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THE EPIDEMIOLOGY OF MULTIPLE MYELOMA

Denise A. Riedel, MPH, and Linda M. Pottern, PhD, MPH

Multiple myeloma, a plasma cell tumor arising in the bone marrow, is a rare cancer with an elusive etiology. Mortality rates for myeloma were not readily available until 1950, at which time myeloma was removed from the general category of "lymphoreticular malignancies" and assigned a unique ICD code (203) in the Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death.[183] This recent ability to track myeloma rates provided a basis to study the descriptive epidemiology, which has since been well reported. However, risk factors for myeloma remain obscure.

DESCRIPTIVE EPIDEMIOLOGY

Incidence in the United States

According to currently available US incidence data (1984 to 1988) from the Surveillance, Epidemiology, and End Results (SEER) Program, multiple myeloma accounts for 1.0% of all malignancies in whites and 2.0% in blacks.[144] The average annual age-adjusted (1970 US standard) incidence rates per 100,000 for whites are 4.7 in men and 3.2 in women, whereas for blacks, they are nearly double, at 10.2 in men and 6.7 in women.[144] Socioeconomic factors, such as household size and family income, do not appear to explain this difference in rates between blacks and whites.[87] Of all the lymphoreticular neoplasms, multiple myeloma accounts for 31% among blacks and 13% among whites, whereas leukemias occur equally in blacks and whites at 31%.[144] The incidence of multiple myeloma has been fairly stable among US whites since the early 1970s (Fig. 1); however, incidence among blacks increased from the 1970s into the early 1980s when it peaked, then decreased slightly.[144] Poverty, as indicated by percent of persons with incomes below the poverty level, did not explain

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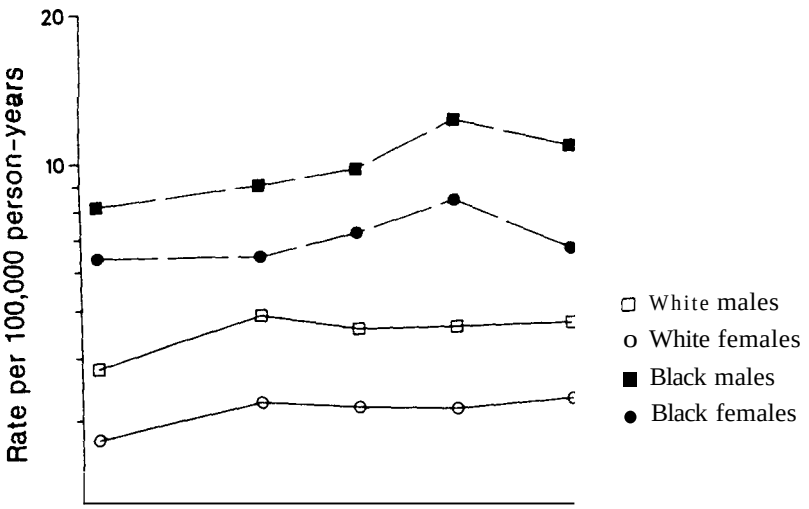

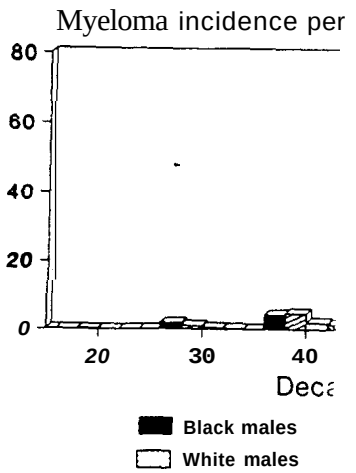

Figure 2. Multiple myeloma average a to 1988. Age plotted as the average of years. *(From* Ries LAG, Hankey BF, M Washington, DC, US Government Prir 2789].)

the excess incidence among blacks, because the rates remained twice those for whites after adjustment.[117]

SEER data for the period 1975 to 1985 indicate that other ethnic groups including native Hawaiians, female Hispanics and female American Indians from New Mexico,' and Alaskan natives[95] also experience higher myeloma rates relative to US whites from the same geographic region. Ethnic groups having lower incidence rates relative to their geographic white counterparts include Chinese and Japanese populations from Hawaii and San Francisco. Rates of the Filipino population of San Francisco and male Hispanics and male American Indians approximate those of whites.[46]

A distinctive feature **of** myeloma is its late age of onset. Compared with the median age of diagnosis for all cancer in the United States for men and women, ages 68 and 66, respectively, the median age at diagnosis for myeloma is slightly higher, 69 for men and **71** for women.'* The average annual age-specific incidence rates increase sharply with age regardless of race or gender, and the rates for blacks are more than twice as high as those for whites at virtually every age (Fig. **2).** A male predominance is seen in both races."'

Although definition of "urban" and "rural" vanes among geographic regions,[52. 124] the incidence for men in urban areas tends to exceed that in rural areas, whereas the rates for women are evenly distributed. However, differences by gender may seem small, because multiple myeloma incidence overall appears to be evenly distributed between urban and rural areas in **13** populations from around the world, including the United States."[52]

International Incidence

Incidence of multiple myel registries from around the world international cancer registry incic the populations served may vary (e.g., pathology versus death c diagnostic precision.'?'[132, 176, 177] In women. Incidence rates in nort American white populations, wht Kingdom, eastern Europe, and ! observed in Asian populations.

Multiple myeloma incidenc including Israel, the Scandinavia vakia, Australia, and New Zeala incidence over time. In Czecho myeloma incidence increased fro from 1955 to 1979,[137] in Malmo, S from 1943 to 1962. In the Danish 1963 to 1982, most likely due to no increase in myeloma was ol 1980s.[100] In general, the increasin been followed recently by a le observed among whites in the U

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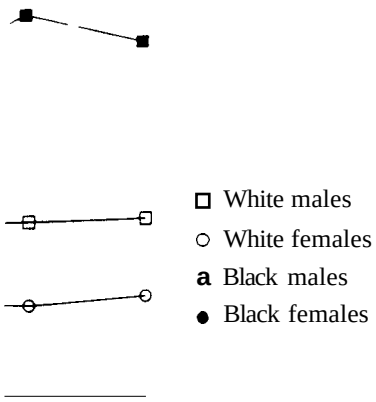

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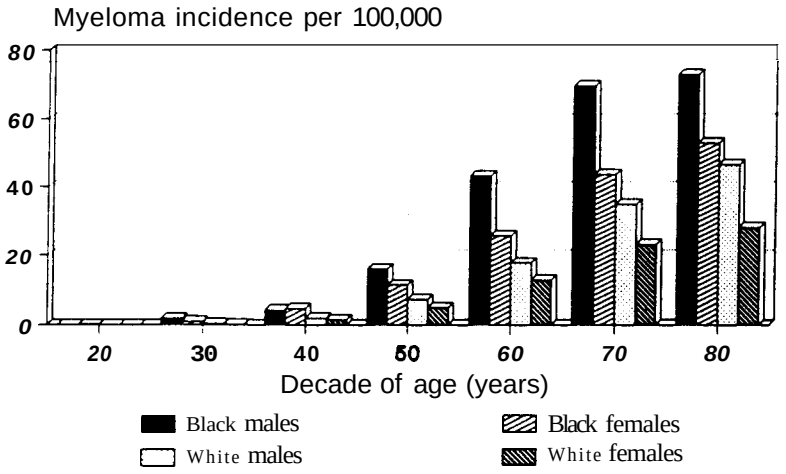

Figure 2. Multiple myeloma average annual age-specific incidence for United States, 1984 to 1988. Age plotted as the average of two five-year age groups. Rates per 100,000 person-years. (*From* Ries LAG, Hankey BF, Miller BA, et al: Cancer Statistics Review 1973–1988. Washington, DC. US Government Printing Office, 1991 (DHHS publication (NIH) No. 91–2789].)

International Incidence

Incidence of multiple myeloma from selected population-based cancer registries from around the world is shown in Figure 3.[124, 176, 177] Comparisons of international cancer registry incidence rates must be made cautiously because the populations served may vary with regard to accuracy of case ascertainment (e.g., pathology versus death certificate only), level of medical care, and diagnostic precision.[124, 132, 176, 177] In most countries, men have higher rates than women. Incidence rates in northern Europe are similar to those in North American white populations, whereas the rates are slightly lower in the United Kingdom, eastern Europe, and South America. Substantially lower rates are observed in Asian populations.

Multiple myeloma incidence surveys conducted in different countries including Israel, the Scandinavian countries, Switzerland, France, Czechoslovakia, Australia, and New Zealand[28, 49, 79, 100, 103, 127, 137, 154, 170] also show increasing incidence over time. In Czechoslovakia[79] and Western Australia,[127] multiple myeloma incidence increased from the 1960s to the mid 1980s, in New Zealand from 1955 to 1979,[137] in Malmo, Sweden[im] from 1950 to 1979, and in Denmark[79] from 1943 to 1962. In the Danish survey, however, the rates leveled off from 1963 to 1982, most likely due to changes in diagnostic criteria. In Switzerland, no increase in myeloma was observed between the late 1970s and the late 1980s.[100] In general, the increasing incidence of myeloma over many years has been followed recently by a leveling off. This phenomenon has also been observed among whites in the United States.[47]

Comprehensive incidence data for African populations are largely unavailable. The myeloma rates that have been reported are thought to be an underestimate, mainly owing to limited diagnostic facilities and incomplete case ascertainment.[36] Multiple myeloma case series from Africa in the late 1960s and 1970s have suggested a younger median age at diagnosis than in the

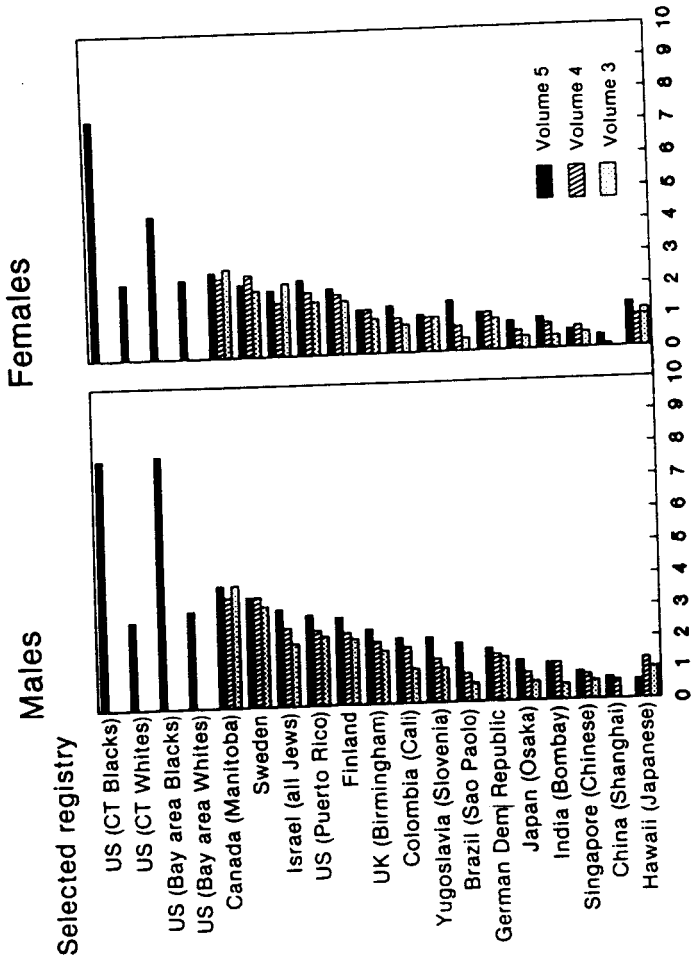

Figure 3. Multiple myeloma, age-adjusted incidence (world standard population) from selected registries. Rates per 100,000 person-years. Years are generally for 1968 to 1972 (Volume 3),[176] 1973 to 1977 (Volume 4),[177] and 1978 to 1982 (Volume 5).[124] (*From* Riedel DA, Pottern LM, Blattner WA: Epidemiology of multiple myeloma. *In* Wiernik PH, Canellos GP, Kyle RA, et al (eds): Neoplastic Diseases of the Blood, ed 2. New York, Churchill Livingstone, 1991, p 347.)

