Malignant Pleural Mesothelioma: World Trends

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1. INTRODUCTION

Asbestos is an umbrella term for a number of naturally occurring fibrous hydrated magnesium silicate minerals. The term encompasses two mineralogic groups: serpentine (chrysotile) and amphibole (crocidolite or riebeckite asbestos, amosite or grunerite asbestos, anthophyllite asbestos, tremolite asbestos, and actinolite asbestos). Serpentine and amphibole can have fibrous or non-fibrous structures; the fibrous type is called asbestos.

Asbestos minerals have long, separable fibres that are strong and flexible enough to be spun and woven. They are also heat resistant. Because of those characteristics, asbestos has been used in a wide range of manufactured goods, mostly building materials (roofing shingles, ceiling and floor tiles, paper products, and asbestos cement), friction products (automobile clutch, brake, and transmission parts), heat-resistant fabrics, packaging, gaskets, and coatings.

Most of the asbestos used in the United States has been serpentine (chrysotile) asbestos. Amphibole asbestos (for example, amosite and crocidolite) has been mined primarily in South Africa, India, Bolivia, and Australia; it has been less used worldwide. The other amphibole varieties anthophyllite asbestos, tremolite asbestos, and actinolite asbestos have no significant industrial applications at the present time.

The use of asbestos in the United States peaked during and after World War II. Major asbestos mining, processing, and manufacturing installations currently flourish in developing countries; in developed countries, such installations are under intense public pressure to cease operations.

Mesothelioma is a rare cancer of the membranes lining the lungs, chest, heart, and abdominal cavity. Three histologic types have been described: epithelial, spindle cell, and mixed. Almost all mesothelioma cases are linked to asbestos exposure. The symptoms of the disease usually do not appear until 20–40 years after the first exposure to asbestos.

Mesothelioma incidence is often interpreted as an index of past exposure to airborne asbestos. Projections of the number of mesothelioma cases over time may be used to evaluate various asbestos health management interventions, including exposure limits and product bans. Mesothelioma projections also provide a foundation for estimating the number of potential lawsuits from persons claiming occupational exposure to asbestos or exposure resulting from use of previously manufactured asbestos-containing products.

Exposure in the workplace has been significant for asbestos miners and millers, and for people employed in secondary manufacturing with asbestos. Historically, construction workers have had very heavy inhalation exposures as a result of mixing and spray ing asbestos on the job. In the United States, use of asbestos declined when fibreglass insulation was introduced from about 1965; it declined further after the U.S. Occupational Safety and Health Administration regulated workplace asbestos exposure in 1972.

However, the use of asbestos has continued to increase in the developing world. One example of the dynamic pattern of worldwide use of asbestos is illustrated by a recent World Trade Organization decision that upheld a ban by France on the import and use of chrysotile. That decision is likely to increase the pressure on producers to target the developing world for sales and use of asbestos. Hence, patterns of occupational exposure to asbestos are complex, dynamic, and quite difficult to estimate in both the United States and the developing world. The present article reviews the incidence, mortality, risks, treatment, and survival, and prognostic factors for mesothelioma.

2. MESOTHELIOMA INCIDENCE AND MORTALITY AROUND THE WORLD

Mesothelioma incidence and mortality rates are age-standardised with the “world standard population” to take into account differences in the age structure of the populations being compared. Because of the high case-fatality rate for mesothelioma, the incidence and mortality rates are nearly equivalent.

2.1 Incidence Rates and Trends in the United States

In the United States, incidence rates for pleural mesothelioma among white males have increased over
time. Rates are highest in seacoast areas (for example, Seattle, San Francisco—Oakland, Hawaii), where asbestos manufacturing plants or shipyards were or are located. The incidence rates in males showed an increasing trend throughout the 1970s and early 1980s. This trend has been attributed to occupational exposure in the shipbuilding industry during World War II, in manufacturing, and in building construction. The significant secular change was attributed both to period (date of diagnosis) and to cohort (date of birth) effects. Connelly et al.\(^5\) showed that incidence rates for pleural mesothelioma among white males were nearly 50% higher in the 1980–1984 period than in 1975–1979. The cohort effect peaked for the 1905–1909 birth cohort and then declined. Those effects probably reflect changes in asbestos exposure patterns in the past and changes in clinical awareness and coding rules for mesothelioma.

Price\(^6\) studied the trend of mesothelioma incidence rates during 1973–1992 in the United States. For women, the age-adjusted rates were flat (0.30 per 100,000 population). The estimated lifetime risk for women was 2.5×10^{-4}, independent of birth cohort. The projected average annual number of cases in women was about 500. For men, the age-adjusted rate increased solely because of the group aged 75 years and older. Lifetime risk for men peaked at 2×10^{-3} for the 1925–1929 birth cohort and then declined to 5×10^{-4} for the 1955–1959 birth cohort. The rates of risk for men peaked at 2×10^{-3} for the 1925–1929 birth cohort and then declined to 5×10^{-4} for the 1955–1959 birth cohort.

The pattern of rates reflected in the age and birth-cohort model suggested a peak of 2300 in the annual number of mesothelioma cases for men before the year 2000. The number of cases would then drop toward 500 annually during the next 50–60 years. Those trends reflect the American trend in raw asbestos consumption and reductions in workplace levels of airborne asbestos.

