Original article

Exposure to occupational carcinogens and lung cancer risk. Evolution of epidemiological estimates of attributable fraction

Sara De Matteis, Dario Consonni, Pier Alberto Bertazzi

University of Milan, Milan and Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena. Milan, Italy

Abstract. *Background and aim of the work:* Lung cancer is the leading cause of cancer death world-wide. Among the possible causes, occupational risk factors play a major role and are potentially preventable. We reviewed the scientific evidence about lung cancer burden due to occupation. *Methods:* We reviewed the literature and selected population case-control and cohort studies which provided estimates of the proportion of lung cancers attributable to occupational carcinogens (population attributable fraction, PAF). Different methods were used to evaluate occupational exposure to suspected/known lung carcinogens: lists of high-risk occupations, job-exposure matrix (JEM), expert assessment. Only studies which adjusted for tobacco smoking were included. *Results:* The PAFs reported by the 32 selected Italian and international studies among men vary greatly in time and space: they ranged between 0 to 40% according to different geographical prevalence of hazardous industries (e.g., basic metal industries, shipbuilding and railroad equipment manufacturing). The PAFs estimated using JEM and expert assessment were on average higher. Data for women were usually few and insufficient to calculate stable estimates. *Conclusions:* A significant proportion of lung cancers is attributable to occupational carcinogens. The estimates are extremely variable in time and place and mainly depend on the industrial setting of the area under study; caution is therefore required in generalizing these results to the whole country. Alternative approaches to evaluate occupational lung cancer burden among women are necessary. (www.actabiomedica.it)

Key words: Lung cancer, occupational exposure, occupational carcinogens, population attributable fraction, job-exposure matrix

Introduction

Lung cancer is the leading cause of cancer death world-wide, with more than 1.2 million deaths in 2002 (1). Rates in men have peaked in some areas of the world, but in women they are still increasing (2). Although smoking is by large the most important cause, occupational factors play an important role. It has been estimated worldwide in year 2000 that 10% of lung cancer deaths in men (88,000 deaths) and 5% in women (14,300 deaths) were attributable to exposure to selected occupational lung carcinogens (arsenic, asbestos, beryllium, cadmium, chromium, diesel fumes, nickel, and silica); the corresponding numbers of years lost due to morbidity or premature mortality (disability-adjusted life years, DALYs) were 825,000 (men) and 144,000 (women) (3-5). In the same year in Europe, assuming attributable fractions of 7-15% (men) and 2-9% (women) the estimates deaths were over 32,000 (29,300 men, 3,200 women) with about 300,000 DALYs (275,000 in men, 28,000 in women) (3). In US, using 1997 mortality data and attributable fraction estimates of 6.1-17.3% (men) and 2% (women), about 6,800 to 17,000 lung cancers were estimated to be caused by exposure to chemicals at the workplace (6).

The frequency of exposure to occupational carcinogens is still high: in 1990-93, in the European Union, among 32 millions of exposed roughly 9 millions of workers were exposed to the lung carcinogens mentioned above (not including like polycyclic aromatic hydrocarbons, radon, and environmental tobacco smoking) (7). The corresponding estimates for Italy were 4.2 and 1.4 million (8% of the Italian workforce) for lung carcinogens (8); ten years after (2000-03) only a modest decrease (1.2 millions) was found (9).

In the context of a study on lung cancer recently completed in Lombardy, we conducted a review of the role of occupational factors in causing lung cancer. In particular, we were interested in the proportion of lung cancer cases which are attributable to occupational factors in different areas of the world (and therefore potentially preventable). To this end, we selected population case-control and cohort studies conducted in Italy and abroad that presented estimates of the risk of lung cancer for selected occupations and calculated the population attributable fraction (PAF) or at least reported the information necessary to calculate it.

Materials and methods

We searched trough MEDLINE the studies on occupational lung cancer published in peer-reviews journals in the last 30 years, including reviews of such studies. We selected population case-control and cohort studies conducted in Italy (10-19) and abroad (20-42) which estimated lung cancer risk and/or calculated the population attributable fraction (PAF) of lung cancer associated to occupational exposure. The PAF may be defined as the fraction of disease in the population that would not have occurred if the effect associated with the risk factor of interest were absent (43-45); consequently, it is a measure of the proportion of disease that could be prevented if the exposure to the factor were eliminated.

