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Epidemiology of Mesothelioma

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Abstract: Since 1973 the International Agency for Research on Cancer has classified asbestos as a certain carcinogen, but today it is still used in several countries. To date, mesothelioma risk is certainly linked not only to occupational exposures but also to environmental exposures. The incidence and mortality are increasing worldwide, especially in developing countries where asbestos is still often used without adequate measures for worker safety. The epidemiological surveillance systems of related asbestos diseases are instruments of public health adopted internationally. The experience and the operating methodology of the Italian mesothelioma registry and the data produced from 1996 to 2015 highlight how in countries where the asbestos ban has been active for over 20 years the risk of asbestos remains present, especially in the construction sector as well as for the environmental exposures of the resident population near companies that used asbestos in their production cycle. Worldwide, it is necessary to introduce the ban on the extraction, processing, and marketing of asbestos as claimed by the international scientific community.

Keywords: asbestos; mesothelioma; incidence; mortality; surveillance systems; mesothelioma Registry; public health; review

1. Asbestos: Consumption, Exposure, and Ban

Asbestos is a natural mineral, which in all its mineralogical varieties has fibrous morphology (actinolite, amosite, anthophillite, chrysotile, crocidolite, and tremolite). It has been used all over the world and also in Italy, and its use dates back to the time of the ancient Persians, Greeks, and Romans. It is characterized by high resistance to heat, as well as chemical and biological agents, abrasion, and wear. Asbestos is an environmental carcinogen, asbestos fibers, when mechanically disturbed, divide longitudinally, generating even thinner fibers (fibrils), which, when inhaled, may be responsible for fibrotic (asbestosis) or neoplastic processes (mesothelioma, lung cancer).

The two historical epidemiological studies that established with certainty the causal role of asbestos in the onset of pulmonary carcinoma and pleural mesothelioma were, respectively, Doll's 1955 [1] and Wagner's and collaborators in 1960 [2]

In 1964, the world conference on the biological effects of asbestos was held, organized by the New York Academy of Sciences, whose proceedings were published in 1965, the year in which the scientific community reached unanimous agreement on the carcinogenic action of this material [3].

In 1973, the International Agency for Research on Cancer (IARC) classified asbestos (all types: actinolite, amosite, anthophyllite, crocidolite, tremolite, and chrysotile) as certain carcinogens for humans [4]. In a 2012 IARC monograph, [5] asbestos was confirmed as the only certain risk factor for mesothelioma in a series of target organs including the pleura, the peritoneum, the pericardium, and the vaginal tunic of the testicle. The monograph confirms asbestos as a certain carcinogen for lung cancer, and for the first time it defines asbestos as a certain carcinogen for laryngeal and ovarian cancer.

It also assesses that the scientific evidence is limited for association between asbestos and tumors of the pharynx, stomach, and colon. Because of the close correlation between asbestos consumption and mortality from related asbestos pathologies, an analysis of the distribution in time and space of asbestos consumption is of great importance for epidemiological analysis [6]. Marinaccio et al. 2005, analyzed the per capita consumption of asbestos in different countries of the world demonstrating how the mortality curve for mesothelioma significantly reflects the consumption trend after a long latency period [7].

The increase in world production levels is constant from the second postwar period to the mid-seventies, a period in which it reached its peak with more than 4.5 million tons/year produced. The total world production of asbestos in the last century reached 173 million tons, of which more than 80% was after 1960, with an annual production (in 2000) of 2,130,000 tons [8]. The asbestos industry continued to extract (2013) about 2 million tons per year, producing "clean" and controlled productions in Europe, "dirty" in other countries. The problem has been moved from Europe to Ukraine, Russia, India, Egypt, Thailand, China, and Brazil, where workers continue to empty their bags by hand without ventilation systems and without protection. The largest producers, up until 2013, were Russia (700,000 tons), China (450,000 tons), Canada (335,000 tons, of which 98% are exported), Kazakhstan (180,000 tons), Brazil (170,000 tons), Zimbabwe (130,000 tons), Greece (35,000 tons), United States (7,000 tons), and Bulgaria (7,000 tons) [9]. More recent data are reported from the Asbestos Ban Secretariat (2019) related to 2015 (Table 1).

Table 1. Asbestos Trade Data (2015).

Fiber Producers (Tons)	
Russia	650,000
Brazil	270,000
China	210,000
Top five Users (Tons)	
India	370,000
China	287,000
Brazil	163,000
Russia	124,000
Indonesia	120,000

Source: http://www.ibasecretariat.org/ 10/6/2019. Updated 16 May 2019.

