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Role of Ultrafine Nanoparticles in Lung Cancer

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Abstract

Lung cancer is the most widely recognized disease and it is the main reason of cancer demise in men and the second driving reason for tumor passing, after breast cancer, in ladies. Recently, the International Agency for Research on Cancer (IARC) has categorized particulate matter, a large element of air pollution, as cancer-causing to people, supported adequate proof that exposure is related to associate multiplied risk of lung carcinoma. Urban particles consist of three modes: ultrafine particles (UFPs), accumulation mode particles and coarse particles. UFPs (<0.1 μm diameter) contribute very little to the total mass, but are very high in number in the urban air. The potential of particles to cause unfavorable health effects is connected to their capability to enter the lungs, probably carrying variety of cytotoxic compounds with them. UFPs have vital health effects as a result of their terribly high alveolar deposition fraction, massive extent, chemical composition, ability to initiate inflammation and potential translocate to the circulation. Over the previous years there has been an increasing assortment of clinical and medical specialty information associated with air pollution health effects and proof linking exposure to urban air pollutants. In particular, link between particulate matter (PM10 or PM2.5) with lung cancer is generally consistent, although formal statistical significance was not always reached. However, knowledge and awareness remain limited, regarding the carcinogenic effects of UFPs and some clinical studies are still unrecognized. Our purpose, during this review, is to review and synthesize the literature relating to the malignant neoplastic disease impact of UFPs, particularly the associations between the exposure to UFPs and risk for carcinoma.

Keywords: UFPs; NPs; Lung cancer

Introduction

Lung cancer is the main reason of cancer death in men and the second driving cause of cancer death, after breast cancer, in women [1]. At the beginning of the 20th century incidence of lung cancer was very low, but now its incidence is increasing rapidly [2,3]. According to the GLOBOCAN 2012 report, incidence of lung cancer globally was of 1.8 million new cases in 2012, representing 12.9% of the total estimating cancer incidence in the year 2012. The worldwide lung cancer mortality rate amounted to 1.59 million deaths in 2012, accounting for 19.4% of total cancer deaths. Lung cancer is the most common cancer in men worldwide (1.2 million, 16.7% of the total) with the highest estimated age-standardized incidence rates in Central and Eastern Europe (53.5 per 100,000) and Eastern Asia (50.4 per 100,000). Notably, low incidence rates are observed in Middle and Western Africa (2.0 and 1.7 per 100,000 respectively). In women, incidences rates are generally lower with a geographical pattern little different, reflecting different exposure to tobacco smoking. Highest estimated rates are in Northern America (33.8) and Northern Europe (23.7) and lowest rates in Western and Middle Africa (1.1 and 0.8 respectively) [4].

Four potentially modifiable risk factors, including: smoking, low intake of fruits and vegetables, indoor smoke from household use of solid fuels and urban air pollution are associated with 74% of lung cancer deaths. Moreover, living in a polluted area can negatively affect the prognosis and quality of life of lung cancer patients [5,6].

The International Agency for Research on Cancer (IARC), recently, has classified particulate matter, a wide component of air pollution, as carcinogenic to humans, based on adequate evidence that exposure is associated with an increased risk of lung cancer [7-9].

Urban particles consist of three modes: ultrafine particles (UFPs), accumulation mode particles (which together form the particle mode) and coarse particles. UFPs (<0.1 μm diameter) contribute very little to the overall mass, but are very high in number in the urban air (Figure 1). Even though there are a lot of particulate natural sources, the smallest one seem made mainly by human activities. With increasing road traffic density and emission from automotive combustion engines, environmental exposures have become more widespread in the general population. In particular, the vehicle traffic represents the main fine and ultrafine particulates source, generating the 50-60% of global air pollution. Not least is the contribution coming from UFPs inside the buildings (called indoor pollutants) where cooking, heating, smoking and combustion processes are great pollution producers.

In terms of particle size, the attention of scientific studies has shifted from mass (PM 10 or PM 2.5), to surface area and particle number concentrations to the last of which is largely comprised of UFPs [10-12].

The potential of particles to cause adverse health effects is linked to their capacity to enter the lungs, potentially carrying a number of toxic compounds with them. From a mechanistic point of view, UFPs have important health effects because of their large surface area, their chemical composition, their high alveolar deposition fraction and their ability to induce inflammation and translocate to the circulation [13-20].