When not reported in the original article, we calculated PAF from the published data using the formula 100xPEC(OR − 1)/OR (44, 45) where OR is the odds ratio adjusted for potential confounders and PEC is the proportion of cases exposed to a given factor. Although PAF depends on the disease risk, the main determinant of PAF is the prevalence of exposure in the population, which varies between genders and in space and time; this measure is therefore sex-, place-, and period-specific. Since PAF can be estimated only from population-based studies, we selected population-based and hospital-based case-control studies in which the hospital(s) represented the main reference for the population. Only studies with a detailed work history and information on smoking habits, being the major confounder, were included; two studies on non-smokers were also selected.

The selected studies used different methods to evaluate occupational exposure (46-50): 1) job title: subjects that worked in selected occupations/industries known (IARC group 1) to be carcinogenic for the lung (List A) (Tab. 1); 2) job-exposure matrices (JEM): matrices with a wide range of occupations/industries on one axis and a list of agents on the other: every cell contains a number which is a combination of intensity, frequency, and probability of exposure to the specific agent; 3) expert assessment: exposure to specific lung carcinogens is assessed by technicians like occupational hygienists and engineers according to the specific job, intensity, probability, and frequency of exposure.

In this review we included the multi-centre population-based case-control study Environment And Genetics in Lung cancer Etiology (EAGLE) (http://dceg.cancer.gov/eagle) (51); preliminary results on occupational factors have been reported (12). Information on subjects' work histories (held for at least 6 months) and exposure to selected potentially carcinogenic substances through computer assisted personal interview (CAPI) were collected. Occupational exposure is being evaluated in different ways (for the purpose of this review we will consider only point 1):

1 Carcinogen lists: Occupations and industries coded according to the International Standard Classification of Occupations (ISCO 1968), and the International Standard Industrial Clas-

Table 1. Occupations and industries known to present an excess risk of lung cancer (List A)

Industry	Occupation/Process/Chemicals
Agriculture	Vineyard workers using arsenical insecticides (before 1970)
Mining and quarrying	Arsenic, uranium, iron-ore, granite, and asbestos mining; talc mining/milling
Granite production	Cutting, polishing, etc., of granites stones
Ceramic and refractory brick	Ceramic and pottery workers
Asbestos production	Insulating material production
Metals (iron and steel basic industries)	Iron and steel founding
Metals (non-ferrous basic industries)	Copper, zinc, cadmium, alluminium, nickel, chromates, beryllium
Shipbuilding, motor vehicle, railroad equipment manufacturing	Shipyard and dockyard, motor vehicle, railroad manufacture workers
Gas	Coke plant workers and gas production workers
Construction	Insulators and pipe coverers, roofers, asphalt workers
Other	Painters (construction, automotive industry, and other users)

sification of All Economic Activities (ISIC 1971), respectively; then translated into occupations/industries known/suspected (List A/B) to be associated with lung cancer (46, 52).

2 Selected occupations/industries: Occupations/industries not included in List A/B, with a sufficient number of exposed cases.

3 Job-exposure matrix (JEM): Exposure to 16 suspected/known respiratory carcinogens assigned using a JEM developed by IARC (53, 54).

4 Self-reported exposure (frequency, type, intensity) to a check-list of 26 selected lung carcinogens.

Results

Overall we selected 32 studies, 20 population (10-20, 22-25, 27-30, 32, 36, 38), six hospital (24, 31, 33, 34, 37) three mixed (26, 39, 40) case-control studies, two cohort studies (41, 42), and one meta-analysis (35). We report separately the PAFs estimated with different method of exposure assessment for studies conducted in Italy and abroad. The reported results are only among men, because of the low number of women in occupations/industries known/suspected to be carcinogens for the lung.

We identified six Italian studies that used the List A to evaluate occupational exposure to lung carcinogens (Table 2 and Figure 1). Most of the studies were

Table 2. Population attributable fractions for lung cancer for exposure to occupations/industries classified in List A: Italian studies

Author/Year	Area	Period	Sex	PEC%	OR	PAF%
Ronco/1988	Settimo Torinese	1976-80	M	20.7	2.3	11.9
	Rivoli	1976-80	M	16.0	1.4	4.9
Bovenzi/1993	Trieste	1979-81; 1985-86	M	28.8	2.3	16.0
Simonato/2000	Venice/Mestre	1992-94	M	19.2	1.3	4.4*
	Venice/Centro	1992-94	M	24.7	1.0	0.0*
Richiardi/2004	Eastern Veneto	1990-91	M	12.7	2.5	7.8*
	Turin	1991-92	M	23.7	1.9	11.1*
Fano/2004	Civitavecchia	1987-95	M/F	11.1	1.3	2.6*
Consonni/2006	Lombardy	2002-05	M	10.0	1.4	2.8

