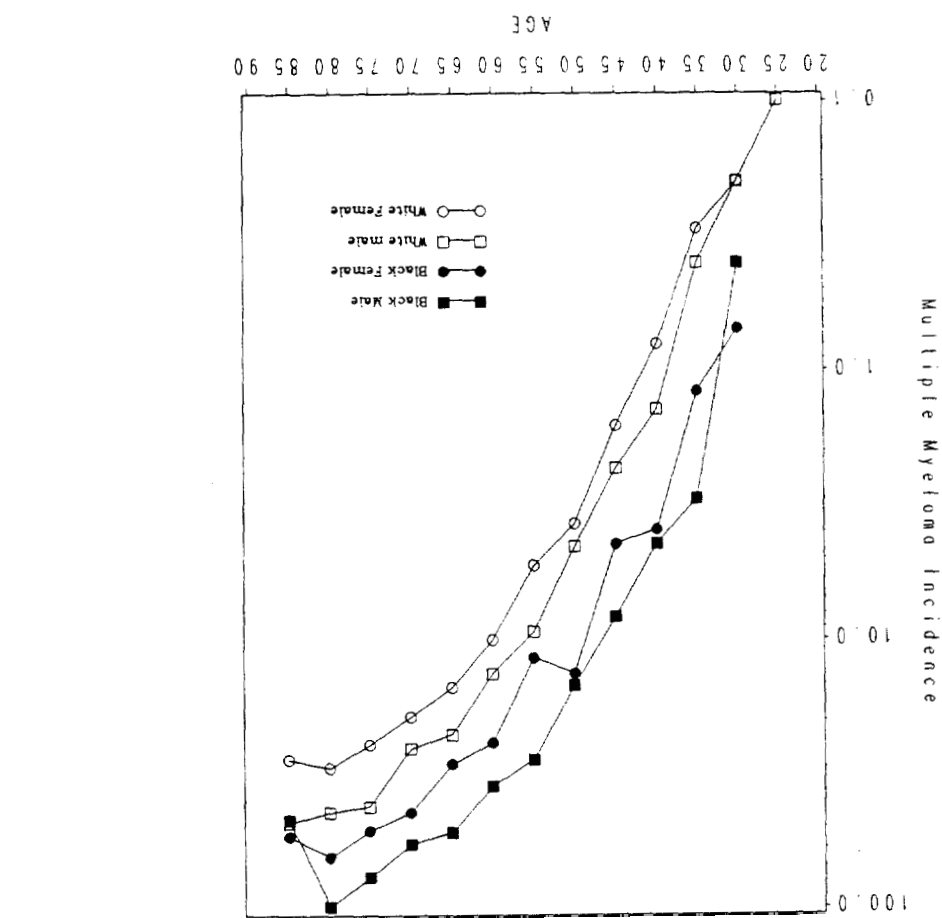
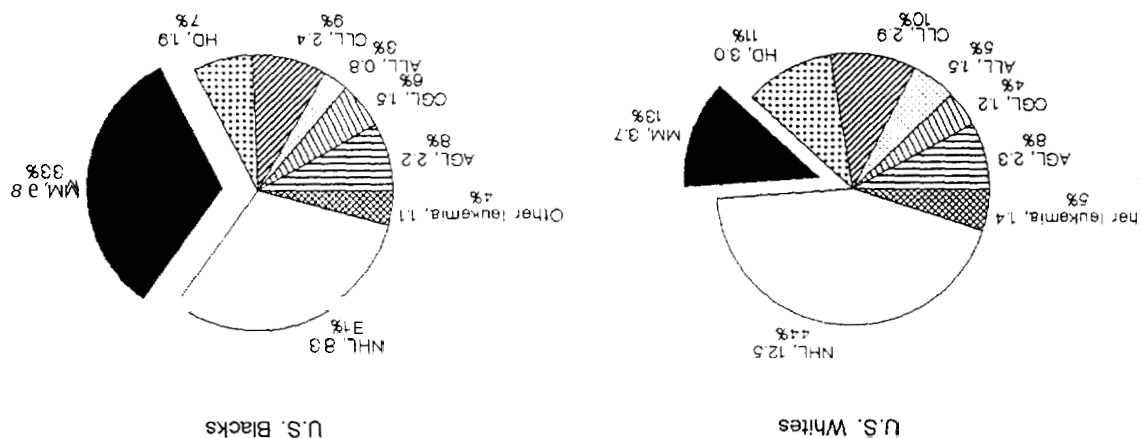


Fig. 23-2. Multiple myeloma average annual age-specific incidence for United States, 1982 to 1986.² Age plotted at beginning of 5-year age interval. Rates per 100,000 person-years.

more than twice those for whites, particularly in the South (Pickle LW, personal communication). In an attempt to investigate the role of changes in diagnostic coding practices, Davis et al.⁹ suggested that the increases were the result of an artifact of disease misclassification. Improved identification of disease among older persons cannot be ruled out, however.

Geographic variations in multiple myeloma mortality have been noted over time. Between 1950 and 1980, U.S. whites experienced particularly high mortality rates in the North Central region.⁷ Rates among white males increased with significantly greater rapidity in the Ohio Valley region, upper Michigan, central plains, southern Florida, southwestern Colorado, and southern Nevada, whereas those among white females were most striking in the mid-Atlantic coast states, eastern Kentucky, southern Indiana, southern Iowa, Missouri, southern Louisiana, eastern Texas, and northeastern New Mexico. The reasons for such geographic variations could include agricultural exposure and pesticide use.

International Incidence

A number of international studies of multiple myeloma incidence are available.¹⁰⁻²⁶ Time trends in incidence from selected population-based registries from around the world are shown in Figure 23-4.²⁷⁻²⁹ Comparisons between international incidence rates of myeloma based on cancer registry data must be made cautiously, since the populations served may vary with regard to age-adjusted rates, in the accuracy of case ascertainment (e.g., pathology versus death certificate only), and in the level of

et al.⁹ found that age-specific mortality has steadily increased, but disproportionately in older age groups. This finding suggests that the dramatic increase in incidence and mortality rates for multiple myeloma may be due in part to improved medical technology and its use in older, high-risk populations.

U.S. Mortality

The age patterns of mortality for multiple myeloma closely parallel the incidence curves. Shown in Figure 23-3 are the age-specific mortality rates for multiple myeloma in the United States from 1950 to 1984 (Devesa SS, personal communication). With few exceptions, non-white rates exceeded white rates in all age groups, increases occurred primarily among those over 60 years of age, and the peak mortality shifted over time from age 60 to age 80. Nonwhite females experienced the highest increase over the 35-year period, 330 percent compared with 304 percent for males. Increases were one-half as great among white males and females, 154 percent and 146 percent, respectively (Devesa SS, unpublished data). Since the 1950s, multiple myeloma mortality increased approximately 15.0 percent per 5-year interval among whites, ranking third behind lung cancer and melanoma among males and second behind lung cancer among females.⁷ Among nonwhites, mortality rates increased 21.6 percent among males, and 23.3 percent among females per 5-year interval, ranking second only to lung cancer.⁸ During the 1970s, mortality rates increased 50 percent more rapidly among nonwhites than among whites and by 1980 in some areas had risen to

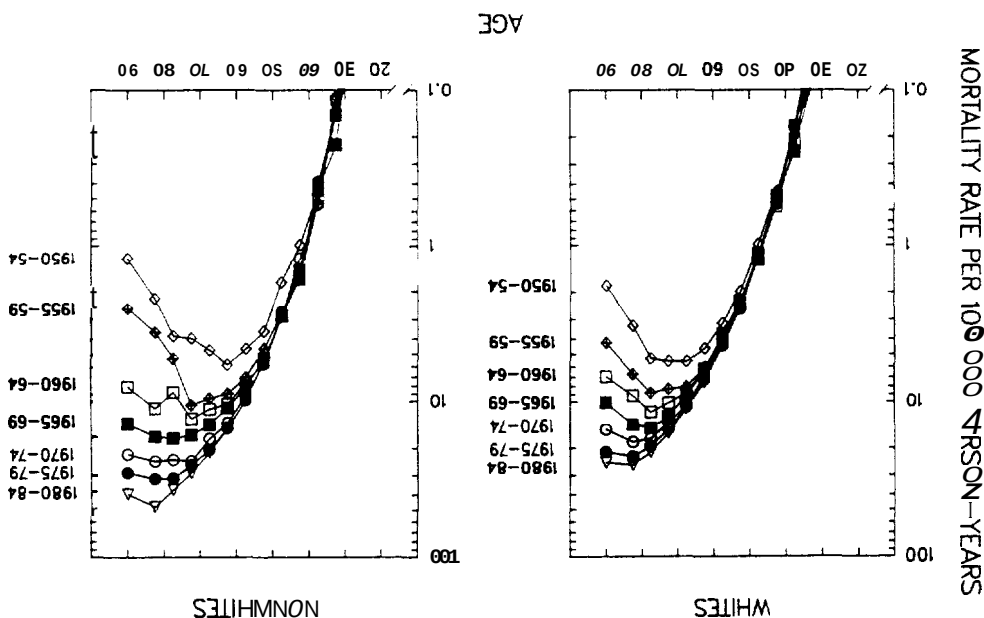


Fig. 23-3. Multiple myeloma, age-specific mortality for U.S. white and nonwhite males and females, 1950 to 1984. Age plotted at midpoint of 5-year age interval, with the exception of the 85+ interval which is plotted at age 90. (Devesa SS: personal communication.)

