Oncogene (2002) 21, 7284–7288
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www.nature.com/onc

The molecular epidemiology of asbestos and tobacco in lung cancer

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Asbestos is a well-known toxin and lung carcinogen. Epidemiologic studies have established tobacco smoke and asbestos exposures synergistically interact to enhance lung cancer risk. The biologic mechanism responsible for this interaction has been the subject of considerable debate. Studies have suggested that asbestos may act as a carcinogen by generating free radical and reactive oxygen species, by inducing tissue injury and subsequent cellular growth, via large-scale chromosome loss and by enhancing delivery of tobacco carcinogens to the respiratory epithelium. Recent molecular epidemiologic approaches further suggest that asbestos enhances the mutagenicity of tobacco carcinogens and that it acts, at least in part, independent of the tissue damage responsible for fibrosis.
Oncogene (2002) **21,** 7284–7288. doi:10.1038/sj.onc.1205804

Keywords: lung cancer; asbestos; tobacco

Introduction

Asbestos is a natural occurring fibrous hydrated magnesium silicate mineral that has multiple commercial uses as a result of its indestructible character. The majority of asbestos used in the United States has been serpentine chrysotile asbestos, while amphibole asbestos (notably amosite and crocidolite) has been mined primarily in South Africa, India, Bolivia and Australia and seen less (albeit significant) use world-wide (Wilt *et al.*, 1998). Asbestos has been used primarily in products that require heat resistance (e.g. insulation). Its use in the United States peaked during and after World War II as a result of its extensive use in shipbuilding and commercial construction.

Exposure in the workplace has been significant for asbestos miners and millers, as well as for those exposed during secondary manufacturing uses (Rom, 1998). Construction workers (particularly asbestos insulators or 'laggers') have had historically very heavy inhalation exposures as a result of mixing and spraying asbestos on the job. In the United States asbestos use diminished when fiberglass insulation was introduced (circa 1965) and declined further after OSHA regulated workplace asbestos exposure in 1972. However, the use of asbestos has continued to increase in the developing world (Huncharek, 1993). One example of the dynamic pattern of worldwide use of asbestos is illustrated by the recent World Trade Organization decision upholding France's ban on the import and use of chrysotile. This decision is likely to increase the pressure for producers to target sales and use of asbestos to the developing world (Kazan-Allen, 2001). Hence, patterns of occupational exposure to asbestos are complex, dynamic and quite difficult to estimate in both the United States and the developing world.

Asbestos has long been known as a potent occupational toxin and lung carcinogen (Blot and Fraumeni, 1996; Rom, 1998; Russi and Cone, 1994). While tobacco smoke is clearly the single greatest risk factor for lung cancer, significantly increased risks for lung cancer have been observed in both non-smokers and smokers exposed to asbestos (Blot and Fraumeni, 1996; Selikoff *et al.*, 1968). A large body of epidemiologic evidence has demonstrated that smoking and asbestos exposure, occurring together, have a more than additive action in causing lung cancer (Selikoff *et al.*, 1968; Vainio and Boffetta, 1994). The relationship between these exposures has been termed 'synergistic,' meaning that they act in a multiplicative fashion (Rothman, 1976). Quantification of the magnitude of these risks is problematic as they clearly are dose and time dependent, but in epidemiologic studies of workers with significant exposure to both asbestos and tobacco smoke, asbestos exposure alone is associated with an approximate fivefold increase in lung cancer risk (above unexposed workers), smoking alone with about a 10-fold risk and in workers with both exposures risk has been estimated at about 50-fold above that for the unexposed (Selikoff *et al.*, 1968). Measures of this interaction across studies have shown considerable variation, but studies of the highest exposures point to an interaction that is multiplicative (Vainio and Boffetta, 1994). The epidemiologic data addressing the lung cancer risk from asbestos exposure and the accepted interaction with tobacco smoke exposure have been intensively analysed. The interaction appears to hold for all histologic subtypes (Vainio and Boffetta, 1994). Further, although fraught with uncertainty, the

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dose extrapolations are also consistent with a linear dose-response for the interactive risk.

