Abstract. Asbestos has been used extensively and, in spite of many countries having banned most of its uses, professional, domestic and environmental exposure has not ceased worldwide. Inhaled asbestos fibers can lead to malignant mesothelioma, lung cancer and non-cancerous conditions, while the substance persists indefinitely in the lung and pleural tissue, resulting in continuous damage. Exposed individuals may be offered medical surveillance or compensation, but nothing is currently being done to lower their specific cancer risk: chemoprevention seems a promising approach. A web search and a PubMed review of the literature on chemoprevention trials in individuals exposed to asbestos have been conducted. Forty-six articles on five projects were found and newly reviewed but, surprisingly, no novel trials have been set up for twenty years, although considerable advances have been gained in cancer chemoprevention. A re-consideration of possibilities offered by chemoprevention should be encouraged. New trials based on the most recently characterized molecules should be planned, taking into account specific issues such as the need for a very large number of participants and a long follow up or, alternatively, the use of biomarkers as surrogate endpoints. The long latency of asbestos related diseases may offer delayed intervention opportunities. The lack of chemoprevention trials for asbestos exposure highlights the urgent need for research in this field.

Asbestos fibers have high tensile strength and chemical, electrical and heat resistant properties which make them extremely useful as building and insulation material. This material became increasingly popular among manufacturers and builders in the late 19th century, and was used extensively throughout the world in the last century. Around 1900, the overall production of asbestos was around 30,000 tons per year. Asbestos mining expanded steadily thereafter, peaking in 1975 when almost five million tons were extracted, and then declined.

Asbestos fiber inhalation can lead to neoplastic diseases such as malignant mesothelioma (MM) and lung cancer (LC) as well as to non-cancerous conditions, namely asbestosis, pleural effusions, and pleural plaques (1). The first reports regarding asbestos toxicity for the respiratory system date to the beginning of the XX century (2). Asbestos has been declared a proven human carcinogen by the International Agency for Research on Cancer of the WHO-EPA (3) and by the U.S. Environmental Protection Agency (4).

The necessity of an asbestos ban has been very slowly recognized by regulators, but since the mid 1980s, most uses of asbestos have been banned or severely restricted in many
countries, starting from Scandinavia. Nowadays, asbestos is still in use in a number of countries. The quantity of asbestos mined throughout the world was 2,200,000 tons in 2008 (5). Russia produced half of this amount, followed by China, Brazil, Kazakhstan and Canada.

Occupational exposure may still represent a health problem, even in the countries where asbestos use has been stopped or diminished after the ban. In some cases, the asbestos industry has shifted from manufacture to stripping/removal work, creating a novel source of exposure. A study conducted in 31,302 stripping/removal workers in the Great Britain Asbestos Survey found a higher than expected mortality rate for all causes and for all types of cancer, including MM, LC, and laryngeal cancer (6).

Often environmental or domestic exposure is still present – increasing the risk of cancer – after asbestos factories have closed (7). In addition, inhaled asbestos fibers persist indefinitely in lung and pleural tissue, resulting in continuous damage. Individuals that were exposed in the past remain at increased risk throughout their life, as asbestos-linked tumors typically have long latency: at least 10 years for LC, up to 50 years for MM (1).

Environmental exposure may be exceptionally high, where mineral fiber-containing materials have been used for building constructions: e.g. in Biancavilla, Italy (8) and in Turkish villages with high exposure to erionite (9). Unexpected clusters of exposure of unrecognized origin may be found comparing exposure for MM at a municipal level (10).

Prevention strategies at the population level focus mainly on reducing/eliminating the exposure to carcinogenic fibers. Ecological studies have demonstrated that per capita utilization of asbestos is associated with mortality trends for MM and asbestosis (11).

Many observations support the recommendation that all countries should adopt regulations aimed at eliminating asbestos use. Regarding pleural MM, a plateau phase seems to have been reached in some countries, after the rising incidence of the last decades (12).

On the other hand, individually oriented strategies are needed for those who were exposed in the past and still are at high cancer risk. In most western countries, workers who were exposed to asbestos are offered medical surveillance, and are entitled to compensation. Studies based on medical surveillance are relatively rare, and aimed either at registering the exposed population (13), or at monitoring clinical parameters such as pulmonary function and radiological abnormalities (14, 15).

