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*EPIDEMIOLOGY OF MULTIPLE MYELOMA**

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Multiple myeloma, a plasma cell tumor arising in the bone marrow, is a rare cancer with an elusive etiology. According to 1994 estimates by the American Cancer Society, the 12,700 cases and 9,800 deaths from multiple myeloma occurring annually in the United States account for approximately 1.0 percent of all newly diagnosed malignancies and 2.0 percent of all cancer deaths.[1]

DESCRIPTIVE EPIDEMIOLOGY

Mortality

Age-specific mortality data have shown that rates increase exponentially beginning at age 30 and peaking at age 80 and older among whites and blacks of both sexes.[2,3] Mortality rates are consistently higher among men than women and among blacks than whites in each age group, although the male/female ratio is greater at older ages than at younger ages, and the black/white ratio is 3.0 among persons under age 50 compared with 1.5 among older individuals.[2,3]

Since 1950, age-adjusted mortality rates have risen continuously; in 1985 to 1989 such rates were approximately 2.3 and close to 4.0 times those in 1950 to 1954 among whites and nonwhites, respectively (National Center for Health Statistics, unpublished data). These increases were among the highest observed for any cancer during this time interval.[1,3] Rates for blacks, monitored separately from data for nonwhites (consisting of the combined group of American blacks, Asians, and Indians) since 1970, have shown the greatest proportional increase among all racial groups, increasing 30 percent for men and 46 percent for women between 1970 to 1974 and 1985 to 1989. During the last two decades, the highest age-adjusted myeloma rates have been observed in black men, followed by black women, and then white men, with the lowest rates occurring in white women.[2,3]

To further evaluate the increases in mortality during the past four decades, we examined rates according to age group and year of birth to determine whether (1) the increases were confined to certain age groups or were seen among adults of all ages, and (2) persons born in earlier time periods had a similar or different mortality experience than those born more recently. As shown in Figure 24-1, the increase in mortality during the past four decades occurred primarily among older whites and blacks of both sexes, with little change among persons under age 50. The increases were progressively more rapid in the older age groups. The **nsk** for multiple mveloma rose among individuals born in the late 1800s and early 1900s, with more recent birth cohorts experiencing little change in risk.

International mortality data have revealed that the highest rates occur in northern Europe, North America, Australia, and New Zealand, with the lowest rates in Japan, Yugoslavia, and Greece.[4] Based on 1960 to 1989 mortality data from the World Health Organization files, the rates of increase in myeloma mortality have diminished over the past three decades. The largest proportional increases have occurred in the older age groups for both women and men. Greater increases were also observed in countries with lower baseline death rates, and rates are now stable in most