Since asbestos is well known to cause interstitial fibrosis, it has been suggested that the fibrosis is central to the lung cancer process (Browne, 1986; Weiss, 1988b). This question has proven particularly controversial and presents a vexing epidemiologic problem; both interstitial fibrosis and lung cancer are dose-related and disentangling their various independent contributions to disease requires extremely large study groups with documented and variable exposure histories (Blot and Fraumeni, 1996; Craighead and Mossman, 1982; Mossman *et al*., 1983). While large studies have been conducted, there may not be adequate data resources to answer this question with the epidemiologic approach. The idea that asbestos-induced lung cancers follow an etiologic pathway that includes fibrosis flows from the observations that asbestos fiber deposition occurs primarily in the lower lobes of the lung and can be followed by induction of asbestosis and the formation of a 'scar' carcinoma (adenocarcinoma). Many studies have supported this general mechanism, reporting an increased proportion of lower lobe tumors among asbestos exposed populations (Craighead and Mossman, 1982; Jacob and Anspach, 1965; Kannerstein and Churg, 1972; Karjalainen, 1993; Soutar *et al*., 1974; Talcott and Antman, 1988; Weiss, 1988a; Whitwell *et al*., 1974), as well as an increased proportion of adenocarcinomas in asbestos exposed lung cancer patients (Auerbach *et al*., 1979; Browne, 1986; Hourihane and McCaughey, 1966; Husgafvel-Pursiainen *et al*., 1999; Johansson and Albin, 1992; Karjalainen, 1994; Mollo *et al*., 1995; Raffin *et al*., 1993; Talcott and Albin, 1988; Whitwell *et al*., 1974). However, these associations have not been reported by all studies (Auerbach *et al*., 1984; Brodkin *et al*., 1997; Churg, 1985; deKlerk *et al*., 1996; Hillerdal *et al*., 1983; Huuskonen, 1978; Kannerstein and Churg, 1972; Lee *et al*., 1998; Vainio and Boffetta, 1994), and as the proportion of adenocarcinoma and lower lobe tumors have steadily increased among non-asbestos exposed populations (i.e. women and former smokers) the implications of these patterns have become less clear.

The epidemiologic data also have little to say about the biologic basis of either the carcinogenic effect of asbestos alone or the combined effect of asbestos and tobacco smoke exposure. *In vitro* studies have shown asbestos to be cytotoxic, clastogenic and, although it is not an Ames assay mutagen, asbestos is mutagenic in systems that detect large deletions of DNA (Both *et al*., 1994; Hei *et al*., 1992; Jaurand *et al*., 1986; Okayasu *et al*., 1999). Asbestos fibers can induce chromosomal aberrations and large deletion events by interfering with mitotic machinery resulting in the abnormal segregation of chromosomes (Ault *et al*., 1995; Cole *et al*., 1991; Dopp *et al*., 1995; Hesterberg and Barrett, 1985; Jensen *et al*., 1996; Kodama *et al*., 1993; Palekar *et al*., 1987; Sincock and Seabright, 1975; Valerio *et al*., 1983; Yegles *et al*., 1993). Workers exposed to asbestos have been reported to have increased levels of sister chromatid exchanges (Fatma *et al*., 1991; Rom *et al*., 1983), as do non-smokers with high environmental asbestos exposures (Donmez *et al*., 1996). In addition, exposed workers have an elevated incidence of DNA double-strand breaks in lymphocyte DNA (Marczynski *et al*., 1994).