In the United States, approximately 340 tons of asbestos was imported in 2016 [10]. Italy has the distinction of having had the first mine opened on its territory "for commercial purposes" in 1870; therefore, it was the only country in the European Union, together with Greece, where asbestos mines were active. So, it is a country that is both an importer and a producer. Until the end of the 1980s, Italy was the second largest European fiber asbestos producer after the Soviet Union and the largest in the European community. The Italian production comes almost exclusively (if modest quantities are excluded from the Val Malenco fields) from the Balangero chrysotile mine (20 km north of Turin), the most important field in terms of size and plant in Western Europe. In Italy, from the postwar period (1946) to the 1992 announcement, 3,748,550 tons of raw asbestos (over 160,000 tons/year in the period 1976–1980) was produced, and 1,900,885 tons of raw asbestos was imported from Australia, Canada, and South Africa [11,12]. Raw asbestos imports remained above 50,000 tons/year until 1991. The use of asbestos in Italy in the last century has grown to around 220,000–240,000 tons/year, reached in the second half of the 1970s. In the 1980s, use gradually decreased, although later and more slowly than in other European countries, until the ban in 1992.

Asbestos is still used in developing countries and in some countries of the European Union, despite the directive 2003/18/CE of the European Parliament and of the Council of 27 March 2003 provides for the obligation to completely stop the use by 15 April 2006. The Italian law n. 257 of 27 March 1992 declared the "cessation of the use of asbestos", and in particular the ban on the extraction, import, export, marketing, and production of asbestos products and products containing asbestos.

However, the law did not prohibit indirect use, and, therefore, several million tons of compact materials containing asbestos and many tons of friable asbestos are still present in many contaminated sites, both industrial and nonindustrial, public, and private, throughout the Italian territory. In Italy the raw asbestos produced or imported, taking advantage of its remarkable material insulating properties and low cost, has been used in a wide range of industrial activities: in the sectors of industrial production of asbestos-cement manufactured articles, textile manufactures containing asbestos, shipbuilding, repair and demolition of railway rolling stock, construction, and in many other sectors of economic activity. For these reasons, the number of exposed workers in Italy is very significant [13].

Several respiratory and neoplastic diseases can be caused by environmental pollutants, such as asbestos, polycyclic aromatic hydrocarbons, carbon monoxide, heavy metals, gases, and formaldehyde [14–20].

In fact, in addition to occupational exposure, the risk of mesothelioma is now certainly linked to exposure to the environmental type of asbestos, be it of anthropic origin (for example, a residence near industries or polluted sites) or of natural origin (in areas where there are natural outcrops of asbestiform minerals of asbestos and not). In Italy there are also asbestosimic fibers, such as fluoro-edenite [21], an asbestiferous fibers of natural origin present in the area of Etna capable of inducing mesothelioma, and balangeroite, an asbestiform fiber that has been identified in some rocks present in the Balangero mine (Turin).

Recently, as part of the SENTIERI-ReNaM project, cases of mesothelioma have been found not only in sites where asbestos is explicitly recognized as a source of contamination, but also in numerous territories defined as being of national interest for other reasons of pollution. These data confirm that the spectrum of economic activities, work, and living environments involved in exposure to asbestos is very wide, and it is not possible to limit it to industrial sectors with direct use of the material as raw material [22].

Data provided by the Italian National Research Council (32 million tons of asbestos cement still to be reclaimed) and ISPRA (Higher Institute for Environmental Protection and Research), in the chapter on special waste of the 2011 Yearbook, reports that waste containing asbestos produced in Italy in 2009 amounted to about 380,000 tons. If the estimates prove to be exact based on the asbestos still present in the national territory (32 million tons) and the annual amount removed (380,000 tons), at this rate of annual removal, the disposal process could last another 85 years [8].

In Italy, from the 1992 announcement, the time distance from the end of the occupational exposure for the subjects exposed in the past is now on the order of 25 years. From the day of the call for tenders, the workers' protection legislation has guaranteed adequate information and training to work in protected conditions for those who work today for the demanufacturing and removal of materials containing asbestos. Mesothelioma (any site) and lung cancer arising from occupational exposure to asbestos have been included in the Italian list of occupational diseases since 1994 [23,24].

2. Malignant Mesothelioma (MM)

Malignant mesothelioma (MM) is a rare tumor, rare tumors are those with incidence <6/100,000 per year (RARECARE) [25], that originates from the inner lining of the body's serous cavities (pleura, peritoneum, pericardium, and vaginal tunic of the testicle). It has a bad prognosis and is characterized by a short survival (about 12 months) [26,27]. It is considered a "sentinel event" of past exposure to asbestos in all areas where exposure to other risk factors for MM can be ruled out [28].