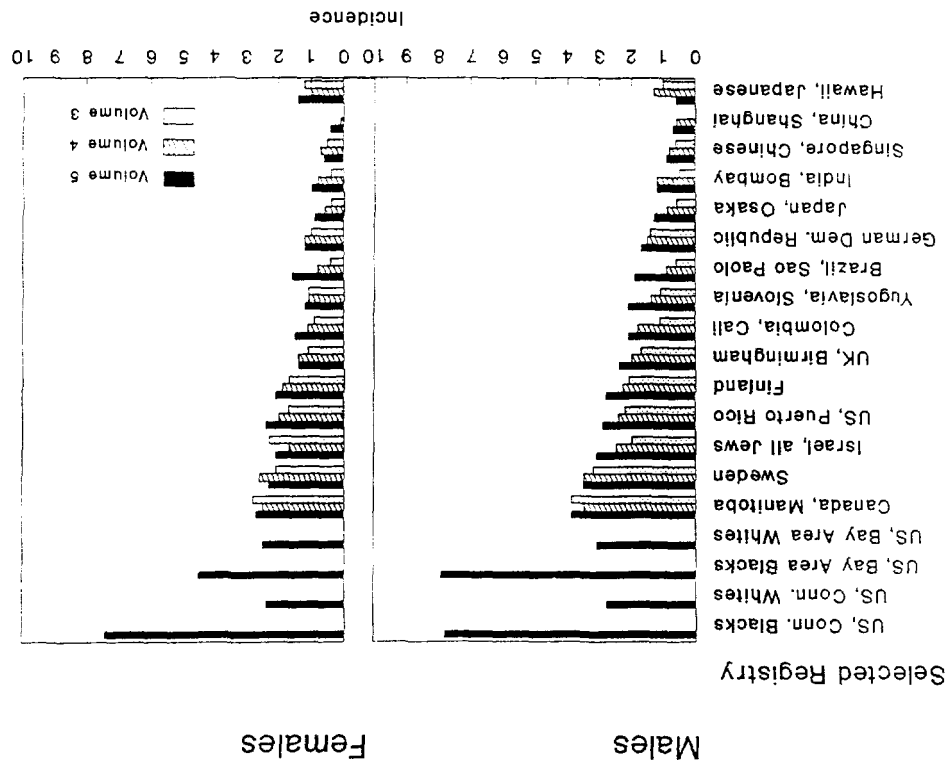


Fig. 23-4. Multiple myeloma, age-adjusted incidence (world standard population) from selected registries. Rates per 100,000 person-years. (From *Cancer Incidence in Five Continents*, Vol. 3, 1966 to 1973; Vol. 4, 1971 to 1977; Vol. 5, 1977 to 1982.²⁷⁻²⁹)

The incidence rates in Scandinavia are similar to those in the North American white population, while the rates are slightly lower in England and Eastern Europe and substantially lower in Asian countries (Fig. 23-4). The incidence data for multiple myeloma in South America are generally unavailable. In Norway,²⁴ multiple myeloma is the most frequent form of lymphoreticular malignancy (32 percent), with higher incidence rates in the rural population over 60 years of age, a finding that parallels that of Kyle et al.³¹ in the United States. High rates were also suggested for Ireland^{15,16} and Scotland,^{13,22} although on the basis of small numbers of cases. In a study of hematopoietic malignancies in southern France,¹² multiple myeloma was the fourth most common of these diseases. A cancer incidence study from Czechoslovakia reported an increase in incidence of multiple myeloma between 1968 and 1985.¹⁴ Ludwig et al.¹⁹ reported a relatively low incidence of multiple myeloma in Austria between 1969 and 1979 and commented that the apparent north-south gradient in

Europe could result from diversity in quality of diagnosis and registration, although ethnic differences could not be ruled out. This conclusion was supported by an analysis of U.S. mortality data, which also showed a north-south gradient and a statistically significant ethnic association with persons of Scandinavian ancestry.³² Unfortunately, comprehensive incidence data for African populations are largely unavailable, but such data are necessary to provide valuable insights into variations within the black population around the world. Excess incidence of multiple myeloma among blacks has been noted previously.^{2,33-34} High incidence rates occur in American black populations (Fig. 23-4) on both the East and West Coasts.² Low rates occur among African blacks, perhaps because of the small percentage of older blacks, limited diagnostic facilities, and incomplete ascertainment of African cases. A previous report of myeloma in South African blacks³⁵ suggested that rates may actually be higher, since some persons might not seek conventional medical care. Case series from French West Africa,³⁶ Rhodesia,³⁷ Zambia,³⁸ Nigeria,³⁹⁻⁴¹ Kenya,^{42,43} and South Africa⁴⁴ suggest a younger median age at diagnosis and a sizeable male excess of multiple myeloma. In a case survey of all black Zimbabwean patients presenting at two central hospitals in Harare from 1982 to 1984,⁴⁵ multiple myeloma accounted for 21.3 percent of lymphoreticular malignancies (including leukemia, non-

tion may occur because of differences in the quality and reporting of data. Data from Western Australia⁵⁴ revealed that multiple myeloma incidence increased 26.7 percent among males and 17.7 percent among females between the decade 1960 to 1969 and the 5-year period 1980 to 1984. Over each period, the male rates rose for all age groups except for the 80+ age group. A similar trend pattern was seen in a study of multiple myeloma incidence in Malmö, Sweden, from 1950 to 1979.⁵⁵ There was a small and statistically significant trend of increasing incidence among males, but not among females. Turesson et al. suggested that the relatively small increase in incidence may be attributable to the stability of the population and to the comprehensive health care system available in Sweden. In a Danish study of multiple myeloma incidence trends,⁵³ rates increased from 1943 to 1962, but not after 1962. The more precise diagnostic criteria employed after 1962 may have contributed to the leveling off of incidence rates during the period 1963 to 1982.

International Mortality

Shifts in the age distribution of a population and improved survivorship (as a result of better therapy) can influence mortality trends. Changes in incidence rates may result from increases in exposure to an environmental agent, which may cause similar increases in mortality from multiple myeloma. When specimens are not reviewed by trained pathologists using standard criteria, misdiagnosis or misclassification of the disease may result. Changes in the coding for death certification, increased awareness of the clinical manifestations of multiple myeloma by physicians, greater access to medical care, and errors in population enumeration may result in artificial changes in mortality rates. Referral bias may spuriously increase mortality rates in areas with medical institutions that serve patients from outlying areas. In-correct inferences concerning mortality trends may also occur when an investigation is conducted that is not representative of the population at risk of the development of multiple myeloma.

Multiple myeloma mortality is increasing in a number of countries.^{56,57} For 1960 to 1975, rates were high in Northern Europe, North America, Australia, and New Zealand; however, mortality in Great Britain was not as high as in the Scandinavian countries, the United States, and Canada.⁵⁸ The lowest rates were reported in eastern Europe, southern Europe, and Japan.⁵⁹ Countries with lower multiple myeloma mortality rates, such as Japan, had experienced the largest increases in mortality over time. Cuzick et al.⁵⁹ suggest that since high-quality medical care has been available in Japan for a number of years, the increase in multiple myeloma mortality is not related to underdiagnosis. Factors related to increased affluence, such as greater availability and utilization of health care, may be related to the increased incidence of multiple myeloma. In countries with high mortality, such as Sweden, increased rates occurred only among

Hodgkin's lymphoma, Hodgkin's disease, and multiple myeloma), and 25.7 percent from 1979 to 1981. These percentages of multiple myeloma are dramatically lower than those from the latest SEER incidence data² (see Fig. 23-1). However, a recent survey of cancer in developing nations³⁰ revealed that African cancer registries generally reported myeloma incidence rates that did not exceed 0.8 per 100,000 population, in sharp contrast to Western nations. The dramatic differences in rates may reflect differences in recognition of disease in limited sectors of the total population. National cancer registries for African nations reported the age-adjusted proportion of myeloma out of all cancers to be less than 1 percent. Rates appear to be high among Jamaicans, in whom the median age at diagnosis is 50 to 55 years, and survival time is short.⁴⁶

Multiple myeloma incidence rates for Maori people of New Zealand approximated those of U.S. whites.²⁶ Incident myeloma cases from Tasmania¹⁸ were more likely to have a rural residence than control subjects early in life, which may indicate the role of a prenatal or childhood exposure.

