

# Lung cancer and related risk factors: an update of the literature

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**Summary** At the present time, lung cancer is the leading cause of cancer-related death in males. Diagnostic difficulty makes detection complicated and this, in conjunction with the low survival rate, renders the disease a serious health problem. In-depth knowledge of associated risk factors is therefore called for, in order to prevent or at least reduce the appearance of lung cancer and to open new avenues of research. Although the disease has a multicausal aetiology, tobacco accounts for 85-90% of all cases. This paper reviews the current situation, dividing the risk factors, for study purposes, into two groups; intrinsic (non-modifiable) and extrinsic (modifiable).

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## Introduction

Lung cancer is a serious public health problem. Although it is one of the most studied cancers, its world incidence is still increasing. The highest incidence for men is found in Eastern Europe, followed by North America. Among women, the incidence is clearly higher in North America.<sup>1</sup> Indeed, lung cancer has been the most commonly occurring cancer in men and women in the USA since 1987.<sup>2</sup>

Apart from its high incidence, the seriousness of this type of cancer resides in its high lethality. In the last 30 years, prognosis for lung cancer has witnessed hardly any improvement, with 5-year

survival currently standing at 13%<sup>3</sup> and total survival at only 12%.<sup>4</sup> This is because the symptoms and signs of lung cancer are highly non-specific.

There are multiple risk factors for lung cancer, with some having greater importance than others. A review of the literature on such risk factors was thus undertaken, with these being grouped into two broad categories, namely: factors inherent to the individual (intrinsic factors) and factors extraneous to the individual (extrinsic or environmental factors). While the former category features intrinsic aspects, such as genetic susceptibility, family history of cancer, sex, race, age and previous respiratory diseases, the latter category includes extrinsic aspects, such as tobacco use, diet, occupation and environmental pollution.

The search strategy that was employed is described extensively elsewhere.<sup>5</sup> Briefly, Medline and EMBASE were searched from 1985, making

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specific searches for each of the risk factors. We excluded editorials, commentaries and published articles with less than 50 cases.

## Extrinsic factors

### Tobacco use

Smoking is the principal risk factor for lung cancer. It is estimated that approximately 85-90% of all pulmonary neoplasias derive from this habit.<sup>6</sup> This drug possesses over 3500 different chemical substances, and at least 20 of these are proven pulmonary carcinogens in humans or animals.<sup>7</sup> These carcinogens can be divided into three major groups of chemical compounds, i.e. polycyclic aromatic hydrocarbons, aromatic amines and *N*-nitrosamines.<sup>8</sup> Special mention must be made of benzo(a)pyrene among the polycyclic aromatic hydrocarbons, and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) among the *N*-nitrosamines, since both substances are extremely carcinogenic. The risk of developing smoking-related lung cancer depends on several factors, e.g. duration of habit, intensity of habit (number of cigarettes per day), age at initiation and type of tobacco.<sup>9</sup> It has been observed that, owing to the characteristics of cigarette smoke, black-tobacco smokers are more prone to develop cancers of the pharynx, larynx and oral cavity, while blond-tobacco smokers are more prone to develop lung cancer.<sup>10</sup> The amount of time that must elapse before the level of risk faced by ex-smokers reverts to that of non-smokers is controversial. It is thought that the risk posed to ex-smokers will approach, although never equal, that of lifetime non-smokers by at least 15 years after cessation of smoking.<sup>10</sup> The decrease in risk becomes evident from the time a smoker quits the habit. In response to the publication of findings pointing to the carcinogenicity of tobacco, the filter was introduced and cigarettes were produced with a lower nicotine and tar content. Nevertheless, smokers were observed to increase the depth and number of inhalations in order to satisfy their nicotine addiction.<sup>8</sup>