Because of their physical characteristics, asbestos fibers remain in the lung, regional lymph nodes, and pleural cavity and induce chronic inflammation through the production of reactive oxygen/nitrogen

species. As a consequence, immunocompetent cells can have their cellular and molecular features altered by chronic and recurrent encounters with asbestos fibers, all of which eventually lead to decreased tumor immunity [29–33].

Potential cofactors for the development of MM are also exposure to other elongated mineral particles (EMPs) such as synthetic materials (ceramics, nanoparticles), ionizing radiation, and SV-40 virus infections [34,35]. Genetic factors can also play a role in the onset of MM. Indeed, family clusters in blood relatives have been described [36–39].

Many studies have shown that polymorphism in the genes involved in xenobiotic and oxidative metabolism or in DNA repair processes may play an important role in the etiology and pathogenesis of these diseases. [40,41] Early symptoms of MM are usually nonspecific, and diagnosis may be delayed. There are a number of comprehensive studies in the literature investigating potential biomarkers for the early diagnosis of MM in symptomatic patients exhibiting past exposure to asbestos. Among these, Mesothelin is one of the several well-known biomarkers used in the diagnosis of pleural MM [42–45]. Other studies showed that miRNA expression in tissue and body fluids is aberrant in various tumors, revealing miRNAs as promising diagnostic biomarkers [46].

It is a disease characterized by a long latency interval between the onset of exposure and the appearance of the disease (from 20 to 40 years and over) [47]. The average overall survival rates (OS) range from 4 to 13 months for untreated patients and from 6 to 18 months for treated patients, only 7% of patients are still alive at five years from the diagnosis [8,27,48].

A better survival was reported with multimodal surgical-based therapy. The Surveillance, Epidemiology, and End Results (SEER) database was explored from 1973 to 2009 to identify all 14,228 cases with diagnostic certainty. In multivariate analyses, female sex, younger age, early stage, and treatment with surgery were independent predictors of longer survival. Despite the development of surgical techniques, prognosis has not improved in the last four decades [49].

After the cessation of use at work, the public health danger is the presence of both large quantities of materials containing asbestos in a friable matrix, in civil and industrial buildings as well as in transport sector facilities (e.g., naval), and significant quantities of material containing asbestos in a compact matrix whose progressive deterioration can cause the release of fibers with consequent risk to human health.

In addition, asbestos is extremely widespread and can be hidden in living areas and in everyday objects (ironing board covers, curtains, cardboard, toys, etc.) [50].

The analysis of data provided by epidemiological studies has shown that the risk of MM increases with the increase in exposure to asbestos fibers, so there are no doubts regarding the proportional relationship between cumulative dose and MM frequency [51–53]. It is also agreed that the most recent exposure has a lower role, but not a null one [54]. As with all carcinogens, however, there is no safety "threshold" below which there is no risk [53].

The incidence is increasing worldwide, and it is expected to reach its peak in the coming years, especially in developing countries where asbestos is still used and often without adequate control measures [55]. Because of the long latency period of the disease, deaths are expected to peak between 2015—2025 and, according to some experts, even in 2040 [8,55–61].

3. International Data

3.1. The Epidemic Waves

The first wave, which began in the 1920s until the 1980s, was the extraction and manufacture of materials with asbestos. The second period was dominated by the industrial use of materials that contained it: insulation in shipbuilding and railway rolling stock, the production of textile products, use in the metalworking industry, and in manufacturing activities for thermal and acoustic insulation. The third wave, which persists even after the ban in the various countries, is that of occupational exposure to asbestos fibers, in the sites where it was already used, for maintenance, renovation,

and demolition work. Today it is possible to identify a fourth phase: that relating to those who work in reclamation and disposal and to those who work or live in buildings with the presence of materials containing asbestos (MCA) [62–66].

Fifty-four countries have adopted rules of total or partial prohibition of the use of asbestos. Despite this, the use of this carcinogen is allowed in some of the most populous countries in the world, such as China, India, and Russia, resulting in an important health impact although presumably underestimated [64].

On a global level, the problem of exporting asbestos from the producing countries (in particular Russia, China, Kazakhstan, and Brazil) to the middle-low income countries of Asia, Africa, and Latin America remains [66,67].

Despite the reduction in global asbestos consumption and production resulting from the prohibition or limitation of asbestos uses in more than 50 countries since the 1970s, asbestos is still used, imported, and exported to different countries, and the number of mesothelioma deaths could increase in the next few decades in these countries [68,69].

In Ukraine, ten factories work at full capacity, importing almost half a million tons of raw material from Kazakhstan and Russia to turn them into slabs, pipes, and fireplaces. In Greece (sixth producer in the world) there is, to date, adequate health protection, while in Turkey the number of open-air fields is of great concern. In Cappadocia, asbestos is still used to build and insulate houses [70].