PEC = Proportion of Exposed Cases
OR = Odds Ratio adjusted for tobacco smoking
PAF = Population Attributable Fraction
* Calculated by us

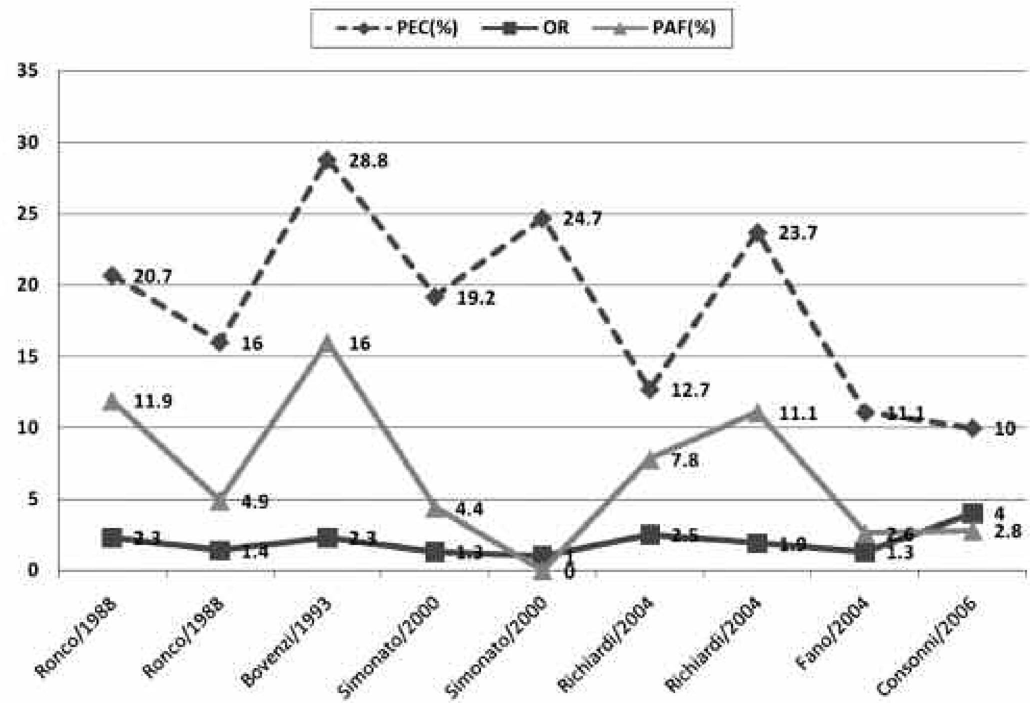

Figure 1. Population attributable fractions for lung cancer for exposure to occupations/industries classified in List A: Italian case-control studies. (PEC= Proportion of Exposed Cases; OR= Odds Ratio adjusted for tobacco smoking; PAF= Population Attributable Fraction)

conducted in Northern Italy in highly industrialized areas. There was a large variability in PAF estimates (0-16%), mainly because of a large variability in the proportion of exposed cases. The largest PAFs were found in the areas near Turin and Trieste. We noted a general tendency towards a decline in the proportion of exposed cases over time (Fig. 1).

In the studies conducted abroad using the same approach an even wider variability was found, with PAFs ranging from 3% to 40% (Tab. 3), reflecting very different patterns of occupational exposures even within the same country; for example, in the USA, in areas with similar industrialization levels the PAFs varied from 3 to 17%. The highest estimate was found in Sweden, with a very high prevalence of workers in iron ore mining. The two studies conducted among nonsmokers reported very low or null PAFs.

The Italian studies which used JEM and expert assessment (Tab. 4), conducted in the highly industrialized areas of Lombardy and Piedmont, found higher estimates of PAFs. This is due to greater specificity (with lower degree of non-differential misclassification) and sensitivity (with larger proportion of exposed cases) of these approaches.

In the studies performed abroad (Tab. 5), the PAF estimates ranged from 4.6 to 27.7%. The largest ones were found in central-eastern Europe where the economy even in recent years was still based on basic industries and agriculture and a less developed occupational hygiene system was present.

Discussion

The aim of this review was to estimate the burden of lung cancer due to occupational exposure among different populations. As expected we found a great variability across populations in different periods. Among Italian studies the largest PAFs were found in areas (Settimo Torinese, Trieste, Turin) with a high prevalence of non-ferrous metal basic industries, shipbuilding, and railroad equipment manufac-

Table 3. Population attributable fractions for lung cancer for exposure to occupations/industries in List A: International studies.