Passive smoking is also a risk factor for lung cancer. Environmental tobacco smoke has been defined by the US Environmental Protection Agency (EPA) as a human carcinogen.<sup>11</sup> It should be borne in mind here that, while active smoking only affects the smoker, passive smoking affects everyone in the immediate vicinity. The risks observed to date are not very high, ranging around 1.5.<sup>12,13</sup> However, exposure to environmental tobacco smoke (ETS) is very difficult to measure. The standard practice is

to ascertain whether anyone (the spouse in particular) in the home smokes and the period of cohabitation. However, the person being studied may well be exposed to ETS in the workplace or spend little time with his/her spouse. In addition, there is the possibility that the home in question may be very well ventilated. All these aspects may lead to inaccurate classification of exposure, and so to over- or underestimation of the risk. The ideal solution in such cases would be to have biological markers capable of indicating the true ETS exposure faced by such individuals. The problem is that the biological markers of exposure which have been most used to date, such as serum or salivary cotinine, reflect exposure to tobacco in the preceding 48 h, thus rendering them invalid for the purpose of retrospective studies. They are, however, very useful in prospective or prevalence studies.<sup>14,15</sup>

### Occupation

It has been estimated recently that 23% of workers in the European Union are exposed to carcinogens in their work.<sup>16</sup> It is worth bearing in mind that the sum total of known attributable fractions can be more than 100%, since there are many risk factors that can act in synergy. For any disease, the sum of all aetiological fractions of the complementary causes of that disease is higher than 100%.

According to the International Information System on Occupational Exposure to Carcinogens (CAREX),<sup>17</sup> the most common occupational exposures to carcinogens are: solar radiation, ETS, silica and wood dust. The last three have been shown to be pulmonary carcinogens.<sup>19-21</sup> Many professions are known to pose a risk of suffering lung cancer (Table 1). Individuals engaged in occupations in which chemical compounds are handled, and workers in contact with dust or

**Table 1** Occupations and activities with a known risk of lung cancer (adapted from Ahrens and Merletti<sup>84</sup> and Ward et al.<sup>85</sup>).

|   |
|---|
| Mining and quarrying  |
| Chemical exposures and chemical processes   |
| Asbestos production (insulators, textile, cement products)  |
| Refineries, foundries and activities that entail handling metals (chromium, nickel, copper and cadmium) |
| Construction workers  |
| Painters  |
| Shipbuilding and motor-vehicle industry   |
| Wood-related activities   |
| Rubber industry   |
| Ceramic and brick industry  |
| Exposure to diesel exhaust (taxi, lorry and bus drivers)  |

microscopic particles (asbestos, wood dust, silica) are the occupational groups that face a relatively higher risk of developing lung cancer.<sup>21-23</sup> Among these groups, the best known are: construction workers (due to asbestos exposure); carpenters, joiners, wood and timber workers (due to sawdust exposure); and employees working in factories dealing with different types of chemical substances.<sup>24,25</sup> It should be stressed that construction workers and workers exposed to wood dust constitute two major occupational groups involving a large number of people.

In all likelihood, occupation plays a greater role in the development of lung cancer than has been acknowledged until now, given that the average 8-h working day constitutes a very long period of time during which subjects may be exposed to noxious substances. It has been observed that blue-collar workers, i.e. those that are exposed to carcinogenic substances, tend to smoke more than their white-collar counterparts.<sup>26</sup> The existence of this possible interaction has not been highlighted—with the exception of asbestos and tobacco—since the great majority of occupational studies tend to be based on records that do not reflect tobacco use.

## Diet

Diet has been shown to have a dual effect on the appearance of lung cancer, possessing both protective and harmful elements. Protective elements include intake of fruit and vegetables, due to their antioxidant-vitamin content (A, C and E),<sup>27-30</sup> with the greatest protective effect being ascribed to carotenoids in general and beta-carotene in particular.<sup>31</sup> However, a number of studies have reported no protective effect for intake of vitamin supplements. Large-scale intervention trials have been undertaken, such as the Carotene and Retinol Efficacy Trial (CARET),<sup>32</sup> Alpha-Tocopherol and Beta-Carotene Study (ATBC)<sup>33</sup> and Physician's Health Study (PHS),<sup>34</sup> in which no protective effect was found for intake of beta-carotene, retinol or alpha-tocopherol. These results are even more remarkable given that the first two studies (CARET and ATBC) focused on designated risk populations, namely smokers and asbestos workers. Indeed, CARET had to be halted as the interim results indicated an excess mortality of 28% among subjects who were taking these supplements.