It is estimated that today around 125 million people in the world are professionally exposed to the risk of asbestos in the workplace [64]. The true dimensions of mesothelioma epidemics worldwide are still unknown, mainly due to the lack of data from industrializing countries [11], and recent estimates state that the epidemic has not disappeared [71–73].

3.2. Mortality

Every year in the world, according to WHO estimates, more than 100,000 deaths are due to the consequences of occupational exposure to asbestos (mesothelioma, lung cancer, and asbestosis). In Western Europe, projections for asbestos mortality predict 500,000 deaths in the first thirty years of 2000 [64,71,73]. The underlying level of the mortality rate from mesothelioma is about 1–2 per million/year [74,75]. Estimates of the global annual number of cases of MM based on mortality data report about 14,000 cases in 89 countries according to Park (2011) (which still considers this an underestimate) and about 59,000 for Prüss Ustün (2011) [11,58].

In the ecological study, Park (2011) [11], assuming that mortality reflects the incidence of this fatal form of cancer, hypothesized that the national frequency of mesothelioma is a consequence of the historical cumulative use of asbestos. The study covered 89 countries that had information on the frequency of mesothelioma and or the use of asbestos at the national level. These countries represented 82.6% of the world population in 2000. Of these countries, 56 had data for both mesothelioma frequency and asbestos use, and 33 had no mesothelioma frequency data but had data for the use of asbestos. The total use of asbestos in the period 1920–1970 was 51.2 million tons in the 56 countries with data on the frequency of mesotheliomas and the use of asbestos, and it was 14.2 million tons in the 33 countries that had given only use of asbestos. This was a total of 65.4 million tons in all 89 countries analyzed. Among the 56 countries with data on deaths from mesothelioma and use of asbestos, the total number of deaths in the 15 years between 1994–2008 was about 174,300. There was a linear and significant relationship between MM deaths and the use of asbestos. The data extrapolated to the group of 33 countries that did not report data on mesotheliomas estimate about 38,900 deaths from mesothelioma in the 15 years between 1994–2008. The conservative estimate based on the use of asbestos until 1970, globally, indicates that one case of mesothelioma is underestimated for every four or five reported cases. The estimated total number of MM cases was 213,200 (cumulative mortality of 15 years during 1994–2008). This is equivalent to an annual average of around 14,200 cases.

No information on the mortality of mesothelioma has been reported to the World Health Organization (WHO) by Russia, China, and India [11,71]. The mortality rate has increased in Japan

but is estimated to be decreasing in Europe and the United States [76–79]. The mortality data for MM recorded in the WHO Database for the period from 1994 to 2008 reported 92,253 deaths in 83 countries. The mortality rates adjusted for age were 6.2 and 4.9 per million inhabitants for males and females, respectively, and the average age at death was 70 years. Sex and age-specific mortality reported rates of 9.0 per million for males compared to 1.9 per million for females. The male:female ratio was 3.6: 1. Regarding anatomical sites, the pleural site represented 41.3% of all mesotheliomas [78].

In Brazil and Colombia, countries that are still producers and users of asbestos, deaths for MM in a five-year period are, respectively, 340 and 255, and even these should be considered as underestimates, particularly in relation to the complexity of diagnosis [80–82]. For Brazil, Algranti (2015) reports the trend from 2000 to 2012 and estimates an increase in mortality up to 2030 with a peak between 2021 and 2026. The delay compared to industrialized countries reflects the trend in consumption in the country [83].

In Spain, an increase in pleural MM mortality is expected up to 2020, based on an age–period–cohort model [84]. In France, a peak mortality is estimated with 1300 cases in 2040 [85]. In Great Britain in 2017, there was a mortality peak of 2197 men and 398 women [86]. Based on the report on asbestos consumption and related asbestos diseases, forecast models of the trend and number of mesothelioma cases expected in Italy over the next few years have been developed. The projections, based on different models that use asbestos consumption as estimates of actual exposure, predicted a peak of pleural MM among men of about 800–1000 deaths per year between 2010 and 2020 or between 2012 and 2025, followed by a relatively rapid decline [64,87–89].