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Mortality in the United States

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International Mortality

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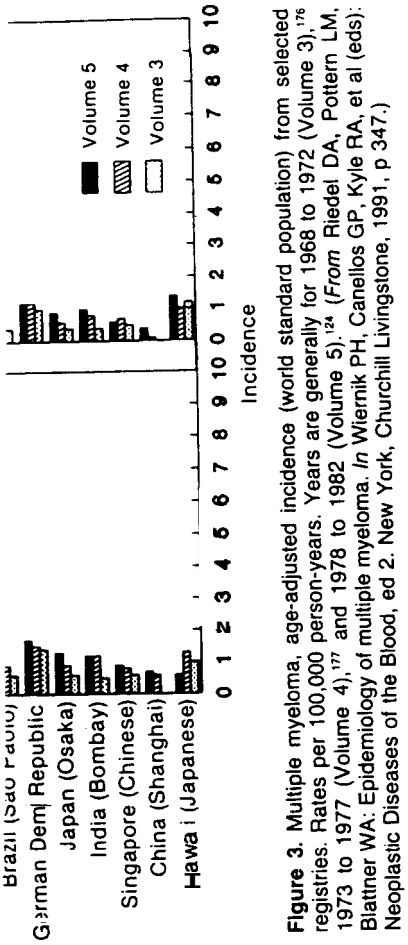

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United States, reflecting a younger population and a sizable male excess.".[143] These findings have persisted in an update of a Kenyan case series.[125]

Mortality in the United States

Historically, mortality data in the United States have been available over a longer period of time than incidence data. Myeloma mortality has been monitored since the early 1950s, whereas the SEER program has provided incidence data since 1973. Rates among nonwhites exceed those among whites for mortality as well as for incidence. Among nonwhites over age 55, mortality has increased dramatically between 1950 and 1988, whereas increases for whites over 55 have not been as great. The dramatic increases in mortality rates may be due in part to improved medical technology, particularly in older, high-risk populations,",[170] or due to a true upward shift in the risk for individuals born into the cohort of maximum risk in the late 1800s.[150] Over the past 20 years, mortality appears to have become more stable, as has the incidence. Age-specific rates reveal that myeloma mortality has increased disproportionately in older age groups since the 1950s, especially among those over age 60 years (Fig. 4). Peak mortality has shifted over time from age *60* to age *80.*

International Mortality

Multiple myeloma mortality has been increasing in a number of countries, and the increase has been most pronounced in individuals age 55 and older.* Some view the increased mortality in the older age group as a result of better and earlier diagnosis and increased longevity,[113] whereas others consider the increase to be real."

The countries where death rates have been lowest (including Greece, Japan, and Hungary) have had the largest increases for the period 1970 to 1985. This is in contrast to countries with traditionally high rates, such as Norway, New Zealand, and Finland, or countries with moderate rates, including England and Wales, and France, where the rate of increase is intermediate. The largest percent increase in mortality during the period was in the 70 to 74 age group." Because men and women have shown a similar pattern of increase, a common environmental exposure, rather than an occupational exposure, may have more influence on multiple myeloma mortality."

Survival

The prognosis for multiple myeloma is poor. Based on SEER cases diagnosed from 1981 to 1987, US blacks had a slightly higher 5-year relative survival rate than whites, *28.3%* and 26.3%, respectively.[144] The relative survival rates were higher for women than for men regardless of race: 29.3% versus 27.5% for blacks and 27.5% versus 25.0% for whites.[144] Survival is generally more favorable among those with higher income and education, regardless of race.[68, 133, 147] Other studies did not support this finding, however.".[178] In a clinical study of US multiple myeloma patients," survival was related to the patient's ability to travel to receive treatment, perhaps reflecting better prognosis. Blacks had a more favorable survival than whites after adjustment for potential

confounding variables including center."

RADIATION EXPOSURES

Exposure to ionizing radiation: myeloma. DNA, and particularly is believed to be the target of damage." Multiple myeloma occu survivors exposed to high doses suggest a link with long-term, low

Atomic Bomb Survivors

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Radiation-Related Occupations

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Increases in the incidence and who were ever employed in the US noted."" Large exposures to radium radium-containing paint to make fi were lacking. Greater incidence and length of employment than with **intr**

Diagnostic and Therapeutic X-Rays

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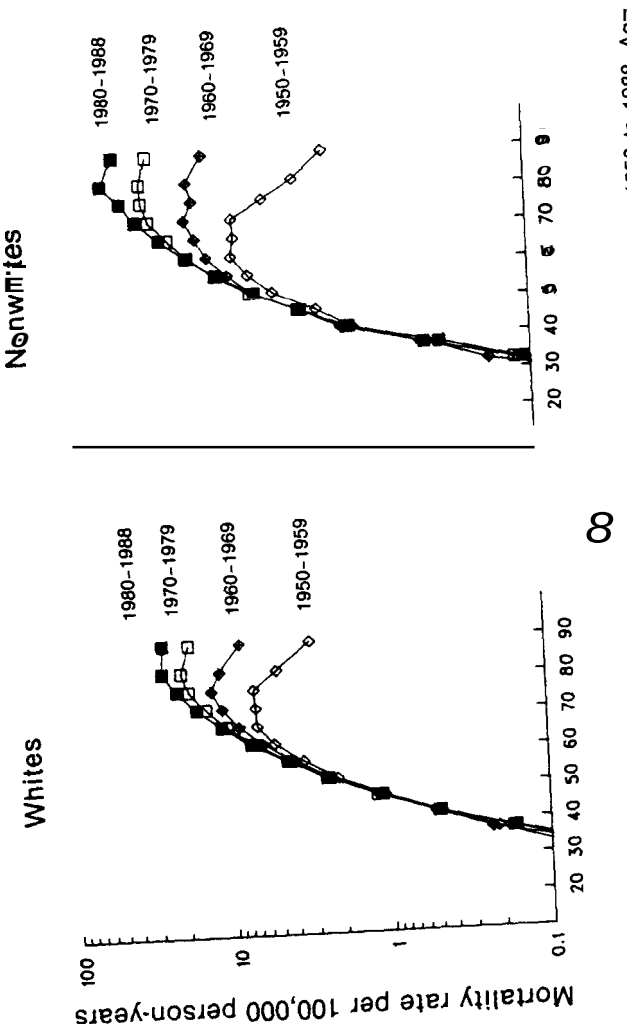


Figure 4. Multiple myeloma, age-specific mortality for US whites and nonwhites, 1950 to 1988. Age plotted at midpoint of 5-year age interval, with the exception of the 85+ interval which is plotted at age 90. (Courtesy of S. S. Devesa.)

confounding variables including age, sex, education, therapy, and treatment center.[99]

RADIATION EXPOSURES

Exposure to ionizing radiation is the most convincing risk factor for multiple myeloma. DNA, and particularly proto-oncogenes or "cancer genes" in DNA, is believed to be the target of potentially carcinogenic ionizing radiation damage." Multiple myeloma occurs after a long latent period in atomic bomb survivors exposed to high doses of radiation,[155] but studies of radiologists suggest a link with long-term, low-dose exposure to radiation.[101, 114]

Atomic Bomb Survivors

The strongest evidence linking radiation to myeloma has been provided by cancer mortality studies of atomic bomb survivors.[81, 155] Those who entered bombed areas of Hiroshima City within 3 days after the blast had nearly 60% greater risk of myeloma mortality than those not exposed.[81] Nearly one third of myeloma deaths between 1950 and 1985 among atomic bomb survivors have been attributed to the atomic radiation in 1945.[155]

Radiation-Related Occupations

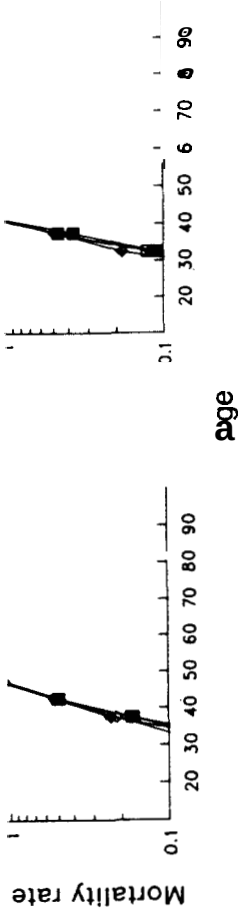
Studies on the mortality experience of radiologists and radium dial painters have provided further information on the risk of multiple myeloma due to radiation. The excess of myeloma deaths among radiologists was observed nearly 30 years ago.[101] In a more recent study, radiologists exposed to lower doses of long-term radiation had a twofold excess myeloma risk.'"

Increases in the incidence and mortality from myeloma among women who were ever employed in the US radium dial painting industry have been noted.[163] Large exposures to radium resulted from licking brushes dipped into radium-containing paint to make fine tips." Accurate measures of exposure were lacking. Greater incidence and mortality were more strongly linked with length of employment than with internal radium intake.

Diagnostic and Therapeutic X-Rays

Diagnostic x-ray exposure has not been clearly linked with multiple myeloma. Some studies of diagnostic x-ray exposure have shown a small, nonsignificant increased risk of myeloma associated with this exposure,",[59, 61] whereas others have not.[35, 41, 62] Members of a prepaid health plan had an excess myeloma risk for more frequent x-ray exposure.[18] In a study of over 27,000 Chinese diagnostic x-ray workers, no excess myeloma incidence was reported over a 30-year period when compared with workers in other medical occupations in which x-ray exposure was not likely.'"

The effects of therapeutic irradiation on myeloma risk are inconsistent.[15, 16] Studies of patients receiving therapeutic radiation for ankylosing spondylitis have suggested an association with multiple myeloma.[37, 39] Myeloma mortality increased over time since first irradiation treatment among the spondylitics,



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but the trend was not significant.]' A nested case-control study also reported a nonsignificant increase in myeloma risk for x-ray treatment.[14] The mortality experience of US women, based on cancer registry data, who were initially irradiated for cervical cancer has shown no excess of myeloma.[15]

Nuclear Facilities

Several studies have indicated an increased risk of multiple myeloma mortality among workers in the nuclear industry,[53, 66, 111, 158] but not in another study.[6] Most excesses of multiple myeloma mortality have been related to exposures between 10 to 15 years prior to death.[66, 158] In an analysis of combined mortality data from the Hanford site, Oak Ridge National Laboratory, and Rocky Flats Nuclear Weapons Plant, multiple myeloma was the only cancer with a significantly increased risk.[65] The significance was mainly driven by the high risk among the Hanford workers. These studies suggest that chronic exposure in the workplace to low levels of radiation may be involved in the development of multiple myeloma.