Price and Ware\(^7\) further compared analyses based on data for 1973–1992 with follow-up to 2003. They found a slower decline in cases in men immediately after a peak in 2000–2004. Analysis confirmed that the annual number of mesothelioma cases in men, which had increased steeply from the 1970s through the mid 1990s, levelled off in both the age-adjusted and the absolute number of cases. After a peak of approximately 2000 cases, the level is expected to return to background levels by the year 2055. The total projected number of mesothelioma cases in men for 2003–2054 is approximately 71,000. The maximum lifetime risk for men, which occurs for the 1925–1929 birth cohort, is 1.8×10^{-3}. The age-adjusted rate for women is constant, and the lifetime mesothelioma risk for women across birth cohorts is 3.6×10^{-4}. The time pattern of cases for women supports the existence of a threshold exposure level for mesothelioma and a quantifiable background rate (Figures 1 and 2)\(^8\).

The age-adjusted mesothelioma incidence (Figure 1) indicates a consistently higher rate for men than for women across all years. Over the years, the trend increased for men and remained at an almost constant low rate for women. Accounting for mesothelioma's latency period of 20–40 years, the increased incidence for men reflects the gender characteristic of the workforce, the increased use of asbestos in the United States, and the high levels of occupational exposure before the late 1960s, when formal workplace exposure limits were established. The age-adjusted rates for men peaked in the 1990s. Projections of future mesothelioma cases in men indicate that the number of cases per year will decline.


2.2 Asbestos Consumption in the United States and the World

In the late 1960s and early 1970s, consumption of asbestos in the United States increased at a rate of 3% - 4% annually. In the 1980s and 1990s, consumption declined by 5% annually (Figure 3). Worldwide, the use of asbestos has declined. The world production of asbestos can be used as a rough guide of world consumption (Figure 3). World production declined from 5.09 million tonnes in 1975 to about 1.93 million tonnes in 1999.

Canada is the only developed country that still produces (almost entirely for export) significant quantities of asbestos fiber. In 2000, Canada was the second-largest producer (behind the Russian Federation) of asbestos and also the world’s leading exporter, being responsible for approximately 16% of world production. Much of the rest came from five developing countries: the Russian Federation (37%), China (17%), Brazil (10%), Kazakhstan (9%), and Zimbabwe (8%) 11. The Russian Federation, China, and Brazil have significant local markets for their asbestos. Other countries such as Thailand, India, South Korea, and Japan are major importers of the mineral. In 2000, consumption in selected countries as a percentage of total world production was as follows: Russian Federation, 22%; China, 20%; Brazil, 9%; Thailand, 6%; India, 6%; Japan, 5%; and South Korea, 1% 11. The reported incidence of asbestos-related disease is unreliably low in developing countries, because epidemiology research has not been carried out systematically in many of those countries.

Table 1 compares mesothelioma incidence rates for 28 countries worldwide: Algeria and Zimbabwe in Africa; Cuba in the Caribbean; Costa Rica in Central America; Argentina and Brazil in South America; Canada and the United States in North America; China, Japan and South Korea in East Asia; Thailand and Singapore in Southeast Asia; India in South-Central Asia; Israel in Western Asia; the Russian Federation, Slovenia, and Poland in Eastern Europe; Sweden, Norway, and Finland in Northern Europe; Italy in Southern Europe; the United Kingdom, Spain, France, and Germany in Western Europe; and Australia and New Zealand in Oceania 11.

2.3 Mesothelioma Incidence and Mortality Outside North America

In Italy during the period 1969 – 1994, the mortality rate related to malignant pleural mesothelioma (MPM) increased by 15% every 5 years, and MPM deaths increased from 900 to 500 every year 12. Mortality related to MPM is higher in areas where shipyards or industries associated with asbestos exposure are present. Turin is the capital of Piedmont, where a quarry of asbestos and some cement works are located. In Casale (a town with many cement factories), MPM is 11 times more frequent than in most other Italian towns 11.

<table>
<thead>
<tr>
<th>Region</th>
<th>Males</th>
<th>Females</th>
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<tbody>
<tr>
<td>Algeria (Algeria)</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td>Zimbabwe (Harare: Africans)</td>
<td>0.2</td>
<td>0.0</td>
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<tr>
<td>Cuba (Villa Clara)</td>
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<td>0.0</td>
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<tr>
<td>Costa Rica</td>
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<td>0.0</td>
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<tr>
<td>Argentina (Bahia Blanca)</td>
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<td>0.0</td>
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<tr>
<td>Brazil (Campinas)</td>
<td>0.2</td>
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</tr>
<tr>
<td>Canada (Quebec)</td>
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<td>0.4</td>
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<tr>
<td>U.S.A. (New Orleans: whites)</td>
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<td>0.7</td>
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<tr>
<td>China (Beijing)</td>
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<td>0.2</td>
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<td>Japan (Osaka prefecture)</td>
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<td>India (Mumbai)</td>
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<td>0.1</td>
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<tr>
<td>Israel (Jews born in Europe or North America)</td>
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<tr>
<td>Australia (Western)</td>
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<tr>
<td>New Zealand</td>
<td>1.9</td>
<td>0.2</td>
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TABLE 1: Age-standardised mesothelioma incidence rates per 100,000 male or female population in regions or ethnic groups with the highest rates, 1993 – 1997
Merler et al. found that, between 1968 and 1992, the highest incidence of mesothelioma registered in both sexes by 150 cancer registries worldwide occurred in the population of Genova and Trieste, Italy, where large shipbuilding facilities were located. That high incidence fitted well with the pattern of unprotected industrial use of asbestos occurring in most industrialised countries of Western Europe and also with the gender characteristics of the workforce employed in activities with asbestos exposure. Italy introduced a ban on asbestos use in 1992. However, considering that asbestos seems to act as an initiator for mesothelioma, the trend in male mortality for primary pleural tumours will not peak for two or three more decades.

