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Surveillance and intervention studies on respiratory cancers in asbestos-exposed workers

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A systematic review of the literature on the surveillance of workers at presumed increased risk for respiratory cancer because of their exposure to asbestos revealed surveillance programs at the national, population, industrial, and factory (workplace) levels. Furthermore, 3 randomized chemoprevention trials involving workers exposed to asbestos were found. The nationwide programs to survey problems related to occupational exposure to asbestos were conducted in Europe. Some of the countries have policies for the surveillance of workers exposed either currently or formerly to asbestos. The results of the chemoprevention trials suggest that there are, as yet, no practical tools for efficient, safe chemoprevention of asbestos-induced respiratory malignancies.

Key terms cancer risks, chemoprevention, medical surveillance, prospective studies, respiratory cancers, smoking habits, trials.

Exposure to asbestos causes cancer and mesothelioma in human lungs in addition to asbestosis and pleural plaques and thickenings. Both nonsmokers and smokers exposed to asbestos fibers develop lung cancer, the risk being greatly increased in smokers (1). (For a review see reference 2.) A latency period of at least 10—20 years between the first exposure to asbestos and the clinical manifestation of lung cancer is generally observed; the latency period is even longer for mesothelioma. Convincing evidence of the carcinogenic risk for asbestos exposure to humans resulted in risk management actions in several countries, varying from exposure limits to the banning of asbestos and asbestos-containing materials.

It is a long-standing occupational health practice to place asbestos workers under medical surveillance during employment, with the aim of detecting early signs of asbestos-related diseases. Such surveillance is usually undertaken as part of a broader set of actions, inclusive of surveillance exposure at the workplace and monitoring of individual members of the work force for the presence of effects that are not seen clinically. Medical surveillance is used for the purposes of compensation to verify the absence of asbestos-related diseases or to classify any that occur as a result of occupational exposure and to reduce individual exposure through changes in the workplace. Studies based on follow-up tend to be restricted to the period of employment, although the carcinogenic hazard represented by asbestos tends to accumulate despite reduction or cessation of current exposure (3).

Exposure to asbestos at work is usually some order of magnitude greater than that of the general population (4) so that workers are at high risk for cancer. Furthermore, because of their biopersistence and slow dissolution, asbestos fibers tend to accumulate in the lungs. Asbestos-exposed workers are therefore often included in trials for evaluating the efficacy of cancer preventive strategies through early detection or primary prevention, with special reference to lung cancer.

Several screening techniques for lung cancer have been used on asbestos-exposed workers over the last 10 years, including repeated lung X rays, sputum cytology, or both. The difficulty of surgical excision of the lung tumors detected represents a limitation to such exercises, however, because of the concomitant impairment of respiratory capacity due to asbestosis. Furthermore, the effectiveness of screening for lung cancer with respect to an increase in survival or the avoidance of death from the disease has not been proved in controlled trials (5, 6).

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Studies of the effectiveness of chemoprevention (ie, chemical agents added to a person's usual regimen) in reducing the occurrence of respiratory cancers among asbestos workers have been undertaken recently, particularly on the possible preventive potential of beta-carotene.

The objective of this paper is to present a review of the published literature on surveillance and intervention studies, including chemoprevention trials, among workers at increased risk of developing respiratory cancer because of exposure to asbestos.

Materials and methods

The MEDLINE and CANCERLIT data bases for 1969 to 1996 were consulted to identify intervention studies, chemoprevention trials, smoking cessation programs, and medical surveillance programs for asbestos-exposed workers. As additional sources, we used the IARC directories of on-going research in cancer epidemiology (1977—1996) and some summary reviews on smoking cessation programs and their effectiveness (7, 8). No limitations were placed on the characteristics or quality of the studies when they were selected for this review.

Results

The available scientific literature can be divided into 3 main categories: surveillance programs in factories or industrial sectors, surveillance programs at the national or subnational level, and chemoprevention trials.