Particle's toxicity can be ascribed to compounds bound to it, several

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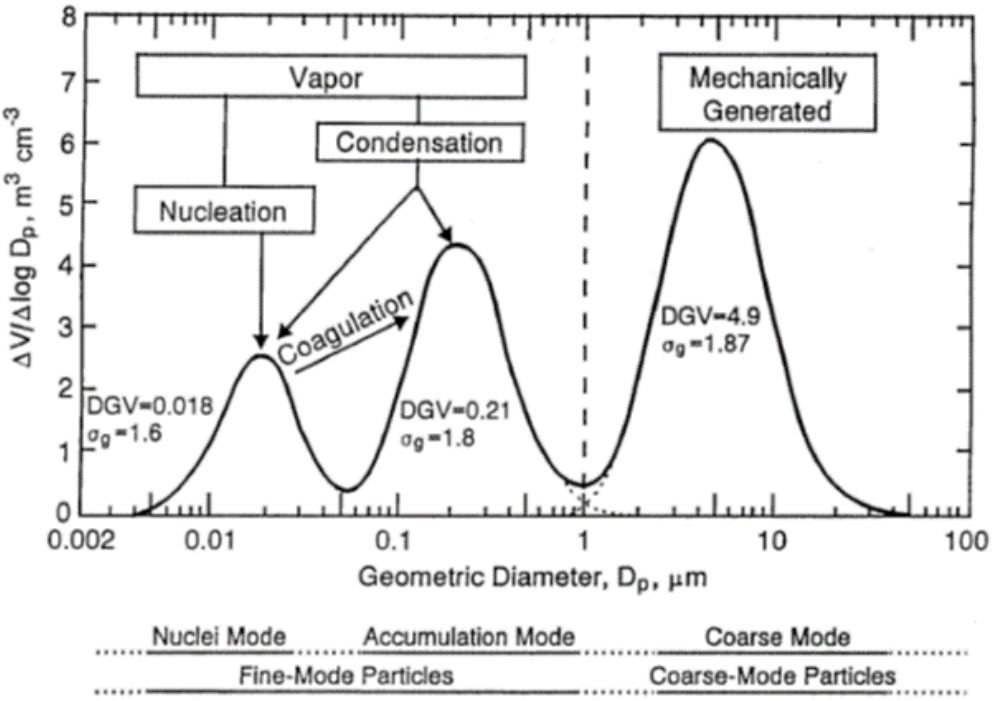

Figure 1: Trimodal urban particle size distribution indicating particle sources and coagulation processes (EPA 1996).

of which have been classified by the IARC in the Group 1, carcinogens. Among these, polycyclic aromatic hydrocarbons (PAHs) and some heavy metals (As, Cd, Ni) could be considered major contributors to human exposure through the respiratory tract.

Several cohort and case - control studies have indicated higher risk for lung cancer in association with different measures of exposure to ambient air pollution, in particular to UFPs and nanoparticles (NPs).

Over the past years there has been an increasing collection of clinical and epidemiologic data related to ambient air pollution health effects and evidence linking exposure to urban air pollutants. In particular, link between particulate matter (PM10 or PM2.5) with lung cancer is generally consistent, although formal statistical significance was not always reached.

However, knowledge and awareness remain limited, regarding the carcinogenic effects of UFPs and some clinical studies are still unrecognized.

Our purpose, in this article, is to review and synthesize the literature regarding the carcinogenic effect of UFPs, especially the associations between the exposure to UFPs and risk for lung cancer.

Methodology

Methods were developed relying on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. We selected the most relevant contributions to the literature in clinical and epidemiologic fields starting with the information retrieved from PubMed, Scopus and Web of Science using the following keywords "ultrafine particles" OR "UFPs" OR "urban air pollution" AND "health effects", AND "cancer" OR "cancerogenesis" OR "lung cancer" and other synonymous terms and our own extensive collection of ultrafine particles publications. Additional articles were identified from the reference lists of selected relevant articles. The research has been delimited to all articles relating to lung cancer over the last 17 years. The Collected studies were subsequently reviewed manually, in which the authors examined the relevance of the topics through an internal grading process. PM10, NO_2, SO_2, Environmental Air Pollution Particles were excluded. The search yielded about 31 articles which were further reviewed; at the end of this selection process 9 articles were deemed relevant to this review and were examined with a particular emphasis on carcinogenic effects of UFPs, in particular the association with lung cancer.