In Europe, mesothelioma incidence rates are mostly still rising, although, in some countries, slow-downs are found. In 2003, Montanaro et al. summarised the geographic and incidence trends of pleural mesothelioma in Europe. Geographic distribution for the risk of mesothelioma was greatly varied, with annual rates ranging from about 8 per 100,000 male population in Scotland, England, and the Netherlands, to less than 1 per 100,000 male population in Spain (0.96), Estonia (0.85), Poland (0.85), and Vojvodina, Yugoslavia (0.56).

The ranking of the incidence rates for women was similar to that observed for men, but the rates themselves were considerably lower.

Between 1978 and 1987, incidence rates in men increased significantly in all countries except Denmark. In the 10 years after 1987, that trend decelerated, and a significant increase was found only in England and France. In addition, the magnitude of the trends in younger men was generally lower than that estimated for older men. In certain European populations, a decline may begin in the next few years, considering the deceleration of observed trends of asbestos exposure and mesothelioma, and recent bans on asbestos use.

Since the start of record-keeping, 50,000 people in the United Kingdom have died of mesothelioma, most of them being labourers, builders, and dockers. Before the 1980s, asbestos was widely used in the manufacture of household appliances, brakes, and clutches, and in building construction. The number of newly diagnosed patients under the age of 50 in the United Kingdom has been falling steadily since 1990 as a result of efforts since the late 1970s to remove environmental asbestos and to tighten controls on the use and disposal of the mineral. But the incidence of mesothelioma is still rising in people aged over 60 years. The annual number of deaths from the disease reached 1700 in 2003, up from fewer than 200 in the 1960s. But the numbers will continue to rise, peaking at 2000 annually by 2010.

In Norway, the importation of asbestos increased after World War II, peaking in 1970. Stringent regulations took effect in 1977, and, for all practical purposes, importation and use of asbestos ended in Norway in the late 1970s. Importation was finally prohibited in 1982. Ulvestad et al. analysed the incidence of mesothelioma in Norway over time and studied the consequences of the use of asbestos and the effectiveness of the asbestos ban. An age-period cohort model was used to analyse time trends for pleural mesothelioma. From 1965 to 1999, the annual number of pleural mesothelioma cases rose gradually in both men and women. The highest annual number of pleural mesothelioma cases was recorded in 1999, when 73 new cases were diagnosed. Cohort-specific risks increased for men born up to approximately 1935. After that, the risks seemed to stabilise. The delayed period-effect of the asbestos regulation of the late 1970s will probably be noticeable in the mesothelioma rates of 2010.

2.4 Epidemiologic Links Between Asbestos and Mesothelioma

Epidemiology data on peritoneal mesothelioma are scarce; however, exposure to asbestos is an identified risk factor. To characterise the disease, its time trends, its age-incidence relationships, and its occupational risk factors, Hemminki and Li studied peritoneal mesothelioma for a 38-year period (1961–1998) in Sweden. Peritoneal mesothelioma was rare: only 96 cases in men and 113 cases in women were recorded during that time. The age-standardised incidence of the disease increased for men until 1985 and levelled off thereafter. The incidence in women was equally high, but continued to increase toward the end of the study period. The maximal incidence occurred at an age of about 80 years for both sexes. In men, 29% of the cases had typical asbestos-related jobs with a standardised incidence ratio (SIR) of 1.70. Bricklayers and plumbers had the highest risk (SIR of 7.22 and 5.12, respectively). Within the limits of the sample size, no evidence for risk from environmental exposures to asbestos was noted, because the risks for farmers and for urban residents were not different.

Hemminki and Li also characterised the time trends and the regional, socioeconomic, and occupational risk factors for pleural mesothelioma in Sweden in the years from 1961 to 1998. A total of 1298 cases in men and 233 cases in women were recorded during the 38-year period. The age-standardised incidence of the disease was highest in residents of large industrial and shipbuilding cities. In those populations, the trend also increased. In the final time period, the rate for men was about 10 times that for women. In male socioeconomic groups, manual workers showed the highest (and an ever-increasing) SIR. Among men, plumbers and seafarers had the highest risk (SIRs of 4.56 and 2.83, respectively). Farmers showed an SIR of 0.28, indicating that the population at large was at four times higher risk than farmers were. The SIRs of many academic or college-educated groups were twice to six times higher than that of farmers, suggesting indirect exposure to asbestos in the former groups.

Using registry data for Australia from 1945 to 2002, Leigh and Driscoll analysed time trends in mesothelioma incidence. They found that, from 1945
to 2001, Australia had 7027 cases, with 488 more for January 2002 through June 2003. Incidence rates in 1999 for Australia per million population aged 20 years or older were men, 53.3; women, 10.2; and overall, 31.8. Those rates, which had been continually increasing, were the highest reported national rates in the world. Western Australia had the highest rate (47.7 overall in 1999), but the most cases were seen in the two most populated eastern states, New South Wales and Victoria. Australia’s high incidence of mesothelioma is related to high asbestos use in the past (all fibre types, in a wide variety of settings). The number of cases is expected to reach about 18,000 by 2020, with about 11,000 of those yet to appear.

Takahashi and Karjalainen compiled information about asbestos issues for 10 Asian countries (China, Indonesia, Japan, Korea, Malaysia, Philippines, Singapore, Taiwan, Thailand, and Vietnam). Only Singapore and, recently, Japan have adopted a total ban on asbestos. China, a major producer of chrysotile, shows an increasing consumption trend, which is typical of less industrialised countries.

