A Note from History:
Much Overlooked Causes of Lung Cancer

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In 1950, two studies identified tobacco smoking as an etiologic factor of lung cancer [1,2]. In 1964, the Surgeon General of the United States announced that cigarette smoking is causally related to lung cancer. Epidemiologic studies during the ensuing years showed that 88-90% of lung cancers in males and 68-75% in females can be attributed to cigarette smoking [3]. These observations imply that factors other than cigarette smoking play cardinal roles in induction of cancer in up to one third of the lung cancer patients. The purpose of this review is to survey the carcinogens other than tobacco that cause lung cancers.

**Radon-222** is a naturally occurring decay product of radium-226 and uranium-238, which are ubiquitous in soils and rocks. Radon is an invisible, odorless, and tasteless gas. Its radioactive decay products, polonium, bismuth, and lead, emit alpha particles into indoor and outdoor air and are highly harmful to the epithelial cells of the lung. The damage is done to pulmonary epithelial cells when the radiation interacts either directly with DNA in the cell nucleus or indirectly by the generation of free radicals [4].

In 1879, autopsy findings documented for the first time an occupational risk of lung cancer in miners in the Erz mountains in Europe [5]. Subsequently it was shown that high levels of radioactivity from emission of radon can be measured in mines in the Erz mountains and in underground mines worldwide and that cigarette smoking was an unlikely contributor to the miners’ lung carcinoma [6].

The most common source of radon in indoor air is the soil, rocks, and concrete beneath building structures, but building materials such as bricks, granite, plaster, and cement also contribute to low levels of radiation exposure. Recent studies show that low dose radiation may be as oncogenic as high dose radiation exposures [3,6]. According to U.S. Environmental Protection Agency estimates, one in every 15 homes nationwide has an elevated radon level [7]. It has been observed in multiple case-control studies, that there is increasing lung cancer risk with increasing exposure to household radon, after adjusting for cigarette smoking [3,8].

Radon in the general environment and building structures is estimated to be responsible for 10-14% of all lung cancers [3,9,10]. In 1988, the International Agency for Research on Cancer classified radon as a Group I carcinogen to humans [11]. In 2005, radon was recognized as the second-leading cause of lung cancer in the United States and it was estimated that more than 20,000 Americans die of radon-related lung cancer each year [7]. Similarly, radon is responsible for about 2% of all deaths from cancer in Europe [12]. An association of radon and smoking in induction of lung cancer has been linked in two studies [13,14]. It appears that in certain individuals, radon gas and radioactive decay products may act synergistically with cigarette smoke in the causation of lung cancer [15].

**Asbestos** is a naturally occurring fibrous mineral. Industrial exposures to amphibole and chrysotile asbestos in mining operations and in the manufacture of insulation and friction products and asbestos cement carry increased risk of pulmonary fibrosis and scarring; there is approximately 23% risk of lung cancer [16,17]. The occurrence of lung carcinoma in asbestos workers was first reported in the 1930s. It was found that among workers with asbestosis the incidence of lung carcinoma was 6% [18]. However, residents of industrialized countries accumulate a substantial number of asbestos fibers in their lungs as well. It is estimated that low levels of environmental exposures to asbestos cause 1 of 50,000 lung cancer deaths in the general population [3,17].
Carcinogenic effects of exposures to man-made mineral fibers (glass filaments, ceramic fibers, and slag wool) have been demonstrated in animals. In humans, slag wool and glass production workers have been shown to have elevated lung cancer risks [19,20].

Arsenic in inorganic form is a constituent of soil and occurs in copper, lead, and zinc ores. Arsenic is removed during the smelting and may be inhaled by refinery workers and by residents in the neighborhood of industrial plants. In 1969, a threefold increase in mortality from lung cancer was observed among workers at a copper smelter [21]. Subsequently, it was found that copper, gold, and tin miners exposed to arsenic-containing dust also had threefold excess of lung carcinoma [22]. During the last two decades, confirmatory reports from many countries showed that inorganic arsenic is a pulmonary carcinogen to humans [11].