More recently, radiological techniques such as low dose computed tomography (LDCT) has been proposed to screen asbestos-linked cancer in exposed individuals. Most of the published trials resulted in diagnosis of early and late LC and, in limited cases, MM (16, 17). The highest LC prevalence (4.28%, 8 cases) was found in a selected cohort of 187 highly exposed individuals, 89% of whom were smokers (18). LDCT still needs fine tuning, as it has high sensitivity but low specificity, resulting in detection of high numbers of nodules that may lead to undue interventions with high costs, discomfort and pain. The identification of soluble proteins, i.e. mesothelin, megakaryocyte potentiation factor, and osteopontin, as markers of early lesions or even of pre-clinical asbestos-related tumors, disclose intriguing screening perspectives (19).

However, it is rather unpredictable if early detection strategies can positively affect cancer prognosis of those who have been exposed. Early-stage LC may be effectively treated, however, it is questionable whether diagnosis of late-stage LC or MM may lead to a benefit in terms of survival length or quality of life, in the absence of efficacious therapeutic options.

In many countries, individuals exposed to asbestos may apply to social security programs for compensation. Two basic models can be identified: no-fault systems based on worker compensation or social security, or tort systems (employers inexcusable fault), based on employer, public or general/producer liability. In general, no-fault systems do not pay for non-economic losses, whereas the tort system can provide higher awards.

Smoking cessation must obviously be actively encouraged, as it reduces LC risk and ameliorates respiratory function, however, it is ineffective in reducing MM risk. Nothing is currently being done to lower individual cancer risk due to asbestos exposure.

Chemoprevention seems a promising approach regarding risk reduction in those exposed to asbestos. However, very few trials have been undertaken and reported in scientific literature (20).

According to Greenwald (21), “chemoprevention of cancer aims to prevent, arrest or reverse either the initiation phase of carcinogenesis or the progression of neoplastic cells to cancer”. Chemopreventive agents have been classified into two broad groups: blocking agents that prevent carcinogen interaction with DNA, and suppressive agents that prevent downstream effects. A requirement for any chemopreventive agent is efficacy and lack of toxicity (22). As carcinogenic activities are usually complex, it is apparent that a mixture of chemopreventive agents should be required to counteract all the damaging activities (23).

We here perform an evaluation of the scientific literature, having searched the web for chemoprevention trials conducted in asbestos-exposed individuals. New intervention strategies will be hopefully proposed.

**Materials and Methods**

A systematic search for articles was performed using the PubMed database (National Library of Medicine, National Institutes of Health,
Bethesda, MD, USA - http://www.ncbi.nlm.nih.gov/ PubMed) being up to date until the of 30th January 2012. The search strategy included the use of specific key words (MESH terms [mesh]), and common research terms, along with PubMed free text (words in title or abstract field [tiab]), or phrase search (more words in quotes in title or abstract field [tiab]) tools. The first group referred to main concepts related to MM and asbestos (mesothelioma[mesh] OR asbestos[mesh] OR asbestos[tia] OR mesothelioma[tia]). The second group referred to chemoprevention studies (chemoprevention[mesh] OR chemoprevention[tia] OR chemo-prevention[tia] OR "prevention trial*"[tiab] OR "prevention protocol*"[tiab] OR "supplementation trial*"[tiab] OR dietary supplementation[mesh]). Only original articles were included (NOT review[pt] OR letter[pt] OR news[pt] OR case reports[pt] OR congresses[pt]).


In addition, newly gathered information and new results regarding published or planned trials were gained, when possible, through direct contact with participating investigators.

Results

Forty-six citations were retrieved in the PubMed database and were manually reviewed. The large majority of these articles (n=21) addressed different issues of the Beta-Carotene and Retinol Efficacy Trial study (CARET), three were on the Wittenoom Crocidolite Industry Program, one described the results of the Tyler Asbestos Workers Program, and one reported on a trial planned for the workers of a French asbestos cement factory (see Table I for references). In addition, three papers evaluated the chemopreventive properties of different chemicals against MM in vitro and in mice (see below). No currently active chemoprevention trial for asbestos-exposed individuals was found through web searches.

Table I reports the basic data of the four trials that were found through the literature search, plus one that was only mentioned as being planned in a review paper (9).

The four trials started between 1985 and 1991. The chemopreventive agent was β-carotene, alone or in combination with retinol or other antioxidants. The rationale for its use came from observational studies demonstrating that people eating more fruits and vegetables, which are rich in β-carotene and retinol and those having higher serum β-carotene concentrations had lower rates of LC. It was a shock when in 1996, the largest of these studies (CARET) had to be stopped in advance as the participants experienced an excess of LC incidence and mortality at interim analysis (24). These results were highly consistent with those found for β-carotene in the Alpha-Tocopherol Beta-Carotene (ATBC) Cancer Prevention Study of 29,133 male smokers in Finland (25).