Mechanism of Action

Pulmonary and cardiovascular diseases and cancer have been associated to exposure to ambient air particulate matter (PM) in epidemiologic studies [21,22]. In ambient air, measure of the particulate matter (PM) is usually reported as the mass of particles with an aerodynamic diameter less than 2.5 µm (PM2.5) or 10 µm (PM10). Differently, it may be reported as the number concentration and size distribution of UFPs. There has been considerable attention on the pulmonary effects of UFPs because it has been showed that they can reach the alveoli and translocate to circulation. Particles of larger size, instead, deposit mainly in the upper airways and can be cleared by the mucociliary system and ingested [23].

In the last years, interest has focused on the UFP fraction with a diameter ≤ 0.1 µm, which are abundant in numbers but contribute little to particle mass. The deposition of inhaled UFP in the respiratory tract is ruled by diffusional processes, but there are notable differences within the UFPs size range with respect to the efficiency of their maximal deposition in different regions of the respiratory tract [24]. UFPs are

not predominantly retained on the epithelium but penetrate into the interstitium [25].

For these reasons it is of great importance to understand mechanisms by which UFPs and NPs exert their effect on lung disease and impair lung functions. Oxidative stress, inflammation and genotoxicity are the pathobiological processes considered most relevant to lung injury.

Oxidative stress is caused by disequilibrium between production of reactive oxygen species (ROS) and biological system's ability to neutralize the reactive intermediates. It may be caused directly by generating reactive oxygen species (ROS) in the vicinity or inside the cell or could indirectly affect mitochondrial respiration or deplete antioxidant species within the cell. Severity of the oxidative stress may be an important step in triggering some detrimental biological processes, like aging. Cells treated with NPs or animal models exposed to NPs inhalations have oxidative stress as common endpoint. Furthermore, ROS are the main factors involved in inflammatory processes. Oxidative stress-responsive signaling pathways can induce inflammation, resulting in the expression of pro-inflammatory genes involved in the recruitment and activation of cytokines, chemokines, and adhesion molecules. Inflammation genes are under control of transcription factors such as NF-KB and AP-1, both of which are redox sensitive and both of which have been demonstrated to be activated in macrophages exposed to carbon black NPs [26]. Both *in vivo* and *in vitro* studies have shown that NPs of various compositions (fullerenes, carbon nanotubes, quantum dots and automobile exhaust) generate ROS [27-29].

Reactivity of the surface area itself or the species absorbed to the outer surface of the particles (transition metals, organics) may contribute to their reactivity and oxidative potency [30]. There are many studies demonstrating that NPs and UFPs can trigger inflammatory responses. The small size, the shape and the large surface area appear to be centrally involved in promoting inflammation. The exact mechanism by which NPs induce pro-inflammatory effects is unknown; it has been suggested that they generate ROS, and thereby modulate intracellular calcium concentrations, activate transcription factors, and induce cytokine production [31].

Inoue et al. found that dosing mice with diesel NPs exacerbates lung inflammation induced by LPS (endotoxin or lipopolysaccharide). Lung homogenates derived from the LPS+NPs mice tended to have an increased TNF-α level and chemotaxis activity for polymorphonuclear leukocytes [32].

Results on pro-inflammatory effects of NPs have also been reported from clinical studies in humans. In a recent explorative analysis, the increase of particulate and gaseous air pollution was associated with multiple changes in the differential white blood cell count in patients with chronic pulmonary diseases. The researchers found an immediate decrease of polymorphonuclear leukocytes in response to an increase of particulate pollutants. Lymphocytes increased within 24 h in response to with all gaseous pollutants but showed only minor effects in regard to particulate air pollution. Monocytes showed an increase associated with ultrafine particles and nitrogen monoxide. The effect had two peaks in time, one 0-23 h before blood withdrawal and a second one with a time lag of 48-71 h [33,34].

PM fraction of air pollution contains number of constituents that may increase the generation of ROS by a variety of reactions, such as transition metal catalyses, metabolism, redox cycling of quinones and inflammation. In addition, polycyclic aromatic hydrocarbons and volatile organic compounds (e.g. benzene) may be metabolically activated to reactive species that form adducts on the DNA. These effects are quite easily investigated in cell free systems or cell cultures, while in animal experimental models there are other questions to consider when interpreting the harmful effect of UFPs and NPs. In particular, some factors including dose, dimension, deposition, durability and defense systems must be taken into account when interpreting health effects, such as lung tumor development [35].

Moreover, UFPs and NPs may cause genotoxicity through both primary and secondary mechanisms. A genotoxic substance deleteriously impacts the genome of a cell either by direct or indirect damage to the cellular DNA including effects on the cellular pathways that monitor and protect genome integrity. Primary genotoxicity is caused by direct binding of the particle with the DNA or component of the cell division machinery such as centromeres or microtubule spindle or intrinsic free radical production [36]. Pulmonary exposure to UFPs and NPs may cause genotoxicity through the induction of chronic inflammation leading to persistent oxidative stress.