Country	Author/Year	Area	Period	Sex	PEC%	OR	PAF%
USA	Blot/1978	Georgia	1970s	M	20.7	1.6	8.8
USA	Blot/1980	Virginia	1970s	M	28.3	1.7	16.0
USA	Blot/1982	Florida	1970-75	M	21.8	1.4	15.4
USA	Blot/1983	Pennsylvania	1980s	M	23.9	1.9	11.3
Sweden	Damber/1985	Sweden	1980s	M	41.7	8.9*	40.0
China	Levin/1988	Shanghai	1980s	M	13.2	1.4*	3.9
USA	Vineis/1988	Pennsylvania	1974-77	M	43.0	1.4	17.0
		Virginia	1976	M	32.0	1.3	10.0
		Florida	1976-79	M	25.0	1.4	10.0
		New Jersey	1980-81	M	26.0	1.4	11.0
		Louisiana	1979-83	M	16.0	1.2	3.0
Germany	Jockel/1998	Germany	1988-93	M	41.0	1.6	15.4
Europe	Pohlabeln/2000§	Italy, Germany, Sweden, Portugal, Spain, France, UK	1988-94	M	12.0	1.5	4.0*
Europe	Zeka/2006§	Czech Republic, Hungary, Poland, Romania, Russia, Slovakia, UK	1998-02	M	4.0	0.4	-

PEC = Proportion of Exposed Cases
OR = Odds Ratio adjusted for tobacco smoking
PAF = Population Attributable Fraction
* Calculated by us
§ Only non-smokers

Table 4. Population attributable fractions for lung cancer for exposure estimated through Expert Assessments/JEM: Italian studies

Author/Year	Area	Period	Sex	PEC%	OR	PAF%
Berrino/1980	Saronno	1976-77	M	39.5	3.0	26.4
Riboli/1983	Pioltello	1976-79	M	41.7	1.7	16.6
Pastorino/1984	Saronno	1976-79	M	34.3	2.7	21.6*
Ciccone/1988	Settimo Torinese	1976-80	M	50.0	4.1	37.9

PEC = Proportion of Exposed Cases
OR = Odds Ratio adjusted for tobacco smoking
PAF = Population Attributable Fraction
* Calculated by us

turing. It's interesting that in the study of Ronco et al. even in the same area there was a great difference in the PAFs estimates because of the different industrial profiles: foundries, chemical, and rubber industries in Settimo Torinese, mechanical industries in Rivoli.

In the EAGLE study a lower PAF, as a result of a lower frequency of exposure (10%), and a lower OR estimate (1.4), was found. There are several explanations for these finding. First, the study was the most recent, and occupational exposures to carcinogens probably decreased over time (for instance, asbestos use in Italy was banned in 1992). Second, the study found a lower proportion of cases exposed to occupational lung carcinogens (notably, asbestos). This apparently low PAF corresponds, in absolute terms, to a high number of cases: considering that the annual number of lung cancer cases among men in Lombardy is around 5,000 (55, 56), a PAF of 2.8% means that

Table 5. Population attributable fractions for lung cancer for exposure estimated through Expert Assessments/JEM: International studies

Country	Author/Year	Area	Period	PEC%	OR	PAF%
UK	Martischnig/1977	Newcastle	1972-73	28.9	2.4	16.9*
USA	Hinds/1985	Ohio	1980s	5.0	12.6	4.6
UK	Pannet/1985	UK	1980s	54.5	1.4	15.3
USA	Vena/1985	New York	1957-65	36.2	1.2	6.3
Norway	Kvale/1986 §	Norway	1966-78	23.0	2.6	13.3
Norway	Kjuus/1986	Telemark and Vestfold County	1979-83	39.2	2.3	22.2
USA	Schoenberg/1987	New Jersey	1980-81	31.0	1.7*	13.0
Sweden	Damber/1987	Sweden	1980s	13.0	2.5	7.7
USA	Morabia/1992	USA	1980-89	13.5	3.1*	9.2
Greece	Chatzis/1999	Athens	1987-88	11.5	2.9	10-17**
Sweden	Gustavsson/2000	Stockholm	1985-90	41.0*	1.3*	9.5
Western-Europe	Veglia/2007 §	Sweden, Denmark, Norway, Netherlands, UK, France, Germany, Spain, Italy, Greece	1992-98	71.0*	1.3	16.3
Central-Eastern Europe	Bardin-Mikolajczak/2007	Czech Republic, Hungary, Poland, Romania, Russia, Slovakia	1998-01	83.0	1.5	27.7*

PEC = Proportion of Exposed Cases
OR = Odds Ratio adjusted for tobacco smoking
PAF = Population Attributable Fraction
§= Cohort study
* Calculated by us
** Calculated assuming PEC of 5-10%

