ASBESTOS-RELATED DISEASES

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Asbestos-related diseases include asbestosis, pleural plaques, pleural thickenings and several neoplasms.

Asbestosis

Asbestosis is defined as diffused interstitial fibrosis of the lung, as a consequence of exposure to asbestos fibres, often associated with pleural plaques. Diagnosis of asbestosis, according to the American Thoracic Society (2004) is based on the following criteria:

1. hystopathological or imaging demonstration of structural alterations compatible with asbestos-related disease;
2. previous asbestos exposure demonstrated by occupational or environmental anamnestic data, or by specific markers like pleural plaques or thickenings;
3. exclusion of other causes;
4. documented impairment of lung function. In some cases, moderate fibrosis can be present together with major respiratory impairment. Some cohort studies have shown asbestosis to be the cause of 12-20% of observed deaths, or even more (Lemen, 2005).

Asbestosis symptoms include cough, dyspnea and lung base crepitus sound. Respiratory function impairments include alterations of haematic gas exchanges and occurrence of constrictive disorders. Asbestosis is generally associated to elevated asbestos exposure. The computed tomography is particularly suitable to detect radiological signs of parenchymal lesions, with special reference to early lesions not detectable by X rays.

Asbestosis is a progressive disorder even in the absence of further exposures. Asbestosis patients show an increased risk of lung cancer and mesothelioma.

There is general consensus on the notion that asbestosis is linearly correlated to cumulative exposure, and since low concentrations do not determine radiological signs, a threshold model is hypothesized.

Pleural plaques

Pleural plaques are bilateral, marked, frequently calcified plaques, generally located on parietal pleura, and slowly evolve into more extended thickenings (see below). Latency times of pleural plaques can be of some decades since onset of exposure. They can be observed in large proportions (even over 50%) in their progressions can cause restrictive impairment of lung function. As reported by Hillerdal (2001) they generally do not cause harm, but, since they are associated to asbestos exposure, they are predictors of risk of asbestosis, lung cancer and mesothelioma.

Diffuse pleural thickenings

Diffuse pleural thickenings, or visceral pleura fibrosis, is a fibrous capping that can, is some instances, penetrate lung parenchyma with its fibrous septa. Pleural thickenings have been reported in 2-7% of asbestos exposed subjects after 15-20 years, and in advanced stages they may cause pleural calcification. Symptoms include thoracic pain, dyspnea and restrictive functional respiratory impairment (Miles *et al.*, 2008).

Asbestos-related neoplasms

In May 2009 the International Agency for Research on Cancer (IARC) revised the scientific evidence about asbestos carcinogenicity, reaching the following conclusions: there is sufficient evidence of a causal association between asbestos exposure and mesothelioma of pleura, peritoneum, pericardium and tunica vaginalis of testis, and of carcinoma of lung, larynx and ovary. There is, furthermore, limited evidence of an association with pharynx, stomach and colorectal cancer (IARC, 2012).

Mesothelioma

According to Park *et al*. (2011), the overall number of mesothelioma cases recorded in the 56 countries that have a registration system, is of about 174,000 in the time window 1994-2008. As shown by Tossavainen (2004) and Park (2011), the use of asbestos showed a peak in the Seventies in most European countries, and subsequently declined.

Current patterns of asbestos production and use at a global level are discussed by Marsili and Comba (2013).

Following early observation by Newhouse (1969), Newhouse and Berry (1979) and Seidman *et al*. (1979), and a large number of subsequent studies, it was clearly demonstrated that mesothelioma risk is a function of cumulative asbestos exposure and lung fibre burden (see for a recent review Pinto *et al.*, 2013). No threshold is known as shown by Iwatsubo *et al.* (1998), the dose-response relationship is observable at exposure levels as low as 0.5 ff/mL/year; the same study showed that risk associated with continuous exposure is higher than risk associated with intermittent exposure.

Modelling approaches to mesothelioma risk have consistently shown that occurrence of disease: a) is a linear function of cumulative exposure (as already mentioned); b) depends on fibre type; c) is proportional to the 3^{rd}-4^{th} potency of latency (Peto *et al*., 1985; HEI, 1991), there is thus general consensus that time gives more weight to early exposures.

Latency time of mesothelioma was investigated by Irving Selikoff and workers in the frame of the well-known insulator cohort study (Ribak *et al.* 1988); in that study the average latency time was of about 34 years. Subsequent studies showed that the shortest observed latency times are of about 15 years, and the longest ones may approach 60-70 years (Lamphear & Buncher, 1992; Bianchi *et al*., 1997; Neumann *et al.,* 2001; Leight *et al.,* 2002). The median latency time reported by the Italian National Mesothelioma Registry is of 46 years (INAIL, 2012).

A possible reduction of risk after exposure cessation, suggested by some epidemiologic studies with long follow-up (Berry *et al*., 2004; Barone Adesi *et al.*, 2008) could be explained by asbestos fibre clearance (Musk *et al*., 2002; Berry *et al*., 2009). The issue, though is still debated (Pinto *et al*., 2013).

As extensively discussed by IARC (2012), the pathogenetic mechanisms underlying asbestos carcinogenicity include:

- *fibre dimensions*: higher risk from longer and thinner fibres;
- *surface chemistry*: higher risk associated with free radical release;
- *biopersistence*: higher risk from amphiboles than chrysotile;
- *genotoxicity*: induction of direct DNA damage through reactive oxygen species, interference with mitotic apparatus, induction of chromosomal alterations;
- *persistent inflammation*, macrophagic activation, stimulation of cell proliferation and survival, activation of signal transduction pathways, epigenetic alterations.

Asbestos can thus be defined as a complete carcinogen, that contributes to both early and late stages of carcinogenesis.

Asbestos-related lung cancer

Lung cancer is a disease characterized by multifactorial aetiology, the main risk factor being cigarette smoke. A variable proportion of lung cancer cases can be attributed to occupational asbestos exposure in different populations. According to a recent estimate (Mc Cormack *et al.*, 2012) about 4% of male lung cancer cases in industrialized countries could be attributed to asbestos; this would correspond, indicatively, to two cases of asbestos-related lung cancer for each case of pleural mesothelioma.

There is a well ascertained dose-response relation between asbestos and lung cancer. According to Hodgson and Darnton (2000) there is an extra risk of 5% per f/mL/year for amphibole exposed cohort, and 0.1-0.5% Ø per f/mL/year for chrysotile-exposed cohorts (cohort with mixed exposures show extra risks of less than 1%). No threshold is known. All hystotipes of lung cancer can be observed among asbestos-exposed subjects; latency times are generally over 15-20 years (Rom, 1998; Shottenfeld & Fraumeni, 1996).

Asbestosis subjects have an increased risk of lung cancer, but it has been demonstrated that an increased incidence of cancer occurs in asbestos exposed subjects also in the absence of asbestosis (Weiss, 1993; Wilkinson *et al.*, 1995).

Lung cancer risk associated to the joint exposure to asbestos and cigarette smoke exceeds the risk that could be predicted if these determinants of the disease were independently operating (Saracci, 1977; Hammond *et al*., 1979; Doll & Peto, 1985).

Asbestos exposures can anyhow induce lung cancer even in the absence of cigarette smoke. The joint presence of the two risk factors determines a number of extra cases higher to the corresponding numbers resulting from each exposure taken by itself. The interaction is probably intermediate between an additive and a multiplicative model. The underlying hypothesized mechanisms include an impairment of lung fibre clearance, a “carrier” role of fibres with respect to carcinogenic chemicals and a catalytic role of fibres in the generation of reactive intermediate compounds.

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