In the US, 3000 people die every year, and an estimated 100,000 deaths are expected over the next 40 years [85,90]. To better understand the most recent mesothelioma trends in the United States, all mesothelioma deaths reported by the Centers for Disease Control and Prevention (CDC) in the period 1999–2015 were analyzed. During the period 1999–2015, a total of 45,221 deaths were reported from malignant mesothelioma. Age-adjusted mortality rates decreased from 13.96 per million in 1999 to 10.93 in 2015. The birth cohort of the 1920s is prevalent, while the percentage of younger cohorts has steadily decreased over time, confirming a decline in occupational exposure in these cohorts. The M/F ratio has fallen over time, suggesting a greater percentage of environmental cases [10,91–93]. In Korea, Kim (2016) predicted mortality from asbestos-related diseases per year, from 2014 to 2036, depending on the amount of asbestos used, and the estimated deaths are between 1942 and 3476 by 2036 [94].

3.3. Incidence

The most recent incidence data available for the USA, reported by the surveillance program Epidemiology (Surveillance, Epidemiology, and End Results (SEER)) of the National Cancer Institute (NCI), are published in the SEER Cancer Statistics Review (CSR), 1975/2016. The annual publication of the research and surveillance program of the NCI provides a report with the most recent incidence, mortality, survival, and prevalence data [95] (Tables 2 and 3).

Table 2. Surveillance, Epidemiology, and End Results (SEER) 1975–2016 incidence rates by sex.

Mesothelioma: Age-Adjusted SEER Incidence Rates × 100.000 by Year, Race, and Sex			
Year of Diagnosis: 1975–2016 All Races	Total	Males	Females
	0.99	1.84	0.39

Source: https://seer.cancer.gov/csr/ the SEER web site, Updated 10 June 2019.

Table 3. SEER 2012–2016 incidence rates by sex and age.

Mesothelioma **SEER Incidence Rates × 100.000 Age-Adjusted and Age-Specific Rates, by Race and Sex**			
SEER Incidence Age at Diagnosis Age-Adjusted Rates, 2012–2016 All Races	Total	Males	Females
All ages	0.9	1.6	0.4
Under 65	0.2	0.3	0.2
65 and over	5.8	10.9	2.1

Source: https://seer.cancer.gov/csr/ the SEER web site, Updated 10 June 2019.

In Europe, the average incidence is 20 per million inhabitants/year. The incidence varies between 7 per million in Japan and 40 per million in Australia [96,97]. The incidence has steadily increased in the last twenty years in Europe in the industrialized countries and is expected to peak around 2020–2025 [56,76]. Only in countries where asbestos control measures were taken during the 1970s, such as Sweden and the United Kingdom, is there a tendency for incidence rates to fall [72]. The world epidemic is at its beginning where consumption has grown, as in developing countries [98,99], and in countries that produce and/or use asbestos, such as China, India, Russia, Zambia, Colombia, and Kazakhstan, where a strong increase in incidence is expected [100,101]. An increase in incidence is reported for nonoccupational exposures (e.g., housewives), in family members of professionally exposed individuals, and in subjects with environmental or residential exposure. In Italy, the clusters of environmental exposure cases are mainly linked to the presence of industrial asbestos plants (Casale Monferrato, Broni, Bari), shipbuilding and ship repair activities (Monfalcone, Trieste, La Spezia, Genoa), and soil contamination (Biancavilla in Sicily) [102–104]. The most recent incidence data (2000–2007) for Europe are available on RARECARE, which estimates the frequency of rare cancers in Europe. Its objective is to provide an operational definition of "rare cancer" and a list of tumors that correspond to this definition. The project provides incidence, survival, prevalence, and mortality data based on data from the 94 population cancer registries of 24 European countries participating in the RARECAREnet project [25] (Table 4).

Table 4. RARECARE incidence of malignant mesothelioma (MM) 2000–2007.

Tumor	**Crude Incidence Rate Per 100,000**	**95% Confidence Interval**		**Number of Cases Collected in the RARECAREnet Database from 2000–2007**	**Estimated New Cases EU 2013**
Malignant mesothelioma	2.14	2.12	2.16	33.552	12.526
Mesothelioma of pleura and pericardium	1.83	1.80	1.85	28.676	10703
Mesothelioma of peritoneum and tunica vaginalis	0.13	0.12	0.13	2.065	746

Source: http://www.rarecarenet.eu/analysis.php, Updated 10 June 2019.