The Tyler Asbestos Workers Program started in 1985 in Texas: 755 asbestos-exposed workers were randomized to receive either β-carotene (50 mg) plus retinol (25,000 IU) on alternate days, or placebo. No statistically significant difference was found in sputum cellular atypia after at least 6 months on the protocol (26).

The CARET study enrolled 14,254 heavy smokers or former smokers and 4,060 asbestos-exposed individuals that received either 30 mg β-carotene plus 25,000 IU retinol (retinyl palmitate) per day or placebo, after randomization (24). The trial was started in 1983 in the U.S. with two pilot studies and was stopped in 1996, 21 months earlier than planned, when an increased risk of LC incidence was observed in the intervention group compared to the placebo group (relative risk RR=1.28; 95% confidence interval CI=1.04-1.57). The excess risk of LC that persisted after intervention cessation was subsequently shown to be restricted primarily to females (27). The LC risk was marginally increased in the asbestos exposed sub-cohort (RR=1.40; 95% CI=0.95-2.07). After prolonged follow-up, an increased MM risk in the arm of active treatment vs. placebo was recently found in the asbestos-exposed individuals (RR=1.51; 95% CI=0.80-2.84) (28).

In the Wittenoom Crocidolite Industry Program, conducted in Australia from 1990 to 1995, 1,024 exposed workers received assistance to stop smoking plus either 30 mg β-carotene or 25,000 IU retinol per day. The risk of MM was reduced in the retinol arm compared to the β-carotene arm (RR=0.24; 95% CI=0.07-0.86), while for LC incidence treatment with β-carotene and retinol resulted in similar effects (29). Comparing the 1,024 individuals in the program to a group of 996 asbestos-exposed workers who chose not to join the program, a non significantly reduced mortality due to both MM and LC was observed, with an adjusted RR=0.77 for MM (95% CI=0.38-1.55), and 0.67 for LC (95% CI=0.33-1.37); however, the lack of a placebo-controlled arm possibly introduced serious biases affecting such a comparison (30).

Published evidence concerning the French asbestos cement factory trial is lacking. The study started in 1992 but no final report has ever been produced (31). Different cocktails containing N-acetyl-cysteine, β-carotene, selenium, α-tocopherol, ascorbic acid, riboflavin and fenretinide were to be administered to 300 workers of an asbestos cement factory (26).

The intention to offer ranpirnase treatment to those living in erionite villages in Cappadocia with high mesothelin levels in serum has been anticipated by Carbone and colleagues (9). However, no further reports have been published.

Discussion

The most important finding of this review is therefore the complete lack of new results: in the last twenty years, no actual trial on individuals exposed to asbestos was started. There are
Table I. Chemoprevention trials in asbestos-exposed individuals.