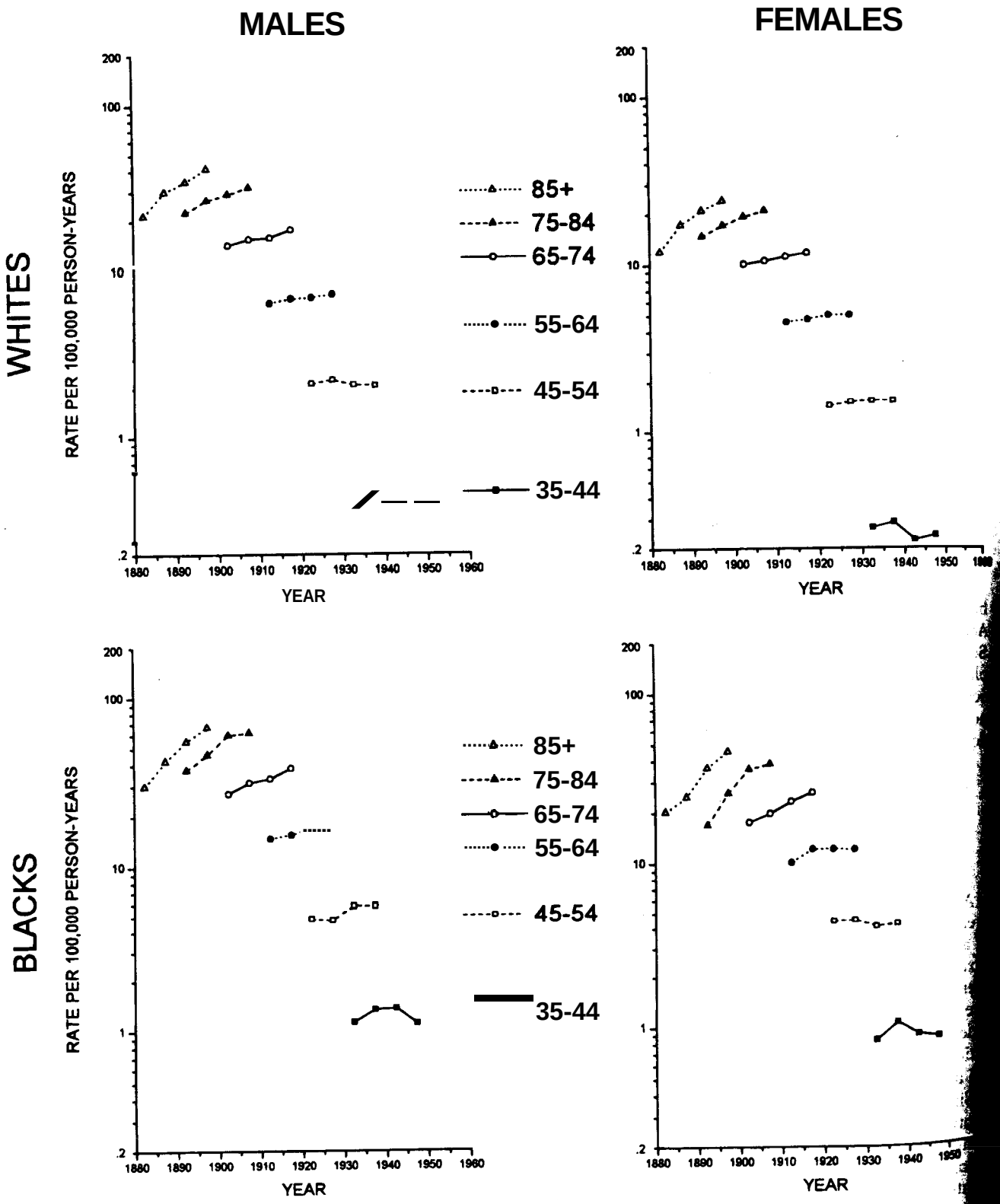


Fig. 24-1. Trends in U.S. age-specific mortality rates for multiple myeloma by cohort year of birth: 1880–1960 by race and gender.

ntries where previously the rates were high[4]; these terns may be partly related to improvements in gnosis.

Incidence

Incidence data were collected from several geo-aphic areas during the 1969 to 1971 Third National ancer Survey and have been obtained on an ongoing sis since 1973 by the Surveillance, Epidemiology, and d Results (SEER) Program.[5] A distinctive feature of ultiple myeloma is the late age of onset. Multiple my-oma onset is rare prior to age 30; thereafter, age-spe-ic incidence rates rise exponentially with age, with e rate of increase less rapid at older ages (Fig. 24-2). all age groups, multiple myeloma incidence rates are ore than twice as high in blacks than they are in hites, and higher in black women than in white en.[2,6] The male/female ratio is greater among older an among younger adults for both blacks and whites. cidence curves are similar to mortality curves in ape, with age-specific incidence higher than the cor-sponding mortality rates.[2]

In contrast to the notable increases in national age-djusted mortality rates, particularly for blacks, the in-dence of myeloma in five geographic areas (Atlanta, etroit, San Francisco-Oakland, Connecticut, and owa) rose only modestly between 1970 and 1990 (Fig. 4-3).[3,5] The incidence among whites rose more rapidly uring the 1970s than during the 1980s. Data from a U.S. community in which population-based incidence rates for myeloma have been monitored since 1945 also demonstrated a small increase between 1945 to 1977 and 1978 to 1990.[1] Similarly, between 1950 and 1979, the incidence of myeloma rose only slightly in Malmo, Sweden, where comprehensive medical surveillance among the elderly has been the norm for several decades.[8]