Recent research on animals that were given vitamin supplements<sup>35</sup> suggested a rise in the incidence of lung cancer through the induction of phase-I (cytochrome-P450 family) enzymes that activate exogenous compounds and favour their bonding with DNA. Another explanation might lie in

the existence of physiological changes in the lungs of smokers, which cause these nutrients to metabolize differently than in non-smokers, with a predominance of oxidated forms.<sup>36</sup> In contrast, certain foodstuffs (watercress, for instance) have been observed<sup>37</sup> to contain specific substances, such as phenethylisothiocyanate (PEITC), that are capable of inhibiting the effect of potent carcinogenic substances present in tobacco. Moreover, animal-based studies attribute a certain protective effect to the consumption of olive oil, via a mechanism akin to that described above.<sup>38</sup>

Diet can also contain risk factors for lung cancer, particularly in the form of saturated fats, yet the risks observed are not high.<sup>39-42</sup> Speculation has centred on more than one possible mechanism of action, with cellular oxidation or alteration of the permeability of the cell membranes being postulated as possible explanations for carcinogen penetration of cells.<sup>43</sup> Whatever the case, however, it can be stated that, proportionally speaking, the risk is of a far lower magnitude than the protective effect attributed to fruit and vegetables.<sup>44</sup>

## Environmental pollution

Environmental pollution has also been linked to risk of lung cancer. Nowadays, the principal sources of pollution are motor-vehicle exhaust fumes, heating systems, power stations and other industrial emissions. Risk of lung cancer has been observed to be higher in urban rather than rural settings, and fluctuates at around 1.6 for men and 1.9 for women,<sup>45</sup> although these risks may be greater in high-pollution areas<sup>46</sup> (Table 2).

The effects of environmental pollution are very difficult to study since exposure is complicated to measure. Ecological studies lack information on certain confounders, such as tobacco use (city-dwellers smoke more) or the mobility of subjects. Measurement of environmental pollution at an aggregate level assumes that all individuals residing in a given area will face the same level of exposure to environmental pollution.

One study conducted in Athens into air pollution and tobacco concluded that pollution was probably unrelated to lung cancer among non-smokers, but among smokers, air pollution might have a synergic effect vis-à-vis certain histological types.<sup>47</sup> In a further cohort study, risk was observed for exposure to ozone, sulphur dioxide and microscopic particulate matter. This risk was higher for men than for women.<sup>48</sup> Using spatial analysis, other authors have reported higher risks of lung cancer with proximity to the city centre and an

**Table 2** Environmental pollution and risk of lung cancer.

| Study and year                                | Design                                     | Results  |
|---|--|--|
| Katsouyanni and Pershagen, <sup>46</sup> 1997 | Review                                     | It is suggested that urban air pollution may be a risk factor for lung cancer, with estimated relative risks in the order of up to about 1.5 in most situations  |
| Nielsen et al., <sup>86</sup> 1996            | Case (healthy bus drivers) and 60 controls | Environmental pollution raises the levels of DNA-PAH adducts   |
| Biggeri et al., <sup>49</sup> 1996            | Case-control                               | The mortality risk of lung cancer is higher in the city centre and decreases when moving away  |
| Beeson et al., <sup>48</sup> 1998             | Cohort                                     | Increased risks of incident lung cancer were associated with elevated long-term ambient concentrations of particulates smaller than 10 µm and sulphur dioxide  |
| Engholm et al., <sup>87</sup> 1996            | Cohort                                     | It is suggested that an association between outdoor air pollution and lung cancer is identifiable only above a certain pollution level. This study did not find any risk since pollution in Copenhagen is very low |
| Pope et al., <sup>88</sup> 2002               | Cohort                                     | Long-term exposure to combustion-related fine particulate air pollution is an important environmental risk factor for lung cancer mortality  |
| Jedrychowski, <sup>18</sup> 1990              | Case-control                               | Higher risk of lung cancer for subjects exposed to high levels of particulate matter and sulphur dioxide   |
| Katsouyanni, <sup>47</sup> 1991               | Case-control                               | Higher risk of lung cancer due to pollution for smokers. No effect was observed for non-smokers  |