<table>
<thead>
<tr>
<th>Study</th>
<th>First author, year (ref)</th>
<th>Numbers</th>
<th>Study group</th>
<th>Definition of asbestos exposure</th>
<th>Endpoint</th>
<th>Intervention</th>
<th>Main results</th>
<th>Comments</th>
<th>Additional results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tyler McLarty, Asbestos Workers Program (Texas, 1985-1993)</td>
<td>McLarty, 1995 (26)</td>
<td>755</td>
<td>Asbestos workers, 95% males, 60% current SMK, 20% former SMK</td>
<td>Asbestos exposure, sputum cytology in subjects completing 26 months on the protocol (median 5 years)</td>
<td>Sputum cytology in subjects</td>
<td>β-Carotene 50 mg plus retinol 25 000 IU on alternate days or placebo</td>
<td>No significant difference in sputum atypia: 213 sputum atypia, 4 malignant out of 349 actively treated subjects</td>
<td>Blinded (but skin yellowing)</td>
<td>Smoking and drinking were associated with lower serum concentrations of β-carotene (baseline and after supplementation)</td>
</tr>
<tr>
<td>CARET (US multicentric, 1985-1996)</td>
<td>Omenn, 1996 (24)</td>
<td>18 314</td>
<td>SMK or former SMK, 66% males, 50-60 years; 4060 asbestos exposed, 100% males, 45-69 years</td>
<td>First exposure on the job 15 years before randomization and either a chest x-ray positive for asbestos-related lung disease or having worked in specified high-risk trades</td>
<td>Primary: LC incidence</td>
<td>β-Carotene 30 mg plus retinol (retinyl palmitate) 25 000 IU per day or placebo</td>
<td>388 LC cases. For active treatment vs. placebo: Total RR 1.28 (95% CI 1.04-1.57) Asb exp RR 1.40 (95% CI 0.95-2.07) Current heavy SMK RR 1.42 (95% CI 1.07-1.87) Former heavy SMK 0.80 (95% CI 0.48-1.31)</td>
<td>The trial was started in 1983 with two pilots (816 asbestos exposed subjects and 1029 heavy SMK), it was expanded in 1988 and 1991, it was stopped 21 months earlier than planned in 1996. Statistical analysis by intention to treat.</td>
<td>23 MM cases: 14 in the active treatment group, 9 in the placebo group (no stat sign effect) Death (any cause) RR=1.18 (95% CI=1.02-1.37) Death (cardiovascular causes) RR=1.26 (95% CI=0.99-1.61) Overall MM incidence of 1.62 per 1000 person-years (5 MM, 0.36 in the SMK cohort)</td>
</tr>
<tr>
<td>Subramanian, 2006 (28)</td>
<td></td>
<td>4060</td>
<td>Asbestos-exposed, 100% males, 45-69 years</td>
<td>First exposure on the job 10 years before randomization and either</td>
<td>Predictors of MM occurrence after 16 years of follow-up</td>
<td>β-Carotene 30 mg plus retinol (retinyl palmitate) 25 000 IU per day</td>
<td>40 MM cases. For active treatment vs. placebo: RR 1.51 (95% CI 0.80-2.84)</td>
<td></td>
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</tr>
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</table>
Table I. Continued

<table>
<thead>
<tr>
<th>Study (Country, date)</th>
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<th>Numbers</th>
<th>Study group</th>
<th>Definition of asbestos exposure</th>
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<th>Intervention</th>
<th>Main results</th>
<th>Comments</th>
<th>Additional results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wittenoom Crocidolite Industry Program (Australia, 1990-1995)</td>
<td>Musk, 1998 (30)</td>
<td>2199 Enrolled</td>
<td>92% Males, mean age 57 years, 1203 randomized for the program</td>
<td>H3 positive for asbestos-related lung disease or having worked in specified high-risk trades ≥5 years</td>
<td>MM and LC incidence, death from any cause, other cancers, cardiovascular diseases</td>
<td>Program: assistance to stop smoking plus either β-carotene 30 mg or retinol 25 000 IU per day.</td>
<td>RR of MM=1.33 (95% CI=1.2-1.5)</td>
<td>RR of LC=0.66 (95% CI=0.51-0.85)</td>
<td>Relative mortality rate program/placebo.</td>
</tr>
<tr>
<td>De Klerk, 1998 (29)</td>
<td>1024 Randomized</td>
<td>92% Males, mean age 57 years, 21% current SMK, 275 never SMK</td>
<td>H3 Crocidolite. Duration: median about 190 days, range 1 day to over 15 years; Time since first exposure: range 25 to 45 years</td>
<td>H3 Crocidolite. Duration: mean 381 days (program), 276 days (comparison)</td>
<td>MM, LC and any cancer incidence, death from any cause, other cancers, cardiovascular diseases</td>
<td>Either β-carotene 30 mg or retinol 25 000 IU per day.</td>
<td>Relative mortality rate program/placebo=0.64 (95% CI=0.47-0.88)</td>
<td>Relative mortality rate program/placebo=0.64 (95% CI=0.47-0.88)</td>
<td>No placebo.</td>
</tr>
<tr>
<td>Asbestos Cement Factory Prevention Trial</td>
<td>Pluygers, 1992 (31)</td>
<td>900 Planned</td>
<td>150 Active workers ≥50 years old, asb exp ≥2 years;</td>
<td>Serum levels of TPA, ferritin, CEA (Yearly assessment of serum)</td>
<td>If TPA or ferritin levels are high, intervention</td>
<td>19 Active workers evaluated; 5 had high serum levels</td>
<td>19 Active workers evaluated; 5 had high serum levels</td>
<td>MM incident cases: on retinol observed=3, predicted=8.8 on β-carotene observed=12, predicted=9.0</td>
<td>Peculiar study design</td>
</tr>
</tbody>
</table>
Currently no chemopreventive agents for which efficacy against LC or MM has been demonstrated in clinical trials.

