Perspective

Malignant pleural mesothelioma: an epidemiological perspective

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This paper reviews the aetiology, distribution and projected future incidence of malignant mesothelioma. Asbestos exposure is the most thoroughly established risk factor. Debate continues regarding the relative importance of the different asbestos fibre types and the contribution of Simian virus 40 (SV40). Disease incidence varies markedly within and between countries. The highest annual rates of disease, approximately 30 case per million, are reported in Australia and Great Britain. The risk of disease increases with age and is higher in men. Time from asbestos exposure to disease diagnosis is on average greater than 40 years. Non-occupational asbestos exposures contribute an increasing proportion of disease. With the exception of the United States, incidence continues to increase. In developed countries peak incidence is expected to occur before 2030.

Key Words: Asbestos; epidemiology; incidence; malignant mesothelioma

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Malignant mesothelioma is a tumour arising from the mesothelial lining of the pleura, peritoneum, pericardium and tunica vaginalis. Pleural mesothelioma is the most common of these, accounting for approximately 90% of disease (1,2). Patients commonly present with dyspnoea, chest wall pain and pleural effusion (3). Diagnosis is often made at an advance stage of disease and in untreated patients median survival is less than one year (4).

Disease aetiology

The association of mesothelioma with asbestos exposure is well established, with an aetiological fraction above 80% (5). Indeed, incidence of the disease prior to the widespread commercial production of asbestos was rare (6,7). The link was first demonstrated by Wagner *et al*. (8) in 1960, who described crocidolite asbestos exposure in 33 cases of mesothelioma in South Africa's North Western Cape. Confirmation of the association came with eight case control studies conducted between 1965-75, which reported relative risk of exposure between 2.3 and 7.0 (9). Finally, McDonald (10) summarised 43 cohort mortality studies finding proportional mortality ratios for exposed subjects ranging from 2.5 to 102.3.

There are six types of asbestos that may be divided into two forms, serpentine and amphibole. The only serpentine type, chrysotile, also known as white asbestos, is made up of curled fibres and accounts for approximately 95% of all asbestos used worldwide (11). The amphibole group includes amosite, crocidolite, tremolite and anthophyllite (12). Their straighter, needle-like, friable fibres distinguish them from chrysotile. Of the amphiboles, amosite (brown asbestos) and crocidolite (blue asbestos) had the most industrial usage. The relative oncogenicity of the main asbestos fibre types, chrysotile in particular, is controversial. Hodgson and Darnton (13) examined average cumulative exposure in seventeen published cohorts and calculated a risk ratio of 1:100:500 for chrysotile, amosite and crocidolite respectively. Others argue that chrysotile is not carcinogenic and that the observed cases are due to contamination by the amphibole tremolite (14). Reviews of the epidemiological literature have yielded conflicting conclusions regarding the malignant potential of chrysotile (15-17). Studies of retained lung fibres in affected patients have reported increased odds ratios for amphibole fibres, as well as for chrysotile fibres alone (9). The evidence has been deemed sufficient by the World Health Organisation (WHO) to conclude that all types of asbestos cause cancer in humans (18).

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Table 1 Current incidence and projected future case load for malignant mesothelioma

Country	Year	Cases	Annual incidence per million[†]	Male-Female ratio	Predicted peak	Estimated future cases	Period of estimate
Australia (35)	2008	661	29	4:1	2014-2021	6,500[§] (36)	2004-2060
United Kingdom (37)	2009	2,560	29	4.9:1	2011-2015	65,000 (38)	2002-2050
USA (39)	2009	-	10	4.6:1	2000-2005	85,000 (2)	2008-2054
Italy (40)	2004	-	24	2.6:1	2015-2024	800/year (41)	2012-2024
Japan (42)	2007	1,068	8[‡]	3.5:1	2027	66,000 (43,44)	2003-2050