In Bulgaria, 25,000 exposures were recorded between 1977 and 1989, with around 1000 deaths per year. Bulgaria totally banned the import, production, and use of asbestos in 2005, but they produced and used asbestos products in the last 3–4 decades of the 20th century. There has been an increase in the incidence of mesothelioma from 5 to 58 cases per 100,000 from 1993 to 2013 [70]. In Sweden, where asbestos consumption has fallen earlier, there is already a decrease in mortality and incidence rates [97]. However, despite the 1982 ban and the introduction of strict security measures for occupations that include manipulation or exposure to asbestos in the removal activities, after 35 years of the ban and a first-rate decline, a total of between 1961 and 3716 incident mesotheliomas were recorded in 2009 (21.1% in women). The risk of MM is significantly increased in 24 occupations, for example, among male

plumbers (SIR, 4.99; confidence interval of 95%, 4.20–5.90) and among female seamstresses. One of the reasons for this recent increase may be the long latency of mesothelioma [105]. Around 70,000 new cases are expected in the United States over the next 20 years [85]. In Quebec, the total number of MM accidents for both sexes is estimated at 315 cases per year in the period 2008–2032 [106]. In Australia between 1982 and 2011, 13,036 new cases of MM were diagnosed. The age-standardized incidence rate has risen over the last 10 years (2.8 per 100,000 in 2011). The incidence peak in Australia is expected in 2020 [65,107].

4. Epidemiological and Health Surveillance

Surveillance means the collection, integration, and analysis of data and the prompt dissemination of information to interested parties. In health care, the concept applies both to monitoring the health status of a population or group exposed to a harmful agent (epidemiological surveillance) and to the follow-up of individuals exposed to the risk of illness (health surveillance). From a public health point of view, there is interest in forecasting the evolution of the MM epidemic. This follows the progressive adoption in Western countries of measures to contain exposure to asbestos, or an actual ban, and to clarify the questions still unresolved on mesothelioma risk trends after termination of occupational exposures as well as on the entity of the risk for different categories of subjects exposed for employment or environmental reasons. Epidemiological surveillance of incident cases of mesothelioma is recognized, both nationally and internationally, to be of primary importance for the understanding of health damages from exposure to asbestos. It is also important for the identification of exposure circumstances still present in the environment, for evolution of "proper" or "improper" exposures to asbestos, and for employing protection mechanisms for patients and their families. The registration of mesothelioma cases is an essential tool for the development of epidemiological knowledge and a support to research activities. It is an instrument of control and prevention of risks as well as an indicator to guide the choices and organization of health services in terms of population needs [23,108]. Ferrante in 2016 conducted a review of the international surveillance experiences of malignant mesotheliomas, summarized below in Table 5 [109].

Table 5. International experiences in the epidemiological surveillance of MM.

State	Coverage-Type Detection	Occupational Exposure Detection	Environmental Exposure Detection
Italy	national incident cases	individual questionnaire	individual questionnaire
Australia	national incident cases	individual questionnaire	individual questionnaire
South Korea	national incident cases	individual questionnaire	individual questionnaire
France	30% incident cases	individual questionnaire	individual questionnaire
Germany	professional disease national	documents	no
UK	Deaths national	death certificate	no
Holland	professional disease national	documents	no
Scandinavian countries	national incident cases	documents	no
USA	28% incident cases	no	no

Source: Ferrante P, Binazzi A, Branchi C, Marinaccio A. National epidemiological surveillance systems of mesothelioma cases]. Epidemiol Prev. 2016 Sep-Oct;40(5):336-343. Modified.

In Italy, the epidemiological surveillance of mesothelioma cases is entrusted by the Decree of the President of the Council of Ministers n. 308/2002 to the National Mesothelioma Registry (ReNaM) established at the National Institute for Insurance against Accidents at Work (INAIL) [110].

The competences of the National Registry are (DPCM 308/2002):

- estimate the incidence of mesothelioma cases in Italy;
- collect information on past exposure to asbestos of registered cases;
- contribute to the evaluation of the effects, of the industrial use of asbestos, and to the recognition of sources of contamination still unknown; and
- promote research projects for the evaluation of the association between mesothelioma cases and exposure to asbestos.

The National Mesothelioma Registry covers the entire national territory for the detection of mesothelioma cases by a regional operations center (COR) in each region, whose fundamental activities are the active search for incident cases (through health facilities in the area of their competence, which diagnose and treat cases) and the definition of the modalities of exposure to asbestos (through the interview on the subjects' occupational, residential, and family history). The detection of MM cases is carried out at competent health facilities that diagnose and treat cases (occupational health services, anatomy and pathological histology, pneumology departments, thoracic surgery, and oncology). Exhaustive and complete checks of the data collected are made with the use of hospital discharge cards (SDO), of the death cards encoded by Istat, and of the data of population cancer registers, where present. Classification of cases according to the level of certainty of diagnosis takes place following a reference scheme defined at the national level and published in the ReNaM guidelines. The guidelines describe the territorial development and coverage of the survey, the operating procedures, and the criteria for classifying and coding diagnosis and exposure. The results of the activity of the national mesothelioma registry are published in periodic reports and in Italian and international scientific journals [111,112].

