



OPEN Past exposure to PM₁₀ and lung cancer risk in the EAGLE case–control study

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Within the EAGLE population-based case-control study, the present study aims to integrate previous analyses which suggested an increased lung cancer risk associated with particulate matter $\leq 10 \mu\text{m}$ (PM₁₀) exposure estimated 2–5 years before diagnosis (year 2000), by considering pollutant levels estimated 12–15 years before diagnosis (year 1990), i.e., in a potentially more relevant time window. Odds ratios (OR) and 95% confidence intervals (CI) were calculated through multivariate unconditional logistic regression. Mean PM₁₀ levels were higher in 1990 than in 2000 (68 vs. 46.6 $\mu\text{g}/\text{m}^3$). Contrary to what we previously observed, among 1,665 cases and 1,808 controls we found no association between 1990 PM₁₀ concentrations and lung cancer risk (OR: 0.96, 95%CI: 0.75–1.24). We further confirmed this difference also considering exposure from the two years combined, mutually adjusting for one another (0.89, 0.87–1.00 in 1990 and 1.49, 1.06–2.08 in 2000). The observed differences might be related to several factors: distinct methodologies used to estimate exposure, coarser granularity of 1990 exposure estimates, dissimilar levels in pollutant concentrations. However, our results might also suggest a greater relevance of more recent exposures in the carcinogenic process, thus contributing to the intriguing hypothesis that air pollution might act as a promoter of cancer development.

Keywords Lung cancer, Air pollution, PM₁₀, Carcinogenesis, Environmental health, Case-control study

Lung cancer is the leading cause of cancer morbidity and mortality worldwide, with almost 2.5 million new cases in 2022 which represent about 12% of all cancer diagnoses¹. It is also the leading cause of cancer deaths globally (18.7%)² having a poor prognosis, with a 5-year survival rate that tends to be below 20% in most countries³. Incidence and mortality for this cancer are very different between countries, depending mainly on the distribution of smoking habits across populations⁴. Tobacco smoking is by far the main risk factor for lung cancer, but other determinants do play an important role, including environmental tobacco smoke, many occupational agents, and radon decay products⁵. Investigations on two very large study populations (i.e., the American Cancer Society [ACS] cohort and the Harvard Six Cities study) found that also long-term exposure to air pollution could increase the risk for lung cancer mortality^{6–9}. In the ACS cohort, exposure to particulate pollution was considered as the median of a 5-year period occurring one to ten years preceding death, while in the Harvard Six Cities study, 1-year to 5-year lagged moving averages before death were used. In 2013, the International Agency for Research on Cancer (IARC) classified outdoor air pollution as a Group 1 carcinogen based primarily on evidence for lung cancer¹⁰. After the IARC evaluation, other studies reported positive associations between air pollution and lung cancer. In 2014, a meta-analysis summarizing 18 studies (17 cohort studies and one case-control study, mostly from Europe and the USA) estimated meta-relative risks for lung cancer of 1.09 (95% confidence interval [95%CI]: 1.04–1.14) and 1.08 (95%CI: 1.00–1.17) associated to a 10 $\mu\text{g}/\text{m}^3$ increase in concentrations of particulate matter with diameter $\leq 10 \mu\text{m}$ (PM₁₀) and $\leq 2.5 \mu\text{m}$ (PM_{2.5}), respectively¹¹. These represent two different fractions of particulate pollution (with PM_{2.5} being itself a fraction of PM₁₀) and, at least in urban areas, share most of the same sources (i.e., nonindustrial combustion and road transport)¹². Kim et al., in 2018, conducted a meta-analysis including 30 cohort studies from the USA, Europe, and China. The summary relative risks (RR) for lung cancer mortality for 10 $\mu\text{g}/\text{m}^3$ increase in PM₁₀ and PM_{2.5} concentrations were 1.07 (95%CI: 1.03–1.11) and 1.14 (95%CI: 1.07–1.21), respectively¹³. A more recent meta-analysis selected 15 high quality studies published between 2004 and 2019 to summarize the evidence on the association between particulate matter and lung cancer risk. The authors estimated summary relative risks of

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1.23 (95%CI: 1.05–1.40) and 1.16 (95%CI: 1.09–1.23) for an increase of 10 $\mu\text{g}/\text{m}^3$ in PM_{10} and $\text{PM}_{2.5}$ exposure, respectively¹⁴. Also a study based on a large US cohort of adults (i.e., 1.5 million subjects from the National Health Interview Surveys conducted in 1986–2014, with mortality linkage through 2015) pointed out the role of air pollution in lung cancer mortality (HR: 1.13, 95%CI: 1.00–1.26, per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$)¹⁵.