Surveillance programs in factories or industrial sectors

Studies of workers in factories and industrial sectors with potential exposure to asbestos are summarized in table 1 for those in which the method used for identifying the exposed is specified (9—18). Other methods have been proposed or tested to identify workers who have either been exposed to asbestos or have asbestos-related diseases, with the implicit aim of implementing a surveillance program thereafter. These include a method to identify cohorts with substantial exposure to asbestos in New Jersey (United States), as a first step in a program to notify individuals of their risks (19), a surveillance scheme of work-related occupational respiratory diseases (named SWORD) established in the United Kingdom through periodic contact with chest and occupational physicians, who provided data on new cases of parenchymal asbestosis and benign pleural disease (20), and the use of hospital discharge data to identify new cases of asbestosis (21). The last 2 studies resulted in the identification of a large number of affected subjects who would otherwise have gone undetected.

Most of the studies summarized in table 1 were conducted in the United States and involved workers in industries or factories. These programs, in general, share a lower participation rate than health education programs. Only 2 of the studies included a smoking cessation program based on counseling by a physician and an evaluation of the proportion of those who had not resumed smoking 1 or 2 years later. The smoking cessation program for shipyard workers at the naval shipyard in Charleston, South Carolina, in the United States (12) involved a comprehensive questionnaire on the workers' knowledge, attitudes, and beliefs about the adverse effects of smoking (11).

Surveillance programs at the national or subnational level

Large surveillance programs have been launched or are in progress in some European countries (table 2) (22—35). Programs at these levels result in large numbers of workers and high participation rates.

The appropriateness of the new standard for asbestos introduced in the United Kingdom in 1969 was evaluated by examining the health of exposed subjects and evaluating their mortality prospectively after the new regulations had been applied (22—24). Information on exposure in the factories was collected in parallel. The program required periodic medical examinations, including a standardized interview on exposure and smoking habits.

The German program (25, 26) was a result of pressure from insurance bodies on former and current asbestos-exposed workers to accept health examinations after leaving employment, with the aim of using the collected individual information for better compensation of asbestos-related diseases. It is worth noting that, in 1992, Germany decided to stop the trading of asbestos and asbestos-containing materials. In both the United Kingdom and Germany, data on smoking status were collected in order to evaluate whether smoking modifies the cancer risk related to exposure to asbestos.

The approaches used in Finland (27—29) and Norway (30—35) were developed to identify subjects who had been exposed to asbestos in the past in order to persuade them to reduce their smoking habit. A law prohibiting the use of asbestos came into effect in both countries before the programs started. The surveillance program in Finland was carried out with other actions aimed at reducing the use of and exposure to asbestos, including a ban in 1990 on the manufacture, import, and use of asbestos-containing products. Through the use of various record systems efforts were made to identify and contact subjects who had had significant occupational

Table 1. Surveillance programs in factories and industrial sectors with exposure to asbestos.

Reference	Factory or industrial sector reference(s)	Characteristics of surveillance program and methods		Results
		Health surveillance	Health education	
Hurst et al, 1979 (9), United States	Factory in Texas where asbestos insulation products were manufactured (1954—1972), extension to other asbestos workers in the area	Identification of 1095 previous workers through health examination records and invitation to participate Questionnaire, physical examination, posteroanterior lung X rays, left lateral view, sputum cytology, respiratory function tests	Smokers, on an individual basis	Not presented
Felton 1979 (10), United States	Long Beach naval shipyard, a facility of the United States Navy in Los Angeles, opened in 1943	In 1977, all personnel offered a chest X ray (6640 attendees, 88.6% of total); register established for those with an X ray indicative of asbestos-related disease and known work history; program planned on a yearly basis: each worker leaving employment offered a yearly examination	Workers dealing with asbestos or having asbestos-related diseases (the latter: 18.1%) were offered an "educational effort" on the health consequences of asbestos	Not presented
Li et al, 1983, 1984 (11, 12), United States	Naval shipyard in Charleston, South Carolina	Work history, smoking habits, pulmonary function testing, chest X ray, sputum cytology collected for 3991 eligible civilian shipyard workers	All participants given a pamphlet outlining a smoking cessation strategy; smokers categorized as having normal or abnormal pulmonary status (1231 eligible, 871 participants) encouraged to join a smoking cessation study, randomly assigned to receive a simple warning of 3—5 min of behavioral cessation counseling from a physician; smoking status of both groups evaluated at 3- and 11-month intervals	8.4% still not smoking 11 months after behavioral counseling compared with 3.6% of those who received a minimal warning only
Tuch et al, 1986 (13), Israel	Former workers in a cement-asbestos plant	2800 subjects invited by mail to an interview on work history, medical examinations, pulmonary function tests	Smoking cessation program offered; method not presented	184 attendees (6.6%); no results on smoking cessation
Tillet et al, 1986 (14), United States	Three cohorts of asbestos workers, 1 of members of the Flint Glass Workers' Union	Periodical medical surveillance offered to workers and family members; 854 members identified and notified	Smoking cessation offered; method not presented	Particiption rate 70%; results on smoking not presented
Meyerowitz, 1989 (15), United States	Workers in a plant in Minnesota for at least 5 years and with at least 15 years of latency	Invited to attend screening and educational program (325 invited, 219 attending)	Educational program offered; method not presented	Not presented
Kilburn 1990 (16); Kilburn & Warshaw 1992 (17), United States	Union members who were or had been exposed to asbestos in construction, metal trades, shipyards	Selection of 4183 (out of 8749 members) whose exposure had begun 15 or more years earlier and lasted at least 5 years; questionnaire, chest X ray, spirometry, and measurement of alveolar carbon monoxide	Smoking cessation program offered: (physician counseling) current smokers (2627 subjects) asked by mail about smoking status 6 months later	Subjects with lung impairment appeared more inclined to quit smoking
Munafo' et al, 1992 (18), Italy	Railroad workers at repair workshops with at least 30 d of work between 1960 and 1980	14 887 invited, 9303 participants in 1991; questionnaire on work history and smoking, medical examination, chest X ray, respiratory function tests, asbestos bodies in sputum used		Not presented