A study of the incidence of multiple myeloma in northern Israel from 1970 to 1979²³ found the overall incidence of multiple myeloma to be similar to that of Central European countries.¹⁹ Incidence was significantly higher among males compared with females, Jews compared with Arabs, urban areas compared with rural areas, and among persons over age 65.²³ Incidence for all these groups rose significantly over time. Among the Jewish population, annual incidence of multiple myeloma was significantly higher for European Jews versus Afro-Asians or native Israelis; this variance may be attributable to differences in cultural factors, including nutrition, and to living in an urban environment, which may increase the chances of exposure to industry and pollutants, rather than to genetic differences.

The incidence of myeloma is low in several Asian countries, including the People's Republic of China,²⁰ South Korea,¹⁷ and Japan.^{10,26,47} Rates in U.S. Oriental populations closely resemble those of their native countries.²⁶ A low rate of differentiated B-cell malignancies (including non-Hodgkin's lymphoma, multiple myeloma, and chronic lymphocytic leukemia) in Japan was reported previously.⁴⁷ The low rates of these malignancies probably reflect genetic factors³⁶ as well as the excess of T-cell malignancies. T-cell malignancies occur because regions of Japan that are endemic for adult T-cell leukemia (ATL) coincide with areas endemic for the viral etiologic agent, human T-cell leukemia/lymphoma virus type I (HTLV-I).^{48,49} A role for genetic factors is also suggested by the higher percentage of immunoglobulin D (IgD) myeloma in Orientals.^{50,51} Since IgD involves a less-differentiated plasma cell, this increase may be consistent with the tendency of Orientals to develop undifferentiated, as opposed to differentiated, forms of B-cell neoplasms.⁵²

Several investigators from various countries have monitored incidence trends of multiple myeloma.⁵³⁻⁵⁵ Comparisons of these studies are difficult, as trend varia-

multiple myeloma occurs after exposure to high doses of radiation after a long latent period, as in atom bomb survivors. By contrast, several other studies indicate a causal link with long-term, low dose exposure, as in radiologists and others exposed to diagnostic and thera-

Atom Bomb Survivors

The strongest evidence linking radiation to myeloma has been provided by several studies on the mortality and incidence of cancer among atom bomb survivors.⁷⁰⁻⁷² All three studies reported an increased risk and incidence of multiple myeloma associated with radiation exposure for extended periods of follow-up, reflecting the long latency for emergence of multiple myeloma. Wakabayashi et al.⁷² reported that survivors who received high doses of radiation, ≥ 100 cGy, had a significantly higher risk of multiple myeloma than did those who received lower doses of 0 to 9 cGy. Elevated serum Ig levels⁷³ and chromosomal aberrations in B lymphocytes⁷⁴ have also been reported, perhaps representing subclinical markers of multiple myeloma risk.

Radiologists

Studies on the mortality experience of radiologists have provided information on the risk of multiple myeloma caused by occupational exposure to radiation. Lewis⁷⁵ observed five multiple myeloma deaths among 425 American radiologists who died between 1948 and 1961. Whether this significant excess was solely attributable to radiation exposure is uncertain, since actual radiation measurements were not available and possibly imprecise dose estimates were used.⁷⁶ Maratoski et al.⁷⁷ also found excess deaths of myeloma among approximately 6,500 radiologists who were followed from 1920 to 1969 and hypothesized that long-term, low dose exposure may have had an etiologically related immunosuppressive effect. Leukemia risk was high for radiologists who entered practice in the earlier years, when radiation dose levels were higher. By contrast, there was a twofold excess of myeloma among those who entered practice more recently, suggesting that long-term exposure to low levels of external radiation is a risk factor for myeloma.⁷⁸

Diagnostic and Therapeutic x-Rays

Evidence that diagnostic x-rays contribute to the risk of multiple myeloma is weak. Two studies have indicated no difference in exposure to x-rays among multiple myeloma cases and controls,^{79,80} while nonsignificant excess risks have been observed by others.⁸¹⁻⁸³ Blair and Hayes⁸⁴ discussed mortality patterns among U.S. veterinarians and noted that the proportionate mortality for multiple myeloma for practitioners who began their careers between 1908 and 1957 was elevated over proportionate mortality for practitioners who began their careers between 1958 and 1987.

RADIATION EXPOSURES

survival may be the result of differences in severity of the disease. In a comparative hospital-based record review conducted by Savage et al.,⁶⁷ clinical variables and poverty indicators were compared for 52 black patients with myeloma at Harlem Hospital Center (HHC) and for 46 black and 46 white patients with myeloma at Columbia Presbyterian Medical Center (CPMC). Blacks with myeloma at HHC had poorer survival rates than did the other two patient groups mainly because they presented with more advanced disease. Crowded living conditions and poverty level also influenced the poorer survival rates among HCC patients. Savage et al. suggested that the effect of low socioeconomic status (e.g., crowding, below-median family income, and a higher percentage of families living below the poverty level) was as important as, or more important than, the effects of either race or clinical features of the disease on survival.

Using clinical and socioeconomic status data from 153 multiple myeloma patients who participated in the North Carolina case control study,⁶⁸ Weston et al.⁶⁸ found that survival was not associated with current or highest income, education level, type of dwelling, or crowdedness of dwelling. By contrast, clinical factors such as hypocalcemia and renal insufficiency were closely correlated with survival. No differences in survival rates between blacks and whites were found.

Overall, the descriptive epidemiology of multiple myeloma has shown that it is a disease of older age. In the United States, myeloma rates for blacks are highest and continue to outpace myeloma rates among white populations. Improved diagnosis and better recognition of this cancer in older high-risk patients may be contributing to the increased incidence seen in this group. Internationally, incidence rates are highest in industrialized countries and are lowest in developing countries. The differences in rates reflect the presence of registries, usually in industrialized countries, that cover a larger proportion of the total population within a country and reflect greater access to medical care. Investigations of the role of socioeconomic status on myeloma risk have revealed a link with high socioeconomic status, GNP, and myeloma mortality. By contrast, no associations have been found for socioeconomic status and myeloma incidence. Studies of multiple myeloma survival point to an association between low socioeconomic status and poor survival; however, clinical factors are also important. It is possible that the measures of socioeconomic status available do not adequately describe myeloma risk and that differences in risk observed reflect the availability and level of medical care available.

reers earlier. Risk of leukemia, like that of multiple myeloma, was higher among veterinarians who practiced during the 1950s and 1960s, when x-ray use was more widespread and safety precautions were not as stringent. By contrast, a cancer incidence study of 27,011 Chinese diagnostic x-ray workers over a 30-year period reported no excess multiple myeloma as compared with workers in other medical occupations in which x-ray exposure was not likely.⁸⁵

Nuclear Facilities

Some studies have indicated an increased risk of multiple myeloma mortality among workers in the nuclear industry. Four cases of myeloma occurred among workers at the Windscale Nuclear Processing Plant in Great Britain over 1950 to 1974, versus one expected case. Three of these workers were exposed to radiation, two of whom had accumulated doses of 4 and 3.3 rem, respectively, and one of whom had worked with plutonium. Retired and ex-workers were omitted, possibly producing an underestimate of the occurrence of myeloma in this population.⁸⁶

Excess multiple myeloma mortality has been reported among male employees engaged in plutonium manufacturing at the Hanford Works in Washington state (11 observed myeloma deaths versus 7.6 expected).⁸⁷ However, only eight of these workers were exposed to radiation. Reanalysis of these data by Darby and Reissland⁸⁸ revealed that there was an excess of myeloma by two to three deaths for those workers whose total dose was ≥ 5 rem. 10 years previous to death.

Most associations between multiple myeloma mortality and radiation have been observed when exposures 10 to 15 years before death are considered. In an updated analysis of mortality data from the Hanford site, Gilbert et al.⁸⁹ noted a statistically significant increase in myeloma mortality over a 30-year period. The strongest trend and significant dose-response relationship was noted when exposures occurring at least 10 years prior to death were considered. In a retrospective cohort study of workers at the Sellafield plant of British Nuclear Fuels,⁹⁰ a statistically significant dose-response relationship of radiation exposure with multiple myeloma mortality was seen for workers who incurred exposures at least 15 years before death. Beral et al.⁹¹ analyzed a cohort of employees of the United Kingdom Atomic Energy Authority who were employed between 1946 and 1979. Approximately one-half of the employees had been monitored over 30 years for whole-body dose radiation that included contributions from x-rays, γ -rays, and neutrons. Worker deaths from multiple myeloma were well below that of the general population of England and Wales. No appreciable dose-response trend for cumulative radiation was evident; however, duration of exposure was not considered. These studies suggest that chronic exposure in the workplace to low levels of radiation may be an important causal link in the development of multiple myeloma.