In Japan, crocidolite had been used for asbestos cement pipe and for spraying, and amosite had been used for building board and for spraying. In the late 1970s, use of these two types of asbestos was stopped in Japan. An extreme increase in imported asbestos was observed between 1960 and 1974. In 1960, 70,000 tonnes of asbestos were imported, and a peak of 320,287 tonnes was reached in 1974. This extreme rise in asbestos imports corresponds with a rapid increase in MPM mortality. Between 1995 and 1999, the estimated mean annual deaths from pleural mesothelioma was about 500. Today, the smoking rate among men in Japan is more than 50%, and so lung cancer deaths caused by the interaction between smoking and asbestos exposure will continue.

Aguilar-Madrid et al. studied the use of asbestos in Mexico at the end of the twentieth century and evaluated data on mortality from malignant mesothelioma in Mexico between 1979 and 2000. Deaths attributable to pleural mesothelioma increased significantly in the period studied. Although imports of asbestos declined, the number of Mexican products containing asbestos tripled. Exports of Mexican asbestos-containing products to Central America grew rapidly in the last 10 years studied. Mexico continues the appreciable use of asbestos and has experienced a significant increase in the occurrence of malignant mesothelioma. Given the many limitations on the control of hazardous work exposures in Mexico, a ban on asbestos is advocated as the most feasible means of limiting an epidemic of asbestos-related disease.

3. ASBESTOS FIBRES AND OTHER ASSOCIATED RISK FACTORS

More than 40 years have passed since occupational crocidolite exposure was found to be associated with development of malignant mesothelial tumours in South African miners 20 – 40 years later. A similar association was not seen in amosite and chrysotile miners.

Epidemiologic and toxicologic knowledge have increased enormously since then, but mortality continues to rise steeply (5% – 10% per year) in most industrialised countries. Even with widespread asbestos abatement efforts, the increase is likely to continue in Western Europe and the United States well into the twenty-first century—at least until 2020. Unregulated use of asbestos in less industrialised countries may cause the epidemic to continue throughout the twenty-first century in those regions.

Asbestos abatement seems to be successful—as evidenced by a decline in the proportion of patients with peritoneal tumours, which are the most common malignancies in heavily exposed individuals. In the 1960s, peritoneal tumours constituted up to 30% of all mesothelioma cases, but in recent years, the proportion has fallen to about 10%. However, the changing ratio might also be attributed to the steady increase in pleural tumours. The difficulty in formulating a connection between asbestos exposure and mesothelioma resulted from an unforeseeable difference in the carcinogenicity of various asbestos mineral fibres, compounded by the very long latency of the disease.

Scattered patches of crocidolite were found in the surface soil of the rural county of Dayao in southwestern China. In 1983, researchers found that residents of two villages in Dayao had hyperendemic pleural plaques and excessive numbers of pleural mesothelioma cases. In a cross-sectional survey, Luo et al. reported that the prevalence of pleural plaque was 20% among peasants more than 40 years of age in Dayao. The average number of mesothelioma cases in a population of 68,000 was 6.6 per year in the 1984 – 1995 period and 22 per year in the 1996 – 1999 period. Mesothelioma cases that were histologically confirmed occurred at a rate of 3.8 cases per year in the 1984 – 1995 period and 9 cases per year in the 1996 – 1999 period. Peasants with higher exposures had a mesothelioma mortality that was five times that of peasants with lower exposures. No cases of mesothelioma were observed in comparison groups from locales where no crocidolite was known to exist in the environment.

The observation of numerous mesothelioma cases at Dayao was a unique finding, attributable mainly to lifetime exposure to crocidolite asbestos. The finding of deaths at a younger age and a relatively high ratio of mesothelioma to lung cancer cases could be another unique result of lifetime environmental exposure to crocidolite asbestos. The commercial use of crocidolite has been officially banned in China since 1984, but the incidence of mesothelioma has continued to increase steadily, particularly among peasants. Because the latency of mesothelioma is approximately 20 – 40 years, the ban had little effect in the 1990s. Increased awareness and changes in diagnosis over time may also be contributing to the increase.
3.1 Types of Asbestos Fibres and Their Relationship to Mesothelioma

To elucidate the features of asbestos that contribute to the induction of human malignant mesothelioma, Suzuki and Yuen used high-resolution analytical electron microscopy to determine the type, number, and dimensions of asbestos fibres in lung and mesothelial tissues in 168 cases of mesothelioma. Asbestos fibres were present in almost all of the lung and mesothelial tissues from the mesothelioma cases. The most common types of asbestos fibres in lung were an admixture of chrysotile with amphibole, amphibole alone, and occasionally chrysotile alone. In mesothelial tissues, most of the asbestos fibres seen were chrysotile. In lung, amosite fibres were greatest in number, followed by chrysotile, crocidolite, tremolite/actinolite, and anthophyllite. In mesothelial tissues, chrysotile fibres were 30.3 times more common than amphibole fibres. In some mesothelioma cases, the only asbestos fibres detected in either lung or mesothelial tissue were chrysotile fibres. The average number of asbestos fibres in both lung and mesothelial tissues was one hundred times the number found in the general population. Most of the asbestos fibres in lung and mesothelial tissue were shorter than 5 μm.

The study results supported the induction of human malignant mesothelioma by chrysotile.

Muscat and Wynder investigated the risks resulting from cigarette smoking combined with asbestos exposure. Mesothelioma cases in men were found predominantly in those who worked in the shipbuilding industry and in the construction or insulation trades. Elevated risk was found for men employed in asbestos-related industries (odds ratio: 8.1)—for example, shipyards (OR: 82.9), construction or maintenance (OR: 8.5), and other asbestos-related jobs (OR: 3.2)—and for men who self-reported exposure to asbestos or insulation (OR: 50.9). A statistically significant trend was found for the risk of mesothelioma with increasing years employed in non-shipyard asbestos-related occupations. Among women, 1 case was found in a woman who worked in an asbestos-related industry, and 2 cases were reported as having had domestic contact with asbestos. No association between cigarette smoking and mesothelioma was found for either men or women.