[†]Age standardised; [‡]Crude rate; [§]State of New South Wales only

The latency of mesothelioma, that is the time elapsed between first exposure to asbestos and the diagnosis of disease, is long. Investigators in New South Wales, Australia reported an average latency of 42.8 years for cases diagnosed between 1972 and 2004, without gender difference. Peritoneal disease had a significantly shorter latency than pleural disease. Longer latency periods were evident in more recent diagnoses (19). A second study, from Italy, reported a mean latency of 44.6 years in 2,544 cases diagnosed in the period 1993 to 2001, with shorter latency in those cases with occupational exposure (20). There is some evidence that disease latency has an inverse relationship with duration or degree of asbestos exposure. In a series of British Naval dockyard workers, Hilliard *et al.* (21) categorised the workers as continuously or intermittently exposed, finding a shorter latency in the more heavily exposed group (42 years, 95% CI, 39.0-45.0, versus 49.5 years, 95% CI, 48.2-50.9). Early studies reporting 20-30 year latency periods often involved insulation workers, a population with heavy asbestos exposure (22).

Although short or low-level asbestos exposures have been linked to the development of mesothelioma, the risk of disease demonstrates dose dependence. In the most closely studied asbestos-exposed population, residents of the Western Australian asbestos mining town Wittenoom, both mine workers and non-mining residents with greater intensity and duration of exposure had higher rates of disease (23,24). Length of employment has similarly been shown to increase mesothelioma risk in Norwegian insulation and asbestos-cement workers (25,26)

Observation of high mesothelioma rates in the Cappadocian villages of Turkey has identified other potential aetiological factors (27). The regionally occurring fibrous mineral erionite has been detected in the villagers' lungs, and is demonstrably carcinogenic in animal models (28). Pedigree analysis in affected families in this region also suggests a genetic susceptibility that is inherited in an autosomal dominant pattern, raising the possibility of a specific gene-environment interaction (29).

The DNA virus, Simian Virus 40 (SV40), has been associated with malignant mesothelioma and has been suggested as a causal co-factor. The most likely route of human infection by SV40 is via contaminated polio vaccines until the late 1970s (30). SV40 inactivates tumour suppressor genes and has demonstrated oncogenic potential in animal experimentation (31). It has a predilection for mesothelial cells and is found in human mesothelioma specimens. It is not however present in all mesotheliomas (32), and PCR-based evidence for tumour infection may have been based on assays prone to false positive results (33). As such the role of SV40 in overall human mesothelioma incidence remains unclear.

Descriptive epidemiology

Worldwide malignant mesothelioma incidence has been rising since the mid 20th century. Analysis of mesothelioma mortality recorded in the WHO mortality database between 1994 and 2008 yielded an age-adjusted mortality rate of 4.9 per million, a mean age at death of 70 years and male to female ratio of 3.6:1 (34). There is marked heterogeneity in malignant mesothelioma incidence within and between countries. *Table 1* outlines up-to-date incidence data in industrialised countries. Some of the most robust data comes from national registries in Australia and the United Kingdom, where age standardised incidence for 2009 was 29 per million of population in both countries. In Australia, male diagnoses dominate and more than 75% of newly diagnosed patients are aged 65 years or older. Incidence has been increasing each year since 16 cases were reported in 1980 (35). Comparable disease distribution is evident in the United Kingdom. Incidence in men has increased five-fold in the 30 years since 1980, and the age-specific incidence peaks at 75-79 years for women and 80-84 for

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men. In the United States, analyses of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program database estimate 2,500-3,000 cases per year, predominantly in elderly men. Furthermore the SEER incidence data suggest a plateau and subsequent decline in new mesothelioma cases since the years 2000-2005 (2,45). Crude incidence rates in a large proportion of Europe are in the range of 10-20 cases per million (22).

Global incidence of mesothelioma is likely to be significantly higher than mortality registries suggest due unreported cases occurring in developing counties. Park *et al*. (46) used the relationship between cumulative asbestos use and disease incidence in countries where both variables are published to estimate unreported cases in countries where only asbestos consumption is known. They describe a "hidden burden of disease" of approximately 39,000 cases in the 15-year period to 2008, predominantly in Russia, Kazakhstan, China, India and Thailand. Furthermore, mortality data in developed countries may underestimate true mesothelioma incidence due to inaccurate death certification (47) and undifferentiated International Classification of Diseases (ICD) codes for pleural malignancy until 1994 (48).