PAH, polycyclic aromatic hydrocarbon.

incinerator.<sup>49</sup> In all, few studies have been undertaken owing to variables that are difficult to measure or control, such as mobility of subjects, variability in pollutant concentrations, and changes in the atmospheric and topographic features of study areas. In order to fine-tune the results, it would be of interest to have access to biological markers capable of indicating pollutant-exposure levels for subjects on an individual basis.

Within the context of environmental pollution, special mention must be made of exposure to radon gas, which not only emits alpha particles on decomposition but, notwithstanding contradictory studies, has shown itself to be a risk factor for lung cancer, accounting for 10-20% of all lung cancers.<sup>50-52</sup> Furthermore, an association has been observed between exposure to Rn222 and mutations in *ras* and *p53* genes.<sup>53,54</sup> Preventive measures are available to reduce exposure to radon gas, as demonstrated by the effectiveness of the Enkavent mat method and the suction pit method, as tested by a University of Florida research team.<sup>55</sup>

## Intrinsic factors

### Sex

Lung cancer is generally diagnosed at an earlier age and survival tends to be better in women than men.

Some authors<sup>56,57</sup> state that, as with exposure to tobacco, women have an approximately 1.5- to 2-fold higher risk of developing the disease than men. There is speculation as to the possibility of female oestrogens playing a role in lung cancer through conferring a slight degree of lability, but no conclusive evidence has yet been produced.

### Age

The highest incidence of lung cancer occurs at around 65 years of age. This finding links lung cancer closely with tobacco use, in that it allows for the requisite induction time for the habit to exert its effect (in view of the fact that most subjects start smoking before the age of 20 years). It has likewise been observed that incidence declines after the age of 80 years,<sup>58</sup> something that could be due to one of two possible causes: a lower prevalence of smoking habit among the oldest cohorts; or a bias or survival effect due to the fact that people who reach such ages are in some way (genetically) resistant to certain risk factors.

### Race

Slight ethnic differences have been observed (higher mortality rates among African-Americans and New Zealand Maoris),<sup>59</sup> and genetic predisposition plays an important role in such differences.<sup>60</sup> In one study it was observed that, for the same level of

tobacco use, relative risk for blacks vs whites was 1.8.<sup>61</sup> Chinese women also have high incidence rates, although it is believed that this could be due to widespread use of wood-fired ovens or to cooking with seed oil.<sup>62,63</sup>

### Previous respiratory diseases

Certain diseases raise the risk of developing lung cancer, such as tuberculosis, chronic obstructive pulmonary disease (COPD) and silicosis. It is suspected that this may be due to inflammation of lung tissue, as this favours cell penetration by carcinogens. COPD entails a higher risk of lung cancer, since 8.8% of COPD patients<sup>64</sup> are said to develop lung cancer within 10 years. It has been suggested that the slower clearance of carcinogens inhaled by COPD sufferers may raise the risk of the advance of lung cancer.<sup>65</sup> Sarcoidosis is also linked to increased risk.<sup>66</sup>

### Family history

After due adjustment for tobacco use, family history of lung cancer has been associated with a rise in risk.<sup>67</sup> Specifically, risk is higher in people under the age of 59 years with a history of lung cancer among first-degree blood relatives.<sup>68</sup> Similarly, observation has shown that first-degree blood relatives of any cancer sufferer have a 2.4-fold excess risk of developing lung cancer, and that lung cancer is more common in those families with a record of breast and ovarian cancer.<sup>65</sup>