The DNA damage caused by asbestos may be related, at least in part, to the generation of oxidative damage (Maples and Johnson, 1992; Schapira *et al*., 1994; Weitzman and Graceffa, 1984; Kamp *et al*., 1992). This mechanism is attractive as it might also be related to the generation of tissue inflammation and cell death related to the pulmonary fibrosis commonly associated with asbestos exposure. There are many lines of evidence that support a mechanistic role for asbestos mediated reactive oxygen species (ROS) in lung cancer (Kamp *et al*., 1992). Antioxidants quench fiber-induced mutagenesis (Dong *et al*., 1994; Goodglick and Kane, 1986; Hei *et al*., 1995; Korkina *et al*., 1992; Mossman *et al*., 1986). Asbestos fibers promote the formation of hydroxyl radicals (Maples and Johnson, 1992; Schapira *et al*., 1994; Weitzman and Graceffa, 1984) a process catalyzed by the presence of fiber-bound metals (Fubini and Mollo, 1995; Lund and Aust, 1992; Park and Aust, 1998; Zalma *et al*., 1987), and asbestos exposure results in elevated 8-OHdG DNA adducts, a biomarker of ROS exposure, both *in vitro* and *in vivo* (Adachi *et al*., 1992, 1994; Chao *et al*., 1996; Chen *et al*., 1996; Fung *et al*., 1997; Marczynski *et al*., 2000; Murata-Kamiya *et al*., 1997; Nejjari *et al*., 1993; Takahashi *et al*., 1997; Takeuchi and Morimoto, 1994; Xu *et al*., 1999)

Smoking also induces cell proliferation, inflammation, and the production of ROS. In fact, very early radiographic changes that mimic an early fibrotic pattern are associated with smoking (Lilis *et al*., 1991). The combination of smoking and asbestos exposure has been shown to increase the occurrence of both lung fibrosis (Lilis *et al*., 1991) and cell proliferation (Sekhon *et al*., 1995). In addition, cigarette smoking may enhance the lifetime accumulation of asbestos fibers (Churg and Stevens, 1995). Increased cell turnover related to the toxic effects of inhaled tobacco smoke and asbestos almost certainly increases the occurrence of somatic alterations in newly dividing cells. Thus, the observations of asbestos and tobacco smoking enhancing airway changes as well as inflammation and fibrosis may, in some part, help to explain the synergy between asbestos exposure and cigarette smoking for lung cancer risk.

Possibly the best mechanistic explanation for the multiplicative effects of asbestos and cigarette smoking involves a model where asbestos fibers serve as a vehicle to deliver concentrated doses of tobacco carcinogens to the nucleus of the target cell (Brown *et al*., 1983; Gerde and Scholander, 1988; Lakowicz *et al*., 1980; Menrad *et al*., 1986). Surfactant phospholipids coating the lung epithelium adhere to the asbestos fibers creating a lipid bilayer where hydrophobic carcinogens such as polycyclic aromatic hydrocarbons (PAH's) may solubilize (Gerde and Scholander, 1988, 1989). This would result in a concentrated smoking

carcinogen exposure at the lung epithelium. If asbestos acts in this fashion, the biologic effects would be indistinguishable from that of cigarette smoke alone except that the dose and dose-rate of carcinogen exposure would be significantly enhanced above non-asbestos exposed individuals. However, it remains unclear whether the synergistic effects of combined exposure depend on the physical interaction between asbestos and tobacco smoke, whether these multiplicative effects reflect saturation of repair mechanisms for ROS, or whether one exposure applies selective pressure for clones initiated by the other exposure (classic tumor promotion).

Epidemiologic studies using a case series approach to study somatic alterations in primary human lung tumors from asbestos-exposed and unexposed patients may be critically useful in delineating the underlying mechanism(s) of the asbestos/smoking synergy. Studies using this approach have demonstrated that asbestos exposure is associated with particular types of somatic gene alterations. Nelson *et al.* (1998) reported asbestos exposure and smoking to be associated with deletion of the *FHIT* gene in lung cancer. Reduced FHIT protein expression and increased LOH observed in the lung tumors of asbestos exposed patients support these findings (Pylkkanen *et al.*, 2002). Asbestos is a well-known clastogen and the enhanced large-scale allele loss observed in these studies is consistent with asbestos acting in this fashion.