Lung Cancer and Ultrafine Pollution

Association between exposure to ambient air pollution and risk of lung cancer has been evaluated in several prospective studies, summarized in Table 1. Despite that statistical significance was not always reached, the evidence linking exposure to urban air pollutants, mainly PM2.5 or PM10 and lung cancer is generally consistent, while they are still poor knowledge on the close association with UFPs. Cohorts from the United States as well as from Europe have found increased risks for lung cancer with higher exposure to PM and other

First Author, year (Ref)	Country	Outcome	Number of subjects	Exposure	RR	95% CI
Mc Donnel, 2000 [37]	USA	Lung cancer mortality	6.338	PM 2.5 PM 2.5-10 PM 10	2.23 1.25 1.84	0.56-8.94 0.63-2.49 0.59-5.67
Turner, 2011 [38]	USA	Lung cancer mortality	188.699	PM 2.5	NA	1.15-1.27
Laden, 2006 [39]	USA	Lung cancer mortality	8.096	PM 2.5	1.27	0.96-1.69
Puett, 2014 [40]	USA	Lung Cancer incidence	1.203.946 person-years	72-month average exposures to: PM 2.5 PM 2.5-10 PM 10	 1.37 1.11 1.15	 1.06-1.77 0.90-1.37 1.00-1.32
Raschou-Nielsen, 2013 [41]	Europe	Lung Cancer incidence	312.944	PM 2.5 PM 10	1.18 1.22	0.96-1.46 1.03-1.45
Katanoda, 2011 [42]	Japan	Lung cancer mortality	63.520	PM 2.5	1.24	1.12-1.37

RR: Risk Ratio; **CI:** Confidence Interval

Table 1: Summary table on prospective study results. Relationship betweewn exposure to air pollution and lung cancer incidence and/or mortality.

substance (PAHs) present in polluted air, with statistically significant risk rations (RRs) ranging from 1.11 to 2.23.

McDonnel et al. correlated the risk of cancer mortality with the fine (PM2.5) or the coarse (PM2.5-10) fractions of PM10 [37]. They concluded that observed associations of long-term ambient PM10 concentration with mortality for males were best explained by a relationship of mortality with the fine fraction of PM10 rather than with the coarse fraction of PM10.

Turner et al. examined the association between mean long-term ambient PM (2.5) concentrations and lung cancer mortality among 188,699 lifelong never-smokers, considering controlled confounders were age, sex, smoking, educational attainment, BMI, chronic lung disease [38]. A total of 1,100 lung cancer deaths were observed during the 26-year follow-up period. Each 10 μg/m^3 increase in PM (2.5) concentrations was associated with a 15-27% increase in lung cancer mortality. The association between PM (2.5) and lung cancer mortality was similar in men and women and across categories of attained age and educational attainment, but was stronger in those with a normal body mass index and a history of chronic lung disease at enrollment ($P<0.05$).

Earlier analysis of the Harvard Six Cities adult cohort study showed an association between long-term ambient PM2.5 and mortality between enrollment in the mid-1970s and follow-up until 1990. Laden et al. extended mortality follow-up for 8 y in a period of reduced air pollution concentrations [39]. The study showed that PM2.5 exposures was associated with lung cancer (RR, 1.27; 95% CI, 0.96-1.69) and cardiovascular deaths (RR, 1.28; 95% CI, 1.13-1.44). Improved overall mortality was associated with decreased mean PM2.5 (10 μg/m^3) between periods (RR, 0.73; 95% CI, 0.57-0.95).

Puett et al. examined the relation of lung cancer incidence with long-term residential exposures to ambient particulate matter and residential distance to roadway, as a proxy for traffic-related exposures [40]. During 1,510,027 person-years, 2,155 incident cases of lung cancer were observed in the study among 103,650 participants. In fully adjusted models, a 10-μg/m^3 increase in 72-month average PM10, PM2.5, or PM2.5-10 was positively associated with lung cancer. When the cohorts was restricted to never-smokers and to former smokers who had quit at least 10 years before, the associations appeared to increase and were strongest for PM2.5.