Throughout the history of automobile development, chrysotile asbestos has been an essential component of vehicle brake linings and pads. Acceptable alternatives were not fully developed until the 1980s, but they have been installed in vehicles produced since that time. Paustenbach et al. analysed what was known over time about the potential environmental and occupational health hazards associated with the presence of chrysotile asbestos in brake linings and pads.

Automobile brakes and brake friction materials were used starting in the early 1900s. Concerns regarding exposure to asbestos among workers involved in the manufacture of friction products were initially raised as early as 1930. The U.S. Public Health Service proposed the first occupational guideline for asbestos exposure in 1938. The causal relationship between asbestos exposure and lung cancer was confirmed in 1955 in asbestos textile workers in the United Kingdom. Later, in 1960, mesothelioma was attributed to exposure to even relatively low airborne concentrations of crocidolite in South Africa. Between 1960 and 1974, initial studies of brake lining wear emissions were conducted. Those studies showed that automobile braking was not a substantial contributor of asbestos fibres longer than 5 μm to ambient air. The first exposure surveys for brake mechanics were conducted during the same period.

In 1971, the U.S. Occupational Safety and Health Administration promulgated the first national standards for workplace exposure to asbestos. Most of the information on the exposure of brake mechanics to airborne asbestos during brake repair was gathered post 1974, primarily from a series of sampling surveys conducted by the National Institute of Occupational Safety and Health in the United States. Those surveys indicated that the time-weighted average asbestos concentrations (about 1 – 5 hours in duration) during brake servicing were between 0.004 and 0.28 fibres per cubic centimetre, and the mean time-weighted average concentration was about 0.05 fibres per cubic centimetre. The data also showed that brake mechanics were not exposed to time-weighted average concentrations above workplace exposure limits in effect at the time of the study.

From 1975 to 2002, more than 25 epidemiology studies were conducted to examine the risk of asbestos-related disease in brake mechanics. Those studies clearly indicated that brake mechanics were not at increased risks of adverse health effects because of asbestos exposure. Specifically, the studies found no increased risk of mesothelioma or asbestosis in brake mechanics, and no evidence that lung cancer in that occupational group could be attributed to exposure to asbestos during brake repair. Those findings could be attributable to one or several factors: the airborne concentration of chrysotile fibres and the duration of the exposure were too small to be significant; that the chrysotile fibres were too short to be biologically important; that chrysotile fibres were substantially less potent than amphibole fibres in inducing lung cancer and mesothelioma; or that other yet-to-be-understood factors were at play. During this same time period, 20 published studies evaluated asbestos exposure or asbestos-related health effects in friction-product manufacturing workers. Those studies indicated that such workers were historically exposed to concentrations of chrysotile fibres perhaps 10 – 50 times greater than brake mechanics experienced, but that the risks of asbestosis, mesothelioma, and lung cancer, if any, were not apparent, except in those workers who had some degree of exposure to amphibole asbestos during their careers.
3.2 Mesothelioma Without Asbestos Exposure

In the past, the increased incidence of mesothelioma has been attributed solely to asbestos. Yet, 20% or more of mesothelioma cases occur in non-exposed individuals. Moreover, among heavily exposed individuals, including crocidolite miners, fewer than 5% develop mesothelioma. Thus, additional factors seem to be causing mesothelioma, alone or in conjunction with asbestos.

Simian virus 40 (SV40) appears to be one of those factors. Poliovirus vaccines used during the years between 1955 and 1963 were contaminated with SV40. It has been estimated that 10–30 million Americans could have received an SV40-contaminated dose of vaccine. Simian virus 40 DNA sequences have been detected in some human cancers, especially pleural mesothelioma, although study results conflict. Strickler et al. examined the relationship between SV40-contaminated poliovirus vaccine exposure and subsequent rates of pleural mesothelioma in the United States. The age-standardized pleural mesothelioma incidence rate in men increased from 0.79 per 100,000 person-years in 1975 to a peak of 1.69 per 100,000 person-years in 1992. Incidence rates increased the most among men who were 75 years of age or older. That age group is the one least likely to have been immunised against poliovirus using a vaccine contaminated with SV40. Incidence rates among men in the age groups most heavily exposed to SV40-contaminated poliovirus vaccine remained stable or decreased from 1975 through 1997. Similar age-specific trends were observed among women. The age-period cohort models for men and women also indicated that trends in pleural mesothelioma incidence were not related to trends in exposure to SV40-contaminated poliovirus vaccine.

Hirvonen et al. failed to detect SV40 in 49 Finns with mesothelioma, but detected SV40 in 3 of 5 mesothelioma cases in U.S. patients. Emri et al. and De Rienzo et al. did not detect SV40 in 29 and 9 Turks with mesothelioma (respectively), but they detected SV40 in mesothelioma biopsies from 2 of 2 Italians and 4 of 11 Americans analysed in parallel. Leithner et al. found SV40 in 3 of 3 tumour samples from the United States and Italy, but did not detect SV40 in 8 mesothelioma samples and 24 bone tumour samples from Austria. The authors of the foregoing publications attributed the negative results obtained in Finland, Turkey, and Austria to the fact that SV40-contaminated poliovirus vaccines were not used in those countries.

4. SURVIVAL AND TREATMENT

Mesothelioma is classified into three general categories: diffuse malignant, localised benign, and localised malignant.