Investigations of residential proximity to nuclear facilities have provided little evidence of an increased risk of multiple myeloma. A recent US nationwide mortality survey found mortality from multiple myeloma among residents of counties with nuclear facilities similar to that among residents of counties without nuclear facilities.[85] Data on multiple myeloma incidence were not available in relation to the accident at the Three Mile Island nuclear power plant; however, increased rates were observed for lymphoma, especially non-Hodgkin's lymphoma.[80] Mortality from myeloma was not elevated among residents living near a nuclear facility in France compared with those living farther away.'' Other studies that have inferred radiation exposure based on residential distance from the nuclear facility''.[60] have found no association with myeloma risk and proximity to the nuclear installations.

A study of British participants in atmospheric nuclear weapons tests revealed increased risk for multiple myeloma among test participants when compared with unexposed controls.[38] More recently, a follow-up study among the New Zealand participants in the same nuclear weapons tests revealed no incident myeloma cases over a 30-year period.''' Exposures incurred by British participants may have been greater, however, because the New Zealanders participated in at most 9 of 21 tests covered in the British study.

OCCUPATIONAL AND ENVIRONMENTAL EXPOSURES

The role of occupational exposures on the risk of multiple myeloma remains unclear. The overwhelming majority of occupational associations with myeloma have been in agriculture[143] and have been most consistent for farming occupations. Nonspecific associations for metal, rubber, benzene, wood, leather, textile, petroleum, and miscellaneous occupations and industries have been reported in the epidemiologic literature. However, a very recent case-control study conducted in the Montreal area reported some elevation in myeloma risk based on detailed job descriptions.''' Owing to the wide variety of potential exposures incurred in many of the occupations, causal associations with specific chemical agents or type of work are lacking. Some studies may also be of insufficient size to detect an association.

Agriculture

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'AL EXPOSURES

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Agriculture

A number of epidemiologic studies have indicated a significant increased risk for multiple myeloma in agriculture (predominantly farming),'.[14, 23, 26, 35, 59, 62, 126, 171, 180] but a few have shown no association.[22, 25, 142, 169] Multiple myeloma has been reported by some to be associated with hog production,[26] dairy farming,'" sheep farming,"' exposure to beef cattle,'" working with farm animals,[116] and orchard farming.[137] Agriculturally related exposures linked to an increased myeloma risk include grain dust,' dusty occupations,"' aflatoxins,[130] and engine exhaust[59] from farm equipment. A study in Sweden suggested that agriculture workers may encounter exposures that evoke both allergic reactions and multiple myeloma.'" Because of the variety of associations reported in these studies, it is impossible to determine from these studies whether oncogenic zoonotic viruses, animal insecticides, agricultural chemicals, or some combination of these exposures are responsible for the increased risk of multiple myeloma.

Increased risk of myeloma has occurred among farmers born more recently,[11, 26, 137, 140] particularly in industrialized countries, which may reflect a change to modern chemical farming methods over the past 40 years.[27] Epidemiologic studies of both case-control".[26, 27, 96, 123, 138] and prospective[179] designs have explored the association of agricultural pesticides (including herbicides and insecticides) and multiple myeloma. Morns et al[123] reported a 2½-fold risk of multiple myeloma with pesticide use. Boffetta et al[14] found that risk for myeloma was not increased appreciably among those who were exposed only to farming or only to pesticides, but that risk rose dramatically for those exposed to both farming and pesticides (odds ratio = **4.3**). No association was observed between pesticide use and myeloma in an Italian study"' or among a cohort of licensed pesticide applicators.[179]

Few studies have evaluated links between specific pesticide exposures and multiple myeloma. However, herbicides potentially associated with myeloma include phenoxyacid herbicides and chlorophenols.[13, 138] Burmeister[25] found elevated myeloma risk for exposure to the crop insecticides of the organochlorine and carbamate classes, and for the dinitroaniline, thiocarbamate, and urea classes of herbicides.

Metals

Exposures to various metals have been linked with myeloma.[35, 57, 67, 105, 116, 123, 157, 159] A significant increased risk of myeloma has been observed among smelter and metallurgy workers[116] and sheet metal workers,[157] whereas nonsignificant elevations in myeloma risk have been noted for foundry workers.[67, 161] In a case-control study, myeloma was associated with lead vapors and liquid, arsenic, cadmium, and copper powder and fumes.[123] These excesses occurred among whites but not among blacks. Insufficient exposure information has made it difficult to assess whether particular metal fumes, metal dusts, or other exposures explain the observed elevations in risk.

Workers at a Canadian nickel refinery had a significant increase in myeloma mortality.[57] In contrast, no appreciable associations were found for myeloma/lymphoma mortality among Swedish workers grinding stainless steel, who were potentially exposed to chromium and nickel.[165] A positive correlation has been detected for trace levels of lead and cadmium in US water supplies and myeloma mortality.' Lead exposure was not found to be a risk factor for myeloma in a US hospital–based case-control study.[105]

Rubber Manufacturing

Employment in the rubber manufacturing industry may be a risk factor for multiple myeloma.[35] Excess mortality rates of myeloma have been observed among white and nonwhite female rubber workers.'.[122] A majority of these women worked in the industrial products division where rubber bands, hoses, belts, and molded rubber goods were made.[122] A slight increase in myeloma incidence was observed among Swedish male and female rubber workers.[76] Increased incidence was particularly associated with individuals who had a longer exposure time to the chemical weighing and mixing process, because their period of employment encompassed a time when dust control was minimal. Results are inconsistent among white male rubber workers. Greater mortality was observed in one study,[45] but not in another."' A slight excess, based on small numbers, occurred among black male reclaim workers.[45] In a mortality study of male British rubber industry workers, no link with multiple myeloma was detected.[160]

Benzene and Other Chemicals

Benzene has been suggested as a possible etiologic agent of multiple myeloma[42] because its metabolites are known bone marrow toxins. Myeloma incidence has been found to be statistically higher among benzene exposed cohorts," and a statistically significant excess of myeloma and leukemia mortality has been observed among workers exposed to benzene in the manufacture of rubber hydrochloride.[145]

In a nested case-control study of chemical workers,[131] there was a trend association with benzene exposure of 5 years or more, although another case-control study reported no association.[105] A cohort of firefighters was found to have a significant increase in myeloma mortality; however, benzene exposure is only one of the myriad of chemicals present in most structural fires.[83]

An excess of deaths from myeloma and malignant lymphomas combined was noted in a Swedish study of chemical factory workers who were exposed to a variety of established or suspected carcinogens including piperazine, urethane, formaldehyde, benzyl chloride, ethylene oxide, and epichlorohydrin.[77] Risk of myeloma was markedly elevated in a cohort of chemical workers exposed to epichlorohydrin and chemical groups including antioxidants and nitriles."' A significant increase in myeloma mortality was observed among male aircraft maintenance workers exposed to methylene chloride, and female workers exposed to chlorinated and aromatic hydrocarbons including perchloroethylene.[162] A mortality study of Canadian metal workers revealed a significant increase of multiple myeloma among machinists,[63] who were potentially exposed to hard metallic alloys, cutting oils, and mineral oil lubricants in the production of machine parts. A mortality study of metal fabrication workers with similar exposures in New York state found no myeloma excess.[166]

Among embalmers and funeral directors potentially exposed to formaldehyde, funeral directors had a significant excess of lymphatic and hematopoietic cancer mortality, but embalmers did not.[82] The excess occurred among blacks but not among whites.

Wood, Leather, and Textile Industries and Occupations

Associations between myeloma risk and employment in the wood industry have been mostly with the pulp and paper making processes. A nonsignificant

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Petroleum Industry and Fuel Comt

An excess of deaths due to c
observed in several petroleum refi
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work history records did not find sp
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tially exposed to asphalts, tars, gas
report elevated myeloma mortality.[5

Exposures to carbon monoxide a
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products, or chemical solvents.

Hair Dyes

Epidemiologic studies of multiple
or cosmetologist have reported both
(unpublished data).[167] One potential w
Hair dyes contain aromatic, nitro, and
to be mutagenic in laboratory anima
multiple myeloma have specifically a
both found an elevated risk among w
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Permanent hair color than for semi- or
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Miscellaneous Environmental and Oc

Positive associations between mul
have been reported in case-control and

iring industry may be a risk factor for
es of myeloma have been observed
ɔer workers.' [122] A majority of these
, division where rubber bands, hoses,
ade.[122] A slight increase in myeloma
ı male and female rubber workers.[76]
ociated with individuals who had a
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ɔut not in another."' A slight excess,
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ed carcinogens including piperazine,
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eloma mortality was observed among
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idian metal workers revealed a signifi-
ıng machinists,"' who were potentially
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ity study of metal fabrication workers
te found no myeloma excess."'
ɛctors potentially exposed to formalde-
excess of lymphatic and hematopoietic
ɔt.[82] The excess occurred among blacks

and Occupations

and employment in the wood industry
per making processes. A nonsignificant

increased risk of mortality from lymphoma and multiple myeloma combined has been noted among paper and pulp workers in New Hampshire[149] and in paper factory workers in Sweden.[59] Other studies have not shown a relationship between work in wood-related industries and muliple myeloma.'',[35, 62, 92, 119, 126, 138, 141]

Myeloma has been observed in studies of the leather industry. Workers in the leather tanning industry had a nearly twofold nonsignificant increased risk of myeloma,[35] and a study of shoe manufacturing workers noted a twofold increase among men and greater than a threefold increase among women.[174]

An association with myeloma and textile processing is contradictory. A linkage study of Swedish cancer incidence data and occupational census data[116] revealed a nearly threefold increased risk of multiple myeloma among women textile workers in the wool industry, whereas Pottem et al found elevated, nonsignificant risks for Danish women employed in the textile industry (unpublished data). On the other hand, proportional mortality studies of female North Carolina textile workers and male Rhode Island textile workers revealed no significant multiple myeloma mortality.'' [55]

Petroleum Industry and Fuel Combustion Products

An excess of deaths due to cancers of the lymphatic tissue has been observed in several petroleum refinery populations[51, 89, 105, 112, 182] but not in others.[50, 78] A case-control study of the petroleum industry that utilized company work history records did not find specific associations with work category and product exposure.[168] A recent study of highway maintenance workers potentially exposed to asphalts, tars, gasoline, engine exhaust, and lead did not report elevated myeloma mortality.[5]

Exposures to carbon monoxide as a consequence of exposure to diesel, jet fuel, or automobile exhausts, coal fumes, and smoke have been linked with myeloma risk.[35, 59, 123] However, another study'' did not find a significant excess of myeloma cases among subjects exposed to gasoline or diesel exhausts, coal products, or chemical solvents.

Hair Dyes

Epidemiologic studies of multiple myeloma and employment as a beautician or cosmetologist have reported both positive[7, 161] and negative associations (unpublished data).[167] One potential workplace exposure is hair dye application. Hair dyes contain aromatic, nitro, and amino compounds that have been shown to be mutagenic in laboratory animals.[2] Two recent case-control studies of multiple myeloma have specifically assessed hair dye usage, however, and both found an elevated risk among women[185] and men (LM Brown, personal communication, 1991) who dyed their hair. Risk among women was higher for permanent hair color than for semi- or nonpermanent color, and it was higher among users of dark hair-coloring products.[185] Among men, myeloma risk increased with longer duration of hair dye use (LM Brown, personal communication, 1991).