Raaschou-Nielsen et al. aimed to assess the association between long-term exposure to ambient air pollution and lung cancer incidence in European populations [41]. This prospective analysis of data obtained by the European Study of Cohorts for Air Pollution Effects used data from 17 cohort studies based in nine European countries. They assessed air pollution by land-use regression models for particulate matter (PM) with diameter of less than 10 μm (PM10), less than 2.5 μm (PM2.5), and between 2.5 and 10 μm (PM coarse), soot (PM2.5 absorbance), nitrogen oxides, and two traffic indicators. During follow-up (mean 12·8 years), 2095 incident lung cancer cases were diagnosed. The meta-analyses showed a statistically significant association between risk for lung cancer and PM10. For PM2.5 the HR was 1.18 (0.96-1.46). The same increments of PM10 and PM2.5 were associated with HRs for adenocarcinomas of the lung of 1.51 (1.10-2.08) and 1.55 (1.05-2.29), respectively.

Katanoda et al. enrolled 63520 participants living in 6 areas in 3 Japanese prefectures between 1983 and 1985 [42]. Exposure to particulate matter less than 2.5 μm in aerodynamic diameter (PM2.5), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2) was assessed using data from monitoring stations located in or nearby each area. During an average follow-up of 8.7 years, there were 6687 deaths, including 518 deaths from lung cancer. The hazard ratios for lung cancer mortality associated with a 10-unit increase in PM (2.5) were 1.24 (95% confidence interval: 1.12-1.37) after adjustment for tobacco smoking and other confounding factors. In addition, a significant increase in risk was observed for male smokers and female never smokers.

Buonanno et al. studied the characterization of lung cancer risk due to exposure to polycyclic aromatic hydrocarbons and some heavy metals associated with particle inhalation by Italian non-smoking people [43]. A risk-assessment scheme, modified from an existing risk model, was applied to estimate the cancer risk contribution from both ultrafine and super micrometric particles. Exposure assessment was carried out on the basis of particle number distributions measured in 25 smoke-free microenvironments in Italy. The predicted lung cancer risk was then compared to the cancer incidence rate in Italy to assess the number of lung cancer cases attributed to airborne particle inhalation, which represents one of the main causes of lung cancer, apart from smoking. UFPs are associated with a much higher risk than super micrometric particles, and the modified risk-assessment scheme provided a more accurate estimate than the conventional scheme. Among the chemicals considered, heavy metals (in particular, 55% for as, 7% for Cd, and 30% for Ni) made a significant contribution to increased cancer risk, while PAHs only accounted for less than 10%.

The purpose of Liao et al. study was to assess lung cancer risk caused by inhalation exposure to nano/ultrafine particle-bound PAHs at the population level in Taiwan [44]. A probabilistic risk assessment framework was developed to estimate potential lung cancer risk. They found that 90% probability lung cancer risks ranged from 10^{-5} to 10^{-4} for traffic-related NPs and UFPs-bound PAHs, indicating a potential lung cancer risk. Their work emphasizes the need to consider the NP and UFPs particle-bound PAHs data in additional to genetic susceptibility and respiration data in order to obtain a more complete picture of factors influencing potential lung cancer risk caused by inhalation exposure to ambient PAHs. So they showed suggestions of an increased risk of lung cancer at the highest exposure levels of fine particle bound PAHs.

Conclusion

Recently, airborne UFPs and NPs exposure studies (epidemiologic studies and controlled clinical studies in humans, inhalation/instillation studies in rodents, or *in vitro* cell culture systems) have shown that they can contribute to adverse health effects both in the respiratory tract and in extrapulmonary organs.

Epidemiologic studies have found associations of ambient UFPs with adverse respiratory and cardiovascular effects resulting in morbidity and mortality in susceptible parts of the population, whereas other epidemiologic studies have not seen such associations [45-52]. Controlled clinical studies evaluated deposition and effects of laboratory-generated UFPs. High deposition efficiencies in the total respiratory tract of healthy subjects were found and deposition was even greater in subjects with asthma or chronic obstructive pulmonary disease.

In addition, effects on the cardiovascular system, including blood markers of coagulation and systemic inflammation and pulmonary diffusion capacity, were observed after controlled exposures to carbonaceous UFPs [45,51,53-57].

Currently, no information on the potential health risk assessment

of lung cancer related to environmental Nano/Ultrafine particle is available.

Therefore, in light of the mutagenicity, carcinogenicity and ubiquity of UFPs in the atmosphere, the setting of air quality standards and guidelines to limit human exposure should be of primary concern for public health policy. However, setting scientifically based limit values is complicated, owing to the difficulties in interpreting heterogeneous experimental and epidemiological findings.

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