Diffuse pleural mesothelioma accounts for the preponderance of primary pleural tumours.

The “benign mesotheliomas” are usually localised, and they have been reclassified as localised fibrous tumours of the pleura (LFTP). They probably arise from a cell other than the mesothelium. Of all localised mesotheliomas, 10% are malignant, but they are often low-grade and potentially resectable.

The locally invasive and rapidly fatal malignancy of the pleura called MPM, which is linked to asbestos exposure, has a survival time without treatment ranging from 4 months to 12 months. No standard treatment exists for malignant mesothelioma because the tumour is relatively resistant to therapy. However, interest in novel therapies and in conventional treatments used in new ways is currently resurgent. Several treatment modalities have been studied, including surgery, radiotherapy, chemotherapy, and immunotherapy.

Chemotherapy can be administered systemically or directly into the pleura.

Surgical therapy appears to be a promising strategy, because mesothelioma tends to be a localised disease that metastasises late in its clinical course. The two available operative strategies are pleurectomy and extrapleural pneumonectomy (EPP). A pleurectomy removes the parietal or visceral pleura (or both), leaving the denuded surface of the underlying lung. An EPP removes the complete pleural envelope and all of its contents, including the ipsilateral lung, the diaphragm, and a portion of pericardium. Surgical resection is possible only in some patients, and fewer than 15% of them live beyond 5 years.

For patients not treated with curative resection, the median survival duration with supportive care alone has been reported to range from 6 months to 10 months. The median survival time of 337 patients in 11 multicentre chemotherapy trials was 7 months.

Treatment with radiation therapy has been equally disappointing, in part because of the difficulties of irradiating diseased tissue while avoiding toxicity to normal lung, cardiac, and spinal cord tissues.

Azziz et al. reported on 302 patients with MPM who had been referred for assessment between 1989 and 1998. Of the 302 patients, 191 received no specific treatment. Another 47 were treated by decortication/pleurectomy, and 64 had a radical EPP. Intrapleural chemotherapy and systemic postoperative chemotherapy were employed in only 51 patients following their radical surgery. The average survival was 8.9 months for patients treated with palliative care only, 13 months for patients treated with radical surgery only, and 14 months for patients treated with decortication/pleurectomy. However, survival improved to a mean of 35 months for patients treated with radical surgery followed by systemic postoperative chemotherapy. The operative mortality was 9% for EPP and 0% for decortication/pleurectomy. Thus, in selected patients with MPM, complete surgical resection by EPP represented an important initial step in management.
Aziz and colleagues also found that T1 and T2 patients had a much more favourable survival outcome when radical surgery and postoperative chemotherapy were used. Patients with T1 tumours exhibited better long-term survival outcome than those with T2 disease. Patients with T3 tumours had a poor prognosis even when radical surgical resection was achieved. The median survival for T1 tumour patients was 42.8 months. That result was significantly different from the median survivals of 31 months and 14 months for patients with T2 and T3 tumours, respectively. At 1 year and 3 years, survival prevalence was 90% and 70% for T1 patients, and 85% and 36% for T2 patients, and 49% and 0% for T3 patients, respectively. No differences in survival were observed with regard to differences in age, sex, period of asbestos exposure, and preoperative symptoms.

Leigh et al. 15 found a statistically significant trend between lung fibre content (fibres per gram of dry lung tissue) and cell type, ranging from epithelial (low fibre content), through mixed, to sarcomatous (high fibre content). The trend was most apparent for uncoated fibres and for crocidolite. Lung fibre content was also associated with tumour site. Higher lung fibre content was associated with peritoneal tumours. The relationship was significant for all fibre content measures except chrysotile, and it was independent of the relationship between fibre content and cell type. Survival from time of diagnosis was significantly longer for the epithelial cell type (mean: 13 months) and the mixed cell type (mean: 10.2 months) than for the sarcomatous cell type (mean: 5.8 months). Survival time was significantly longer for pleural tumours (mean: 11.4 months) than for peritoneal tumours (mean: 8.6 months).

Sugarbaker et al. 46 found that, with tridimensional therapy (following by adjuvant chemotherapy and radiotherapy) of MPM, three subgroups had an improved prognosis for postoperative long-term survival. Patients with an epithelial cell type had a 2-year survival of 52% and a 5-year survival of 21%. Median survival was 26 months. Negative resection margins on the pathology analysis were associated with a 2-year survival of 44%, a 5-year survival of 25%, and a median survival of 23 months. No evidence of metastases to the extrapleural lymph nodes was associated with a 2-year survival of 42%, a 5-year survival of 17%, and a median survival of 21 months. Patients with all three favourable prognostic variables (n = 31) had the best long-term survival: 68% at 2 years and 46% at 5 years, with a median survival of 51 months.

No known single curative modality yet exists for MPM. Most patients are candidates for chemotherapy at some point in their treatment, but no standard regimen has been established.

Ong and Vogelzang 48 reviewed the available clinical studies in MPM. Response rates have been reported with doxorubicin, high-dose methotrexate, and etoposide at 26%, 37%, and 25%, respectively, but those results have yet to be confirmed. Agents that have produced response rates in 10%–20% of patients include doxorubicin, epirubicin, mitomycin, cyclophosphamide, ifosfamide, cisplatin, and carboplatin. Combination chemotherapy trials did not demonstrate a consistently greater response rate than did single-agent trials. The combination of doxorubicin, cisplatin, bleomycin, and mitomycin demonstrated a response rate of 44%; however, that finding remained unconfirmed. Intraperitoneal therapy using γ-interferon, particularly for small-volume disease, showed promise.