exposure to asbestos and also to submit these subjects to health evaluations. Current smokers who accepted health examinations were encouraged to join a smoking cessation program. After completion of the first phase, however, no additional activities were foreseen.

The Norwegian program involved the population of a restricted area, where asbestos-exposed subjects were identified in a radiological screening program for tuberculosis. The program involved repeated radiological screening and monitoring of the smoking habits of asbestos-exposed subjects who were also smokers. This intervention study is the only population-based program from which evidence has been obtained of a reduced excess risk after the cessation of asbestos exposure and current smoking (33).

In Sweden and Israel (36, 37), programs involving asbestos workers have been suggested, but no information is available on further developments.

Chemoprevention trials

Chemoprevention can be defined as the use of specific natural or synthetic chemical agents to reverse, suppress,

Table 2. Surveillance programs of exposure to asbestos at the national or subnational level.

Nation	Initial year	Description of program and methods		Results
		Health surveillance	Health education	
United Kingdom (England and Wales) (22—24)	1970	National program for workplaces subject to the 1969 asbestos regulations; new workers are to be examined during the 2nd month of employment and every 2 years, as long as they remain in that employment; central record-keeping system; examination consisted of collection of exposure history, smoking habits and respiratory symptoms, clinical examination, chest posteroanterior X ray; all workers included in the mortality study	Not quoted	By end of 1971, 74 767 subjects included in list; results of follow-up mortality study (1971—1991) on 57 402 demonstrated a large excess of lung cancer and mesothelioma among those who started work before the asbestos regulations and a smaller but statistically significant excess of lung cancer among those who started work after the regulations together with an important number of deaths from mesothelioma; overall, the excess for lung cancer was confined to smokers
Germany (25, 26)	1977	National program aimed at identifying factories exposing workers to asbestos and at building up a list of asbestos-exposed workers; insurance institutes asked workers to attend medical examinations regularly (frequency not stated) (questionnaire on work history, chest X ray)	Not quoted	During 1987—1991, 106 984 workers identified in 7643 registered companies; 87 028 subjects invited to attend a medical examination; mortality follow-up (1977—1988) of a subcohort alive at the beginning of the study, > 3 years of exposure, and older than 30 years and validation of accuracy of cause of death reported on death certificates
Finland (27—29)	1989	As part of a general program to prevent asbestos hazards, screening for asbestos-related diseases, aimed at building up list of 55 000 presumably asbestos-exposed workers, through identification and answers to postal questionnaire; 24 000 respondents fulfilling the criteria invited to attend medical examinations including exposure history and chest X ray; all positive X rays referred to specialized centers for further examinations	Information offered at examinations and offer to join a smoking cessation group	24 000 questionnaires mailed; 18 943 subjects examined, 4133 (21.8%) positive tests (lung fibrosis, pleural plaques or thickenings)
Norway, county of Telemark (30—35)	1982	After collection of work history in 1982, asbestos-exposed male workers identified in cross-sectional population-based screening for tuberculosis (involving 28 216 subjects); categorized by level of risks for specific diseases, each becoming the target for "risk-based intervention" based on counseling to stop smoking and attend screening programs involving lung X ray every 4 months and annual exfoliative cytology if aged 50—69 years and at high lung cancer risk; biannually for lower risk category	Information given to smokers by physicians or nurses; counseling on potential lung cancer risk reduction if smoking stopped	Results of follow-up at 8 years (1982—1989) comparing those attending (subdivided according to smoking and asbestos exposure) and not attending screening; reduced lung cancer risk reported for subjects stating they had ceased smoking more than 12 years earlier at the time of screening