During the two decades shown in Figure 24-3, age-adjusted incidence rates were highest among black men, followed by black women, and then white men; they were lowest among white women.[2,3] Although small numbers are involved, native Hawaiians are characterized by a higher age-adjusted incidence of myeloma than whites in Hawaii, and Chinese and Japanese in San Francisco-Oakland and Hawaii have rates lower than whites in those areas.[2] In New Mexico, myeloma rates for American Indians were similar to those of Anglos, but higher than those of Hispanics.[2]

Comparisons of cancer registry incidence data should be made cautiously because the populations served may vary with regard to completeness of case ascertainment, accuracy of diagnosis (e.g., histopathology versus clinical characterization and/or death certificate only), and quality and availability of medical care, particularly among the elderly. Internationally, rates vary approximately 10-fold and are higher in men than women in virtually all populations (Fig. 24-4).[9] For both sexes, the highest incidence is reported among New Zealand Maoris, U.S. blacks in Los Angeles and the

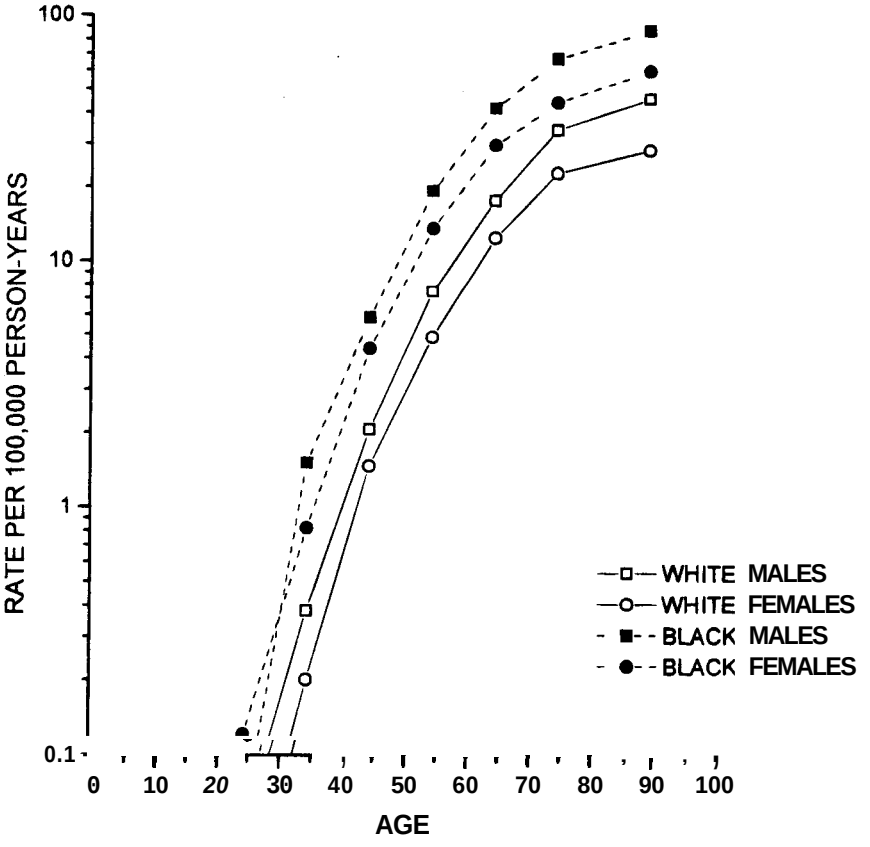
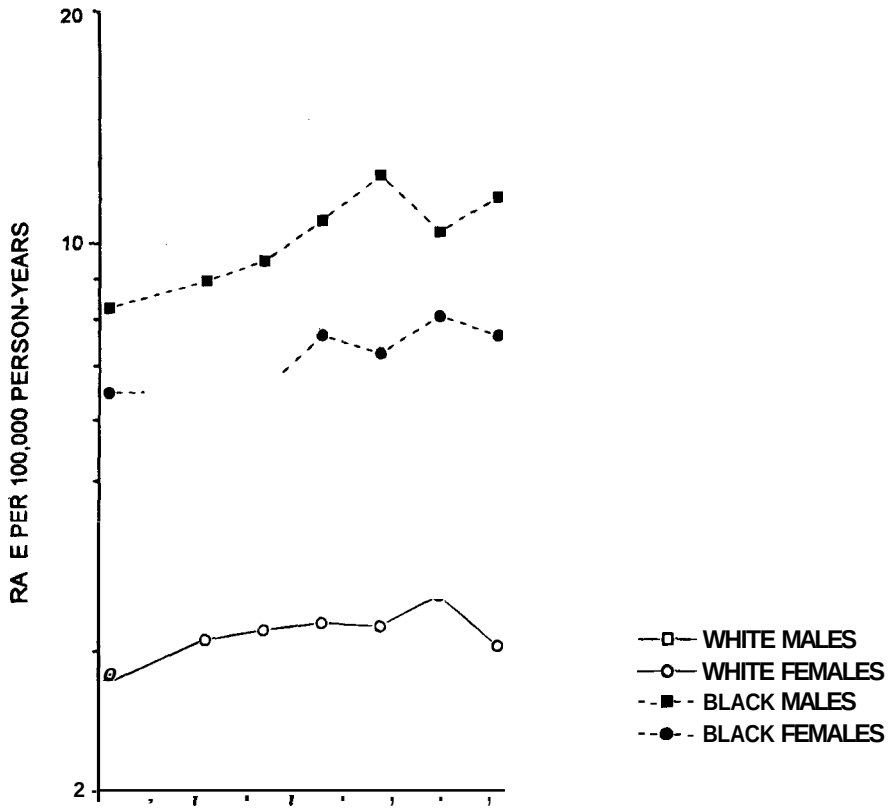