Table 6. Population attributable fractions for occupational exposure to asbestos in Italian studies

Author/Year	Area	Period	Sex	Exposure	PEC%	OR	PAF%
Pastorino/1984	Saronno	1976-79	M	Expert assessment	16.2	1.9	7.7
Bovenzi/1993	Trieste	1979-81; 1985-86	M	Job titles with definite exposure	28.4	2.0	14.2
				Job titles with definite/possible exposure	51.0	1.6	19.0
Fano/2004	Civitavecchia	1987-95	M	Expert assessment	9.2	3.5	6.6

PEC= Proportion of Exposed Cases
OR= Odds Ratio adjusted for tobacco smoking
PAF= Population Attributable Fraction

more than 100 annual cases are attributable to past exposure to carcinogens.

The International inter-study variability in the PAFs was even wider because of the very different pattern of occupational exposures across countries. For example, in the same period (1980s) we observed one of the lowest PAFs in Shanghai still based on a rural economy, and the largest in Sweden, with a very high proportion of workers in iron ore mining. Even within the same country we found wide variability; for example, in areas with similar industrialization levels in the USA the PAFs varied greatly according to the type of occupational exposure (3-17%). Interestingly, these figures were similar to those estimated using an empirical approach by Doll and Peto in 1981 (1-15%) among workers exposed in the 1970s (57).

Two studies conducted were conducted among non-smokers: one reported a low PAF (39), however, the risk estimate was similar to that of other studies, indirectly confirming that the potential confounding effect of smoking is usually overestimated (58-60). The other one found no excess of risk for exposed workers (40).

Considering the studies based on alternative exposure assessment methods (JEM or expert assessment) we observed higher PAFs; for instance, Ciccone et al. (17) estimated a PAF three times larger than Ronco et al. (11) in the same period and area. This was expected because these methods are more accurate than job's title approach: the greater sensitivity increases the proportion of exposed cases and the greater specificity decreases the non-differential misclassification that is known to bias the risk estimate towards the null, particularly in the current conditions of low exposure (35, 61, 62).

Nevertheless, every method has its own advantages and limits due to its imperfect sensitivity and specificity, so that none of them is universally considered the "gold standard" (48, 49). For example, self-reported exposure can be affected by recall bias, i.e., the greater attitude of cases (or controls) to report exposure to hazardous substances, especially to those (e.g., dusts, solvents) easily perceivable.

However, the different exposure assessment methods are less important than the inter-study variability in affecting PAF variation. In fact, also in the studies based on alternative approaches the largest PAFs were estimated in areas with a high proportion of cases exposed.

Among the international studies the multi-centre study conducted in central-eastern Europe, despite of being the most recent selected, estimated one of the largest PAFs, perhaps due to a less developed economy, based until recently on basic industries, and with probably worse occupational hygiene conditions.

Asbestos is the single occupational agent causing the highest number of lung cancers, particularly in our country where hundreds of thousands of workers have been exposed until the 1992 ban (8, 9). If we consider the studies that evaluated exposure to asbestos in different industries and occupations (Tab. 6), the PAFs ranged from almost 7% to 19%. These figures are similar to those found in other European countries (63). When considering only asbestos production industry, the number of exposed workers is usually very limited: only one study (11) had a number of cases sufficient to calculate lung cancer risk and found a PAF of 2.8%.

We did not report estimates for women because the number of exposed cases is usually very low and the estimates are highly unstable. This is explained by the fact that occupational lung carcinogens were discovered in epidemiology studies conducted mainly among male work-forces. Alternative approaches are therefore necessary to adequately evaluate occupational carcinogenic risks among women.

Conclusions

We have reviewed Italian and international literature to estimate the global burden of lung cancer attributable to occupational exposure. Even considering similar studies we observed very different PAFs that cannot be explained by the different exposure assessment methods, but mainly by the extremely varied proportion of exposed subjects in different populations. This proportion depends partly on time, with a decreasing trend due to the general industrial hygiene improvement and to the introduction of more protective laws for the workers. However, the most important factor is place, because the distribution of occupations/industries involving exposure to lung carcinogens varies greatly across and within countries. In fact, the largest PAFs were estimated in highly industrialized areas with a great prevalence of shipbuilding and railroad equipment manufacturing, metal basic, and chemical industries, with similar estimates even in different countries.

It is important to keep in mind that most of the studies were conducted in areas with a high incidence of lung cancer or where cohort studies had already detected occupational cancer risks. Therefore, caution is required in generalizing these estimates to the whole country.