Investigations have also been conducted to determine

whether residential proximity to nuclear facilities increases the risk of multiple myeloma; however, a majority of the studies have failed to provide evidence of an elevated risk. Mortality studies by Forman et al.⁹² and by Cook-Mozzafar et al.⁹³ attempted to explore this association but did not quantify radiation dose information and inferred exposure by considering distance from the nuclear facility. While Forman et al.⁹² found a significant decrease in risk of multiple myeloma with increasing proximity to nuclear installations, Cook-Mozzafar et al.⁹³ were unable to find mortality from multiple myeloma that was significantly different from the rest of England and Wales. These findings are contradictory to the occupational studies by Smith and Douglas⁹⁰ and by Gilbert et al.,⁸⁹ who had access to radiation dosimeter measurements. Dousse⁹⁴ compared observed cancer mortality in the area of the Beaumont-Hague district of Normandy, France, which includes the La Hague nuclear facility, with the expected cancer mortality for the period 1975 to 1982. No significant excess of multiple myeloma mortality was found. However, a 7-year latent period may not have been long enough to observe an effect from radiation.

In a study of cancer incidence near Denver, Colorado, in areas surrounding the Rocky Flats nuclear weapons plant,⁹⁵ the number of lymphomas and myelomas combined exceeded the expected number for males. Increases in similar cancer types that were in excess among survivors of the atom bombings at Hiroshima and Nagasaki were noted in the Colorado population. As a consequence of the 1979 accident at the Three Mile Island (TMI) nuclear power plant near Harrisburg, Pennsylvania, cancer incidence in the region has been evaluated. A review of bone marrow examinations at a community hospital serving patients within a 10-mile radius of TMI revealed no increase in the number of myeloma cases seen for the 5-years since the accident.⁹⁶

Jessop and Horsley⁹⁷ initiated a case control study to investigate an area of Britain in which a cluster of multiple myeloma was previously reported. A nuclear fuel reprocessing plant was thought to be responsible for the apparent excess of myeloma. Patients lived longer in coastal regions than did control patients and may therefore have had greater exposure to marine discharges of radioactive material. However, it was concluded that the radiation exposure was unlikely to be large enough to induce multiple myeloma.

Participants in atmospheric nuclear weapons tests have also been studied to determine whether such exposures cause an increased incidence and mortality of cancer including multiple myeloma. A British case control study of multiple myeloma among servicemen and male atomic weapons employees who were participants in atmospheric nuclear weapons tests in the Pacific Ocean⁹⁸ revealed significant differences for multiple myeloma mortality and incidence between test participants and unexposed controls. Investigation of excess multiple myeloma mortality among participants grouped by recorded doses of external radiation or type of test con-

are not included. These data must be interpreted with caution, since some of these statistical associations may have occurred by chance alone as a consequence of multiple occupations or exposures being compared in a single study. Results from studies using death certificates in particular should be viewed carefully to prevent possible misclassification of occupation codes or cause of death or lack of detailed occupational information.

Agriculture

Of the studies listed in Table 23-1, an overwhelming majority have indicated a statistically significant positive association between multiple myeloma and agricultural farming (not represented in Table 23-1), who noted a statistically significant association between farming occupations and death from multiple myeloma among white male decedents from Washington state. Statistically elevated risks among farmers have also been detected in an ecological mortality study in Texas by Agu et al.¹¹⁸ While information is lacking with regard to which specific type of farming may elevate risk of multiple myeloma, a correlational study by Priester and Mason¹¹⁹ found an excess of multiple myeloma among residents of the southeastern United States, in counties with large poultry populations. At least two other studies^{104,105} have reported positive associations between chicken farming and risk of death from multiple myeloma. The significance of exposure to chicken production is unclear but may support the role of a zoonotic oncogenic virus in the etiology of multiple myeloma. This hypothesis was suggested by previous experiments involving the agent of Marek's disease, a malignant lymphoma in chickens; the lymphoma was grown in mammalian cells¹²⁰ and was found to have cross-reacting antigens with human tumors.¹²¹

Other investigations have found associations of multiple myeloma with hog production,¹⁰⁴ dairy farming,¹⁰¹ sheep farming,¹¹¹ exposure to beef cattle,¹¹¹ working with farm animals,¹⁰⁸ and orchard farming.¹¹⁰ Because of the variety of associations reported, it is impossible to determine whether onco-genic zoonotic viruses, animal insecticides, agricultural chemicals, or some combination of these exposures are responsible for the increased risk of multiple myeloma.^{30,82,112,122} Additional studies have suggested that agricultural exposures, such as grain dust¹²² and engine exhaust⁸² from farm equipment, may influence the development of multiple myeloma. Gallagher et al.⁸⁰ reported increased risks of multiple myeloma among farm workers, for those workers exposed to processed

ducts were inconclusive, owing to the small sample size. Because a large percentage of the participants are still alive, and because an adequate latent period must be considered to assess radiation exposure, further follow-up evaluation of this cohort is warranted.⁹⁹

Radium Dial Workers

Siebbings et al.¹⁰⁰ conducted a mortality study of women employed in the U.S. radium dial painting industry prior to 1950. Notable increases in the incidence and mortality of myeloma were evident for those ever employed, and significant increases were found for workers employed prior to 1930, when exposures to radium were reportedly higher. The excesses of incidence and mortality were particularly elevated among those employed longest. A statistical association of four living incident cases with varying internal measurements, based on the expectation of myeloma deaths, was stronger when duration of employment was considered rather than internal radium intake. Siebbings et al. contend that external γ-radiation may be the biologically significant exposure. Associations with internal radium intake such as from tipping the brush in the mouth were weak because of lack of a good measure of internal exposure. Multiple myeloma occurrence among persons exposed to radiation is well documented, with increased risks reported primarily among older persons. The strongest association between multiple myeloma risk and radiation exposure has been observed among atom bomb survivors who experienced high doses instantaneously and among radiologists and radium dial workers who experienced a lower dose over a long period of time. Risk associated with exposure to diagnostic and therapeutic x-rays is contradictory. With the advent of nuclear power, concern for cancer risk has increased among power plant workers and local residents. Among nuclear plant workers, the strongest associations of radiation exposure and multiple myeloma have been observed for low dose exposures occurring over a 10- to 15-year period. Associations of multiple myeloma in areas situated near nuclear facilities have generally proved negative. Evidence from geographic cancer clusters, hospital record reviews, and case control studies of environmental radiation exposure is weak, partly because of lack of reliable exposure data and adequate sample size.

ENVIRONMENTAL AND OCCUPATIONAL EXPOSURES

Over the past decade, much information on potential environmental and occupational risk factors for multiple myeloma has been ascertained from epidemiologic investigations of various design. Table 23-1 presents positive associations between specific occupations/industries and multiple myeloma reported from case control, prospective, and proportionate incidence/mortality studies. Ecologic mortality studies and correlational studies

Table 23-1. Reported Positive Associations Between Occupational Exposures and Multiple Myeloma