Exposure mapping within countries reveals high regional variability in incidence and mortality. In Italy, significant municipal clusters of disease have been identified close to asbestos cement industries, shipyards, oil refineries and petrochemical industries (49). Similarly in the UK, the highest mesothelioma mortality rates are recorded in areas with a history of ship building, such as Barrow-in-Frness, Plymouth, Portsmouth, Tyneside and Southampton (50). Regional variability is also evident in the registries contributing to the SEER Database. In 1998 the incidence ranged from 4.5 per million in Hawaii to 23.3 per million in Seattle-Puget Sound, an area historically associated with maritime industry (51). Small clusters of very high incidence have also been described secondary to environmental exposures. Villages in Turkey (52) and New Caledonia (53) with incidence rates above 1,000 per million are examples.

Given the role of asbestos in the aetiology of malignant mesothelioma, it is unsurprising that the relative risk of various occupational exposures have been extensively addressed in the epidemiological literature. Three waves of disease have been described. The first affected miners and millers of raw asbestos and in the manufacture of asbestos products. Former Wittenoom workers have been closely followed. Berry *et al*. (54) recently published 50-year follow-up in a cohort of 6,908 Wittenoom employees, reporting mesothelioma death rates of 4.7% and 3.1% for male and female workers respectively. Malignant mesothelioma accounted for 10% of known deaths in men and 8% in women in this cohort. A second wave of disease subsequently became evident in workers who used asbestos products in industry. Carpenters, plumbers, defence personnel, shipbuilders, and insulation installers are typical of the occupations affected (55).

Since the 1990s changing risk groups have been identified (56), prompting classification of a third wave of disease, in people with often unknown, short term or low level exposure to asbestos. Cited examples of these frequently non-occupational exposures include, domestic (family of asbestos workers), air pollution from nearby asbestos industry, or exposure to asbestos in place (buildings containing asbestos) (57). In Western Australia, increasing disease incidence attributed to exposure during home maintenance and renovation exemplifies the epidemiological shift (58). Non-occupational exposures of this type were found to account for 8.3% of cases in the period 1993-2001 in Italy (59), but have been implicated in up to 30% of current presentations in the US and are predicted to account for an increasing proportion of disease (55).

Projections of future disease burden

An estimation of future mesothelioma disease burden was first undertaken using a birth-cohort model in British men (60). The model indirectly accounted for asbestos exposure and predicted a proportional hazard of mesothelioma mortality by age and year of birth. The projection predicted a peak of 2,700-3,300 deaths in Britain in the year 2020. This methodology was widely reproduced in different populations, but has subsequently been shown to overestimate peak incidence (61). Using improved modelling techniques, Price and Ware (2) further described reductions in incidence projections over time in the SEER data. Recent models allow more sophisticated estimation of asbestos exposure and mortality variation within birth-cohorts (36,43,48).

With the exception of the United States, current predictions suggest peak mesothelioma incidence has not yet been reached (*Table 1*), and that in developed countries, this will occur in the second and third decades of the century. The late peak in Japan can be explained by a historical delay in heavy asbestos usage in that country (44). Future expected caseloads for each country or region are estimated from the annual incidence rate and expected peak year. They demonstrate that in industrialised nations alone, the disease

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is likely to affect hundreds of thousands of people in the next 50 years. High asbestos consumption in developing countries, particularly in Asia, is likely to cause additional future disease, however this is difficult to quantify (62).

Conclusions

Despite a clear understanding of malignant mesothelioma aetiology, the worldwide incidence continues to climb. The long latency of this disease and the continued distribution and consumption of asbestos products ensure that the toll of asbestos exposure will continue well into 21st century. The large future caseload underlines the ongoing importance of research directed towards early diagnosis and disease management.

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