Miscellaneous Environmental and Occupational Exposures

Positive associations between multiple myeloma and exposure to paint have been reported in case-control and prospective studies.[10, 35, 110, 123] A recent

study in New Zealand reported higher myeloma risk among car, spray, and sign painters than general painters.[10] Risk for spray painters may be higher because of increased exposure to nonvolatile components in the paints.

The association between multiple myeloma and exposure to asbestos has been reported in some case-control studies[35, 105] and one prospective study[139] but not in other studies.[14, 96, 123, 148] A significant exposure-response gradient was reported for individuals with multiple myeloma who were exposed to asbestos for at least 10 years as compared with hospital controls.[35] Also associated with a nonsignificant excess risk of myeloma was photography and exposure to electric cable.[35] An increased risk was reported for janitors and cleaners, and for exposure to cleaning agents and disinfectants.[157] An association between occupational exposure to electromagnetic fields and multiple myeloma was not shown in two studies attempting to evaluate this relationship.[118, 135]

A cohort study of Swedish chimney sweeps reported a marginally significant increase in multiple myeloma incidence.[75] Potential occupational exposures included polycyclic aromatic hydrocarbons (formed by combustion of coal, wood, coke, and oil) and metals such as arsenic, nickel, and chromium." A nonsignificant excess of multiple myeloma was reported among a cohort of abrasive manufacturing workers whose potential work exposures included dusts from aluminum oxide and silicon carbide processing.[56]

Nonoccupational Exposures

Prescription and over-the-counter medications have been suggested as myeloma risk factors in several case-control studies. Friedman[61] found propoxyphene use to be predictive for multiple myeloma. A possible association with prior use of phenytoin, phenobarbital, diazepam, propranolol, ibuprofen, diet drugs, stimulants, and laxatives has been suggested.[105] A mortality study of health plan members in California found a significant elevation in myeloma for prior use of erythromycin, chlorpheniramine, gentamicin sulfate, sulfamethoxazole, and terpin hydrate.'" It is unclear whether the responsible factor for the increased myeloma risk was the prescription drug or the medical condition that was being treated with the drug; however, the probability of chance findings cannot be ruled out.

Multiple myeloma has not been found to be strongly related to either cigarette smoking or alcohol consumption. One Swedish case-control study reported inconsistent results; ex-smokers had an elevated risk, but current smokers did not.[59] Several other case-control studies[14, 20, 21, 62, 71, 105] have found no increased risk for tobacco use. An increased myeloma risk for ever having smoked cigarettes has been reported in a follow-up study of Seventh Day Adventists, with significant trend associations for number of cigarettes smoked and years smoked.[120] No such pattern was observed in a cohort study of US veterans.[82a]

Previous case-control studies have found no appreciable association between alcohol consumption and myeloma[14, 62, 105] A recent case-control study of white men found a significant increased risk for myeloma and alcohol consumption, particularly among those who consumed combinations of beer, wine, and hard liquor (LM Brown, personal communication, 1991). Biologc mechanisms linking myeloma etiology to alcohol consumption have not been adequately explored.

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Familial and Genetic Factors

Familial occurrence of myelor
has been no conclusive evidence
disease. Recent research has foc
human leukocyte antigen (HLA),
environmental variables that corr

Case Reports Among Family Me

Previous reports documented
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members." [73, 106] Associations with
history of autoimmune disorders'
diseases," and a nonsignificant e
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suggested by cases of multiple my

Genetic Marker Studies

Over the last decade, several
been conducted to determine the
cases have with respect to immuno
tested 68 myeloma patients and 3
differences in HLA type; however,
studies revealed a significant increa
controls. An HLA typing of two si
antigens; however, the sisters had
did they share a common M-prc
myeloma in nontwin brothers wh
monoclonal immunoglobulin of the
Early studies of HLA and multi
B locus"'; however, more recent ass
An association of multiple myelor
allotype was reported in a study of 2
controls.[97, 98] As part of a popula
myeloma among US blacks and wh
of HLA-Cw2 was observed for cases
white men.[138a] Although myeloma
for both black and white men, it d
cancer among black men.

Chromosomal Abnormalities

One important cytogenetic abn
myeloma is the 14q+ abnormality,

myeloma risk among car, spray, and
sk for spray painters may be higher
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Familial and Genetic Factors

Familial occurrence of myeloma has been well established; however, there has been no conclusive evidence implicating multiple myeloma as an inherited disease. Recent research has focused on various genetic markers including human leukocyte antigen (HLA), chromosomal abnormalities, oncogenes, and environmental variables that correlate with multiple myeloma.

Case Reports Among Family Members and Spouses

Previous reports documented multiple myeloma occurring among siblings and spouses. Of 37 families with at least two members with myeloma, the cancer occurred among siblings in 25 of the families.[156] Three families in Northern Ireland had multiple myeloma in two first-degree relatives concurrently, although the monoclonal type of immunoglobulin varied in both cases within each family.[115] In another family, a sister had kappa light chain myeloma and two brothers both had monoclonal IgG kappa myeloma.% Case-control studies have also reported the occurrence of multiple myeloma in related family members.[19, 73, 106] Associations with myeloma include significant links with family history of autoimmune disorders[106] and degenerative central nervous system diseases,') and a nonsignificant elevated risk for family history of myeloma among first-degree relatives.[19] An environmental role in myeloma etiology is suggested by cases of multiple myeloma occurring among spouses.[24, 88, 90, 94, 104]

Genetic Marker Studies

Over the last decade, several genetic studies of multiple myeloma have been conducted to determine the similarities and differences that myeloma cases have with respect to immunogenetic markers.[72, 108, 109] Ludwig and Mayr[109] tested 68 myeloma patients and 3000 controls for HLA types and noted no differences in HLA type; however, a larger analysis including data from other studies revealed a significant increase of HLA-B5 among cases compared with controls. An HLA typing of two sisters with myeloma revealed identical HLA antigens; however, the sisters had no common chromosomal abnormality, nor did they share a common M-protein.[108] Grosbois et al[72] reported multiple myeloma in nontwin brothers who were identical for the HLA genotype of monoclonal immunoglobulin of the IgG kappa isotype variety.

Early studies of HLA and multiple myeloma found an association with the B locus"); however, more recent associations have been found with the C locus. An association of multiple myeloma with HLA-Cw5 antigen and G3m(g5) allotype was reported in a study of 22 black myeloma patients and 138 laboratory controls.[97, 98] As part of a population-based case-control study of multiple myeloma among US blacks and whites, a significantly higher gene frequency of HLA-Cw2 was observed for cases compared with controls for both black and white men.[138a] Although myeloma risk appears to be enhanced by HLA-Cw2 for both black and white men, it does not explain the higher incidence of the cancer among black men.

Chromosomal Abnormalities

One important cytogenetic abnormality of etiologic relevance to multiple myeloma is the 14q+ abnormality, first reported by Wurster-Hill et al[184] in

1973. Gould et al[70] examined 115 myeloma patients for karyotypic abnormalities and found that the translocation t(8;14)(q24;q32) was statistically associated with IgA myeloma protein. The same translocation has been associated with 80% of all Burkitt's lymphoma cases.[151] Another translocation, t(11;14)(q13;q32), has been observed in various B-cell abnormalities including multiple myeloma, chronic lymphocytic leukemia, and plasma cell leukemia.[48] B-lymphoproliferative disorders are often associated with chromosomal abnormalities of the light chain immunoglobulin loci, on chromosomes 2 and 22, and the heavy chain immunoglobulin locus on chromosome 14." A recent case review of the cytogenetic literature from the 1960s through the 1980s[48] revealed 453 myeloma patients of whom 124 had a complete karyotype analysis. Of these 124 patients, 32% had various chomosomal abnormalities involving chromosome 14. Other structural and numerical chromosomal aberrations in myeloma patients have been reported[102]; however, at this time no specific chromosomal abnormality has been linked to multiple myeloma.

Oncogenes

Recent studies have implicated malignant transformation by oncogenes in the pathogenesis of multiple myeloma.[4, 58, 70, 128, 129, 153] Increased levels of c-myc mRNA have been detected in myeloma plasma cells in 9 of 37 myeloma patients, and two of these patients had c-myc gene rearrangements.[153] A case series from Japan found 4 of 11 advanced myeloma patients had high *c-myc* RNA expression that in turn correlated with high levels of myeloma cellular proliferation.'" This suggests that transformation of myeloma cells occurs only in response to increased expression and activation of the c-myc gene. Co-amplification of c-myc and the pvt-locus in myeloma is rare,[4] and the role of other genes in tumor development remains unknown. One investigation noted an activated *ras*[n] gene in a myeloma cell line that had a rearranged myc allele.[58] Other oncogenes that so far have an undefined role in myeloma etiology include the B-cell lymphoma/leukemia genes *bcl*-1 and *bcl*-2.[48]

PRE-EXISTING MEDICAL CONDITIONS

Because multiple myeloma is a plasma cell tumor, the role of the immune system in the cancer's etiology is of primary interest. An excess of certain pre-existing immune-stimulating medical conditions has been observed in myeloma cases, suggesting that chronic antigenic stimulation (CAS) of the immune system may be an important factor in the development of myeloma. However, not all studies have reported the same findings owing to inconsistencies in defining CAS, differences in the lag time between the medical condition and the diagnosis of myeloma, and the quality of medical information obtained. Recent epidemiologic studies[14, 31, 35, 62, 71, 93, 105, 138, 181] have explored the CAS hypothesis by utilizing medical history information, namely, past exposures to viral or bacterial illnesses, immunizations, allergies, or autoimmune disorders.

A number of case-control studies have examined the relationship between myeloma and history of certain medical conditions. A study in Italy" found that scarlet fever, BCG vaccination, and chronic bacterial disease were significant risk factors for multiple myeloma. Risk rose with increasing number of bacterial illnesses. A nonsignificant twofold risk was observed for history of herpes zoster, pyelonephritis, tuberculosis, and malaria. In contrast, no increase in risk was found for scarlet f malaria in a British study and No association between myeloma was observed in a study conduc based case-control study in four myeloma risk was found for ir study also reported significantly mononucleosis, and rheumatic tuberculosis, urinary tract infecti for gonorrhea.'" A separate anal a nonsignificant increase in risk f and hepatitis. Risk was not elev chain cases, unlike for the more

Three case-control studies[62] allergy-related conditions. Risk o fever,[138] "any allergic condition," but nonsignificant, risks were de and food allergies, whereas no allergies."" Risk was also increa conditions among light chain mye of the other autoimmune disease: icant increase in risk in one of either allergic conditions or autoi case-control studies.[14, 31, 35, 71, 105]

A nested case-control study medical conditions reported an e contrast, no association between n two other case-control studies."[62]

The following medical condit with myeloma in at least two ca chickenpox and mumps)," [71, 93] vac [71, 93] previous lymphoid tissue s bronchitis,'.'[93] tuberculosis,[14, 62] h myeloma diagnosis.".[93] In a recent data from the two US prepaid hea risk were detected for disc dise eczema, and bronchitis (for plan o 1991). Twofold nonsignificant ele infection, and herpes zoster. Mod urinary tract infection, hay fever, a rheumatic fever, and degenerative tencies in the medical conditions r CAS, when evaluated in this man to adequately-evaluate the role of multiple myeloma.