Fig. 24-2. Age-specific incidence rates for multiple myeloma by race and gender for nine SEER areas, 1975–1991.


20
10
2
RA E PER 100,000 PERSON-YEARS
WHITE MALES
WHITE FEMALES
BLACK MALES
BLACK FEMALES

race.[10–12]

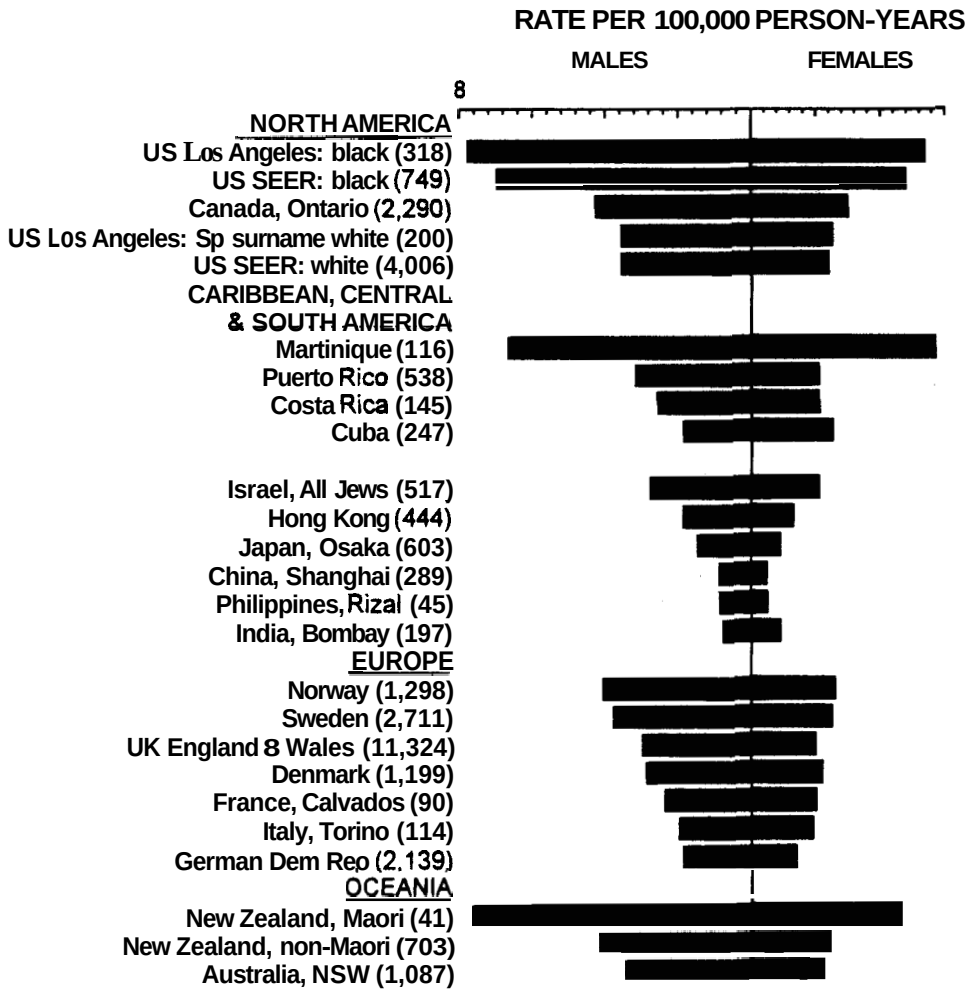


Fig. 24-4. International variation in multiple myeloma incidence (age-adjusted, world standard) by gender, 1983–1987. (Data from Parkin et al.[9])

findings of an increased myeloma risk associated with atomic bomb irradiation have been refuted in a recent report of myeloma incidence data for the years 1950 to 1987; no evidence of an excess risk of myeloma or a significant dose response was observed.[16] Differences between the earlier data sets and the present data were evaluated to determine the reasons for this disparity. In the most recent report,[16] it was determined that the change in the risk estimates was due to more complete follow-up (an additional 12 years of incidence data), more stringent diagnostic criteria, and the exclusion of myeloma cases classified as second primaries. The relationship between atomic bomb radiation and multiple myeloma is still under investigation.

Radiation-Related Occupations

The mortality experience of radiologists and other radiation-exposed workers has provided additional information on multiple myeloma risk due to radiation. An excess of myeloma deaths among American radiologists was first reported over 30 years ago.[17] More recently myeloma risk was reported to be two times higher among radiologists exposed to lower doses of radiation than among physicians in other specialties.[18] Among over 27,000 Chinese diagnostic x-ray workers, however, no excess incidence of myeloma was observed over a 30-year period when compared with medical workers unlikely to have had occupational x-ray exposure.[19]