References

1. WHO. *Revised Global Burden of Disease (GBD) 2002 Estimates*. 2008 [cited February 22, 2008]; Available from: http://www.who.int/healthinfo/bodgbd2002revised/en/index.html

2. Devesa SS, Bray F, Vizcaino AP, Parkin DM. International lung cancer trends by histologic type: male:female differences diminishing and adenocarcinoma rates rising. *Int J Cancer* 2005; 117 (2): 294-9.
3. Driscoll T, Nelson DI, Steenland K, et al. The global burden of disease due to occupational carcinogens. *Am J Ind Med* 2005; 48 (6): 419-31.
4. Fingerhut M, Nelson DI, Driscoll T, et al. The contribution of occupational risks to the global burden of disease: summary and next steps. *Med Lav* 2006; 97 (2): 313-21.
5. Nelson DI, Concha-Barrientos M, Driscoll T, et al. The global burden of selected occupational diseases and injury risks: Methodology and summary. *Am J Ind Med* 2005; 48 (6): 400-18.
6. Steenland K, Burnett C, Lalich N, Ward E, Hurrell J. Dying for work: The magnitude of US mortality from selected causes of death associated with occupation. *Am J Ind Med* 2003; 43 (5): 461-82.
7. Kauppinen T, Toikkanen J, Pedersen D, et al. Occupational exposure to carcinogens in the European Union. *Occup Environ Med* 2000; 57 (1): 10-8.
8. Mirabelli D. [Estimated number of workers exposed to carcinogens in Italy, within the context of the European study CAREX]. *Epidemiol Prev* 1999; 23 (4): 346-59.
9. Mirabelli D, Kauppinen T. Occupational exposures to carcinogens in Italy: an update of CAREX database. *Int J Occup Environ Health* 2005; 11 (1): 53-63.
10. Bovenzi M, Stanta G, Antiga G, Peruzzo P, Cavallieri F. Occupational exposure and lung cancer risk in a coastal area of northeastern Italy. *Int Arch Occup Environ Health* 1993; 65 (1): 35-41.
11. Ronco G, Ciccone G, Mirabelli D, Troia B, Vineis P. Occupation and lung cancer in two industrialized areas of northern Italy. *Int J Cancer* 1988; 41 (3): 354-8.
12. Consonni D, Bertazzi PA, Pesatori AC, et al. Occupational risks for lung cancer in the population-based case-control study "Environmental and Genetic Lung cancer Etiology" (EAGLE) study. 28th International Congress on Occupational Health; Milan (June 11-16, 2006), p. 39.
13. Fano V, Michelozzi P, Ancona C, Capon A, Forastiere F, Perucci CA. Occupational and environmental exposures and lung cancer in an industrialised area in Italy. *Occup Environ Med* 2004; 61 (9): 757-63.
14. Richiardi L, Boffetta P, Simonato L, et al. Occupational risk factors for lung cancer in men and women: a population-based case-control study in Italy. *Cancer Causes Control* 2004; 15 (3): 285-94.
15. Simonato L, Zambon P, Ardit S, et al. Lung cancer risk in Venice: a population-based case-control study. *Eur J Cancer Prev* 2000; 9 (1): 35-9.
16. Berrino F, Crosignani P, Pastorino U, Riboli E, Adami R, Gervasio A. Valutazione del rischio attribuibile alle esposizioni professionali. *Epidemiol Prev* 1980; 10/11: 70-7.