or prevent carcinogenic progression to invasive cancer. The definition does not include compounds ingested as part of the normal diet (38); instead the agents are added to a person's usual regimen.

Most of the chemoprevention trials initiated during the last decade involved the testing of micronutrients for possible preventive effects against epithelial cancers (39). This rationale is based on the results of observational studies and laboratory experiments, which showed that certain human dietary habits and the administration of some micronutrients to animals are associated with low risks for cancer of several organs, including the lung, and inhibition of carcinogenic processes in animals (40, 41). One of the most promising micronutrients for cancer prevention is beta-carotene, because of evidence of its possible antioxidant action. Four chemoprevention trials based on beta-carotene and on retinol (3 trials) or other potential chemopreventive agents (1 trial) involved asbestos-exposed workers, alone or together with other high-risk groups (42—61). The chemoprevention trials on asbestos workers are summarized in table 3.

Three trials were fully randomized. One, the Beta Carotene and Retinol Efficacy Trial (CARET), was a placebo-controlled primary prevention trial with a beta-carotene and retinol treatment group, and one, the Australian study, was based on randomization of subjects into 2 treatment groups, with no placebo group. In the latter study, base-line end-point rates were estimated from those for the general exposed population.

The McLarty trial addressed workers heavily exposed mainly to amosite (42); the Australian study involved workers exposed exclusively to crocidolite (62). The CARET trial involved asbestos-exposed subjects who were also current smokers or who had smoked during the last 15 years. Two trials (the CARET and Australian studies) aimed at testing the potential preventive action of treatment on both lung cancer and mesothelioma, while the McLarty study evaluated the effect on lung

Table 3. Chemoprevention trials involving workers exposed to asbestos. (TPA = tissue popypeptide antigen, CEA = carcinoembryonic antigen)

Reference	Enrolled population	Current exposure to asbestos	Study design	End point	Regimen	Other strategies	Plasma levels after treatment	Current status of results
McLarty, 1992 & 1995 (42—44), United States	755 men at asbestos factories or asbestos workers in Texas	Undefinable	Randomized double-blind, placebo-controlled	Sputum atypia	Beta-carotene 50 mg/day; retinol, 25 000 IU on alternate days	None	Beta-carotene 5—6 times base line; retinol no significant difference	No significant difference between treatment and placebo
Beta-carotene and retinol efficacy trial (CARET), 1988—1996 (45—57), United States	4060 asbestos-exposed men, aged 45—69 years, current or ex-smokers (14 254 heavy smokers or recent ex-smokers)	Yes	Factorial, pilot; randomized, placebo	Lung cancer and mesothelioma	Beta-carotene, 50 mg/day; retinol, 25 000 IU/day; both; placeb	Antismoking advice	Both chemicals 6—7 times base line	Both chemicals: excess lung cancer, general and cardio-vascular mortality (asbestos workers and smokers)
Musk, 1994 (58, 59) Australia	1024 ex-miners	No	Randomized between 2 treatments; no placebo	Lung cancer and mesothelioma	Beta-carotene, 30 mg/day; retinol, 25 000 IU/day	Undefinable	Undefinable	Preliminary: lower lung cancer and mesothelioma rates in retinol compared with beta-carotene group
Pluygers, 1991—1992 (60, 61) France	300 asbestos-cement workers	Yes	Randomized into those positive for biomarkers; TPA, > 200 U/l; ferritin, > 400 ng/lt; CEA, > 3 ng/ml	Asbestos-related malignancies	Acetyl-cysteine (600 mg/day), beta-carotene (30 mg/day), selenium (100 µg/day), alpha-tocopherol (30 mg/day), ascorbic acid (20 mg/day), riboflavin (20 mg/day)	None	Not reported	On-going