Investigators	Study Population and Size	Design	Risk Estimate	Adjustments*
Boffetta et al. (1989) ⁸¹	American Cancer Society Prevention Study Volunteers (<i>n</i> = 1,410) Exposure: Farmers Farming and pesticides	Case control within prospective	OR = 3.4 ^{ad} OR = 4.3 ^d	CR
Brownson et al. (1989) ¹⁰²	Missouri Cancer Registry 1984-1988 (<i>n</i> = 15,000) White male farmers	Case control	OR = 1.4	A
La Vecchia et al. (1989) ¹⁰⁷	Hospital patients from greater Milan, Italy 1983-1988 (<i>n</i> = 506)	Case control	OR = 2.0 ^d	E
Cuzick and De Stavola (1988) ⁷⁹	Referral center patients, England and Wales (<i>n</i> = 798)	Case control	RR = 1.8 ^d	CR
Levi et al. (1988) ⁶³	Vaud Cancer Registry, Switzerland, agriculture workers, 1977-1984 (No. cases = 53)	Proportional mortality	PMR = 210 ^d	J
McLaughlin et al. (1988) ¹⁰⁸	Swedish Cancer Environment Registry: National Swedish Cancer Registry, males (No. cases = 808) Exposure: Farmers	Nonconcurrent prospective	SIR = 1.7 ^d (incidence)	P
Flodin et al. (1987) ⁸²	Selected Swedish hospital registries and clinics (<i>n</i> = 562)	Case control	RR = 1.9 ^d	CR
Morris et al. (1986) ¹⁰⁹	SEER registrants (Washington, Utah, metropolitan Detroit, metropolitan Atlanta) (<i>n</i> = 2,381)	Case control	OR = 2.6 ^{ad}	H
Nandakumar et al. (1986) ⁹²	Leukemia and Allied Disorders Registry: Cancer Registry of Western Australia, descendants 1975-1984 (<i>n</i> = 1,245)	Case control (mortality)	OR = 1.44	CR
Pearce et al. (1986) ¹¹¹	New Zealand Cancer Registry, male interviewees (<i>n</i> = 391) Exposure: Farming Sheep farming Beef cattle	Case control	OR = 1.7 ^d OR = 1.9 ^d OR = 1.7 ^d	E E E
Steinack and Wilkink (1986) ¹¹²	1960 Swedish Population and Housing Census Respondents, Swedish Cancer Environment Registry (<i>n</i> = 2,739), males	Nonconcurrent prospective	RR = 1.2 ^d	P
Vagero and Persson (1986) ¹¹³	Self-employed Swedish male farmers, Swedish Cancer Environment Registry 1961-1979 (No. cases = 347)	Nonconcurrent prospective	SMR = 115 ^d (morbidity)	P
Delzell and Grufferman (1985) ¹⁰⁶	Decreased nonwhite North Carolina farmers, 1976-1978 <65 years old (No. cases = 10)	Proportional mortality	PMR = 250 ^{ad}	G
Pearce et al. (1985) ¹¹⁰	New Zealand Cancer Registry, 1977-1981 males (<i>n</i> = 410) Exposure: Farming (age 20-64)	Case control	OR = 2.0 ^{ad}	A
Cantor and Blair (1984) ¹⁰⁵	Deceased male Wisconsin farmers (<i>n</i> = 1,337) Exposure: Farming Fertilizer use	Case control	OR = 1.4 ^{ad} OR = 1.7 ^{ad}	K K

(continued)

Table 23-1. (continued) Reported Positive Associations Between Occupational Exposures and Multiple Myeloma

Investigators	Study Population and Size	Design	Risk Estimate	Adjustments ^a
Farming Occupation (continued)				
Burmeister et al. (1983) ¹⁰⁴	Decceased white male Iowa farmers (<i>n</i> = 1,650) 1964-1978	Case control	OR = 1.48 ^{a,d} OR = 1.83 ^{a,d} OR = 2.65 ^{a,d} OR = 1.96 ^{a,d}	cf cf cf cf
Gallagher et al. (1983) ⁸⁰	A. Maxwell Evans Clinic patients. Vancouver, B.C. (<i>n</i> = 252) Exposure: Farm workers Processed grain Industrial occupation	Case control	OR = 2.2 ^d OR = 2.4 ^d OR = 2.1 ^d	cf cf cf
Burmeister (1981) ¹⁰³	Decceased white male Iowa farmers. 1971-1978 (No. cases = 133)	Proportional mortality	PMR = 127 ^{a,d}	A
Bross et al. (1978) ¹⁰¹	Roswell Memorial Park cancer patients: Buffalo, New York (<i>n</i> = 14,000; No. cases not available) 1956-1965 Exposure: Dairy farming	Prospective	RR > 2.0	A
Metal Exposure				
Sorahan and Cooke (1989) ¹³⁰	Male U.K. steel foundry workers 1946-1985 (No. cases = 9)	Nonconcurrent prospective	SMR = 122 (mortality)	G
Cuzick and De Stavola (1988) ⁷⁹	Referral center patients, England and Wales, exposed ≥ 10 years to metals/dusts 1978-1984 (<i>n</i> = 798)	Case control	RR = 1.1	cf
McLaughlin et al. (1988) ¹⁰⁸	Swedish Cancer Environment Registry: National Swedish Cancer Registry. male smelter/metalurgy workers (No. cases = 18)	Nonconcurrent prospective	SIR = 1.7 (incidence)	B
Morris et al. (1986) ¹⁰⁹	SEER registrants (Washington, Utah, metropolitan Detroit, metropolitan Atlanta) (<i>n</i> = 2,381)	Case control	OR = 1.5 ^d	H
Giles et al. (1984) ¹²⁸	Residents of Tasmania, 1972-1980 (<i>n</i> = 232) Male metal workers Male foundry workers	Case control within prospective	RR = 1.0 RR = 1.5	cf cf
Gallagher and Threlfall (1983) ¹²⁷	Male metal workers in British Columbia (No. cases = 33)	Proportional mortality	PMR = 128 ^c	A
Greene et al. (1979) ¹²⁹	Male employees of U.S. printing office. 1948-1977 Whites (No. cases = 8) Nonwhites (No. cases = 2)	Proportional mortality	PMR = 219 ^{a,d} PMR = 246 ^{a,d} PMR = 153 ^c	B G B
Rubber Manufacturing				
Cuzick and De Stavola (1988) ⁷⁹	Referral center patients, England and Wales 1978-1984 (<i>n</i> = 798)	Case control	RR = 1.4	cf
Gustavsson et al. (1986) ¹³⁸	Male Swedish rubber workers (No. cases = 5)	Nonconcurrent prospective	SMR = 128 (morbidity)	G
Dezell and Grufferman (1985) ¹⁰⁶	White male union rubber reclaim workers. 1940-1971 (No. cases = 6)	Nonconcurrent prospective	RR = 4.5 ^d	G
Andjelkovich et al. (1978) ¹³⁵	U.S. white female rubber workers. 1964-1973 (No. cases = 2)	Nonconcurrent prospective	SMR = 234	I
Monson and Nakano (1976) ¹³⁶	Female rubber workers in Akron, Ohio (No. cases = 9)	Nonconcurrent prospective	SMR = 214 ^c	G

(continued)

Table 23-1. (continued) Reported Positive Associations Between Occupational Exposures and Multiple Myeloma

Investigators	Study Population and Size	Design	Risk Estimate	Adjustments ^a
Benzene				
Rinsky et al. (1987) ¹⁴¹	White male Ohio rubber plant workers 1940-1965 (No. cases = 4)	Nonconcurrent prospective		
Wood, Leather, and Textile Industries, and Occupations				
Cuzick and De Stavola (1988) ⁷⁹	Referral center patients England and Wales exposed to leather tanning 1978-1984 (<i>n</i> = 798)	Case control	RR = 1.9	cf
McLaughlin et al. (1988) ¹⁰⁸	Female Swedish textile workers (No. cases = 11)	Nonconcurrent prospective	SIR = 2.7 ^d	8
Flodin et al. (1987) ⁸²	Swedish cases from selected medical clinics and population controls exposed to fresh wood (<i>n</i> = 562)	Case control	RR = 3.2 ^d	A
Walrath et al. (1987) ¹⁵²	Employees of leather shoe manufacturing company, 1960-1979 Males (No. cases = 10) Females (No. cases = 8)	Proportional mortality	PMR = 193 ^{cd} PMR = 346 ^{cd}	G G
Millham (1983) ¹⁴⁵	Deceased Washington state paper and pulp mill workers (No. cases = 19)	Proportional mortality	PMR = 182 ^{cd}	3
Petroleum Refining, Petroleum Production, and Fuel Combustion Products				
Flodin et al. (1987) ⁸²	Selected Swedish hospital registries and clinics (<i>n</i> = 562)	Case control	RR = 2.6 ^d	A
Linert et al. (1987) ¹⁶⁴	Hospital patients, Baltimore, MD (<i>n</i> = 200)	Case control	OR = 3.7 ^{cd}	F
Kaplan (1986) ¹⁵⁸	Male U.S. petroleum refinery workers (No. cases = 16) as of 1980	Nonconcurrent prospective	SMR = 123	A
Morris et al. (1986) ¹⁰⁹	SEER registrants (Washington, Utah, metropolitan Detroit, metropolitan Atlanta) (<i>n</i> = 2,381)	Case control	OR = 1.8 ^d	H
Rushon and Alderson (1983) ¹⁵⁷	Male British oil distribution center employees, 1950-1975 (No. cases = 11)	Nonconcurrent prospective	SMR = 117 (mortality)	G
Thomas et al. (1982) ¹⁵⁶	Deceased white male members of Oil, Chemical and Atomic International Union (No. cases = 9)	Proportional mortality	PMR = 204	G
Miscellaneous Exposures				
Raffin et al. (1989) ¹⁷⁴	Male Danish asbestos cement industry workers, 1928-1984 (No. cases = 8)	Nonconcurrent prospective	SMR = 168 (mortality)	G
Cuzick and De Stavola (1988) ⁷⁹	Referral center patients England and Wales, 1978-1984 (<i>n</i> = 798)	Case control	RR = 3.5 RR = 1.9 RR = 2.0 ^d RR = 6.0 RR = 3.0	cf cf cf cf tr