Employment in nuclear facilities and risk of myeloma has been investigated in several studies. Although mortality from myeloma was lower than that observed in the general population (probably due to the healthy worker effect), an association between this cancer and radiation exposure was seen in two nuclear facilities[20,21] and among a large cohort of British radiation workers from many facilities.[22] No myeloma deaths (with a 10-year lag) were observed among workers in the Oak Ridge National Laboratory or in the Rocky Flats Nuclear Weapons Plant.[23]

Residential and Atmospheric Radiation Exposures

Investigations of the relation of residential proximity to nuclear facilities have provided little evidence of an increased risk of multiple myeloma.[24–26] In addition, a

recent U.S. nationwide mortality survey reported similar myeloma mortality among residents of counties with and without nuclear facilities.[27]

Increases in multiple myeloma incidence and mortality have been observed among British military men who participated in atmospheric nuclear weapons tests when compared with unexposed controls.[28] Among New Zealand military participants in the same nuclear weapons tests, no incident myeloma cases were seen over a 30-year period.[29] Exposures incurred by the New Zealanders may have been lower since they participated in fewer tests than the British subjects.

Diagnostic and Therapeutic X-Rays

Diagnostic x-ray exposure has not been clearly linked with multiple myeloma. Most epidemiologic studies have reported no association with diagnostic x-rays.[30–35] Among members of a prepaid health plan, no excess risk of myeloma associated with diagnostic x-rays was observed, although a trend with increasing number of x-rays received was seen regardless of the lagging interval.[36] Of historic interest is the significantly increased risk of myeloma observed among women who had received injections of Thorotrast (*a*-emitting x-ray contrast medium) for cerebral arteriography[37]; fortunately Thorotrast has not been used for many years because of the recognized health risks.