cancer by assessing the frequency of an early lesion, sputum atypia. The French study uses "asbestos-associated malignancies" as end points, defined on the basis of serum biomarkers (tissue polypeptide antigen, carcinoembryonic antigen, serum hyaluronic acid and ferritin) (60, 61). Two trials (the CARET and Australian studies) reported power estimations for the lung cancer end point, while one (McLarty) was based on smaller numbers because of the higher frequency of the end point.

Two chemoprevention trials involved cohorts of asbestos workers who had been identified earlier and followed for cancer risk. They were workers at an asbestos factory in Texas, summarized in table 1 (9), and crocidolite miners in Wittenoom, Australia (62). The 4 trials have the use of beta-carotene as a preventive agent in common, but the administered dose varied from 30 to 50 mg/day. Retinol was also administered in 3 trials, at doses from 25 000 IU on alternate days to 25 000 IU/day. The factorial design of the CARET trial should allow an evaluation of the effect of retinol independently of that of beta-carotene.

In the CARET study, all the subjects were offered participation in a special program to stop smoking, and 30% abstinence was observed after 2 years, the abstinence being equally distributed between the 2 groups of the study. In the French study, dietary advice was given to increase fruit and vegetable intake.

The base-line results of the McLarty study showed that the serum levels of beta-carotene were increased in the treated group. This finding suggests that there was adequate compliance. The retinol serum levels did not vary significantly between the 2 groups, but the administered dose was low (25 000 IU on alternate days), with the stated aim of limiting metabolic conversion of beta-carotene to retinol. The blood levels of beta-carotene were lower in the smokers and drinkers in both groups of the study. The end point of the study, sputum atypia, was not affected by the treatment (44).

The CARET study was interrupted after an average of 4 years' supplementation because of adverse results in the interim analysis. Treatment significantly modified the plasma levels of both beta-carotene and retinol (55), but combined treatment significantly increased the incidence of lung cancer (5.92×1000 versus 4.62×1000) and mortality from all causes (14.45×1000 versus 11.91×1000) and cardiovascular disease in comparison with the group receiving the placebo. The results for the asbestos-exposed subjects did not differ from those for smokers, although the excess lung cancer incidence found in this subgroup was not significant because of the small numbers (6.05×1000 versus 4.33×1000, $P = 0.08$) (57).

Very preliminary results from the chemoprevention trial in Australia, comparing groups treated with retinol and beta-carotene, indicate slightly fewer lung cancers

and mesotheliomas in the retinol group, there being 4 lung cancers and 3 mesotheliomas in the retinol group, 6 lung cancers and 12 mesotheliomas in the beta-carotene group (de Klerk N, personal communication). Even if this difference is confirmed, however, the possible effect of beta-carotene in comparison with base-line rates should be taken into account.

The French study is still in progress.

Discussion

Surveillance programs in factories

The sources used to identify the studies may not have been adequate, and the number of surveillance studies on asbestos workers and on smoking cessation programs may have been underestimated. Those that were identified suggest, however, that few long-term surveillance programs on asbestos-exposed workers have been carried out in factories or industrial sectors, and those reported involve a limited number of workers. Furthermore surveillance studies are too often restricted to the period of actual exposure. When factories are closed or workers retire or leave the workplace, health authorities are often unable to take over the surveillance activities performed in factories, and workers who were previously the target of health examinations automatically become "lost to follow-up". Lists of exposed subjects are usually unavailable or are not sent to the health authorities, since this is not a legal requirement in most countries.

Most programs to survey asbestos workers can be defined as "passive", as they consist of (repeated) follow-up of the same cohort over time to evaluate mortality, but no "active" intervention is undertaken. Ascertainment of vital status does not require any direct contact between subjects and the health structure. Few surveillance programs include activities other than simple medical surveillance, such as smoking cessation programs. Furthermore, the published protocols on the activities are limited (7), and even fewer results have been published on their efficacy.