We previously conducted a study to evaluate the association between exposure to PM_{10} and lung cancer risk within the Environment And Genetics in Lung cancer Etiology (EAGLE) population-based case-control study, performed in Lombardy, North-West Italy in 2002–2005. We found suggestive evidence of a positive association, with an odds ratio per 10 $\mu\text{g}/\text{m}^3$ of 1.28 (95%CI: 0.95–1.72). Average PM_{10} levels for year 2000 (i.e., 2–5 years before diagnosis) were estimated at each residential address from models integrating land-use regression (LUR) methodologies and aerosol optical depth (AOD) data from the Moderate Resolution Imaging Spectroradiometer (MODIS) satellite¹⁶. Several solid tumors occur many years or decades after exposure to carcinogenic agents. Therefore, starting from our earlier study, we integrated it by reconstructing pollutant levels estimated 12–15 years before diagnosis (year 1990), i.e., in a potentially more relevant time window from an etiological point of view, with the aim to deepen the knowledge on the relationship between lung cancer risk and long-term exposure to PM_{10} . We could not move further away in time because of the unavailability of data from emission sources before 1990.

Materials and methods

The EAGLE study

EAGLE is a population-based case-control study conducted to investigate genetic and environmental risk factors for lung cancer, for which details can be found at the National Cancer Institute website¹⁷. Briefly, 216 municipalities belonging to five Lombardy areas were included: Brescia, Milan, Monza, Pavia, and Varese (Fig. S1). Two-thousand and ninety-nine incident lung cancer cases (participation rate: 86.6%) were recruited from April 2002 to June 2005 among subjects admitted to 13 hospitals, mostly located in the Milan metropolitan area. Two-thousand one-hundred and twenty healthy controls (participation rate: 72.4%) were randomly selected from the general population and frequency matched to lung cancer cases by gender, area, and age. Subjects of the study were of both genders, resident in one of the 216 municipalities, and with age between 35 and 79 years¹⁸. Informed consent was obtained from all individual participants included in the study. All participants signed informed consent regarding publishing their data as aggregate results of the study (single participants are not identifiable). All methods were performed in accordance with the relevant guidelines and regulations.

For each study subject, information on factors associated with lung cancer, including smoking, dietary habits, and occupational history were collected, and blood samples were taken.

Subjects' addresses were translated into spatial coordinates using the web tool GPS Visualizer¹⁹. Using QGIS²⁰ all subjects were subsequently georeferenced into their cell of residence and assigned the corresponding estimated PM_{10} annual average value for year 1990.

Exposure assessment

PM_{10} concentrations for the year 1990 were reconstructed by an Air Quality Modelling System (AQMS) based on the Flexible Air quality Regional Model (FARM)^{21,22} that considers the processes involving pollutants in the atmosphere, e.g., chemical reactions, transport, dispersion and deposition^{23,24}. A detailed description of the adopted AQMS is reported in the Supplementary Material (in particular, Fig. S2 reports the AQMS scheme). FARM is the main component of the MINNI system, one of the models contributing to the Copernicus regional air quality production systems. It has been validated and compared with other similar models by numerous verification activities²¹. The air quality simulations have been performed considering two nested computational domains covering Northern Italy (with 9 km grid spacing) and Lombardy region (with 3 km grid spacing) respectively (Fig. S3).

The FARM model was coupled with the meteorological model WRF, which is a consolidated reference meteorological modelling system²⁵. WRF was applied on 3 nested computational domains (Fig. S4) covering continental Europe and central Mediterranean, Northern Italy and Lombardy respectively (Fig. S3). Model results have been compared with meteorological observations available in Lombardy for the target period to verify the reliability of the meteorological reconstruction (Fig. S5–S6).