Since 1948, when the first report of deaths from lung cancer in five workers manufacturing arsenic-containing pesticides was published [23], twofold excess of lung cancer was found in workers involved in the production of arsenical pesticides [24]. Similarly, twofold excess risk of lung cancer was detected in individuals living near pesticide manufacturing plants [25]. Arsenic is used in a wide variety of insecticides, fungicides, and herbicides. Increased incidence of lung cancer was reported in vineyard workers in Germany and France [26]. These workers were exposed not only by inhaling arsenic-containing dust, but by drinking wine and water contaminated with arsenic residues. Recent epidemiologic studies have confirmed that arsenic exposure via drinking water is associated with increased risk of lung cancer [27]. Arsenic is widely employed in production of semiconductors and silicon wafers, and it is a constituent of certain wood preservatives [3,28].

Silica and quartz have long been known to produce a pulmonary disease, i.e., silicosis. In 1934, 14 cases of silicosis and lung cancer were published [29]. As far back as the 1940s, it was shown that workers in granite, stone, and tunneling industries, stonemasons, sandblasters, and metal grinders had a 40% elevated risk of laryngeal and lung cancers [30]. Subsequently it was shown conclusively that there is substantial risk of pulmonary cancer among workers who develop silicosis by working in metal, glass, ceramic, brick, stone, and related industries [31]. For such workers, the overall excess lung cancer relative risks ranged from 1.5 to 5.0 [32]. In most underground mines, the dust contains 30% respirable free silica and the odds ratios for lung cancer in such mines, including chromium, lead, gold, and silver ore mines, after adjustment for smoking and other factors, range from 1.75 to 3.25 [33,34].

Probable industrial carcinogens are too numerous to consider all in this brief review, but some notable examples merit attention. Acrylonitrile is a chemical used in manufacturing plastic and synthetic rubber. The association between industrial exposure to acrylonitrile and lung cancer was first reported in 1980 [35], and has been confirmed in subsequent studies. Beryllium is a metal used as a hardening agent in manufacturing alloys and ceramics. It is also widely used in the electronics industry as an insulating agent. In 1980, a 40% increase in lung cancer mortality was reported among beryllium-exposed workers [36]. In a follow-up study, the increase in lung cancer in patients with beryllium disease was confirmed and the elevated incidence of lung cancer was apparently unaffected by smoking [37]. Cadmium is widely used in the plastics and paint industries as well as in the manufacture of batteries. Investigators reported twice the expected number of lung cancers in cadmium production workers [38].

Chromium compounds are used in electroplating of metal surfaces to provide insulation and a non-tarnishable finish. Epidemiological investigations have demonstrated increased risk of lung cancer among chromate workers [39]. Formaldehyde is used in production of plywood, rubber, leather, cosmetics, photographic films, explosives, and as embalming fluid in the mortuary industry and and tissue preservative in pathology laboratories. Mortality experience has shown an exposure-response relationship between lung cancer and formaldehyde [40]. Nickel compounds have been identified as pulmonary carcinogens for workers in nickel refineries [41].

Air pollution by industrial plants, vehicles, and residential furnaces contaminates the air with a variety of carcinogens. Workers exposed to emissions from coal and gas plants had a risk of lung cancer twofold higher than unexposed workers [42]. Roofer exposed to coal tar fumes were reported to have 50% increase in lung cancer risk [43]. Due to 40% increase of lung cancer in railroad workers [44], in 1990, the World Health Organization listed diesel engine exhaust as a probable carcinogen. Undoubtedly, vehicular pollutants are major contributors to the presence of carcinogens such as polycyclic hydrocarbons and benzopyrene in the urban air. Historically, it has been estimated that 10% of lung cancers can be attributed to air pollution. In 1996, a case-control study in China suggested that in nonsmoking women, the use of coal, air pollution, exposure to coal dust, frequent frying of food, and a
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Diet plays a considerable role in the induction of many cancers, although none of the putative relationships between diet and lung cancer have been conclusively proven. Results from case-control studies indicate that people who eat more fruit and vegetables have a lower risk of lung cancer than those who eat less fruit and vegetables [3]. Studies [47,48] have shown an increased risk of lung cancer with low intake of dietary carotenoids and vitamin A. Four-fold increase in the risk of lung cancer with low dietary intake of vitamin A was reported [49]. Also, low dietary levels of vitamin C and vitamin E have been associated with increased risk of lung cancer [50]. An elevated lung cancer risk was also observed in hard liquor drinkers [51].