National surveillance programs

Europe is the only area of the world where surveillance programs on asbestos workers have been carried out at the national level. The experiences vary by country. A common denominator, which makes these programs possible, is the availability of a national record-keeping system based on the transmission of lists of asbestos-exposed workers to health authorities. All of the programs that have evaluated the cancer experience of asbestos workers show high rates of respiratory cancer, even among subjects, like those in the United Kingdom, who were hired after the application of a new hygiene standard.

Only the Finnish and Norwegian programs included health education. Current smokers who accepted health examinations were encouraged to join a smoking cessation program. After 8 years of follow-up, a reduction in lung cancer was observed among people who gave up smoking in Norway.

Industrialized nations should have national "asbestos" programs to eliminate the hazards of asbestos, including a policy for surveillance and intervention among currently and formerly exposed workers. Few countries have developed such a policy, although the congressional mandate on shipyard workers in the United States and the Italian policy for railroad workers (table 1) may be considered surrogates limited to workers involved in some industrial sectors

The European Community, within the framework of the regulation on occupational exposure to asbestos (which did not include a ban on asbestos use already applied in several member countries), approved a directive (83/477/CEE) that requires lists to be kept of exposed workers at the national level, with the aim of encouraging health surveillance beyond the cessation of employment. No data are yet available about the implementation of the directive in member states.

Chemoprevention trials

Chemoprevention trials involving asbestos-exposed workers have encountered several problems. In the CARET study, asbestos-exposed subjects were chosen as a high-risk group for lung cancer, together with heavy smokers, on the basis of the hypothesis that micronutrients prevent carcinogenic processes due to various carcinogenic agents. In fact, the effect was comparable in the 2 groups of subjects at risk, with an increased risk for mortality from both lung cancer and cardiovascular diseases. This result is consistent with that found for heavy smokers in another large chemopreventive trial involving beta carotene (63), while an American trial with physicians who were mostly nonsmokers and were given a lower dose of beta-carotene showed no effect on lung cancer incidence (64).

Because of lack of power it is difficult to evaluate the effect on mesothelioma in the 2 trials (the CARET and Australian studies) that considered this neoplasm as an outcome. The available observational and experimental evidence of a possible preventive effect of micronutrients on nonepithelial cancers, and specifically on mesotheliomas, is very weak (65). An evaluation of the independent effect of retinol in the CARET study (the only study that could conduct such an evaluation) has not yet been reported. The McLarty trial provides substantially negative results with regard to squamous-cell atypia; the

small numbers and the short follow-up prevent comparison of the results for mortality from lung cancer and cardiovascular disease with those of the CARET study.

Of the on-going trials, the French one is the most problematic. In this trial, laboratory tests are being used to identify subjects who have or may develop asbestos-related malignancies, but no convincing validation of their predictive value in terms of end point has been given (60, 61). Treatment is a mixture of drugs, some of which have not been shown to have preventive potential. The period of treatment, the end points, and the monitoring of side-effects have not been clearly described, and the power estimate of the study has not been reported. This trial involves workers still exposed to asbestos, as does, at least partially, the CARET study, and no clear strategy for ceasing or at least reducing current exposure has been given. The Australian and McLarty studies address only previously exposed workers; however, the incompletely randomized design of the Australian study (no placebo group) leaves some doubt about the interpretation of the results. As the treatment is practically identical to that used in the CARET study, any differences in the results from this study would need validation.

The results of the aforementioned studies should be interpreted by comparing them with those of other chemoprevention trials using the same agents and similar end points. The consistency of the CARET trial and that described by The Alpha-tocopherol, Beta-carotene Cancer Prevention Study Group (63) and their compatibility with the Physicians Health Study (64) suggest that the beta-carotene hypothesis for preventing lung cancer in asbestos-exposed workers should be abandoned, as it has for other high-risk groups (57). The results of the McLarty study lead in the same direction. The effect of retinol has not yet been evaluated, but some results should appear from the CARET trial, now in its analytical phase. It would seem wise, after the experience with beta carotene, not to begin new trials with retinol before the CARET results have been made available. The evidence for an effect of any chemopreventive agent on mesotheliomas is currently inadequate to justify randomized trials.