The Italian (Istituto Superiore per la Protezione e la Ricerca Ambientale, 2022) and the MACCity (ECCAD) emission inventories have been processed by the Emission treatment sub-system (Fig. S2) to provide the time-varying emission data needed by FARM. Fig. S7 shows hourly NO emission fluxes for a January 1990 weekday at 8:00 AM over Northern Italy and Lombardy produced by the Emission treatment sub-system. The variation recorded by air pollutant emissions from 1990 to 2010 and the contribution attributable to the human activity sectors are illustrated in Fig. S8, highlighting the decline of energy and industrial production emissions due to the occurred de-industrialization and to industrial emissions control measures. While SO_2 and NO_x emissions have been reduced by about 89% and 48% respectively from 1990 to 2010, PM_{10} showed a 16% only reduction due to the increased contribution of non-industrial combustion (mainly due to wood burning for residential heating), partially compensating the decrease of emissions from the industrial and transport sectors. The air quality boundary conditions were provided by the System for Integrated modelling of Atmospheric composition (SILAM) continental scale retrospective air quality reconstruction²⁶.

PM_{10} concentrations over the Lombardy region have been then computed and stored with hourly time resolution. Fig. S9 and S10 show the yearly average concentration field and the comparison between observed and predicted levels at selected stations, confirming the capability of the modelling system to reconstruct the seasonal variability of PM_{10} levels.

Mean annual PM_{10} levels for the year 2000, which have been used for comparison and adjustment (see below), had been estimated at each subject's residential address through a hybrid spatial-temporal model that

integrates a LUR model and satellite measurements of AOD²⁷. A complete description of the methods already applied to the EAGLE study population can be found in Consonni et al.¹⁶.

Statistical analysis

Analyses were performed only on subjects with a complete history of tobacco smoking and who had not changed their residence since 1980. Odds ratios (OR) and 95% confidence intervals (CI) were calculated through multivariable unconditional logistic regression^{28,29}. Adjustment variables were selected a priori, either because they were matching variables or because they were plausibly related to both the exposure and the outcome at study, thus acting as potential confounders. For each analysis, we fitted two main models with additional levels of adjustment. Model 1, adjusted for the matching variables: gender, age (categorical, nine levels) and area (categorical, five levels) education level (none, elementary, middle, high, university), and smoking variables: ever smoked cigarettes, number of pack-years (in linear, quadratic and cubic transformations), years since quitting (categorical, eight levels), ever smoking other types of tobacco (i.e. cigars, cigarillos, pipe), and exposure to environmental tobacco smoking (in childhood, at work, or within the family). Model 2, further adjusted for occupational exposure to carcinogens (asbestos, respirable crystalline silica, polycyclic aromatic hydrocarbons, diesel motors exhausts and nickel/chromium compounds) and other factors possibly associated with lung cancer (assumption of red and processed meat³⁰, fruit and vegetables³¹). In the present study we report results from Model 2: those deriving from model 1 can be found in the Supplementary Material. Several steps of analysis were performed. First, the association between PM₁₀ exposure and lung cancer risk was assessed using exposure estimates for the year 1990, also evaluating its potential for nonlinearity by using cubic splines, with knots at the 25th, 50th, and 75th percentiles of the pollutant distribution. As a sensitivity analysis, we also performed this model in never and former smokers only (trying to rule out the effect of the most relevant carcinogen we have information on) and verified effect modification between smoking status and PM₁₀. Second, results from the first analysis were compared to those obtained using exposure estimates for the year 2000 and already published¹⁶. Third, the two sets of exposure values (i.e., annual means for 1990 and 2000) were considered together in the same model. In the above analyses, where exposure levels are considered as a continuous variable, results are expressed per 10 µg/m³ increase in PM₁₀ concentration and reported for the entire study sample, the Milan area alone and the other four areas combined. Finally, to try to improve the resemblance between the two models used to estimate air pollution levels in the two time points, we rescaled the spatial resolution of the exposure estimates for the year 2000 (available at each subjects' residential address) to the same 3 × 3 km grid used for the year 1990 (i.e., by averaging exposure values estimated in 2000 for each subject who resided within each 3 × 3 km cell), assigned the annual average of exposure in each cell to each study subject (according to his/her residential address), and re-ran the models performed to assess the association between PM₁₀ and lung cancer risk in the year 2000.