Large randomised trials that are currently ongoing or that have been performed in recent years will yield important answers regarding the role of chemotherapy and the efficacy of various single and combination chemotherapy agents, including drugs to inhibit vascular endothelial growth factor and its receptor, epidermal growth factor receptor, and platelet-derived growth factor receptor. Furthermore, biologic and genetic studies of mesothelioma have identified several tyrosine kinase receptors that are aberrantly expressed in the tumours. Orally available small-molecule inhibitors of several tyrosine kinase receptors have been developed and are now being evaluated in clinical trials.

Tans et al. 49 treated 20 consecutive patients who had histologically proven MPM secondary to environmental exposure to asbestos or erionite with cisplatin, mitomycin C, and α-interferon. They administered 82 treatment cycles to 19 evaluable patients. Of the 19 patients, 2 attained a partial response. Stable disease was seen in 11 patients, and 6 patients experienced disease progression. Toxicities included interferon-related fever and flu-like symptoms, and vomiting. The median actuarial survival was 15 months. Three patients were alive at 20+ months, 21+ months, and 27+ months. The authors concluded that, although the addition of α-interferon to cisplatin and mitomycin C did not result in an objective response higher than that previously reported with the same cytotoxic agents alone, the trend towards an improvement in median survival as compared with well-matched historical controls suggested some benefit from the inclusion of interferon.

Vogelzang et al. 51 conducted a phase III trial to determine whether treatment with pemetrexed and cisplatin would result in survival time superior to that achieved with cisplatin alone. A total of 456 patients were accrued to the trial: 226 received pemetrexed and cisplatin, 222 received cisplatin alone, and 8 never received therapy. Median survival time in the pemetrexed/cisplatin arm was 12.1 months versus 9.3 months in the control arm. Median time to progression was significantly longer in the pemetrexed/cisplatin arm: 5.7 months versus 3.9 months. The response rate was 41.3% in the pemetrexed/cisplatin arm versus 16.7% in the control arm. In patients with MPM, treatment with pemetrexed plus cisplatin and vitamin supplementation resulted in superior survival time, time to progression, and response rate as compared with treatment with cisplatin alone. The addition of
folic acid and vitamin B₁₂ significantly reduced toxicity without adversely affecting survival time.

Berghmans et al. conducted a systematic qualitative and quantitative overview of the literature and suggested that the most active chemotherapeutic regimen was a combination of cisplatin and doxorubicin (objective response rate of about 28%) and that the best single agent was cisplatin (objective response rate of about 23%). The combination of the two drugs can be recommended as a control arm for future randomised phase III trials. Khalil et al. also reviewed the results of the most recent trials and the most promising advances in the treatment for malignant mesothelioma.

Pass and Donington investigated the use of intracavitary photodynamic therapy as adjuvant therapy after EPP. Photodynamic therapy is based on the systemic administration of light-sensitive molecules that localise in neoplastic cells and that produce toxic singlet oxygen when activated by light of a particular wavelength. Porphyrin dye is readily absorbed from the bloodstream by human cells. Non-malignant cells are able to excite the dye rapidly; malignant cells are not. The result is a relatively selective retention of dye within malignant cells at 48 hours after intravenous administration. The dye is excited by exposure to a single wavelength of light from a laser. The activated dye produces intracellular oxygen free radicals that ultimately cause cell death.

Table II summarises results of various treatment modality combinations. The relatively poor outcome for mesothelioma suggests that opportunities are potentially available for further improvements in the management of the disease. A scatter plot of patient numbers against median survival time (Figure 4) shows that the medians are concentrated in the region from 5 months to 15 months.

Magnani et al. analysed survival after malignant mesothelioma in the population-based Registry of Malignant Mesothelioma of Piedmont, Italy (4.5 million total population). In 1990 – 1998, 590 patients had a histologic diagnosis of pleural mesothelioma. Vital status was ascertained at the municipalities of residence at January 1, 2000. At the end of follow-up, 58 patients (9.8%) were alive, and 20 (3.4%) had been lost to follow-up. (In some other papers, the year of last follow-up and the number of patients still alive at last follow-up are seldom mentioned.) Median survival was 8.5 months. Cumulative survival was 35.9% at 1 year and 14.2% at 2 years. The researchers found no improvement in survival with period of diagnosis. Either the treatment efficacy remained unchanged, or the effect was limited to small subgroups and could not be observed when the analysis included larger categories.

The study by Magnani and colleagues on malignant mesothelioma is the second-largest of three population-based studies in the literature. The other two population-based studies were conducted by Spirtas et al. and Janssen-Heijnen et al., with 1475 and 136 cases respectively. All show similar results. Survival in published clinical series range between 18.4% and 57.6% at 1 year for pleural mesothelioma and 24.1% and 33.8% for peritoneal mesothelioma.

5. PROGNOSTIC FACTORS

Curran et al. determined that poor prognosis in patients with pleural mesothelioma was associated with a poor Eastern Cooperative Oncology Group performance status, a high white blood cell (WBC) count, a probable or possible histologic diagnosis of mesothelioma, male sex, and having sarcomatous tissue as the histologic subtype. Taking these five factors into consideration, patients were classified into two groups: a good-prognosis group (1-year survival rate: 40%) and a poor-prognosis group (1-year survival rate: 12%).

Magnani et al. found that survival was also associated with age (longer survival for younger patients at diagnosis, p < 0.0001) and with histology (longer survival for epithelial mesothelioma, shorter for fibrous, and intermediate for mixed or unspecified types, p < 0.0001).