17. Ciccone G, Ronco G, Mirabelli D, et al. Lung tumors and occupational exposure in an industrial area of northern Italy. *Med Lav* 1988; 79 (1): 54-64.
18. Pastorino U, Berrino F, Gervasio A, Pesenti V, Riboli E, Crosignani P. Proportion of lung cancers due to occupational exposure. *Int J Cancer* 1984; 33 (2): 231-7.
19. Riboli E, Bai E, Berrino F, Merisi A. Mortality from lung cancer in an acetylene and phthalic anhydride plant. A case-referent study. *Scand J Work Environ Health* 1983; 9 (6): 455-62.
20. Schoenberg JB, Stemhagen A, Mason TJ, Patterson J, Bill J, Altman R. Occupation and lung cancer risk among New Jersey white males. *J Natl Cancer Inst* 1987; 79 (1): 13-21.
21. Bardin-Mikolajczak A, Lissowska J, Zaridze D, et al. Occupation and risk of lung cancer in Central and Eastern Europe: the IARC multi-center case-control study. *Cancer Causes Control* 2007; 18 (6): 645-54.
22. Blot WJ, Brown LM, Pottern LM, Stone BJ, Fraumeni JF, Jr. Lung cancer among long-term steel workers. *Am J Epidemiol* 1983; 117 (6): 706-16.
23. Blot WJ, Fraumeni JF, Jr. Changing patterns of lung cancer in the United States. *Am J Epidemiol* 1982; 115 (5): 664-73.
24. Blot WJ, Harrington JM, Toledo A, Hoover R, Heath CW, Jr., Fraumeni JF, Jr. Lung cancer after employment in shipyards during World War II. *N Engl J Med* 1978; 299 (12): 620-4.
25. Blot WJ, Morris LE, Stroube R, Tagnon I, Fraumeni JF, Jr. Lung and laryngeal cancers in relation to shipyard employment in coastal Virginia. *J Natl Cancer Inst* 1980; 65 (3): 571-5.
26. Chatzis C, Danaka G, Linos A, Kales SN, Christiani DC. Lung cancer and occupational risk factors in Greece. *J Occup Environ Med* 1999; 41 (1): 29-35.
27. Damber L, Larsson LG. Underground mining, smoking, and lung cancer: a case-control study in the iron ore municipalities in northern Sweden. *J Natl Cancer Inst* 1985; 74 (6): 1207-13.
28. Damber LA, Larsson LG. Occupation and male lung cancer: a case-control study in northern Sweden. *Br J Ind Med* 1987; 44 (7): 446-53.
29. Gustavsson P, Jakobsson R, Nyberg F, Pershagen G, Jarup L, Scheele P. Occupational exposure and lung cancer risk: a population-based case-referent study in Sweden. *Am J Epidemiol* 2000; 152 (1): 32-40.
30. Jockel KH, Ahrens W, Jahn I, Pohlabeln H, Bolm-Audorff U. Occupational risk factors for lung cancer: a case-control study in West Germany. *Int J Epidemiol* 1998; 27 (4): 549-60.
31. Kjuus H, Langard S, Skjaerven R. A case-referent study of lung cancer, occupational exposures and smoking. III. Etiologic fraction of occupational exposures. *Scand J Work Environ Health* 1986; 12 (3): 210-5.
32. Levin LI, Zheng W, Blot WJ, Gao YT, Fraumeni JF, Jr. Occupation and lung cancer in Shanghai: a case-control study. *Br J Ind Med* 1988; 45 (7): 450-8.
33. Morabia A, Markowitz S, Garibaldi K, Wynder EL. Lung cancer and occupation: results of a multicentre case-control study. *Br J Ind Med* 1992 Oct;49(10): 721-7.
34. Vena JE, Byers TE, Cookfair D, Swanson M. Occupation and lung cancer risk. An analysis by histologic subtypes. *Cancer* 1985; 56 (4): 910-7.