Results

Out of 4,219 subjects (2,099 cases, 2,120 controls), information was available for 4,060 (1,944 cases, 2,116 controls). Sixty-seven subjects were eliminated, as seven of them (3 cases, 4 controls) lacked data on active cigarette smoking, and 60 (35 cases, 25 controls) had no information on passive smoking. From the remaining 3,993 subjects (1,905 cases, 2,088 controls), 3,473 (1,665 cases and 1,808 controls) satisfied our inclusion criteria (i.e., complete history of tobacco smoking and fixed residence since 1980). The subjects included (both cases and controls) were a bit older and had slightly lower education than the excluded ones. In general, there were no substantial differences between cases and controls comparing included vs. excluded subjects (Tables S1–S3).

Most subjects were resident in Milan (2,411), followed by Brescia (400), Varese (258), Monza (204) and Pavia (200). Compared to controls, cases had a higher proportion of males, were slightly older and had lower educational levels. They also had a higher percentage of current smokers (49.8% vs. 24.4%) and a higher number of mean cigarette pack-years. More than 90% of both cases and controls were exposed to secondhand smoking. Adenocarcinoma was the most common morphology (41.1%), followed by squamous cell carcinoma (26%). Most frequent lung cancer stages were IIIA and IV (Table 1).

As regards air pollution exposure, annual 1990 average levels showed large differences when comparing Milan to the other areas (Fig. 1a), with a delta of about 30 µg/m³ between the first and second most polluted areas (80.7 vs. 53.3 µg/m³ as PM₁₀ annual average). When looking at the pollutant mean levels for the year 2000, the different areas showed similar concentrations (Fig. 1b). Overall, median PM₁₀ levels were higher in 1990 than in 2000 (79.1 vs. 47.8 µg/m³, p-value from Wilcoxon signed-rank test < 0.001), even if the distribution of the exposure between the two years was quite similar until the 25th percentile (47.7 in 1990 vs. 44.5 µg/m³ in 2000) (Table 2).

No association was observed between PM₁₀ concentrations in 1990 and lung cancer risk, neither in the overall population, nor separating Milan from the other areas (Table 3A). Analyses among never and former smokers (considered both as separate and conjunct categories) returned comparable findings (Tables S4–S6) and no formal interaction between smoking status and PM₁₀ concentrations was detected. Even investigation of possible nonlinear associations did not show excess in risk (Fig. S11). These results differ from what had been observed considering exposure in 2000 (Table 3B), where increased risks were reported in both overall and stratified analyses. These differences were even more clear-cut in models considering the two years of exposure together (Table 3C): this was evident both in the entire population, where OR was 0.89 (95%CI: 0.87–1.00) in 1990 and 1.49 (1.06–2.08) in 2000, and when limiting the analysis to the Milan area [0.87 (0.76–1.00) vs. 1.87 (1.17–3.00), respectively].

Similar results were observed in models adjusting for fewer confounders (Table S7). Positive associations considering exposure in the year 2000 were observed also after rescaling PM₁₀ estimates to a less fine spatial resolution (3 × 3 km, i.e., the same of the year 1990) (Table S8).

