

Occupational exposure and lung cancer

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ABSTRACT

Lung cancer is the leading cause of cancer death for male and the second most usual cancer for women after breast cancer. Currently there are available several non-specific cytotoxic agents and several targeted agents for lung cancer therapy. However; early stage diagnosis is still unavailable and several efforts are being made towards this direction. Novel biomarkers are being investigated along with new biopsy techniques. The occupational and environmental exposure to carcinogenic agents is an everyday phenomenon. Therefore until efficient early diagnosis is available, avoidance of exposure to carcinogenic agents is necessary. In the current mini-review occupational and environmental carcinogenic agents will be presented.

KEY WORDS

Lung cancer; occupational disease; environmental exposure

J Thorac Dis 2013;5(S4):S440-S445. doi: 10.3978/j.issn.2072-1439.2013.07.09

Lung cancer is estimated to be the leading cause of cancer death worldwide during the last decades. By 2008, there were an approximately 1.6 million of new lung cancer cases (12.7% of all new diagnosis for cancer) while it was the most common cause of cancer death (≈ 1.4 million deaths, 18.2% of the total) (1). Most cases (56% of total) and higher death rates (538/100,000 vs. 410/100,000) are present in less developed countries. A recent study from Europe showed that even though it was the fourth most common cancer—below female breast cancer, colorectal and prostate—it was the leading cause of cancer death (353,000 deaths for 2012) (2). In the USA, lung cancer is the second most common cancer for both sexes but the leading cause of cancer death for both men and women (3). It is worth mention that only recently a trend across decreasing incidence and mortality rates among US women was

detected for the first time (4).

Carcinogenesis is a complex, multifactorial process in which genetic (5,6) as well as and environmental causative factors play an interrelated role that lead to uncontrolled cell growth. Cigarette smoking is considered the leading cause of lung cancer, as it is the main causative agent for about 80% to 90% of cases in countries where the prevalence of cigarette smoking is high (7). Changes of smoking habits in populous, developing countries like China will alter the world map of lung cancer (8).

However it is estimated that about 10-20% of lung cancer cases are detected among never smokers with great geographic variability (9,10). Approximately 300,000 deaths/year due to lung cancer worldwide could not be attributed to cigarette smoking (11). If we categorize lung cancer among never smokers as a separate group we will find that it is the seventh most common cause of cancer death, well above cervix, pancreas or prostate cancer (12). Many etiologic factors of lung cancer—other than cigarette smoking—have been identified: exposure to environmental cigarette smoke (passive smoking) (13); occupational exposure to agents like asbestos and hard metals (14); exposure to radiation, especially radon (15,16); and exposure to indoor and outdoor air pollution (17,18).

Lung cancer, leukemia, and mesothelioma are the most

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Submitted Jul 01, 2013. Accepted for publication Jul 04, 2013.
Available at www.jthoracdis.com

ISSN: 2072-1439

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common forms of occupational cancer (19). Lung cancer is considered to be the most common among occupational related cancers (20). The precise percentage of patients with lung cancer who had been exposed to occupational carcinogens that contributed to the development of the disease is difficult to be estimated due to a wide range in the intensity of exposure, different genetic/ethnicity background and smoking history. However a figure of approximately 10% is referred by some authors (21). Occupational exposure to agents that are associated with lung cancer development is very important as: (I) sometimes physicians do not take detailed occupational history in patients with lung cancer; (II) tobacco smoke has synergic effect with many occupational carcinogens (22,23) and (III) patients with lung cancer after sufficient exposure to an agent which is definitely associated with the disease have the right for financial compensation. On the contrary are often underreported in everyday clinical practice (24).

The International Agency for Research on Cancer (IARC)—an independent scientific section of the World Health Organization—has divided chemical/occupational/environmental/physical and biological agents into 4 categories according to their carcinogenic potential (Table 1) (25). We should mention that in the term “agent” are also included some behavioral or cultural aspects. It is obvious that the above division is a dynamic process which evolves parallel with the current scientific literature (agents of Group 2A may be upgraded to Group 1 in the future). Table 2 presents all carcinogenic agents which are causally related with lung cancer according to the last classification by IARC (26).