Wu et al.<sup>69</sup> reported that women with a family history of lung cancer are more likely to acquire the disease. A further study, again on women,<sup>65</sup> showed that subjects reporting a family history of lung cancer had a 1.9-fold risk (95% CI 0.7-5.6) of developing lung cancer, and those reporting a family history of cancer had a 1.8-fold risk of developing lung cancer (95% CI 1.0-3.2). Another study<sup>70</sup> covering lifetime non-smokers as well as ex-smokers who had quit the habit a long time previously, observed that the risk of lung cancer rose in direct proportion to the number of family members affected by any type of cancer. The aetiological hypothesis for this risk factor postulates genetic inheritance, possibly in areas of tumour suppressor genes and proto-oncogenes, giving rise to an enhanced predisposition to biological disruption.

### Genetic susceptibility

Fortunately, only around 15% of all heavy smokers develop lung cancer. The exact reason for this is not

known, although it is suspected that the phenomenon may be due to the existence of genetic polymorphisms which cause carcinogens to accumulate in the body to a greater or lesser extent; something that implies genetic susceptibility on the part of the individual. These genes, which encode enzymes responsible for the metabolism of exogenous compounds, are generally designated as low-penetrance genes since the risk attributable to each is very low. On the other hand, they are present throughout society so, in population terms, the risk is high. This line of reasoning leads one to conclude that, in essence, such genes act as effect-modifiers with respect to dietary elements, tobacco use, occupation and/or environmental pollution, since they would not exert their effect in the absence of such harmful exposures.

All individuals possess two major enzymatic groups, known as phase-I and phase-II enzymes, encoded by multiple genes. Basically, the former are encoded by genes of the cytochrome-P450 superfamily and the latter by genes of the glutathione S-transferase and N-acetyl-transferase superfamily (NATs). Phase-I enzymes are able to convert exogenous compounds into reactive substances capable of bonding with DNA, thereby favouring the appearance of mutations. Phase-II enzymes facilitate the elimination of such compounds activated by conjugation or enhance their hydrosolubility. Each enzyme metabolizes one or more exogenous substances, with the result that differences in gene sequencing will influence metabolism in any given individual to a greater or lesser extent, depending upon his/her exposure to carcinogens.

To date, the following genes are suspected to have a degree of participation in the appearance of lung cancer: phase-I genes, *CYP1A1*,<sup>71</sup> *CYP2D6*,<sup>72</sup> *CYP2A6*,<sup>73</sup> *CYP2C9*,<sup>74</sup> *CYP3A4*<sup>65</sup> and *CYP2E1*;<sup>75,76</sup> and phase-II genes, *GSTM1*,<sup>77,78</sup> *GSTT1*<sup>78,79</sup> and *GSTP*.<sup>80</sup> Current research<sup>80,81</sup> not only combines phase-I and phase-II genes but also includes the intermediate step of DNA-adduct determination.<sup>82</sup> To date, the genes most associated with lung cancer are *CYP1A1*, *CYP2D6* and *GSTM1*. Whatever the case, to obtain an overall view of individual genetic susceptibility, the different polymorphisms of a multitude of genes must first be ascertained.

### Conclusions

At this point in time, environmental (i.e. extrinsic) factors have a greater relative weight than intrinsic factors in the development of lung cancer, so prevention should be feasible, in theory at least. Tobacco use is clearly the principal risk factor.

Occupation is another risk factor on which it is possible to act, by promoting protection or reducing exposure(s) in the workplace (targeting smokers in particular). Also, new risk factors remain to be studied, such as activities in leisure time.<sup>83</sup> The effects of environmental pollution are very difficult to study since exposure is complicated to measure. The exposure liable to produce the most effective action may conceivably be diet, through encouraging fruit and vegetable intake, especially in the case of smokers. Nevertheless, many nutrients contained in diet could have a specific role in the development of lung cancer.

Application of genetic epidemiology will render it possible for subgroups at greatest risk of developing lung cancer to be identified in the short or medium term, and duly targeted for more effective preventive interventions.

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