Nonetheless, scientific interest and knowledge on chemoprevention has increased steeply: articles on chemoprevention (as defined in the Materials and Methods) and cancer (neoplasms[mesh] OR cancer[tiab]) that have been recorded in PubMed since 1991 number more than 14,300, with an increase from 107 in 1991 to 1399 in 2010.

A review published in 2009 by Hecht and colleagues (23) reported on a list of all the naturally occurring and synthetic agents that prevent lung carcinogenesis in laboratory animals for which a certain effectiveness has been demonstrated (Table II). A rationally constructed mixture of some of these agents could be effective for LC chemoprevention among those exposed to asbestos. Currently some of these compounds (N-acetylcysteine conjugate of phenethyl isothiocyanate, myo-inositol, green tea or polyphenon E, and sulindac) are under investigation in clinical trials for LC prevention among current and/or former smokers, however, no similar trial is ongoing among those exposed to asbestos.

On the other hand, it is not known if any of these substances might be effective in MM prevention, as they were not tested in laboratory animals. In our PubMed search, we found only three studies regarding new molecules evaluated on their preventive (and not therapeutic) properties in MM experimental models. Catalano et al. (32), demonstrated that the nonsteroidal anti-inflammatory compound celoxocib (a COX-2 inhibitor) is effective in reducing of a in vitro proliferation the MM cell line in combination with vascular endothelial growth factor. Apostolou et al. (33) showed that selenium inhibits MM cell growth in a dose-dependent manner, in line with the potential chemopreventive role of selenium in a variety of animal cancer models. Butyrate acted as a repressor of calretinin (CALB2) expression in colon carcinoma cells but not in MM cells (34).

It is time to reassess potentially useful chemopreventive drugs. Any trial using LC and MM incidence or mortality as endpoints would require a very large number of participants and a long follow-up. Expected cases are in the order of magnitude of units of thousands per year. About 10 deaths due to MM per year were registered in the period 1986-2000 in the Wittenoom cohort of 7,000 asbestos-exposed workers (35). In the CARET study, the overall MM incidence was 1.62 per 1,000 person-years in the 4,000 asbestos-exposed individuals (0.36 per 1,000 person-years in 14,000 smokers) (28).

For lessening the need for a large sample size, extensive time commitment, and expense, focus is now turning toward surrogate endpoint biomarkers for lung and pleural carcinogenesis. Acceptable biomarkers must be repeatable, highly sensitive and specific, quantitative, readily obtained
by non-invasive methods, part of the causal pathway of the disease, capable of being modulated by the chemopreventive agent and have high predictive value for clinical disease (21). Such a perfect biomarker is hardly available for this study setting, but the complementary use of different biomarkers could provide reliable evidence.

A mechanism known to mediate asbestos toxicity and carcinogenicity is the generation of reactive oxygen or nitrogen species, whose consequences include genomic instability (36). The extent of genomic instability could be efficiently evaluated using biomarkers of nuclear and mitochondrial DNA damage such as the micronuclei—an intermediate biomarker recently validated as a cancer predictor in healthy individuals (37), 8-hydroxy-2’-deoxyguanosine molecules and the common 4977-bp mtDNA deletion (38). Increased micronuclei frequencies have been found in both MM and LC patients (39, 40). Expected outcomes should be a reduction of genetic instability and of oxidative damage, and, indirectly, of cancer incidence.

In many cases asbestos exposure not only started but also stopped decades ago. The latency period observed in LC pathogenesis is rather long (15 years) and even longer for MM (up to 50 years from the first exposure). Asbestos fibers have no obvious mutagenic activity, however they persist indefinitely in the lung and pleural tissue with continuous generation of reactive species. Persistent oxidative DNA damage can alter signaling cascades and gene expression, induce or arrest transcription, and increase replication errors and genomic instability. The fibers can trigger inflammation through effects on prointerleukin-1b processing by the inflammasome (41) and this may mediate their tumorigenic activity. Inflammation impacts every single step of tumorigenesis, from initiation through tumor promotion, to metastatic progression (42). The long latency period may provide the opportunity to intervene in different steps of carcinogenesis, even when a long time has passed since cancer initiation (43).

In conclusion, asbestos continues to endanger the health and life of people exposed to it and no effective measure is currently offered to reduce cancer risk. It is time to reassess chemopreventive drugs potentially useful in asbestos-exposed individuals and to design and start new trials, aiming at lowering cancer risk.

Competing Financial Interests Declaration

Nothing to declare.

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