Multiple myeloma in relation t A Los Angeles population–based st in multiple myeloma incidence." H myeloma occurring in patients at Epstein-Barr virus genome incorp association may suggest that dereg could predispose one to B-cell neop

in risk was found for scarlet fever or for tuberculosis, BCG vaccination, or malaria in a British study and a US population-based case-control study.'), [93] No association between myeloma and the category of chronic bacterial infections was observed in a study conducted in Baltimore, Maryland.[105] In a population*based case-control study in four areas of the United States, a trend of increased myeloma risk was found for increased number of bacterial illnesses.[93] This study also reported significantly elevated risks for fever blisters, contact with mononucleosis, and rheumatic fever, and nonsignificant increased risks for tuberculosis, urinary tract infections, and syphilis. No increased risk was found for gonorrhea.[93] A separate analysis of the light chain myeloma cases revealed a nonsignificant increase in risk for medical implants, infectious mononucleosis, and hepatitis. Risk was not elevated for having fever blisters among the light chain cases, unlike for the more common form of myeloma.[181]

Three case-control studies[62, 138, 181] reported elevated risks of myeloma with allergy-related conditions. Risk of myeloma was significantly increased for hay fever,[138] "any allergic condition," allergy treatment, and myxedema.[62] Elevated, but nonsignificant, risks were detected for asthma, use of asthma medication, and food allergies, whereas no excess was observed for eczema or drug allergies.'" Risk was also increased for childhood eczema and any allergic conditions among light chain myeloma cases.[181] Rheumatoid arthritis, but none of the other autoimmune diseases evaluated, was associated with a nonsignificant increase in risk in one of the studies.[138] No association was found for either allergic conditions or autoimmune disorders and myeloma in the other case-control studies.".[31, 35, 71, 105]

A nested case-control study that ascertained previous history of various medical conditions reported an excess of diabetes among myeloma cases." In contrast, no association between myeloma and diabetes was reported in at least two other case-control studies.[35, 62]

The following medical conditions have not been shown to be associated with myeloma in at least two case-control studies: childhood illnesses (e.g., chickenpox and mumps),'.[71, 93] vaccinations for childhood and other diseases,[35, 71, 93] previous lymphoid tissue surgery,[35, 62, 105] kidney disease,".[62] chronic bronchitis,"[93] tuberculosis,".[62] hepatitis,[62, 93] and blood transfusion prior to myeloma diagnosis.[35, 93] In a recent case-control study based on medical record data from the two US prepaid health plans, significant elevations in myeloma risk were detected for disc disease and other musculoskeletal conditions, eczema, and bronchitis (for plan only) (MM Doody, personal communication, 1991). Twofold nonsignificant elevations were found for tuberculosis, pelvic infection, and herpes zoster. Moderately elevated risks were noted for boils, urinary tract infection, hay fever, asthma, rheumatoid arthritis, psoriasis, gout, rheumatic fever, and degenerative joint disease arthritis. The overall inconsistencies in the medical conditions reported by case-control studies suggest that CAS, when evaluated in this manner, does not provide sufficient information to adequately evaluate the role of immune stimulation in the development of multiple myeloma.

Multiple myeloma in relation to the AIDS epidemic has also been studied. A Los Angeles population–based study did not reveal an AIDS-related increase in multiple myeloma incidence.[8] However, there have been case reports of myeloma occurring in patients at risk for AIDS,[172, 173] one of whom had the Epstein-Barr virus genome incorporated into the B-cell tumor tissue. This association may suggest that deregulation of the immune system, as in AIDS, could predispose one to B-cell neoplasia.

CONCLUSION

Although myeloma incidence and mortality have been increasing until recently, multiple myeloma remains a relatively rare cancer. In the United States, myeloma rates in blacks continue to outpace those in whites. Internationally, incidence is highest in industrialized countries and lowest in developing countries. The differences in rates reflect the presence of cancer registries, usually in industrialized countries, that cover a larger proportion of the total population within a country and reflect greater access to medical care.

The causes of multiple myeloma are largely unknown; however, potential risk factors include radiation and certain occupational exposures such as farming and pesticide use. The strongest association between multiple myeloma risk and radiation exposure has been observed among atomic bomb survivors, radiologists, and radium dial workers. **Risk** associated with exposure to diagnostic and therapeutic x-rays is contradictory. With the advent of nuclear power, concern for elevated cancer risks has increased among power plant workers and local residents. There is some evidence for elevated risks among nuclear plant workers, but risk among residents near nuclear facilities does not appear to be increased.

Although associations of myeloma with farming and other occupations have been reported in some studies, it is not yet clear what specific agricultural or workplace exposures might be etiologically involved. The strongest candidates include pesticides, benzene, and other organic solvents. Nonoccupational exposures including smoking and alcohol consumption do not seem to be strongly related to myeloma. Associations between myeloma and previous use of prescription drugs have not been well clarified. The role of chronic antigenic stimulation (CAS) in multiple myeloma is incon :usive, mainly because of inconsistencies in the definition of CAS, varying quality of medical history information, and the subsequent contradictory study results.

In addition to environmental risk factors, epidemiologic research of multiple myeloma should focus on potential genetic determinants. Research on chromosomal aberrations, HLA type, and oncogenes will continue to shed light on the pathogenic mechanism of myeloma, as well as provide genetic information that may be useful in the prediction and prognosis of this cancer and other B-cell malignancies.

Incorporation of laboratory-based measures of genetic aberrations and immune function in future epidemiologic studies may be instrumental toward understanding the role of genetics and immune deregulation in the etiology of multiple myeloma.

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References

1. Alavanja MCR, Rush GA, Stewart P, Blair A: Proportionate mortality study of workers in the grain industry. J Natl Cancer Inst 78:247, 1987
2. Ames BN, Kammen HO, Yamasaki E: Hair dyes are mutagenic: Identification of a variety **of** mutagenic ingredients. Proc Natl Acad Sci USA 72:2423, 1975
3. Andjelkovich D, Taulbee J, I manufacturing plant J Occup
4. Bakkus MHC, Brakel-van Peer and the pvt-like region in hum
5. Bender AP, Parker DL, Johnso study: Cancer mortality. Am J
6. Beral V, Inskip H, Fraser P, et Atomic Energy Authority, 1946
7. Berg JW, Burbank F: Correlatior and cancer mortality. Ann NY
8. Bernstein L, Levin D, Menck H Los Angeles County men: **A** co
9. Bertazzi PA, Zocchetti C, Pes population involved in the Sev
10. Bethwaite PB, Pearce N, Fraser Zealand Cancer Registry. Br J I
11. Blair A, Malker H, Cantor KP, Health 11:397, 1983
12. Blair A, Zahm SH: Cancer an Reviews 6:335, 1991
13. Blair A, Zahm SH: Herbicides a. issues. Recent Results Cancer R
14. Boffetta P, Stellman SD, Garfi nested in the American Cancer
15. Boice JD Jr, Day NE, Andersen A for cervical cancer. An internat Cancer Inst 74:955, 1985
16. Boice JD Jr, Engholm G, Kleine risk in patients treated tor canct
17. Boice JD Jr, Land CE, Preston D JF Jr (eds): Cancer Epidemiolog. Press, in press
18. Boice JD Jr, Morin MM, Glass leukemia, lymphoma, and multi
19. Bourguet CC, Grufferman S, **Dt** of cancer. A case-control study.
20. Brown LM, Everett GD. Gibso lymphoma and multiple myelon
21. Brownson RC: Cigarette smokin 1991
22. Brownson RC. Reif JS: A can lymphoma. multiple myeloma a
23. Brownson RC, Reif JS, Chang JC Cancer 64:2381, 1989
24. Brugiatelli M, Comis M, lacopin Acta Haematol 64:227, 1980
25. Burmeister LF: Cancer in Iowa f.
26. Burmeister LF, Everett GD. Var farm practices in Iowa. Am J Ep
27. Cantor KP, Blair A: Farming and study with the use of death certi
28. Carli PM, Bailly F, Tavernier C, in a well-defined population in E
29. Carli PM, Milan C, Lorenzini JL a well defined population in Fra
30. Chen VW, Craig JF, Fontham El in Louisiana: An opportunity for 1990
31. Cohrn HJ, Bernstein RJ, Grufferi of multiple myeloma. A case-con

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ir A: Proportionate mortality study of
r Inst 78:247, 1987
. dyes are mutagenic: Identification of a
Acad Sci USA 72:2423, 1975

3. Andjelkovich D, Taulbee J, Blum S: Mortality of female workers in a rubber manufacturing plant. J Occup Med 20409, 1978
4. Bakkus MHC, Brakel-van Peer KMJ, Michiels JJ, et al: Amplification of the c-niyc and the pvt-like region in human multiple myeloma. Oncogene 5:1359, 1990
5. Bender AP, Parker DL, Johnson RA, et al: Minnesota highway maintenance worker study: Cancer mortality. Am J Ind and Med 15:545, 1989
6. Beral V, Inskip H, Fraser P, et al: Mortality of employees of the United Kingdom Atomic Energy Authority, 1946–1979. Br Med J 291:440, 1985
7. Berg JW, Burbank F: Correlations between carcinogenic trace metals in water supplies and cancer mortality. Ann NY Acad Sci 199:249, 1972
8. Bernstein L, Levin D, Menck H, Ross RK: AIDS-related secular trends in cancer in Los Angeles County men: A comparison by marital status. Cancer Res 49:466, 1989
9. Bertazzi PA, Zocchetti C, Pesatori AC, et al: Ten-year mortality study of the population involved in the Seveso incident in 1976. Am J Epidemiol 129:1187, 1989
10. Bethwaite PB, Pearce N, Fraser J: Cancer risks in painters: Study based on the New Zealand Cancer Registry. Br J Ind Med 47:742, 1990
11. Blair A, Malker H, Cantor KP, et al: Cancer among farmers. Scand J Work Environ Health 11:397, 1985
12. Blair A, Zahm SH: Cancer among farmers. Occupational Med: State of the Art Reviews 6:335, 1991
13. Blair A, Zahm SH: Herbicides and cancer: A review and discussion of methodologic issues. Recent Results Cancer Res 120132, 1990
14. Boffetta P, Stellman SD, Garfinkel L: A case-control study of multiple myeloma nested in the Amencan Cancer Society prospective study. Int J Cancer 43:554, 1989
15. Boice JD Jr, Day NE, Andersen A, et al: Second cancers following radiation treatment for cervical cancer. An international collaboration among cancer registries. J Natl Cancer Inst 74:955, 1985
16. Boice JD Jr, Engholm G, Kleinerman RA, et al: Radiation dose and second cancer risk in patients treated for cancer of the cervix. Radiat Res 116:3, 1988
17. Boice JD Jr, Land CE, Preston DL: Ionizing radiation. *In* Schottenfeld D, Fraumeni JF Jr (eds): Cancer Epidemiology and Prevention, ed 2. Oxford, Oxford University Press, in press
18. Boice JD Jr, Morin MM. Glass AG, et al: Diagnostic X-ray procedures and risk of leukemia, lymphoma, and multiple myeloma. JAMA 265:1290, 1991
19. Bourguet CC, Grufferman S, Delzell E, et al: Multiple myeloma and family history of cancer. A case-control study. Cancer 562133, 1985
20. Brown LM, Everett GD, Gibson R, et al: Smoking and risk of non-Hodgkin's lymphoma and multiple myeloma. Cancer Causes Control 3:49, 1992
21. Brownson RC: Cigarette smoking and risk of myeloma. J Natl Cancer Inst 83:1036, 1991
22. Brownson RC. Reif JS: A cancer registry-based study of occupational risk for lymphoma, multiple myeloma and leukaemia. Int J Epidemiol 1727, 1988
23. Brownson RC, Reif JS, Chang JC, Davis JR: Cancer risks among Missouri farmers. Cancer 64:2381, 1989
24. Brugiatelli M, Comis M, Iacopino P, et al: Multiple myeloma in husband and wife. Acta Haematol 64:227, 1980
25. Burmeister LF: Cancer in Iowa farmers: Recent results. Am J Ind Med 18:295, 1990
26. Burmeister LF, Everett GD, Van Lier SF, Isacson P: Selected cancer mortality and farm practices in Iowa. Am J Epidemiol 118:72, 1983
27. Cantor KP, Blair A: Farming and mortality from multiple myeloma: A case-control study with the use of death certificates. J Natl Cancer Inst 72:251, 1984
28. Carli PM, Bailly F, Tavernier C, et al: Multiple myeloma: Epidemiological features in a well-defined population in Burgundy, France. Int J Epidemiol 18:330, 1989
29. Carli PM, Milan C, Lorenzini JL, et al: Incidence of hematopoietic malignancies in a well defined population in France. Oncology 43:354, 1986
30. Chen VW, Craig JF, Fontham ETH, Correa P: Excessive cancer rates among blacks in Louisiana: An opportunity for physician intervention. J La State Med Soc 142:18, 1990
31. Cohen HJ, Bernstein RJ, Grufferman S: Role of immune stimulation in the etiology of multiple myeloma: A case-control study. Am J Hematol 24:119, 1987