Occupational agents/activities that are associated with increased risk for lung cancer are:

- (I) Mining and usage of asbestos in industry or manufacture (asbestos cement products, thermal and electrical insulation in construction and shipyard work, brakes, textile industry) (27,28). It seems that asbestos fibers size (long and thin) is a strong predictor of lung cancer mortality (29). Even though there is still a controversy in the literature, probably chrysotile is considered less carcinogenic than amphibole forms of asbestos (27,30);
- (II) Usage of arsenic and arsenic compounds (antifungal outdoor wood preservatives, agricultural industry of pesticides, herbicides and insecticides, manufacture of non-ferrous alloys, glass-manufacturing, electronics industry) (31,32);
- (III) Exposure to beryllium and beryllium oxide (nuclear technology, X-ray and radiation technology, dental applications and as beryllium-copper alloys in the electronics, aerospace technology, automotive) (33-35);
- (IV) Exposure to bis (chloromethyl) ether and chloromethyl methyl ether (36,37). Nowadays the possibility for exposure is low because their uses is strictly regulated, are no longer produced in large quantities and almost always are used in closed containers for the synthesis of other chemicals. They are used as a reagent in the manufacture of plastics, ion-exchange resins and polymers;
- (V) Industrial use of cadmium (38,39) [nickel-cadmium (Ni-Cd) batteries is its major use, pigments, coatings and plating in the form of cadmium-alloys, stabilizers for plastics];
- (VI) Exposure to substances as a painter (40-42). Paint is a complex substance that is composed of pigment particles (titanium dioxide, micro-crystalline carbon and azo pigments which are based on aromatic amines), a binder which is usually a resin or a drying oil, a volatile solvent or water and additives in small quantities that give special properties to paints or coatings. Painters are exposed to the chemicals during their application (mainly solvents) and removal (pigments, resins, silica);
- (VII) Nickel-producing industries (mining, milling, smelting, and refining) as well as nickel-using industries (alloys and stainless steel manufacture is its major use, electroplating, welding, grinding and cutting) (43-45). Workers in the former industries are exposed to insoluble nickel whereas soluble nickel is the predominant exposure in the later;
- (VIII) Exposure to chromium (VI) which occurs during production, use and welding of chromium-containing metals and alloys (manufacture of fabricated metal products, machinery and transport equipment); electroplating; production and use of chromium-containing compounds (pigments, paints, catalysts, chromic acid, tanning agents, and pesticides) (46);
- (IX) Exposure to silica dust and its crystalline form (quartz) (47,48). The three main commercial silica product categories are: sand and gravel (manufacture of glass, ceramics, foundry and abrasive activities), quartz crystals (jewellery, electronics and optical components industries) and diatomites (paint and paper industry, synthetic rubber goods, scourer in polishes and cleaners). Also workers in mines and quarries, constructions, crushed stone industries and sandblasting are severely exposed. The presence of silicosis increase further the risk for lung cancer (49);
- (X) Workers in aluminium production who are primarily exposed to polycyclic aromatic hydrocarbons and also to sulfur dioxide and fluorides, various aluminium compounds, chromium and nickel. The risk for lung cancer seems to be increased but studies are still controversial (50-52);

Table 1. Classification of carcinogenetic agents according to the International Agency for Research on Cancer.

Group	Classification	Parameter	Number of agents
1*	Carcinogenic to humans	Sufficient evidence of carcinogenicity in humans and in experimental animals	111
2A	Probably carcinogenic to humans	Limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals	65
2B	Possibly carcinogenic to humans	Limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals	274
3	The agent is not classifiable as to its carcinogenicity to humans	Inadequate evidence of carcinogenicity in humans and in experimental animals	504
4	The agent is probably not carcinogenic to humans	Evidence suggesting lack of carcinogenicity in humans and in experimental animals	1

*An agent can be included in Group 1 in the absence of sufficient evidence for carcinogenicity in humans but there is sufficient data of carcinogenicity in experimental animals and strong evidence that the agent acts through a similar mechanism of carcinogenicity in humans.