(continued)

Table 23-1. (continued) Reported Positive Associations Between Occupational Exposures and Multiple Myeloma

Investigators	Study Population and Size	Design	Risk Estimate	Adjustments ^a
Miscellaneous Exposures (continued)				
Gustavsson et al. (1988) ¹⁷⁷	Swedish trade union chimney sweeps (No. cases = 6)	Nonconcurrent prospective	SMR = 262	G
Schwarz et al. (1988) ¹⁷³	SEER registrants (Washington, Utah, metropolitan Detroit, metropolitan Atlanta) (n = 2,381)	Case control	OR = 1.1	H
Edling et al. (1987) ¹⁶⁸	Abrasive manufacturing, males exposed to aluminum oxide, silicon carbide and formaldehyde dust, 1955-1983 (No. cases = 2)	Nonconcurrent prospective	SMR = 400	G
Linert et al. (1987) ¹⁶⁴	Hospital Patients, Baltimore, MD (n = 200)	Case control	OR = 3.5 ^{b,d}	F
Lundberg (1986) ¹⁶⁶	Swedish paint industry, male workers, 1955-1975 (No. cases = 3)	Nonconcurrent prospective	SMR = 549 ^d	G
Morris et al. (1986) ¹⁰⁹	SEER registrants (Washington, Utah, metropolitan Detroit, metropolitan Atlanta) (n = 2,381)	Case control	OR = 1.3	H
	Exposure: Asbestos		OR = 1.6 ^d	H
Spinelli et al. (1984) ¹⁷⁹	British Columbia, female hairdressers and cosmetologists, 1950-1978 (No. cases = 3)	Proportional mortality	PMR = 619 ^{c,d}	A
Guidotti et al. (1982) ¹⁷⁸	Los Angeles County Tumor Registry	Proportional incidence	PIR = 467	A
	Cosmetologists/hairdressers and manicurists (No. cases = 8)			

^a Adjustments: A, for age; B, for age and area of residence or region; C, for age and familial relationship; D, for age and smoking; E, for age, gender, race, and study site; F, for age and race; G, for age and gender; H, for age and marital status.

^b Estimate of the odds ratio for matched pairs.

^c Death certificate-based study.

^d Statistically significant at the 0.05 level.

^e Calculated by D.A. Riedel.

Abbreviations: cr, unadjusted (crude); No, cases, observed number of myeloma cases.

multiple myeloma. Specific pesticides that might account for the excess of multiple myeloma among farmers have not been identified. Exposure to phenoxy herbicides and chlorophenols,^{124,125} chemicals commonly used in farming, have been associated with an increased risk of lymphomas. Similar links with multiple myeloma are lacking. Studies that have examined exposure to various pesticides have not been able to distinguish between the effects of different groups of chemicals on the risk of multiple myeloma.

Associations with pesticides and multiple myeloma have been shown to occur among farmers born in more recent years,¹²⁶ particularly among farmers from industrialized countries, including the United States, Canada, and Sweden. This phenomenon may reflect a change to modern chemical farming methods over the past 40 years.¹⁰⁵ Both herbicide and insecticide usage were associated with multiple myeloma among male Iowa farmers born in or after 1890, in a case control study using

grain, and for those who worked in dusty occupations. A statistically significant increased risk of myeloma among farm workers remained after controlling for allergies. It was noted that hypersensitivity responses, such as allergic reactions involving the skin, may increase risk of multiple myeloma. Steinbeck and Wiklund,¹¹² in their study of Swedish agricultural workers, also suggested that agriculture workers may encounter exposures that evoke both allergic reactions and multiple myeloma. In a mortality study of grain workers,¹²² 6 deaths from multiple myeloma among grain workers were observed versus 3.3 deaths expected. Owing to the small number of cases, it is unclear whether the culpable exposure(s) arose from work in various grain processing plants or exposure to pesticides as part of grain processing.

Case control studies using death certificates,^{104,105} case control interview studies,^{81,107,109,111} and prospective studies¹²³ have explored an association of agricultural pesticides (including herbicides and insecticides) and

whites. A later case control study by Cuzick et al.⁷⁹ failed to detect an excess of multiple myeloma risk among printers. No specific information was available concerning the kinds of metals involved in these occupations in either of the above studies.

Greene et al.¹²⁹ found a significant excess of myeloma deaths in male employees of the Government Printing Office. Unlike the findings in the correlational study above,³² cases were mainly confined to white compositors, whose major exposure was to inorganic lead and lead vapor.¹²⁹

Data from a case control study¹⁰⁹ revealed an elevated risk of multiple myeloma for employees who reported occupational exposures to metals (i.e., lead vapors and liquid, arsenic, cadmium, and copper powder and fumes). Analysis by race showed a significantly increased risk among whites who were exposed to metals but a nonsignificantly decreased risk among blacks who reported similar exposures. A nonsignificantly elevated risk was observed for exposure to dyes. The presence of trace levels of lead and cadmium in U.S. water supplies has also been positively correlated with mortality from multiple myeloma.¹³¹

A mortality study of Canadian metal workers revealed a significant excess of multiple myeloma among machinists.¹²⁷ Machinists are typically responsible for the production of machine parts, usually from hard alloys, and may be exposed to cutting oils and mineral oil lubricants,¹²⁷ some of which may contain potential carcinogens. In the mouse plasmacytoma model, mineral oil induces myeloma-like tumors in the susceptible strains.¹³³

McLaughlin et al.¹⁰⁸ noted an excess significant risk of multiple myeloma among smelter and metallurgy workers. Studies of foundry workers by Sorahan and Cooke¹³⁰ and by Giles et al.¹²⁸ revealed nonsignificant elevations in risk of multiple myeloma. Giles et al.¹²⁸ did note a significantly increased risk of myeloidproliferative and lymphoproliferative disorders among foundry workers, suggesting that these diseases may share a common etiology with regard to metal exposure.

Rubber Manufacturing

Mason¹³⁴ noted that white males who resided in U.S. counties in which the manufacture of synthetic rubber, synthetic fibers, and plastics occurred had a statistically significant elevation in multiple myeloma mortality rates as compared with total U.S. rates and control counties. Myeloma mortality rates for white females were unremarkable. The major employers in these counties were chemical companies that used vinyl chloride in primary manufacturing processes. Cuzick and De Stavola⁷⁹ reported a nonsignificant excess risk of multiple myeloma among persons reportedly working in rubber manufacturing.

Two other epidemiologic studies^{135,136} reported excess

death certificates.¹⁰⁴ Neither insecticide nor herbicide use was associated with myeloma among those born before 1890. Cantor and Blair¹⁰⁵ noted an association with fertilizer use and acres treated with insecticides in a case control study of Wisconsin farmers who died between 1968 and 1976. Of particular interest was a significant association of multiple myeloma with higher insecticide use among persons born after 1905. Cantor and Blair proposed that this increase in risk from multiple myeloma may be related to more intense use of insecticides after 1945.

A number of case control studies^{81,107,109,111} have examined pesticide use and myeloma in general populations and hospital populations. Morris et al.¹⁰⁹ reported a 2.5-fold risk of multiple myeloma associated with pesticide use. Boffetta et al.⁸¹ found that risk of myeloma did not increase appreciably among those who were exposed either to farming or to pesticide use but that risk rose dramatically for those exposed to both farming and pesticides (odds ratio = 4.3) over the risk for those exposed to neither. Pearce et al.¹¹¹ noted nonsignificant elevated risks for farmers and railway workers who reported potential exposure to phenoxyl herbicides. The study also reported a nonsignificant increase in myeloma risk for exposures incurred by workers maintaining fences, by sawmill and timber workers, and by meat workers, as these activities involve potential exposure to chlorophenols. An Italian study¹⁰⁷ reported no association between pesticide use and multiple myeloma.

A recent study¹²³ reported no increased risk of multiple myeloma in a cohort of licensed pesticide applicators exposed to a plethora of insecticides, herbicides, and fungicides between 1965 and 1982. Results of this study should be regarded as preliminary, as most of the pesticide applicators were exposed infrequently (on a part-time basis), not enough information was gathered concerning individual chemical exposures, and a greater time interval should be considered to evaluate a possible latent effect.