35. Vineis P, Thomas T, Hayes RB, et al. Proportion of lung cancers in males, due to occupation, in different areas of the USA. *Int J Cancer* 1988; 42 (6): 851-6.
36. Hinds MW, Kolonel LN, Lee J. Application of a job-exposure matrix to a case-control study of lung cancer. *J Natl Cancer Inst* 1985; 75 (2): 193-7.
37. Martischnig KM, Newell DJ, Barnsley WC, Cowan WK, Feinmann EL, Oliver E. Unsuspected exposure to asbestos and bronchogenic carcinoma. *Br Med J* 1977; 1 (6063): 746-9.
38. Pannett B, Coggon D, Acheson ED. A job-exposure matrix for use in population based studies in England and Wales. *Br J Ind Med* 1985; 42 (11): 777-83.
39. Pohlabeln H, Boffetta P, Ahrens W, et al. Occupational risks for lung cancer among nonsmokers. *Epidemiology* 2000; 11 (5): 532-8.
40. Zeka A, Mannetje A, Zaridze D, et al. Lung cancer and occupation in nonsmokers: a multicenter case-control study in Europe. *Epidemiology* 2006; 17 (6): 615-23.
41. Kvale G, Bjelke E, Heuch I. Occupational exposure and lung cancer risk. *Int J Cancer* 1986; 37 (2): 185-93.
42. Veglia F, Vineis P, Overvad K, et al. Occupational exposures, environmental tobacco smoke, and lung cancer. *Epidemiology* 2007; 18 (6): 769-75.
43. Levin ML. The occurrence of lung cancer in man. *Acta Unio Int Contra Cancrum* 1953; 9 (3): 531-41.
44. Bruzzi P, Green SB, Byar DP, Brinton LA, Schairer C. Estimating the population attributable risk for multiple risk factors using case-control data. *Am J Epidemiol* 1985; 122 (5): 904-14.
45. Miettinen OS. Proportion of disease caused or prevented by a given exposure, trait or intervention. *Am J Epidemiol* 1974; 99 (5): 325-32.
46. Ahrens W, Merletti F. A standard tool for the analysis of occupational lung cancer in epidemiologic studies. *Int J Occup Environ Health* 1998; 4 (4): 236-40.
47. Bouyer J, Hemon D. Retrospective evaluation of occupational exposures in population-based case-control studies: general overview with special attention to job exposure matrices. *Int J Epidemiol* 1993; 22 Suppl 2: S57-64.
48. 't Mannetje A, Kromhout H. The use of occupation and industry classifications in general population studies. *Int J Epidemiol* 2003; 32 (3): 419-28.
49. Teschke K, Olshan AF, Daniels JL, et al. Occupational exposure assessment in case-control studies: opportunities for improvement. *Occup Environ Med* 2002; 59 (9): 575-93; discussion 94.
50. McGuire V, Nelson LM, Koepsell TD, Checkoway H, Longstreth WT, Jr. Assessment of occupational exposures in community-based case-control studies. *Annu Rev Public Health* 1998; 19: 35-53.
51. Landi MT, Dracheva T, Rotunno M, et al. Gene expression signature of cigarette smoking and its role in lung adenocarcinoma development and survival. *PLoS ONE* 2008; 3 (2): e1651.
52. Mirabelli D, Chiusolo M, Calisti R, et al. [Database of occupations and industrial activities that involve the risk of pulmonary tumors]. *Epidemiol Prev* 2001; 25 (4-5): 215-21.
53. Berrino F, Richiardi L, Boffetta P, et al. Occupation and larynx and hypopharynx cancer: a job-exposure matrix approach in an international case-control study in France, Italy, Spain and Switzerland. *Cancer Causes Control* 2003; 14 (3): 213-23.
54. Ferrario F, Continenza D, Pisani P, Magnani C, Merletti F, Berrino F. Description of a job-exposure matrix for sixteen agents which are or may be related to respiratory cancer. In: Hogstedt C, Reuterwall C, editors. Progress in occupational epidemiology: proceedings of the Sixth International Symposium on Epidemiology in Occupational Health, Stockholm, Sweden, 16-19 August 1988. Amsterdam; New York: Excerpta Medica; New York, NY, USA: Sole distributors for the USA and Canada, Elsevier Science Pub. Co.; 1988. p. xii, 397 p.
55. Inghelmann R, Grande E, Francisci S, et al. Regional estimates of lung cancer burden in Italy. *Tumori* 2007; 93 (4): 360-6.
56. AIRT Working Group. Italian cancer figures-report 2006: 1. Incidence, mortality and estimates. *Epidemiol Prev* 2006; 30 (1 Suppl 2): 8-10, 2-28, 30-101 passim.
57. Doll R, Peto R. The causes of cancer: quantitative estimates of avoidable risks of cancer in the United States today. *J Natl Cancer Inst* 1981; 66 (6): 1191-308.
58. Axelson O. Confounding from smoking in occupational epidemiology. *Br J Ind Med* 1989; 46 (8): 505-7.
59. Blair A, Stewart P, Lubin JH, Forastiere F. Methodological issues regarding confounding and exposure misclassification in epidemiological studies of occupational exposures. *Am J Ind Med* 2007; 50 (3): 199-207.
60. Richiardi L, Forastiere F, Boffetta P, Simonato L, Merletti F. Effect of different approaches to treatment of smoking as a potential confounder in a case-control study on occupational exposures. *Occup Environ Med* 2005; 62 (2): 101-4.
61. Simonato L, Vineis P, Fletcher AC. Estimates of the proportion of lung cancer attributable to occupational exposure. *Carcinogenesis* 1988; 9(7): 1159-65.
62. Vineis P, Simonato L. Proportion of lung and bladder cancers in males resulting from occupation: a systematic approach. *Arch Environ Health* 1991; 46 (1): 6-15.
63. Albin M, Magnani C, Krstev S, Rapiti E, Shefer I. Asbestos and cancer: An overview of current trends in Europe. *Environ Health Perspect* 1999; 107 Suppl 2: 289-98.

Accepted: May 15th 2008
Correspondence: Prof. Pier Alberto Bertazzi
Department of Occupational and Environmental Health
Via San Barnaba, 8 - 20122 Milano, Italy
Tel. +39-02-503-20100
Fax +39-02-503-20126
E-mail: Pieralberto.Bertazzi@unimi.it; www.actabiomedica.it