Studies of the effects of therapeutic irradiation on myeloma risk have been inconsistent. A few case control interview studies have shown an excess risk of myeloma with radiation therapy, and others have not.[34,35,38] A follow-up study of approximately 14,000 patients with ankylosing spondylitis who received a single course of x-ray treatment revealed a nonsignificant elevated risk of myeloma.[39] Among over 180,000 women treated for cervical cancer, no overall excess risk of myeloma was associated with radiation therapy; however, a trend analysis revealed significantly increased risks after the first 10 years of treatment.[40]

Occupational Exposures

The role of occupational exposures on the risk of multiple myeloma is not clear. In case control studies, evaluation of occupational associations is often based on employment in a specific industry or occupation. Because of the small number of individuals employed in any single occupation, statistical power is often insufficient for analysis by job title. Although analysis by industry type has provided some etiologic clues, such information is usually not specific enough to identify particular workplace exposures. Similarly, cohort studies of specific occupational groups have infrequently reported occupational associations with multiple myeloma, because of the rarity of this malignancy. The few studies demonstrating excess risks among occupational cohorts have generally identified small numbers of cases, sometimes as few as three. Most case-control and cohort studies have not included detailed exposure assessments or measurements; thus, specific workplace exposures associated with increased myeloma risk have not been thoroughly evaluated.

Agricultural Occupations and Exposures

A number of epidemiologic studies have evaluated the risk of myeloma among agricultural workers with positive associations reported by many but not all of the studies.[41–44] Suggested agriculturally related exposures that may be associated with an increased myeloma risk include grain dusts,[34,45] engine exhausts and fuels,[38] contact with farm animals,[46,47] and pesticides.[44] Numerous studies have investigated the association between potential pesticide exposure and multiple myeloma; some have reported elevated risks and others have not.[41–43] Only a few studies have evaluated use of specific pesticides.[46–48] In a case-control study of white men in Iowa, nonsignificantlv increased risks of myeloma were associated with handling certain pesticides. Exposure to phenoxv herbicides was significantly linked with myeloma risk in a Swedish study,[47] but this finding was not confirmed in the Iowa study.[48]

Metal Workers

Workers in various metal occupations and industries have been reported to have increased mveloma risk, although these findings have not been consistent.[49–52] Significantly elevated risks have been observed among smelter and metallurgy workers,[51] machinists,[50] and nickel refinery workers.[49] By contrast, other studies have reported no appreciable associations with occupational metal exposures.[53–58] Inadequate exposure data have made it difficult to assess the specific metal exposures that could explain the observed elevations in risk.

Rubber Manufacturing

Some epidemiologic studies have suggested an association between multiple myeloma and employment in the rubber manufacturing industry.[30,59–62] Rubber workers can be exposed to a myriad of substances, including organic solvents, plastic monomers, and rubber additives. The specific exposure(s) linked with excess occurrence of myeloma has not been identified in any of these studies.

Other Industries

At least a dozen studies have investigated the associations between myeloma risk and employment in the wood, lumber, or paper manufacturing industries. Most of the studies showed little or no elevation in myeloma risk.[30,31,34,38,63–68] An excess of deaths caused by cancers of the lymphatic tissue has been observed in several petroleum refinery populations[69–72] but not in others.[73,74] An association between myelloma and employment in textile processing has been suggested in two linkage studies of cancer incidence and occupational census or pension data.[55,75] By contrast, three cohort studies of textile workers revealed no significant

increase in deaths due to multiple myeloma.[76,77a] Excess risks of myeloma among workers employed in the paint manufacturing industry have been noted in several studies.[31,57,78,79]

Specific Occupational Exposures

Benzene has been suggested as a possible etiologic agent for multiple myeloma.[80–82] Although an elevated risk of myeloma has been observed among some benzene-exposed populations of workers ranging in size from 250 to 1,165,[80,82] a cohort study of over 74,000 Chinese benzene-exposed workers demonstrated no excess of myeloma.[83]

Some cohort investigations of chemical workers have revealed excess myeloma mortality,[84,85] while other studies have not.[86,87] Chemical workers have been exposed to a variety of established or suspected carcinogens such as piperazine, urethane, ethylene oxide, and epichlorohydrin,[88] as well as antioxidants and nitrile ~Among aircraft maintenance workers, a significant increase in myeloma mortality was observed for men exposed to methylene chloride and for women exposed to chlorinated and aromatic hydrocarbons, including perchloroethylene.[88] A positive association between myeloma and asbestos exposure has been reported in some,[31,58,89] but not all, studies.[30,57,90,91]

Life-style Factors

Several studies of multiple myeloma have evaluated the role of personal life-style factors, including cigarette and alcohol consumption, hair dye application, and medication use. To date, the possible role of diet has not been fully evaluated.