32. Cook-Mozzaffari PJ, Darby SC, Doll R, et al: Geographical variation of mortality from leukemia and other cancers in England and Wales in relation to proximity to nuclear installations, 1969–78. Br J Cancer 59:476, 1989
33. Croce CM, Shander M, Martinis J, et al: Chromosomal location of the genes for human immunoglobulin heavy chains. Proc Natl Acad Sci USA 76:3416, 1979
34. Cuzick J: International time trends for multiple myeloma. Ann NY Acad Sci 609:205, 1990
35. Cuzick J, De Stavola B: Multiple myeloma-a case-control study. Br J Cancer 57516, 1988
36. Cuzick J, Velez R, Doll R: International variations and temporal trends in mortality from multiple myeloma. Int J Cancer 32:13, 1983
37. Darby SC, Doll R, Gill SK, Smith PG: Long term mortality after a single treatment course with x-rays in patients treated for ankylosing spondylitis. Br J Cancer 55:179, 1987
38. Darby SC, Kendall GM, Fell TP, et al: A summary of mortality and incidence of cancer in men from the United Kingdom who participated in the United Kingdom's atmospheric nuclear weapons tests and experimental programmes. Br Med J 296:332, 1988
39. Darby SC, Nakashima E, Kato H: A parallel analysis of cancer mortality among atomic bomb survivors and patients with ankylosing spondylitis given x-ray therapy. J Natl Cancer Inst 75:1, 1985
40. Davis DL, Hoel D, Fox J, Lopez A: International trends in cancer mortality in France, West Germany, Italy, Japan, England and Wales, and the USA. Lancet 2:474, 1990
41. Davis FG, Boice JD Jr, Hrubec Z, Monson RR: Cancer mortality in a radiation-exposed cohort of Massachusetts tuberculosis patients. Cancer 49:6130, 1989
42. Decoufle P, Blattner WA, Blair A: Mortality of workers exposed to benzene and other agents. Environ Res 30:16, 1983
43. Delzell E, Grufferman S: Cancer and other causes of death among female textile workers, 1976–78. J Natl Cancer Inst 71:735, 1983
44. Delzell E, Grufferman S: Mortality among white and nonwhite farmers in North Carolina, 1976–1978. Am J Epidemiol 121:391, 1985
45. Delzell E, Monson RR: Mortality among rubber workers: X. Reclaim workers. Am J Ind Med 7:307, 1985
46. Devesa SS: Descriptive epidemiology of multiple myeloma. *In* Obrams GI, Potter M (eds): Epidemiology and Biology of Multiple Myeloma. Berlin, Springer-Verlag, 1991, p 3
47. Devesa SS, Silverman DT, Young JL Jr, et al: Cancer incidence and mortality trends among whites in the United States, 1947–84. J Natl Cancer Inst 79:701, 1987
48. Dewald GW, Jenkins RB: Cytogenetic and molecular genetic studies of patients with monoclonal gammopathies. *In* Wiernik PH, Canellos GP, Kyle RA, Schiffer CA (eds): Neoplastic Diseases of the Blood, ed 2. New York, Churchill Livingstone, 1991, p 427
49. Dimitrova E, Plesko I, Somogyi J, Kiss J: Trends and patterns in cancer incidence in Czechoslovakia, 1968–1985. Neoplasma 36:245, 1989
50. Divine BJ, Barron V: Texaco mortality study: III. A cohort of producing and pipeline workers. Am J Ind Med 11:189, 1987
51. Divine BJ, Barron V, Kaplan SD: Texaco mortality study: I. Mortality among refinery, petrochemical, and research workers. J Occup Med 27445, 1985
52. Doll R: Urban and rural factors in the aetiology of cancer. Int J Cancer 47:803, 1991
53. Dolphin GW: A comparison of the observed and the expected cancers of the haematopoietic and lymphatic systems among workers at Windscale: A first report. Harwell, England, National Radiation Protection Board NRPB-R54, 1976
54. Dousset M: Cancer mortality around La Hague nuclear facilities. Health Phys 56:875, 1989
55. Dubrow R, Gute DM: Cause-specific mortality among male textile workers in Rhode Island. Am J Ind Med 13:439, 1988
56. Edling C, Jarrholm B, Andersson L, Axelson O: Mortality and cancer incidence among workers in an abrasive manufacturing industry. Br J Ind Med 44:57, 1987
57. Egedahl RD, Coppock E, Homik R: Mortality experience at a hydrometallurgical nickel refinery in Fort Sash Med 41:29, 1991
58. Ernst TJ, Gazdar A, Ritz J, ras*, in a human multiple 72:1163, 1988
59. Flodin U, Fredriksson M, F wood, and creosote: A cast
60. Forman D, Cook-Mozaffar! Commentary. Nature 329:4
61. Friedman GD: Multiple m radiation and occupation. J
62. Gallagher RP, Spinelli JJ, exposure and risk factors fo
63. Gallagher RP, Threlfall WJ. 129:1191, 1983
64. Gardner M: Cancer among J 296:309, 1988
65. Gilbert ES, Fry SA, Wiggs Hanford Site, Oak Ridge N Plant. Radiat Res 120:19, 19
66. Gilbert ES, Petersen GR, B 1945–1981. Health Physics 5
67. Giles GG, Lickiss JN, Baiki disorders in Tasmania, 1972 Inst 72:1233, 1984
68. Glover CS, Horm J, Christt multiple myeloma survival. , of Multiple Myeloma. Berlin
69. Goldstein BD: Is exposure NY Acad Sci 609:225, 1990
70. Gould J, Alexanian R, Good; Blood 71:453, 1988
71. Gramenzi A, Buttino I, D A myeloma. Br J Cancer 63:76
72. Grosbois B, Gueguen M, Fa immunochemical and immu
73. Grufferman S, Cohen HJ, Dt and central nervous system
74. Guidotti S, Wright WE. Pet Med 3:169, 1982
75. Gustavsson P, Gustavsson sweeps. Br J Ind Med 45:777
76. Gustavsson P, Hogstedt C, Swedish rubber workers, 19
77. Hagmar L, Bellander T, Eng! in a chemical factory. Scand
78. Hanis NM, Shallenberger L study of workers in three Comparisons with U.S. pop
79. Hensen NE, Karle H, Olser Denmark 1943–1982: A stud!
80. Hatch MC, Beyea J, Nieves J plant: Radiation emissions.
81. Hayakawa N, Ohtaki M, Ue among atomic bomb survivor J Med Sci 38:53, 1989
82. Hayes RB, Blair A, Stewart directors. Am J Ind Med 16:r
82a. Heineman EF, Zahm SH, M

nickel refinery in Fort Saskatchewan, Alberta between 1954 and 1984. J Soc Occup Med 41:29, 1991

58. Ernst TJ, Gazdar A, Ritz J, Shipp MA: Identification of a second transforming gene, ras", in a human multiple myeloma line with a rearranged c-myc allele. Blood 72:1163, 1988
59. Flodin U, Fredriksson M, Persson B: Multiple myeloma and engine exhausts, fresh wood, and creosote: A case-referent study. Am J Ind Med 12519, 1987
60. Forman D, Cook-Mozaffari P, Darby S, et al: Cancer near nuclear installations.-Commentary. Nature 329:499, 1987
61. Friedman GD: Multiple myeloma: Relation to propoxyphene and other drugs, radiation and occupation. Int J Epidemiol 15:424, 1986
62. Gallagher RP, Spinelli JJ, Elwood JM, Skippen DH: Allergies and agricultural exposure and risk factors for multiple myeloma. Br J Cancer 48:853, 1983
63. Gallagher RP, Threlfall WJ: Cancer mortality in metal workers. Can Med Assoc J 129:1191, 1983
64. Gardner M: Cancer among participants in tests of British nuclear weapons. Br Med J 296:309, 1988
65. Gilbert ES, Fry SA, Wiggs LD, et al: Analyses of combined mortality data at the Hanford Site, Oak Ridge National Laboratory, and Rocky Flats Nuclear Weapons Plant. Radiat Res 120:19, 1989
66. Gilbert ES, Petersen GR. Buchanan JA: Mortality of workers at the Hantord Site: 1945–1981. Health Physics 56:11, 1989
67. Giles GG, Lickiss JN, Baikie MJ, et al: Myeloproliferative and lymphoproliferative disorders in Tasmania, 1972–1980: Occupational and familial aspects. J Natl Cancer Inst 72:1233, 1984
68. Glover CS, Horm J, Christenson G: Race and socioeconomic status differences in multiple myeloma survival. In Obrams GI, Potter M (eds): Epidemiology and Biology of Multiple Myeloma. Berlin, Springer-Verlag, 1991, p 55
69. Goldstein BD: Is exposure to benzene a cause of human multiple myeloma? Ann NY Acad Sci 609:225, 1990
70. Gould J, Alexanian R, Goodacre A, et al: Plasma cell karyotype in multiple myeloma. Blood 71:453, 1988
71. Gramenzi A, Buttino I, DAvanzo B, et al: Medical history and the risk of multiple myeloma. Br J Cancer 63:769, 1991
72. Grosbois B, Gueguen M, Fauchet R, et al: Multiple myeloma in two brothers. An immunochemical and immunogenetic familial study. Cancer 582417, 1986
73. Grufferman S, Cohen HJ, Delzell ES, et al: Familial aggregation of multiple myeloma and central nervous system diseases. J Am Geriatr Soc 37:303, 1989
74. Guidotti S, Wright WE, Peters JM: Multiple myeloma in cosmetologists. Am J Ind Med 3:169, 1982
75. Gustavsson P, Gustavsson A, Hogstedt C: Excess of cancer in Swedish chimney sweeps. Br J Ind Med 45:777, 1988
76. Gustavsson P, Hogstedt C, Holmberg B: Mortality and incidence of cancer among Swedish rubber workers, 1952–1981. Scand J Work Environ Health 12:538, 1986
77. Hagmar L, Bellander T, Englander V, et al: Mortality and morbidity among workers in a chemical factory. Scand J Work Environ Health 12:545, 1986
78. Hanis NM, Shallenberger LG, Donaleski DL, Sales EA: A retrospective mortality study of workers in three major U.S. refineries and chemical plants. Part 1: Comparisons with U.S. population. J Occup Med 27:283, 1985
79. Hensen NE, Karle H, Olsen JH: Trends in the incidence of multiple myeloma in Denmark 1943–1982: A study of 5500 patients. Eur J Haematol 42:72, 1989
80. Hatch MC, Beyea J, Nieves JW, Susser M: Cancer near the Three Mile Island nuclear plant: Radiation emissions. Am J Epidemiol 132:397, 1990
81. Hayakawa N, Ohtaki M, Ueoka H, et al: Mortality statistics of major causes of death among atomic bomb survivors in Hiroshima Prefecture from 1968 to 1982. Hiroshima J Med Sci 38:53, 1989
82. Hayes RB, Blair A, Stewart PA, et al: Mortality of U.S. embalmers and funeral directors. Am J Ind Med 18:641, 1990