Herndon et al. examined the prognostic importance of pretreatment patient characteristics on the survival of patients with mesothelioma treated by the Cancer and Leukemia Group B (CALGB). The subgroup with the best survival (median survival: 13.9 months) included patients with a performance status of 0 and an age younger than 49 years, and patients with a performance status of 0, an age of 49 years or older, and a haemoglobin level ≥ 14.6. The subgroup with the worst survival (median survival: 1.4 months) included patients with a performance status of 1 or 2 and a WBC count ≥ 15.6 x 10⁹/L.

Edwards et al. assessed the prognostic variables and validated the European Organisation for Research and Treatment of Cancer and CALGB prognostic groups. In univariate analysis, Edwards and colleagues found that significant poor prognostic factors included male sex, older age, weight loss, chest pain, poor performance status, low haemoglobin, leucocytes, thrombocyte, and non-epithelial cell type (p < 0.05). The prognostic significance of cell type, haemoglobin, WBC count, performance status, and sex were retained in the multivariate Cox proportional hazards regression model.

Van Gelder et al. studied 167 new cases (1987 – 1989) of cytologically (15%) or histologically (85%) proven MM in Rotterdam, Netherlands. Univariate analysis identified age, stage, and histopathologic subtype as significant prognostic factors, all of which were confirmed in multivariate analysis. Median survival rates for patients < 65 years, 65 – 74 years, and ≥ 75 years were 12.0 months, 8.1 months, and 4.2 months respectively. Patients with stage I, stage II, or a combination of stages III and IV disease had median survivals of 12.0 months, 4.9 months, and 3.7 months respectively. Mixed histopathologic subtype was less favourable for survival (6.3 months) than...
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<td>81</td>
<td>United States</td>
<td>114</td>
</tr>
<tr>
<td>2002</td>
<td>11.2</td>
<td>52</td>
<td>Australia</td>
<td>115</td>
</tr>
<tr>
<td>2003</td>
<td>14.6</td>
<td>32</td>
<td>Netherlands, Germany</td>
<td>116</td>
</tr>
<tr>
<td>2003</td>
<td>12.1</td>
<td>226</td>
<td>United States</td>
<td>51</td>
</tr>
</tbody>
</table>

*a* Intravenous.

*b* Oral.

*c* Eudratrex alone.

*d* Eudratrex with leucovorin rescue.

*e* Cisplatin and mitomycin.

*f* Cisplatin and doxorubicin.

were the sarcomatous subtype (6.9 months) and the epithelial subtype (8.4 months).

Sugarbaker et al. 122 studied a multimodality approach in patients with MPM. Those researchers found that positive lymph nodes were associated with poorer survival than were negative nodes (p < 0.01). Patients with epithelial variant and negative mediastinal lymph nodes had a survival rate of 45% at 5 years.

Alberts et al. 72 analysed 262 patients with MPM. In a univariate analysis, the significant favourable
neoplasms of localised mesothelioma has been disappointing. Complete surgical resection was the preferred treatment for both types and is usually curative with benign mesothelioma. In more than 80% of cases, LLF is has a benign clinical course; in 50% of patients, it is asymptomatic. The diagnosis is difficult to establish before surgery. Treatment consists of complete resection, including adjacent structures if necessary.

The clinical behaviour of LLF cannot be predicted on the basis of histology only. Broad-based and locally invasive tumours show a higher risk of recurrence. One benign tumour occurred after 1 year and was treated successfully by repeat resection and radiotherapy. Overall, between 10 months and 27 years after the first resection, 13 patients (86%) were alive with no evidence of disease. Hence, long-term follow-up is mandatory in all cases so that early re-resection can be performed at the time of recurrence.

Clear-cell mesothelioma is an extremely rare neoplasm of the pleura that can easily be mistaken for a metastasis to the pleura of clear-cell carcinoma. Desy et al. reported the histochemical, immunohistochemical, and ultrastructural aspects of a case of clear-cell pleural mesothelioma in a 52-year-old man with no known asbestos exposure. He was admitted to hospital for a recurrent, cytologically negative pleural effusion. A partial decortication of the right pleura was performed.

Pericardial mesothelioma is also extreme rare, with a reported incidence of 0.002% among 500,000 mesothelioma cases in a large necropsy study. A relationship to asbestos exposure is possible, but the disease is seen in cases with coexistent asbestos-related pleural disease. In 2004, Suman et al. reported a case of a 19-year-old male student with primary pericardial mesothelioma of epithelial type and no evidence of asbestos in the lung upon post-mortem examination. The patient died 5 months after investigation into the initial presenting symptom of chest pain began. Pericardial mesothelioma generally responds poorly to therapy, and the student’s disease progressed rapidly.

7. CONCLUSIONS

Although the use of asbestos has declined worldwide, some countries are still showing trends of rising consumption and, because of the disease latency period (20–40 years), many new cases of mesothelioma await to surface in the next few decades.

The latency times in 42 cases with definite or probable occupational asbestos exposure showed a log-normal distribution with a median of 37 years and a range of 19–68 years. Mesothelioma is a disease associated with occupational or environmental exposure (or both). Its overall prognosis remains poor, yet the disease could potentially be preventable. A worldwide effort in risk awareness and regulation of asbestos is essential.
Guidelines for the management of mesothelioma are currently being developed by the Lung Cancer Disease Site Group of Cancer Care Ontario\textsuperscript{12}. Guidelines under development include “Use of chemotherapy in patients with malignant pleural mesothelioma” (7-14-1 ES), “Surgical management of malignant pleural mesothelioma” (7-14-2 ES), and “Role of radiation therapy in malignant mesothelioma of the pleura” (7-14-3 ES). Readers are encouraged to review these forthcoming guidelines for more details on the management of this disease.

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