Cigarette Smoking and Alcohol Consumption

Based on the study findings to date, cigarette smoking and alcohol consumption do not appear to be risk factors for multiple myeloma.[30,34,58,92–99] Only one study, a follow-up of Seventh Day Adventists, observed an increased myeloma risk among smokers.[98] No epidemiologic study has reported a relation between alcohol consumption and myeloma.[30,34,58,96]

Hair Dyes

Personal use of hair dyes was evaluated as a risk factor for myeloma in three recent case control studies and two prospective studies.[102–103] Elevated myeloma risk was observed among women who dyed their hair, with the highest risk among users of permanent hair dyes and dark hair coloring products.[99] In another case-control study, no excess risk was found; however, this finding was based on the answer to a single question on regular hair dye use.[102] Men who use hair dye have also been reported to have an elevated risk of myeloma that increases with duration of hair dye use.[101] The American Cancer Society prospective mortality study observed an increased risk of multiple myeloma among woman who dye for 20 years or greater,[103] however, the Nurse's Health Study did not confirm this finding.[104] Epidemiologic studies investigating the association between employment as a beautician or cosmetologist have been inconsistent, with some reporting excess risks[104,105] and others describing no associations.[55,106]

Medication Use

Prescription and over-the-counter medications have been evaluated as myeloma risk factors in several studies.[33,58,107] Significant associations have been observed for myeloma with the use of laxatives[58] and erythromycin.[107] Nonsignificantly elevated risks have been reported for phenobarbital, diazepam, propranolol, ibuprofen, diet drugs, and stimulants.[107]

Precursor Medical Conditions

Several precursor medical conditions have been investigated as possible risk factors for myeloma, including monoclonal gammopathy of undetermined significance (MGUS). A wide variety of other nonmalignant medical conditions, postulated to cause repeated or chronic antigenic stimulation, have also been suspected to play an etiologic role.

Monoclonal Gammopathy of Undetermined Significance

MGUS, considered to be a potential precursor condition for multiple myeloma, is a typically asymptomatic, benign disorder involving proliferation of plasma cells and production of M components.[108] In one of the largest series of MGUS patients followed to date, 19 percent of the 241 MGUS patients developed multiple myeloma within 2 to 29 years.[109] Alterations of interleukin-6 (a growth factor) expression or mutations in oncogenes or tumor suppressor genes (or both) may play a role in the malignant transformation of MGUS (see Ch. 28). However, the factors that may initiate or promote these changes are unknown at the present time.

Chronic Antigenic Stimulation

Based on results from animal studies of induced plasmacytoma ~and on clinical reports,[110–112] it has been postulated that repeated or chronic antigenic stimulation (CAS) of the immune system may lead to myeloma.[42] A number of case-control studies have explored the CAS hypothesis by evaluating myeloma risk associated with past history of chronic infectious, inflammatory, connective tissue, autoimmune, and allergy-related disorders.[42,43] Although elevated myeloma risks have been observed in some investigations among persons with specific medical conditions (e.g., allergic conditions,[34,113] musculoskeletal disorders and disc disease,[114] and rheumatoid arthritis[115,116]), other studies of individuals with these conditions have shown no excess of myeloma.[43,58,117] Such inconsistencies sug-

gest that evaluation of CAS, with this approach does not provide sufficient information to assess the role of immune stimulation adequately in the development of multiple myeloma.[113,118] Even when the CAS hypothesis is evaluated by grouping medical conditions according to their biologically or immunologically related immune response mechanisms, the findings do not support a causal relationship between CAS and myeloma.[113]

The role of viruses in the etiology of multiple myeloma is currently unknown.[119] Several patients with the acquired immunodeficiency syndrome (AIDS) have been reported to have multiple myeloma;[120,121], however, a population-based study did not observe an AIDS-related increase in multiple myeloma incidence.[122]

Familial and Genetic Factors

Familial aggregation of myeloma among first-degree relatives has been documented in numerous case reports, and epidemiologic studies have reported higher frequencies of myeloma and other hematopoietic cancers among cases compared with controls.[124–126] Recent research has focused on various genetic markers including human lymphocyte antigens (HLA), chromosomal abnormalities, and oncogene and tumor suppressor gene mutations.