Metals

Statistical associations have been made between exposures to various metals and occupations believed to entail metal and metal dust exposure.^{79,108,109,127-130} Small numbers of cases and lack of information on actual exposures have made it difficult to assess whether particular metal fumes or dusts or other occupational exposures are responsible for observed elevations in risk. Studies have not been consistent in indicating an excess risk of myeloma among any particular racial group of workers.

Blattner et al.³² observed a significant increase of workers employed in printing and in the manufacture of fabricated metal and machinery within U.S. state economic areas (SEA) with high rates of multiple myeloma mortality. Correlations between occupation and SEAs with high myeloma mortality were restricted to non-

Wood, Leather, and Textile Industries and Occupations

Most associations of multiple myeloma and the wood industry have been with pulp and paper making. Agü et al.¹¹⁸ found a significant correlation of work in the paper industry and multiple myeloma mortality. However, this association disappeared after controlling for race. In another correlation study,³² rates of multiple myeloma mortality were significantly elevated among white males who resided in state economic areas in which a large percentage of people were employed in paper production. Neither of these studies found an association for myeloma mortality and lumber and furniture manufacturing occupations. Millham¹⁴⁵ noted, in an evaluation of occupational mortality in Washington state, that proportional mortality for myeloma was significantly increased among paper and pulp mill workers. Nonsignificant increases were noted for carpenters and plywood workers, while no appreciable association was noted for those who worked in harvesting and milling timber or cabinet making. Subsequently, Millham and Demers¹⁴⁶ suggested that the risk among pulp and paper workers may vary depending on whether the sulfate or sulfite process is used in pulping, since the type of wood processed and chemicals differ in each method.¹⁴⁶⁻¹⁴⁹ Schwartz¹⁴⁹ also noted a nonsignificant increased risk of mortality from lymphoma and multiple myeloma combined among paper and pulp workers in New Hampshire (not shown in Table 23-1). Another study found a significant association of myeloma with fresh wood exposure among persons employed by sawmills and paper factories in Sweden.⁸² By contrast, several case control studies have failed to show any association between work in wood-related industries and multiple myeloma.^{62,79-81,111,115,150,151}

Results from epidemiologic studies of manufacturing of leather have not been consistent. In a clinic-based study by Cuzick and De Stavola,⁷⁹ multiple myeloma cases who reported working in the leather tanning industry had a nearly twofold increase in risk over controls; however, this association was not significant. A mortality study of 4,876 former employees of a shoe manufacturing company in upstate New York indicated a significant excess in mortality from multiple myeloma of twofold among men and over threefold among women between 1960 and 1979.¹⁵² The two correlation studies mentioned previously^{32,118} found no association with leather manufacturing.

Results of studies evaluating an association of myeloma with textile processing appear contradictory. A linkage study of Swedish cancer incidence data and occupational census data¹⁰⁸ revealed a nearly threefold increased risk of multiple myeloma among women textile workers in the wool industry. The correlation study using U.S. data³² reported a slight increase in the number of deaths from multiple myeloma in economic areas with textile manufacturing over the period 1950 to 1969. The correlation study using Texas data¹¹⁸ found a negative

risks of multiple myeloma mortality among female rubber workers. In studies by Monson and Nakano,¹³⁶ the majority of females worked in the industrial products division, where rubber bands, hoses, belts, and molded rubber goods were made. White male employees were not at increased risk.¹³⁷ In the study of Swedish rubber workers, a slight excess of myeloma incidence was also seen.¹³⁸ Among workers who were assigned to weigh and mix chemicals used in processing, excess incidence was associated with those who had a longer exposure time to the mixing procedure, including employment during a period when dust control was minimal.

Delzell and Monson¹³⁹ subsequently reported a statistically significant risk of death from multiple myeloma for white male rubber reclaim workers and a notable excess of death from multiple myeloma among white reclaim workers versus white nonreclaim workers. Risk of death from multiple myeloma among black reclaim workers did not reach significant levels, as there were few blacks in this study. Reclaim workers were exposed to both natural and synthetic rubbers that were ground and devulcanized under heat and pressure as part of the reclaim process. A recent mortality study of male British rubber industry workers found no association with multiple myeloma mortality.¹⁴⁰

Rinsky et al.¹⁴¹ describe an occupational cohort of workers who were exposed to the manufacture of rubber hydrochloride. The manufacturing process included dissolution of natural rubber in benzene. A statistically significant excess of multiple myeloma mortality was observed among rubber workers who were exposed to benzene at low levels. Further analysis indicated a strong dose-response gradient for leukemia, as the number of deaths rose significantly with exposure to benzene. Based on the differences in benzene exposure among those who died of leukemia versus multiple myeloma, Rinsky et al. stated that perhaps low doses of benzene produce well-differentiated cancers such as multiple myeloma, while high doses may lead to leukemia. Decouffe et al.¹⁴² noted that the benzene exposure in a petrochemical plant cohort may have played an etiologic role in the pathogenesis of several tumors of B-cell lineage, since two cases of myeloma and a case of chronic lymphocytic leukemia (CLL) were observed.

Benzene exposure has also been noted in several case reports of multiple myeloma. Aksoy et al.¹⁴³ reported seven cases of multiple myeloma, four of whom were occupationally exposed to benzene (a shoemaker, plastic factory worker, airplane factory worker, and furniture shop owner). A benzene link was also suggested by a case report from Japan by Nakayama et al.¹⁴⁴ of a conjugal cluster in which both husband and wife experienced 30 years of exposure to benzene hexachloride related to agricultural employment.

association of borderline significance. No excess myeloma mortality with employment in the textile industry was observed in a proportional mortality study of female workers in North Carolina.¹⁵³

Petroleum Refining, Petroleum Products, and Fuel Combustion Products

A number of occupational studies have investigated the relationship between employment in the petroleum industry and mortality from multiple myeloma. Blotner et al.³² found a high correlation between multiple myeloma mortality and SEAs where a high percentage of white males were employed by the petroleum industry. Thomas et al.¹⁵⁴⁻¹⁵⁶ evaluated mortality patterns of workers from three Texas oil refineries in several reports. The first report¹⁵⁴ found an excess of multiple myeloma deaths (six cases) among active white male long-time union members, who were union members for 10 or more years and employed in petroleum refining and production of petrochemicals (not shown). In the second study,¹⁵⁵ which included retirees, an additional three multiple myeloma deaths were identified. Interestingly, there were no multiple myeloma deaths among nonwhite workers from all three refineries during the study period. When company work histories of cases and controls were included, no specific associations were found with specific work category/product exposure (not shown).¹⁵⁵ Other occupational studies have reported associations of exposure to petroleum and combustion products with myeloma in British oil distribution centers¹⁵⁷ and U.S. petroleum refineries.¹⁵⁸ An excess of deaths due to cancers of lymphatic tissue has been seen in several petroleum refinery populations,¹⁵⁹⁻¹⁶¹ while similar studies have not found this association.^{162,163} In a case control study by Liner et al.,¹⁶⁴ a significantly elevated risk of multiple myeloma was seen among subjects occupationally exposed to petroleum. An association between myeloma and exposure to engine exhausts was suggested in a case control study conducted by Flodin et al.¹⁶² A statistically significant trend association for myeloma cases occupationally exposed to gases and fumes for at least 10 years has also been reported.⁷⁹ Morris et al.¹⁰⁹ noted a statistically significant elevation in risk of multiple myeloma from purported exposures to carbon monoxide (i.e., exposure to diesel, jet fuel, or automobile exhausts, coal fumes, smoke). Another case control study⁸¹ did not find a significant excess of myeloma cases among subjects exposed to gasoline or diesel exhausts, coal products, or chemical solvents.

Miscellaneous Environmental and Occupational Exposures

Occupational exposures such as paints, chemicals, and asbestos have been evaluated as potential risk factors of multiple myeloma. Paints and chemicals represent broad exposure categories, making it difficult to identify the specific component responsible for an excess risk.