82a. Heineman EF, Zahm SH, McLaughlin JK, et al: A prospective study of tobacco use

and multiple myeloma: Evidence against an association. Cancer Causes Control 3:31, 1992
83. Heyer N, Weiss NS, Demers P, Rosenstock L: Cohort mortality study of Seattle fire fighters: 1945–1983. Am J Ind Med 17:493, 1990
84. Horwitz LJ, Levy RN, Rosher F: Multiple myeloma in three siblings. Arch Intern Med 145:1449, 1985
85. Jablon S, Hrubec Z, Boice JD Jr, Stone BJ: Cancer in Populations Living Near Nuclear Facilities, vol 1: Report and Summary (DHHS publ (NIH) no. 90–874). Washington, DC, US Govt Printing Office, 1990
86. Jacobson RA: Multiple myeloma in sub-Sahara Africa. *In* Obrams GI, Potter M (eds): Epidemiology and Biology of Multiple Myeloma. Berlin, Springer-Verlag, 1991, p 69
87. Johnston JM, Grufferman S, Bourguet CC, et al: Socioeconomic status and risk of multiple myeloma. J Epidemiol Community Health 39:175, 1985
88. Kanoh T Multiple myeloma in spouses (letter). Eur J Haematol 41:397, 1988
89. Kaplan S D Update of a mortality study of workers in petroleum refineries. J Occup Med 28:514, 1986
90. Kardinal CG: Multiple myeloma in a husband and wife. JAMA 239:22, 1978
91. Kato I, Tajima K, Hirose K, et al: A descriptive epidemiological study of hematopoietic neoplasms in Japan. Jpn J Clin Oncol 15:347, 1985
92. Kawachi I, Pearce N, Fraser J: A New Zealand cancer registry–based study of cancer in wood workers. Cancer 64:2609, 1989
93. Koepsell TD, Daling JR, Weiss NS, et al: Antigenic stimulation and the occurrence of multiple myeloma. Am J Epidemiol 126:1051, 1987
94. Kyle RA, Greipp PR: Multiple myeloma. Houses and spouses. Cancer 51:735, 1983
95. Lanier AP, Bulkow LR, Ireland B: Cancer in Alaskan Indians, Eskimos, and Aleuts, 1969–83: Implications for etiology and control. Public Health Rep 104:658, 1989
96. La Vecchia C, Negri E, D'Avanzo B, Franceschi S Occupation and lymphoid neoplasms. Br J Cancer 60:385, 1989
97. Leech SH, Brown R, Schanfield MS: Genetic studies in multiple myeloma. II. Immunoglobulin allotype associations. Cancer 55:1473, 1985
98. Leech SH, Bryan CF, Elston RC, et al: Genetic studies in multiple myeloma. I. Association with HLA-Cw5. Cancer 51:1408, 1983
99. Lenhard RE, Enterline JP, Crowley J, Ho GYF: The effects of distance from primary treatment centers on survival among patients with multiple myeloma. J Clin Oncol 5:1640, 1987
100. Levi F, Te VC, La Vecchia C: Changes in cancer incidence in the Swiss canton of Vaud, 1978–87. Ann Oncol 1:293, 1990
101. Lewis EB: Leukemia, multiple myeloma and aplastic anemia in American radiologists. Science 142:1492, 1963
102. Lewis JP, MacKenzie MR: Non-random chromosomal aberrations associated with multiple myeloma. Hematol Oncol *2307,* 1984
103. Lickiss JN, Giles GG, Baikie MJ, et al: Myeloproliferative and lymphoproliferative disorders in Tasmania, 1972–80: Patterns in space and time. J Natl Cancer Inst 72:1223, 1984
104. Linet MS: Chronic lymphocytic leukemia and multiple myeloma in husband and wife. Am J Med Sci 288:21, 1984
105. Linet MS, Harlow SD, McLaughlin JK: A case-control study of multiple myeloma in whites: Chronic antigenic stimulation, occupation, and drug use. Cancer Res 47:2978, 1987
106. Linet MS, McLaughlin JK, Harlow SD, Fraumeni JR Jr: Family history of autoimmune disorders and cancer in multiple myeloma. Int J Epidemiol 17:512, 1988
107. Lopez AD: Competing causes of death. A review of recent trends in mortality in industrialized countries with special reference to cancer. Ann NY Acad Sci 609:58, 1990
108. Loth TS, Whiteaker RS, Perrotta AL, et al: Genetic aspects of familial multiple myeloma. Milit Med 156:430, 1991
109. Ludwig H, Mayr WR: Genetic aspects of susceptibility *to* multiple myeloma. Blood 59:1286, 1982
110. Lundberg I: Mortality and cancer incidence among Swedish paint industry workers with long-term exposure *to* (1986
111. Mancuso TE. Stewart A, Kn from cancer and other causes
112. Marsh GM, Enterline PE, Mc and chemical plant workers.
113. Marshall M: Experts clash ov
114. Matanoski GM: Risk of cance and other radiation workers. ments, Challenges, and Prosp D 241
115. McCrea AP, Morris TCM: Co 58:394, 1986
116. McLaughlin JK, Malker HS, I Sweden. Arch Environ Health
117. McWhorter WP, Schatzkin AC status to black/white differenc
118. Milham S Jr: Mortality in work Perspect 62:297, 1985
119. Miller B, Blair AE, Raynor HI United States furniture worker
120. Mills PK, Newell GR, Beeson leukemia and myeloma: Resul Inst 82:1832, 1990
121. Monson RR, Nakano KK: Mo employees in Akron, Ohio. An
122. Monson RR, Nakano KK: Mor Am J Epidemiol 103:297, 1976
123. Morris PD, Koepsell TD, Dalir myeloma: A case-control study
124. Muir C, Waterhouse J, Mack 7 (IARC publ no. 88). Lyon, Fra 1987
125. Mukiibi JM, Kyobe J: Pattern (40:20, 1988
126. Nandakumar A, Armstrong B Australia: A case-control stud socioeconomic status and count
127. Nandakumar A, Dougan LE, E of multiple myeloma in Western
128. Nishida K, Taniwaki M, Misaw mosome 14 at band q32.33 in ! phenotype. Cancer Res 49:1275,
129. Nobuyoshi M, Kawano M, Tana may be related to the aggressi Haematol 77523, 1991
130. Olsen JH, Dragsted L, Autrup H: in Denmark. Br J Cancer 58:392,
131. Ott MG, Teta MJ, Greenberg HI chemical manufacturing environ
132. Parkin DM: Cancer Occurrence i France, International Agency for
133. Pasqualetti P, Colantonio D, C sopravvivenza nel mieloma multi
134. Pearce N, Prior I, Methven D, British atmospheric nuclear weap
135. Pearce N, Reif J, Fraser J: Case-c workers. Int J Epidemiol 18:55, 19
136. Pearce NE, Howard JK: Occupati Zealand, 1974–78. Int J Epidemiol

with long-term exposure to organic solvents. Scand J Work Environ Health 12:108, 1986
111. Mancuso TE, Stewart A, Kneale G: Radiation exposure of Hanford workers dying from cancer and other causes. Health Phys 33:369, 1977
112. Marsh GM, Enterline PE, McCraw D: Mortality patterns among petroleum refinery and chemical plant workers. Am J Ind Med 19:29, 1991
113. .Marshall M: Experts clash over cancer data. Science 250:900, 1990
114. Matanoski GM: Risk of cancer associated with occupational exposure in radiologists and other radiation workers. *In* Burchenal JH, Ottegen HF (eds): Cancer, Achievements, Challenges, and Prospects for the 1980s. New York, Grune & Stratton, 1982, p 241
115. McCrea AP, Morris TCM: Concurrent familial myeloma in northern Ireland. Cancer 58:394, 1986
116. McLaughlin JK, Malker HS, Linet MS, et al: Multiple myeloma and occupation in Sweden. Arch Environ Health 43:7, 1988
117. McWhorter WP, Schatzkin AG, Horm JW, Brown CC: Contribution of socioeconomic status to blackiwhite differences in cancer incidence. Cancer 63:982, 1989
118. Milham S Jr: Mortality in workers exposed to electromagnetic fields. Environ Health Perspect 62:297, 1985
119. Miller B, Blair AE, Raynor HL, et al: Cancer and other mortality patterns among United States furniture workers. Br J Ind Med 46:508, 1989
120. Mills PK, Newell GR, Beeson WL, et al: History of cigarette smoking and risk of leukemia and myeloma: Results from the Adventist Health Study. J Natl Cancer Inst 82:1832, 1990
121. Monson RR, Nakano KK: Mortality among rubber workers. I. White male union employees in Akron, Ohio. Am J Epidemiol 103:284, 1976
122. Monson RR, Nakano KK: Mortality among rubber workers. II. Other employees. Am J Epidemiol 103:297, 1976
123. Morris PD, Koepsell TD, Daling JR, et al: Toxic substance exposure and multiple myeloma: A case-control study. J Natl Cancer Inst 76:987, 1986
124. Muir C, Waterhouse J, Mack T, et al: Cancer Incidence in Five Continents, **vol** 5. (IARC publ no. 88). Lyon, France, International Agency for Research on Cancer, 1987
123. Mukiibi JM, Kyobe J: Pattern of multiple myeloma in Kenyans. Trop Geogr Med 40:20, 1988
126. Nandakumar A, Armstrong BK. de Klerk NH: Multiple myeloma in Western Australia: A case-control study in relation to occupation, father's occupation; socioeconomic status and country of birth. Int J Cancer 37:223, 1986
127. Nandakumar A, Dougan LE, English DR, Armstrong BK: Incidence and outcome of multiple myeloma in Western Australia 1960 to 1984. Aust NZ J Med 18:774, 1988
128. Nishida K, Taniwaki M, Misawa W, Abe T: Nonrandom rearrangement of chromosome 14 at band q32.33 in human lymphoid malignancies with mature B-cell phenotype. Cancer Res 49:1275, 1989
129. Nobuyoshi M, Kawano M, Tanaka H, et al: Increased expression of the c-myc gene may be related to the aggressive transformation of human myeloma cells. Br J Haematol 77:523, 1991
130. Olsen JH, Dragsted L, Autrup H: Cancer risk and occupational exposure to aflatoxins in Denmark. Br J Cancer 58:392, 1988
131. Ott MG, Teta MJ. Greenberg HL: Lymphatic and hematopoietic tissue cancer in a chemical manufacturing environment. Am J Ind Med 16:631, 1989
132. Parkin DM: Cancer Occurrence in Developing Countries. (IARC publ no. 75) Lyon, France, International Agency for Research on Cancer, 1986
133. Pasqualetti P, Colantonio D, Collacciani A, Casale R: Stato socioeconomico e sopravvivenza nel mieloma multiplo. Minerva Med 81:713, 1990
134. Pearce N, Prior I, Methven D, et al: Follow **up** of New Zealand participants in British atmospheric nuclear weapons tests in the Pacific. Br J Med 300:1161, 1990
135. Pearce N, Reif J, Fraser J: Case-control studies of cancer in New Zealand electrical workers. Int J Epidemiol 18:55, 1989
136. Pearce NE, Howard JK: Occupation, social class and male cancer mortality in New Zealand, 1974–78. Int J Epidemiol 15:456, 1986