Husgafvel-Pursianinen *et al.* (1993) first suggested that asbestos exposure enhanced the association of tobacco smoke exposure and the occurrence of *k-ras* mutations in adenocarcinoma. Mutations at *k-ras* are primarily G to T transversions at codon 12, and this type of alteration (transversion mutations) has been associated with the action of polyaromatic hydrocarbons and very likely represents the action of tobacco carcinogens at the cellular level (Denissenko *et al.*, 1996). Additional studies have confirmed this observation of asbestos enhancement of smoking-related mutations (Husgafvel-Pursiainen *et al.*, 1995; Nelson *et al.*, 1999; Wang *et al.*, 1995), however, significant potential confounding by histology may obscure the ability to detect associations (Husgafvel-Pursiainen *et al.*, 1999). In addition, it has been shown that these types of transversion mutations at *k-ras* occur in asbestos exposed individuals without evidence of fibrotic alterations (Nelson *et al.*, 1999). That is, this molecular evidence implies that asbestos exposure is related to lung cancer in the absence of asbestosis. Finally, p53 mutations and aberrant protein expression in lung cancer have been associated with asbestos exposure (Husgafvel-Pursiainen *et al.*, 1995; Liu *et al.*, 1998; Nuorva *et al.*, 1994; Wang *et al.*, 1995). The prevalence of G:C to T:A transversion mutations at p53 may be enhanced by asbestos exposure in a fashion related to combined asbestos and tobacco carcinogen dose (Wang *et al.*, 1995). This adds further molecular evidence to the hypothesis that asbestos fibers act by enhancing the delivery of polyaromatic carcinogens to the lung.

Hence, the precise mechanisms responsible for the action of asbestos as a lung carcinogen either alone or in combination with tobacco smoke remain the subject of considerable scrutiny. Studies using a molecular epidemiologic approach are suggesting that the combined exposure results in more mutations that are of the particular type produced by tobacco carcinogens than otherwise occur in the absence of asbestos exposure. In addition, evidence now suggests that the molecular changes may be independent of fibrosis and implies that the pathways for fibrosis and lung cancer are, at least in some critical ways, distinct.

Expansion of the molecular epidemiologic approach may improve our understanding of the asbestos-smoking interaction. For example, little work has been done to date examining other classes of somatic changes that are associated with carcinogen exposure. Several studies have investigated the association of smoking and p16 gene promoter methylation in lung cancer (Kim *et al.*, 2001; Sanchez-Cespedes *et al.*, 2001; Zochbauer-Muller *et al.*, 2001). However, little research has asked if asbestos exposure might enhance the magnitude of this effect (Kim *et al.*, 2001).

It will be difficult to determine with certainty that asbestos is associated with a unique spectrum of genetic alterations. These studies will be limited in their power to attribute changes to asbestos exposure alone as lung cancer in non-smoking asbestos-exposed individuals is (fortunately) becoming more rare in the United States (as exposure in the workplace diminishes). Determining the independent and joint effects of asbestos and tobacco in lung cancer will require investigating large numbers of non-smoking asbestos exposed individuals. It may be useful to examine the types of somatic changes that are found in mesothelioma, a tumor attributable almost solely to asbestos exposure. These studies suggest that there is overlap in the spectrum of genes inactivated in this disease (e.g. p16 inactivation), but the frequency and type of alterations are distinct from lung cancer (Hirao *et al.*, 2002). In addition, all studies of the molecular epidemiology of lung cancer will be limited by their ability to estimate asbestos exposure. At a minimum these studies should include careful occupational histories, noting patient occupation over time in a fashion that might allow for some estimation of duration and intensity of asbestos exposure. Finally, the disturbing experience of the United States with respect to tobacco smoking and the use of asbestos is in the process of being repeated in the developing world. Prevention of this obvious public health emergency must be a priority for all health professionals. However, as this clearly predictable epidemic of lung cancer unfolds, studies of the workers exposed to asbestos are possible and could provide additional information on the mechanism of action of asbestos and tobacco carcinogens in the genesis of lung cancer.

Acknowledgements
This study was supported by NIH grants P42ES5947, ES0002, P42ES07373, CA82354 and CA57494.

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