Familial Cancer

Reviews of the published literature on familial aggregation of multiple myeloma from 1957 to 1987 have revealed a total of 104 cases in 49 families.[123,127] More recent case-control studies have reported a higher frequency of multiple myeloma in related family members among cases compared with controls; however, the numbers were too small to reach statistical significance.[124–126] Excesses of nonmalignant conditions such as autoimmune disorders[127] and degenerative central nervous system diseases.[128] have also been observed among relatives of myeloma patients. By contrast, reports of cases of myeloma among spouses of myeloma patients suggest an environmental role in the etiology of this malignancy.[129–133]

Genetic Marker Studies

Early studies investigating the relationship between HLA and multiple myeloma reported a link with the B locus.[41] More recently, associations have been found with the C locus: HLA-Cw5 antigen was increased among 22 myeloma cases compared with laboratory controls,[134] and HLA-Cw2 was linked with myeloma in a large population-based case control interview study.[135] The environmental and other potential risk factors that may increase myeloma risk among this subset of potentially susceptible individuals have yet to be identified.

Chromosomal Abnormalities

Data from two large case series investigating cytogenetic abnormalities in plasma cell disorders have indicated frequent involvement of chromosomes 1 and 14.[136,137] The 14q+ abnormality occurred in 20 to 25 percent of the cases.[136,137] The t(11;14) and t(11:18) translocations have been observed in myeloma and other B-cell disorders.[138] Other structural and numerical chromosomal aberrations in myeloma patients have also been reported (see Ch. 27).[138] Cytogenetic studies have been a useful aid in predicting prognosis and monitoring remission of myeloma patients.[137] The establishment of etiologic associations with specific chromosomal abnormalities is difficult and has yet to be pursued in epidemiologic investigations. Cytogenetic investigations have led to the identification of the tumor-related genes, thereby providing new information about the pathobiology of myeloma.

Oncogenes and Tumor Suppressor Genes

Several oncogenes and tumor suppressor genes occur at sites of some of the known breakpoints associated with myeloma and other B-cell disorders. Chromosome 14 with the 14q breakpoint is associated with the heavy chain immunoglobulin locus. Chromosome 1 includes the *N-vas* oncogene, which has been implicated in the pathogenesis of multiple myeloma.[136] High levels of c-*MYC* gene expression have been reported in 25 percent of myeloma patients, although only a few cases presented with rearrangement of the c-*MYC* locus.[138] Overexpression of the BCL-2 oncogene has also been observed in some myeloma cases, although cytogenetic breakpoints have not been identified.[137] In addition to oncogene activation, abnormalities in tumor suppressor genes are evident among myeloma patients. Alterations in the *p53* gene on chromosome 17 and the RB-*1* gene on chromosome 13 have been reported in myeloma studies.[137] Identification of the factors that contribute to oncogene expression is an important step in predicting which individuals are at highest risk for developing myeloma.

CONCLUSIONS

Multiple myeloma is an intriguing malignancy from epidemiologic, biologic, and clinical perspectives. It is one of only two hematopoietic cancers (the other is chronic myeloid leukemia) characterized by higher incidence among blacks than whites, and to date epidemiologic investigations have been unable to determine the reasons for these racial differentials.

In general, the causes of multiple myeloma are largely unknown. Several occupations and workplace exposures have been suggested as potential risk factors, but the epidemiologic evidence has been inconclusive. The strongest associations have been with agricultural occupations and those involving exposures to ionizing radiation and organic solvents. Recently, the use of hair

dye has been linked with myeloma, although additional studies are needed to clarify the risk. Nonoccupational exposures including diagnostic and therapeutic radiation, cigarette smoking, and alcohol consumption do not appear to be related to myeloma.

To date, epidemiologic research has primarily focused on the possible role of environmental risk factors in the Occurrence of multiple myeloma. The role of oncogene and tumor suppressor gene mutations in the pathogenesis of multiple myeloma is an emerging area of investigation. Incorporation of laboratory-based measures of genetic aberrations in future epidemiologic studies will be instrumental in understanding the complex interactions between genetics and environmental/life-style risk factors on the development of multiple myeloma.

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