5. ReNaM Data: The Size of the Problem in Italy

The inverse relationship between diagnostic certainty and age at diagnosis is confirmed. The share of certain cases varies between 90% and 73%, up to the age groups "under 84", and is reduced to 42.5% in cases "over 85". The proportion of certain cases does not differ significantly by anatomical site.

The gender ratio M/F = 2.5. Seventy-two percent of the 27,356 archived cases were male.

The percentages of women were 27.4% for pleural mesotheliomas to 32.8% and 41.1%, respectively, for pericardium and peritoneum cases.

Average age at diagnosis was 70 years, with no appreciable gender differences (70.8 years in women and 69.5 in men). Cases with age under 45 years accounted for 2%.

Exposure classification included professional (certain, probable, or possible), family, environmental, out-of-work, unlikely, unknown, to be defined, and not classifiable.

The ReNaM complete archivefrom 1993 to 2015 reported 27,356 cases of MM, of which 21,387 (78.2% of the total recorded cases) cases of MM met the definition of exposure (Table 6).

Table 6. ReNaM data that have been published to date in 6 reports.

Report	Year	Incidence Until
I https://www.inail.it/cs/internet/docs/i_rapporto_renam.pdf?section=attivita	2001	1996
II https://www.inail.it/cs/internet/docs/ii_rapporto_renam.pdf?section=attivita	2006	2001
III https://www.inail.it/cs/internet/docs/iii_rapporto_renam.pdf?section=attivita	2010	2004
IV https://ricercascientifica.inail.it/renam/Report.asp	2012	2008

Table 6. *Cont.*

Report	Year	Incidence Until
V https://www.inail.it/cs/internet/docs/allegato_renam_v_rapporto.pdf	2015	2012
VI https://www.inail.it/cs/internet/docs/alg-pubbl-registro-nazionale-mesoteliomi-6-rapporto.pdf	2018	2015

The data of the VI Report ReNaM, INAIL, 2018. [112].VI REPORT RENAM 1993–2015 = 27,356 cases. **Diagnostic classification**: Four decreasing classes of diagnostic certainty (MM sure, probable, possible, and to be defined). **Diagnosis**: certain MM 22,023 (80.4%), probable MM 2551 (9.3%), and possible MM 2802 (10.2%). **Site**: 25.450 (93.0%) pleura, 1.769 (6.5%) peritoneum, 58 (0.2%) pericardium, and 79 (0.3%) testicular vaginal tunic. **Crude incidence rates** (MM pleura, Italy, 2014): M = 3.84 and F = 1.25 (cases per 100,000) (Table 7).

Table 7. Crude incidence rates (cases per 100,000 residents) Certainly, probable, and possible malignant mesothelioma.

ITALY 2014	*Pleura*	*Peritoneum*	*Pericardium*	*Vaginal Tunic of the Testicle*
Men	3.84	0.20	-	0.01
Women	1.25	0.14	-	-

Among these, 4261 (19.9%) did not present exposure to asbestos, and the exposure was unlikely or unknown. In all cases with defined exposure, 69.2% had a professional exposure (certain, probable, or possible). The Exposure median period was 1959 [1951–1966].

- Occupational exposure 14.818 (69.2%)
- Family Exposition 1047 (4.9%)
- Environmental exposure 939 (4.4%)
- Exposure for hobby activities 322 (1.5%)
- Unknown / unlikely exposure 4261 (19.9%)
- Interview with the subject 11.832 (55.3%)
- Interview with family members 9.044 (42.2%)
- Documentation (extra-interview) 511 (2.3%).

Most involved sectors of activity (1993–2015 period, subjects affected by the illness for professional reasons):

- Building (15.5%)
- Heavy industry (engineering) (8.6%)
- Shipyards (6.1%)
- Textile industry (6.4%)
- Metal product manufacturing activities (5.7%)
- Military defense (4.3%)
- Metallurgy (4%)
- Railway rolling stock (3.2%)
- Cement-asbestos industry (3.1%)

The set of these sectors is responsible for about 60% of the cases registered in the archives of the ReNaM.

Other sectors involved (exposure due to the presence of the material in the workplace and not for direct use):

- production, repair, and maintenance of motor vehicles and motorcycles (4.4%)
- land transport (3.8%),
- Chemical and plastics industry (3.5%)
- food industries (2%)
- maritime sector (2%)
- health (1.9%)
- electricity and gas production (1.6%)
- cargo handling in ports (1.5%)
- glass production (1.3%)
- rubber production (1.3%)
- oil extraction and refineries (1%)
- paper production (0.9%)
- sugar factories (0.8%).