Positive associations between multiple myeloma and exposure to paint have been reported in case control and prospective studies.^{79,109,165,166} Painters are typically exposed to a mixture of aromatic, chlorinated, and aliphatic hydrocarbons, ketones, ethers, and esters.¹⁰⁹ However, the specific chemical exposures that heighten myeloma risk have not yet been identified. A study of Swedish paint manufacturing workers reported a statistically significant excess of multiple myeloma deaths among those employed for at least 5 years.¹⁶⁶ A Swedish cancer morbidity study noted an excess of deaths from myeloma and malignant lymphomas combined among chemical factory workers exposed to esters, urethane, formaldehyde, benzyl chloride, ethylene oxide, and epichlorohydrin (not shown in Table 23-1).¹⁶⁷ A small number of myeloma cases were noted among a cohort of workers from an abrasive manufacturing company with work exposures to dust from processes using aluminum oxide and silicon carbide abrasives.¹⁶⁸

Asbestos exposure has been linked to myeloma in several early case reports¹⁶⁹⁻¹⁷² of miners and others with occupational exposures. At least four case control studies^{79,109,164,173} and one prospective study¹⁷⁴ have reported a positive association between multiple myeloma and exposure to asbestos. In the case control study by Guzik and De Stavola⁷⁹ multiple myeloma cases who reported being exposed for at least 10 years had a significantly greater chance of the development of multiple myeloma than did hospital control patients. A nonsignificant excess risk of myeloma was reported for those employed in photography and for those exposed to electric cable. An association between occupational exposure to electromagnetic fields and multiple myeloma was not shown in two studies attempting to evaluate this relationship.^{175,176}

A marginally significant increase in multiple myeloma incidence among Swedish chimney sweeps was reported in a recent cohort study.¹⁷⁷ Potential occupational exposures include polycyclic aromatic hydrocarbons (formed by combustion of coal, wood, coke, and oil) and metals such as arsenic, nickel, and chromium.¹⁷⁷ Recent studies have reported excess multiple myeloma cases among beauticians and cosmetologists.^{118,178,179} A myriad of organic and inorganic chemicals, including lead-based hair dyes, are handled in this occupation, making the agents responsible for excess risk difficult to assess. One study that evaluated cancer incidence among cosmetologists¹⁸⁰ did not find an association with multiple myeloma.

The role of drugs has been suggested by case reports of myeloma following use of phenytoin¹⁸¹ and sulfapyridazine.¹⁸² Friedman⁸³ ascertained the use of phenytoin and other drugs among multiple myeloma cases and controls. Propoxyphene use was predictive for multiple myeloma (not shown), but no association was observed for phenytoin. In the case control study by Liner et al.,¹⁶⁴ found for prior use of phenytoin, phenobarbital, diaze-

smoke exhaust from a nearby diesel engine parts plant. Of these, weekly insecticide spray was the heaviest exposure and may be the most incriminating. A variety of sprays had been used, some of which contained pyrethrins and perhaps benzene.¹⁸⁸

In 1983, Kyle and Greipp¹⁸⁸ introduced the first report of multiple myeloma in successive spouses. In one instance, a husband had two wives in whom myeloma developed. In the second instance, a woman had two husbands who died from multiple myeloma. Exposure to chemicals, radiation, and other environmental and infectious agents was unremarkable in both situations; however, both husbands who died of myeloma had been exposed to benzene in their occupations as mechanics. McCrea and Morris¹⁹³ studied three families in Northern Ireland in which multiple myeloma occurred in two first-degree relatives concurrently. The monoclonal type of immunoglobulin varied in both cases within each family. Recently, several case control studies have been published that examine the occurrence of multiple myeloma and other disorders in related family members.¹⁹⁴⁻¹⁹⁶ Results from a case control study of multiple myeloma conducted in North Carolina revealed a nonsignificant elevated risk of multiple myeloma associated with a history of multiple myeloma among first-degree relatives.¹⁹⁴

Linet et al.¹⁹⁶ interviewed myeloma cases and controls in Baltimore for family history of autoimmune disorders and cancer among first-degree relatives. Results indicated a statistically significant risk of multiple myeloma associated with family history of autoimmune disorder (mainly rheumatoid arthritis), systemic lupus erythematosus, pernicious anemia, and leukemia.¹⁹⁵

In a recently published case control study,¹⁹⁵ multiple myeloma cases had a higher proportion of first-degree relatives with degenerating or demyelinating central nervous system diseases than did control subjects. Bernard et al.¹⁹⁷ previously noted an association between multiple sclerosis and lymphomas and leukemias. Risk was elevated for cases who had a family history of Parkinson's disease and multiple sclerosis. In addition to shared genetic susceptibility for these diseases among family members, a second environmentally based etiologic step may be required for pathogenesis.

Genetic Marker Studies

Over the past 10 years, several genetic studies of multiple myeloma have been conducted to determine the similarities and differences that myeloma cases and controls have with respect to immunogenetic markers.¹⁹⁸⁻²⁰¹ Ludwig and Mayr²⁰¹ tested three groups of Caucasian patients who resided in the vicinity of Vienna, Austria, for ABO blood group, G1m and Km immunoglobulin complex allotypes, and human leukocyte antigens (HLA) in an effort to describe susceptibility to multiple myeloma. No differences for HLA-A, -B, and -C loci, G1m and Km immunoglobulin allotypes, and ABO blood groups were noted between multiple myeloma patients and con-

tam, propranolol, ibuprofen, diet drugs, and stimulants (not shown). Use of laxatives was significantly associated with risk of multiple myeloma.

The role of occupational exposures on the risk of multiple myeloma remains unclear. To date, the most consistent association has been observed for farming occupations. The epidemiologic literature has found nonspecific associations for metal, rubber, benzene, wood, leather, textile, petroleum, and miscellaneous occupations and industries. However, given the wide variety of exposures incurred in all these areas, links and causal associations with specific chemical agents and type of work are lacking. None of these associations explains the continuing increase of multiple myeloma in the United States.

FAMILIAL AND GENETIC FACTORS

Familial occurrence of myeloma is well established, and a previous review documents that the median age and sex ratio of the 75 reported familial cases resemble those of nonfamilial cases.¹⁰ Although there continue to be reports of siblings affected with myeloma, no evidence has been presented that conclusively implicates multiple myeloma as an inherited disease. Additional research has been conducted to ascertain genetic markers and environmental variables that correlate with multiple myeloma.

Case Reports Among Siblings and Spouses and Other Family Members

Several reports from the past decade document multiple myeloma occurring among siblings.^{183,184} In a review of 37 families with at least two members with myeloma, Shoenfeld et al.¹⁸⁴ noted that the disease occurred among siblings in 25 of these families. Patients with familial myeloma did not differ significantly from those with nonfamilial myeloma with respect to sex, age, distribution of monoclonal proteins, and other clinical data. Isobe et al.¹⁸³ reported multiple myeloma in a brother and sister. The siblings produced different monoclonal immunoglobulins, IgA-k and IgG-k. Ig levels among three children of the sister indicated that all had decreased IgM levels.

Cases of multiple myeloma among spouses have been reported for many years.¹⁸⁵⁻¹⁹² and suggest the role of environmental factors in myeloma etiology. In a report of a multiple myeloma cluster, Kyle et al.¹⁹⁰ noted that two of the six cases were husband and wife. None of the cases appeared to share any unusual exposures, and the cause of the cluster remains unknown.

In 1984, Linet¹⁹¹ reported chronic lymphocytic leukemia in a husband and multiple myeloma in a wife. The diagnoses were made approximately 1 year apart. The couple encountered several shared environmental exposures, including interior wall paint, insecticide spray, embalming fumes or fluid from a work uniform, and

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New research on chromosomal aberrations and oncogenes in myeloma may shed light on the pathogenic mechanism of the disease as well as provide genetic information that may be useful in the prediction and prognosis of myeloma and other B-cell malignancies. While the role of CAS and multiple myeloma is not well understood, future studies should incorporate laboratory-based immunologic measures to explore possible mechanisms within the immune system.

Well-documented risk factors include radiation and certain occupational exposures, such as farming or pesticide use, or both. Radiation-induced multiple myeloma does not fit the age pattern seen for radiogenic leukemia⁹³ (i.e., increases at earlier ages). Instead, radiation appears to amplify the risk of multiple myeloma among exposed groups at the usual age of diagnosis for this cancer. While associations of myeloma with other exposures (e.g., metals, rubber, benzene, wood, petroleum, CAS) have been documented in this review, consistent definitions of the implicated exposures are lacking, making causal inferences with myeloma difficult. Plausible conclusions about myeloma risk on the basis of available epidemiologic studies may be hampered by failure to consider an adequate latent period of the exposure, in addition to the lack of precise and accurate exposure information.

The causes of multiple myeloma and related dyscrasias are largely unknown. Multiple myeloma is a disease of older age. In the United States, myeloma rates are increasing dramatically for both blacks and whites; however, black rates remain higher than white rates. Internationally, incidence rates in industrialized nations are higher than in developing nations, which may be a reflection of greater access to health care and more aggressive cancer registry coverage in the industrialized nations. Socioeconomic status measures have not shown a consistent relationship with myeloma incidence, mortality, and survival. It is likely that other factors, such as availability and level of medical care, not measured by socioeconomic status play a more direct role in myeloma risk.

CONCLUSIONS

In myeloma will become more meaningful. biologically relevant definitions of CAS, the role of CAS immunogenetic measures of immune function and more further laboratory-based investigations that incorporate item used in fighting various disease agents. Perhaps with acerbities and effector mechanisms of the immune sys-

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