Viral etiology of lung cancers has been considered ever since it was demonstrated in 1939 that there was a resemblance of infectious pulmonary adenomatosis (Jaagsiekte disease, later proven to be a retroviral disease) in sheep and adenocarcinoma (later named bronchioloalveolar carcinoma) in man [52]. An impetus for consideration of a viral etiology of lung cancers came from the discovery of human papillomavirus (HPV) in squamous cell carcinoma of the uterine cervix in 1977 [53]. In 1989, HPV was first detected in a series of bronchial squamous cell carcinomas [54]. The authors concluded that HPV infection may have a role in the oncogenesis of squamous cell carcinoma of the lung. Within a few years, HPV-16 and HPV-18 were detected, in addition to pulmonary squamous cell carcinomas, in adenocarcinomas, bronchioloalveolar carcinomas, and oat cell carcinoma [55,56]. In a study from Taiwan [57], where <10% of female lung cancer patients are smokers, it was found that HPV-positive cases were 5 times more common in women than in men. Thus there is mounting evidence that many pulmonary carcinomas, particularly in females, are related to HPV infection [58,59].

Genetic factors in the pathogenesis of lung cancer came to attention during the last three decades. Cytogenetic studies show that several chromosomal alterations are involved in the development of lung cancer. The most common chromosomal abnormality found in lung cancer is a 3p(14-23) deletion [60]. The genes inactivated by this deletion are tumor suppressor genes, which are thought to be important inhibitors of tumorigenesis. One example is the tumor suppressor gene p53 of chromosome 17p13, which was found to be deleted in 20% of lung cancers [61]. It is of interest that 3p14 is one of the most fragile sites in the human genome and deprivation of various essential metabolites may induce deletion. High frequency expression of 3p14 fragile site was detected in lung cancer patients and their relatives [62]. As to activities of oncogenes, it was shown that the nuclear oncogen C-myc was overexpressed in 60% of small cell lung cancers and mutation of the K-ras oncogene was detected in one third of pulmonary adenocarcinomas [63]. There is little doubt that lung cancers are environmental and genetic diseases involving the accumulation of a series of genetic defects. Most of the genetic defects are somatically acquired during life and are probably related to exposure to carcinogens. However, there is evidence that some of the genetic changes are inherited and provide grounds for inborn predisposition to lung cancer [64,65]. The observation that first-degree relatives of lung cancer patients have two-fold risk of developing lung cancer, independent of cigarette smoking, gives credence to the role of genetic factors in pulmonary oncogenesis [66-67]. In recent articles [68-70], molecular changes unique to lung cancer in never-smokers have been reviewed, ranging from increase in chromosome 16p gain and epidermal growth factor receptor mutation to decrease in methylation and p53 mutation. Attention was recently called by investigators in different countries [71-73] to rising incidence of pulmonary adenocarcinoma in nonsmoking young females, suggesting perhaps a role of hormonal factors in induction of lung cancer.

In conclusion, although the complete mechanisms of action of most lung carcinogens are unknown, it is likely that environmental and genetic factors, viral agents, and possibly yet unidentified carcinogens cause lung carcinomas in nonsmokers. In smokers, on the other hand, the various carcinogens that have been discussed in this article may interact with the carcinogens in tobacco smoke, either independently or synergistically.

References
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