137. Pearce NE, Smith AH, Fisher DO: Malignant lymphoma and multiple myeloma linked with agricultural occupations in a New Zealand cancer registry–based study. Am J Epidemiol 121:225, 1985
138. Pearce NE, Smith AH, Howard JK, et al: Case-control study of multiple myeloma and farming. Br J Cancer 54:493, 1986
138a. Pottern LM, Gart JJ, Nam J, et al: HLA and multiple myeloma among black and white men: Evidence of a genetic association. Cancer Epidemiol Biomarkers Prevention, in press, 1992
139. Raffn E, Lynge E, Juel K, Korsgaard B: Incidence of cancer and mortality among employees in the asbestos cement industry in Denmark. Br J Ind Med 46:90, 1989
140. Reif J, Pearce N, Fraser J: Cancer risks in New Zealand farmers. Int J Epidemiol 18:768, 1989
141. Reif J, Pearce N, Kawachi I, Fraser J: Soft-tissue sarcoma, non-Hodgkin's lymphoma and other cancers in New Zealand forestry workers. Int J Cancer 43:49, 1989
142. Reif JS, Pearce NE, Fraser J: Cancer risks among New Zealand meat workers. Scand J Work Environ Health 15:24, 1989
143. Riedel DA, Pottern LM, Blattner WA: Epidemiology of multiple myeloma. In Wiemik PH, Canellos GP, Kyle RA, Schiffer CA (eds): Neoplastic Diseases of the Blood, ed 2. New York, Churchill Livingstone, 1991, p 347
144. Ries LAG, Hankey BF, Miller BA, et al: Cancer Statistics Review 1973–1988 (DHHS publ [NIH] no 91-2789). Washington, DC, US Govt Printing Office, 1991
145. Rinsky RA, Smith AB, Hornung R, et al: Benzene and leukemia. An epidemiologic risk assessment. N Engl J Med 316:1044, 1987
146. Rushton L, Alderson MR: Epidemiological survey of oil distribution centres in Britain. Br J Ind Med 40:330, 1983
147. Savage D, Lindenbaum J, Van Ryzin J, et al: Race, poverty and survival in multiple myeloma. Cancer 54:3085, 1984
148. Schwartz DA, Vaughan TL, Heyer NJ, et al: B cell neoplasms and occupational asbestos exposure. Am J Ind Med 14:661, 1988
149. Schwartz E A proportionate mortality ratio analysis of pulp and paper mill workers in New Hampshire. Br J Med 45:234, 1988
150. Schwartz J: Multinational trends in multiple myeloma. Ann NY Acad Sci 609:215, 1990
151. Secker-Walker LM, Goldman JM: Cytogenetics and leukaemogenesis. In Hoffbrand AV, Lewis SM (eds): Postgraduate Haematology. Oxford, Heinemann Professional Publishing, 1989, p 372
152. Selby JV, Friedman GD, Fireman BH: Screening prescription drugs for possible carcinogenicity: Eleven to fifteen years of follow-up. Cancer Res 49:5736, 1989
153. Selvanayagam P, Blick M, Narni F, et al: Alteration and abnormal expression of the c-myc oncogene in human multiple myeloma. Blood 71:30, 1988
154. Shapira R, Carter A: Multiple myeloma in northern Israel, 1970–1979. Cancer 58:206, 1986
155. Shimizu Y, Kato H, Schull W: Studies of the mortality of A-bomb survivors. 9. Mortality. 1950–1985: Part 2. Cancer mortality based on the recently revised doses (DS86). Radiat Res 121:120, 1990
156. Shoenfeld Y, Berliner S, Shaklai M, et al: Familial multiple myeloma. A review of thirty-seven families. Postgrad Med J 58:12, 1982
157. Siemiatycki J: Risk Factors for Cancers in the Workplace. Boca Raton, Florida, CRC Press, 1991
158. Smith PG, Douglas AJ: Mortality of workers at the Sellafield plant of British Nuclear Fuels. Br Med J 293:845, 1986
159. Sorahan T, Cooke MA: Cancer mortality in a cohort of United Kingdom steel foundry workers: 1946–85. Br J Ind Med 46:74, 1989
160. Sorahan T, Parkes HG, Veys CA, et al: Mortality in the British rubber industry 1946–85, Br J Ind Med 46:1, 1989
161. Spinelli JJ, Gallagher RP, Band PR, Threlfall WJ: Multiple myeloma, leukemia, and cancer of the ovary in cosmetologists and hairdressers. Am J Ind Med 6:97, 1984
162. Spirtas R, Stewart PA, Lee JS, et al: Retrospective cohort mortality study of workers at an aircraft maintenance facility. I. Epidemiological results. Br J Ind Med 48:515, 1991
163. Stebbings JH, Lucas HF, Steh radium dial workers. Am J Ir
164. Steineck G, Wiklund K: Mu Epidemiol 15:321, 1986
165. Svensson BG, Englander V, grinding stainless steel. Am J
166. Teta MJ. Ott MG: A mortality facility in western New York
167. Teta MJ, Walrath J, Wister-M ogists. J Natl Cancer Inst 72:1
168. Thomas TL, Waxweiler RJ, C Texas oil refineries. Am J Ind
169. Tollerud DJ, Brinton LA, Sto North Carolina furniture wor
170. Turesson I, Zettervall O, Cuz multiple myeloma in Malmo, S 310:421, 1984
171. Vagero D, Persson G: Occur Scand J Soc Med 14:151, 1986
172. Voelkerding KV, Sandhaus L acquired immune deficiency s Clin Pathol 92:222, 1989
173. von Keyserlingk H, Baur R, St AIDS. Cancer Detect Prev 14:4
174. Walrath J, Decoufle P, Thomas company. Am J Ind Med 12:61
175. Wang J-X, Boice JD Jr, Li B-X, in China. J Natl Cancer Inst 8C
176. Waterhouse JA, Muir C, Corre (IARC publ no. 15). Lyon, Fran
177. Waterhouse JA, Muir C, Sha Contents (IARC publ no. 42). Cancer, 1982
178. Weston B, Grufferman S, Mac clinical factors on survival in m
179. Wiklund K, Dich J, Holm L-E, Swedish agriculture. Br J Ind M
180. Wiklund K, Holm L-E: Trends J Natl Cancer Inst 77:657, 1986
181. Williams AR, Weiss NS, Koeps in the etiology of light chain my
182. Wong O, Raabe GK: Critical re employees, with a quantitative 1989
183. World Health Organization: Ma Diseases, Injuries, and Causes
184. Wurster-Hill DH, Mclntyre OJ multiple myeloma and plasma
185. Zahm S, Weisenburger D, Bab Hodgkin's lymphoma and multi use (abstract 1024) *In* Prograr American Society of Clinical On

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163. Stebbings JH, Lucas HF. Stehney AF: Mortality from cancers of major sites in female radium dial workers. Am J Ind Med 5:435, 1984
164. Steineck G, Wiklund K: Multiple myeloma in Swedish agricultural workers. Int J Epidemiol 15:321, 1986
165. Svensson BG, Englander V, Akesson B. et al: Deaths and tumors among workers. grinding stainless steel. Am J Ind Med 15:51, 1989
166. Teta MJ, Ott MG: A mortality study of a research, engineering, and metal fabrication facility in western New York state. Am J Epidemiol 127540, 1988
167. Teta MJ, Walrath J. Wister-Meigs J, Flannery JT: Cancer incidence among cosmetologists. J Natl Cancer Inst 72:1051, 1984
168. Thomas TL, Waxweiler RJ, Crandall MS, et al: Cancer mortality patterns in three Texas oil refineries. Am J Ind Med 6:3, 1984
169. Tollerud DJ, Brinton LA, Stone BJ, et al: Mortality from multiple myeloma among North Carolina furniture workers. J Natl Cancer Inst 74:799, 1985
170. Turesson I, Zettervall O, Cuzick J, et al: Comparison of trends in the incidence of multiple myeloma in Malmo, Sweden and other countries, 1950–1979. N Engl J Med 310:421, 1984
171. Vagero D, Persson G: Occurrence of cancer in socieconomic groups in Sweden. Scand J Soc Med 14:151, 1986
172. Voelkerding KV. Sandhaus LM, Kim HC, et al: Plasma cell malignancy in the acquired immune deficiency syndrome. Association with Epstein-Barr virus. Am J Clin Pathol 92:222, 1989
173. von Keyserlingk H, Baur R, Stein H, et al: Multiple myeloma in a patient at risk for AIDS. Cancer Detect Prev 14:403, 1990
174. Walrath J, Decoufle P, Thomas TL: Mortality among workers in a shoe manufacturing company. Am J Ind Med 12:615, 1987
175. Wang J-X, Boice JD Jr, Li B-X, et al: Cancer among medical diagnostic x-ray workers in China. J Natl Cancer Inst 80:344, 1988
176. Waterhouse JA, Muir C, Correa P, et al: Cancer Incidence in Five Continents, vol 3 (IARC publ no. 15). Lyon, France, International Agency for Research on Cancer, 1976
177. Waterhouse JA, Muir C, Shanmugaratnam K, et al: Cancer Incidence in Five Contents (IARC publ no. 42). Lyon, France, International Agency for Research on Cancer, 1982
178. Weston B, Grufferman S, MacMillan JP, Cohen HJ: Effects of socioeconomic and clinical factors on survival in multiple myeloma. J Clin Oncol 5:1977, 1987
179. Wiklund K, Dich J, Holm L-E, Eklund G: Risk of cancer in pesticide applicators in Swedish agriculture. Br J Ind Med 46:809, 1989
180. Wiklund K, Holm L-E: Trends in cancer risks among Swedish agricultural workers. J Natl Cancer Inst 77:657, 1986
181. Williams AR, Weiss NS, Koepsell TD, et al: Infectious and noninfectious exposures in the etiology of light chain myeloma: A case-control study. Cancer Res 494038, 1989
182. Wong O, Raabe GK: Critical review of cancer epidemiology in petroleum industry employees, with a quantitative meta-analysis by cancer site. Am J Ind Med 15:283, 1989
183. World Health Organization: Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death. Geneva, WHO, 1949, 1959, 1969, 1979
184. Wurster-Hill DH, Mclntyre OR, Cornwell GG, et al: Marker-chromosome 14 in multiple myeloma and plasma cell leukemia. Lancet 2:1031, 1973
185. Zahm S, Weisenburger D, Babbitt P, et al: An increased risk of developing non-Hodgkin's lymphoma and multiple myeloma is associated with hair coloring product use (abstract 1024). *In* Program/Proceedings of the 26th Annual Meeting of the American Society of Clinical Oncology, Washington, DC, 1990, p 264

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