Table 2. Carcinogenetic agents related with development of lung cancer according to IARC (first column: with sufficient evidence in humans; second: with limited evidence).

1. Aluminum production	1. Acid mists, strong inorganic
2. Arsenic and inorganic arsenic compounds	2. Art glass, glass containers and pressed ware (manufacture of)
3. Asbestos (all forms)	
4. Beryllium and beryllium compounds	
5. Bis (chloromethyl) ether; chloromethyl methyl ether (technical grade)	3. Biomass fuel (primarily wood), indoor emissions from household combustion of
6. Cadmium and cadmium compounds	
7. Chromium(VI) compounds	4. Bitumens, occupational exposure to oxidized bitumens and their emissions during roofing
8. Coal, indoor emissions from household combustion	
9. Coal gasification	
10. Coal-tar pitch	5. Bitumens, occupational exposure to hard bitumens and their emissions during mastic asphalt work
11. Coke production	
12. Engine exhaust, diesel	
13. Hematite mining (underground)	
14. Iron and steel founding	6. Carbon electrode manufacture
15. MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture)	7. alpha-Chlorinated toluenes and benzoyl chloride (combined exposures)
16. Nickel compounds	
17. Painting	8. Cobalt metal with tungsten carbide
18. Plutonium	
19. Radon-222 and its decay products	9. Creosotes
20. Rubber production industry	10. Frying, emissions from hightemperature
21. Silica dust, crystalline	11. Insecticides, non-arsenical (occupational exposures in spraying and application)
22. Soot	
23. Sulfur mustard	
24. Tobacco smoke, secondhand	12. Printing processes
25. Tobacco smoking	13. 2,3,7,8-Tetrachlorodibenzopara-dioxin
26. X-radiation, gamma-radiation	
	14. Welding fumes

- (XI) Coke-ovens workers (coke production) are mainly exposed to polycyclic aromatic hydrocarbons. Increased risk for lung cancer has been proved by some but not all studies (53,54);
- (XII) Workers in the rubber-manufacturing industry are exposed to dusts and fumes as well as *N*-nitrosamines, polycyclic aromatic hydrocarbons, solvents and phthalates. There is sufficient evidence for excess lung cancer incidence and mortality (42,55-57);
- (XIII) Recently a Working Group of IARC concluded that diesel exhaust is a cause of lung cancer (58) but other authors believe that scientific data from occupational studies is not enough to support the above hypothesis (59);
- (XIV) Second-hand tobacco smoke (passive-smoking) represents an occupational exposure for workers in bars, restaurants, public buildings and educational institutions especially in countries without smoke free legislations in public places (60,61);
- (XV) There is some evidence that workers in the nuclear industry demonstrate an increased risk for lung cancer mortality (62).

As a general rule we could assume that for most carcinogenic agents it has been estimated a dose-response relationship between cumulative exposure and the risk for lung cancer. Also there is usually a lag period that ranges 10-30 years from initial exposure to the time point that relative risk increases to statistical significance. Occupational studies investigating the role of a potential carcinogenic agent on lung cancer incidence or mortality is extremely difficult to come to a definite conclusion due to the presence of various confounders (e.g., cigarette smoking, socioeconomic conditions, diet, air pollution, ethnical differences, simultaneous exposure to several carcinogenetic agents). In patients with lung cancer—especially among never smokers or those with unremarkable smoking history—taking a detailed occupational history (jobs and their duration, the precise workplace and the exact activity, presence of fumes/gases/dusts, use of protective measures) is fundamental but many times physicians underreported it. National Work Health Policy should guarantee a comprehensive plan of occupational hygiene (protection, follow up of air concentration for dangerous agents, regular medical examinations) especially for developing countries with industry expansion.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Spyrtos D, Zarogoulidis P, Porpodis K, Tsakiridis K, Machairiotis N, Katsikogiannis N, Kougioumtzi I, Dryllis G, Kallianos A, Rapti A, Li C, Zarogoulidis K. Occupational exposure and lung cancer. *J Thorac Dis* 2013;5(S4):S440-S445. doi: 10.3978/j.issn.2072-1439.2013.07.09