Only some of the trials included a program on smoking cessation, and only the French trial considered the opportunity of dietary counseling (but not antismoking advice). This lack of concomitant strategies and the lack of action to decrease any current exposure to asbestos are critical, especially in light of the frustrating results of chemoprevention (66).

The main problem in developing a proper strategy for a second generation of prevention trials is that the mechanisms of asbestos carcinogenesis are not yet clearly understood (67). Asbestos is currently considered to give rise to all histological types of lung cancer (68—71), and asbestos fibers may act at multiple stages in neoplastic development (72). These fibers have been shown to induce metaplasia in tracheobronchial epithelium (73) and to alter the expression of the proto-oncogenes that regulate the proliferation of epithelial cells (74). The role of asbestos fibers in the latter stages of tumor progression is unknown. Macrophages are the initial target cells of asbestos fibers. Phagocytosis of the fibers is accompanied by the activation of macrophages, which results in the secretion of a variety of chemical mediators and cytokines. These mediators amplify local inflammatory reactions, which also involve the production of reactive oxygen and nitrogen oxide intermediates. Growth factors for epithelial cells and fibroblasts, such as tumor growth factor-alpha and platelet-derived growth factor, are also released from activated macrophages. It has been hypothesized that an imbalance between cytokines and growth factors may contribute to the pathological effects of asbestos fibers, especially to asbestosis (75). They may also play a role in the multistage carcinogenesis process.

Concluding remarks

The carcinogenic risks related to exposure to asbestos fibers in industrial settings remained unrecognized for a long time, as, until the 1970s, the few existing hygienic standards were limited to preventing the occurrence of lung fibrosis. The standards were not effective, as evidenced by the high prevalence of lung fibrosis and pleural plaques detected for the workers enrolled in the surveillance studies and trials reviewed in this article. A second effect of the limited efficacy of the standards is that asbestos-related cancers have received insufficient compensation (76).

Repeated health examinations, lung X rays, and functional tests to detect asbestos-related lung diseases in the work force were offered regularly in several countries and often imposed by law. The health examinations were usually restricted to the period of employment, however, even though the long latency before the development of lung damage was known. This attitude is inconsistent with the statement that "screening for risk identification presupposes a medical care system which is able to provide continuity of long-term personal care for everyone [p 35]" (77). As a consequence, no evaluation has been published of the effectiveness of periodic examinations in slowing the natural course of fibrosis or in increasing survival. In the countries that recognize the carcinogenic risks due to exposure to asbestos and which have limited or banned the use of asbestos, the policy of periodically examining workers for health effects can be implemented without the criticism that the authorities are choosing "not to attack the situations that determine exposure [p 47]" (77).

With regard to screening for lung cancer, the available evidence goes against the hypothesis that lung can-

cer mortality is reduced significantly by screening based on chest X rays. With the exception of the program in Norway, no attempt is under way to screen workers who have previously been exposed to asbestos for lung cancer. Instead, most of the surveillance programs including the period after exposure have been designed to observe events, rather than to reduce the cumulative risk. It is still not clear whether the cancer risks of active workers who have accumulated relevant exposure can be reduced by eliminating or reducing their current exposure to asbestos (78—80). A reduction in cancer risk would be more plausible if preventive action were not confined to a single factor. The limited diffusion of smoking cessation and dietary programs in the on-going surveillance programs is startling.

The information necessary for planning intervention programs properly includes estimates of the decline in risk after the cessation of exposure among smokers and nonsmokers and the decline in risk for smokers who stop smoking. These data could be obtained by follow-up of target populations after the cessation of exposure(s). Application of this strategy to large cohorts of smokers has helped determine the patterns of decreasing risk after smoking cessation (81—86). A similar effort should be pursued for asbestos workers, for whom information on health status and smoking habits is becoming available. A better integration of the programs being carried out in Europe could also offer an opportunity to incorporate smoking cessation activities.

The results of chemoprevention studies suggest that chemoprevention is not a viable option for asbestos-exposed workers, as the trials published so far on the use of beta-carotene and other supplementations thus far tested have provided no evidence of protection.

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