Unconscious exposure (unknown presence of asbestos in workplaces often open to the public):

- Public administration (1.1%)
- Hotels, bars, and restaurants (0.6%)
- Banks, post offices, and insurance companies (0.5%)
- Education (0.5%)

A new scenario of exposures is represented by the increase in cases with exposure in buildings, which today produces the greatest number of cases and which raises concerns also for the possibility of current exposures. The distribution in the territory of cases originating from this sector is widespread. It is a significant sector for primary prevention. Of particular interest for the possibility of exposures still current is the number of mesothelioma cases registered in so-called 'minor' categories (production and maintenance of transport vehicles, food industry, wood, tobacco, manufacturing industries, agriculture and livestock, catering education, and services in the administrative sector). Activities of the regional registers have brought to light areas of professional activity and economic sectors with exposure to unexpected asbestos that are unrecognized [13].

Examination of the geographic distribution of mesothelioma cases has enabled the identification of clusters in the municipalities with the highest incidence rates, in particular Casale Monferrato, Broni, Genoa, La Spezia, Grugliasco-Collegno, Monfalcone, Trieste, Castellamare di Stabia, Bari, Taranto, Biancavilla, and Augusta. In these municipalities, there were companies that used asbestos in well-defined time periods and up to the ban (shipbuilding, production of insulated rolling stock) and which polluted the surrounding areas (production of asbestos cement). Some of these municipalities (Casale Monferrato, Broni, Trieste, Bari, Taranto, Biancavilla, and Augusta) have been recognized as Sites of National Interest (SIN) for land reclamation [80,113,114].

In Casale Monferrato (Eternit factory), Broni, and Bari (Fibronit factory), a mesothelioma epidemic was recorded among the inhabitants. For 25% of cases in Casale Monferrato and 33% of cases in Broni and Bari a single risk factor was recognized: residing near an asbestos cement factory, which configured an involuntary and unknown environmental/residential exposure. The calculated relative risk was very high (10.5 and 5.25 respectively) for those who lived less than 500 m from the factory, and the fiber load in the lungs of the deceased cases was 10 times higher than in those of other areas [115,116].

From the data reported by ReNaM it appears that in Italy the incidence of MM in women is high, both for nonoccupational (environmental and domestic) and occupational exposure. A total of 10.2% of MM cases derive from unprofessional exposure to asbestos. Cases of familial MM (in blood relatives) are less than 2.5% [53,117]. The economic burden associated with a MM case was estimated at 250,000 euros per case [118].

The data of the ReNaM show that an emerging public health problem is the environmental exposure of the population. [8,88].

About 10% of the cases of MM, for which the previous methods of exposure were reconstructed, were found to be exposed for environmental reasons (residence) or for family reasons (cohabitation with professionally exposed family members) [106]. The activity of the registry has shown the territorial distribution of cases and the methods of exposure (residence near asbestos cement companies, cohabitation with exposed subjects) [119].

The risk of mesothelioma has been studied as a consequence of environmental exposure both anthropic, from residing near sites with important exposure sources, and of natural origin, from its presence on the territory of rock outcrops of asbestos or asbestiform minerals. In women, the percentage of cases with nonoccupational exposure exceeds 20%.

At the Governmental Conference (November 2012) in Venice [23] and in the National Asbestos Plan (2013) [120] the topic of MM cases of environmental origin was indicated as a research priority, with a specific mandate for the ReNaM and the CORs. "The regions will have to investigate the magnitude of the mesothelioma risk associated with non-occupational exposure (environmental or para-occupational) by mandating regional CORs or other relevant structures". As there are environmental exposures, and taking into account the interest of citizens for the protection of public health, elaboration on specific communication interventions is essential in the risk management process. Particularly important are the psychological support interventions in communities affected by mesothelioma [121]. A summary of actions to be undertaken for nonoccupational asbestos exposures, on which the international scientific community agrees, is shown in Table 8.

Table 8. Actions to be taken for nonprofessional asbestos exposure.

Nonemployment Exposures To Asbestos	
Type Of Exposure	***Actions***
Environmental exposure by residence near polluted sites	Reclamation, Restoration, and Monitoring
Exposure to living with family who are occupationally exposed	Protection
Exposure for the use of MCA (materials containing asbestos) in the home or at leisure	Information
Exposure due to the presence of natural outcrops	Research and Surveillance

In conclusion, as the resolution of the European Conference on asbestos held in Brussels in 2005 already recalled, it would be necessary to establish a ban on the use of asbestos in the countries that produce it and export it, in particular for developing countries (East, Africa, South America). Therefore, it is reiterated that, worldwide, it is necessary to introduce and sanction the ban on the extraction, processing, and marketing of asbestos and products containing asbestos. The global ban on asbestos in recent decades is strongly supported by many scientists [61,122–124].

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