	Cases		Controls		Total	
	No.	%	No.	%	No.	%
Total	1,665	100	1,808	100	3,473	100
Sex						
Male	1,318	79.2	1,368	75.7	2,686	77.3
Female	347	20.8	440	24.3	787	22.7
	$p = 0.014^*$					
Age (years)						
Mean (SD)	64.4	(8.1)	63.6	(8.2)	64.0	(8.2)
	$p = 0.004^{**}$					
Category						
35–39	8	0.5	11	0.6	19	0.6
40–44	8	0.5	10	0.6	18	0.5
45–49	35	2.1	44	2.4	79	2.3
50–54	100	6.0	106	5.9	206	5.9
55–59	173	10.4	246	13.6	419	12.1
60–64	291	17.5	317	17.5	608	17.5
65–69	371	22.3	424	23.5	795	22.9
70–74	392	23.5	385	21.3	777	22.4
75–79	287	17.3	265	14.7	552	15.9
	$p = 0.073^*$					
Area of residence						
Milan	1,129	67.8	1,282	71.0	2,411	69.4
Monza	112	6.7	92	5.1	204	5.9
Brescia	196	11.8	204	11.3	400	11.5
Pavia	104	6.3	96	5.3	200	5.8
Varese	124	7.5	134	7.4	258	7.4
	$p = 0.115^*$					
Education level						
None	99	6.0	77	4.3	176	5.1
Elementary	665	40.0	512	28.3	1,177	33.9
Middle	470	28.2	526	29.1	996	28.7
High	345	20.8	484	26.8	829	23.9
University	86	5.2	209	11.6	295	8.5
	$p < 0.001^*$					
Cigarette smoking						
Never	113	6.8	582	32.2	695	20.0
Former (> 6 months)	724	43.5	785	43.4	1,509	43.5
Current	828	49.8	441	24.4	1,269	36.5
	$p < 0.001^*$					
Cigarette pack-years						
Mean (SD)	36.1	(19.5)	14.9	(18.3)	31.2	(28.9)
	$p < 0.001^{**}$					
Secondhand smoking						
Never	93	5.6	155	8.6	248	7.1
Ever	1,572	94.4	1,653	91.4	3,225	92.9
	$p = 0.001^*$					
Lung cancer morphology						
Adenocarcinoma	684	41.1				
Squamous cell carcinoma	432	26.0				
Large cell carcinoma	74	4.4				
Non-small cell carcinoma	173	1.04				
Small cell carcinoma	170	10.2				
Other	57	3.4				
Not available	75	4.5				
Lung cancer stage						
In situ	1	0.1				
Continued						

	Cases		Controls		Total	
	No.	%	No.	%	No.	%
IA	151	9.1				
IB	164	9.9				
IIA	122	7.3				
IIB	94	5.7				
IIIA	301	18.1				
IIIB	157	9.4				
IV	631	37.9				
Not available	44	2.6				

Table 1. Characteristics of the study population. * Pearson’s chi-squared test. ** Student’s t-test.

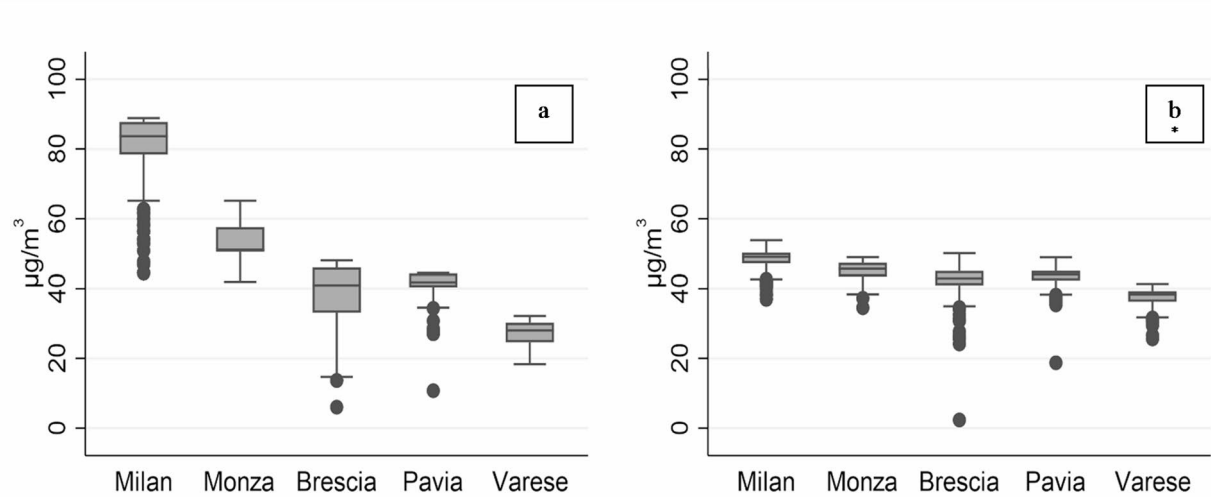


Fig. 1. Distribution of PM₁₀ concentrations by area, 1990 (a) and 2000 (b) (asterisk: adapted from Consonni et al.¹⁶).

Statistics	1990	2000*
Minimum	6.0	2.3
25th percentile	47.7	44.5
Mean	68.0	46.6
Median	79.1	47.8
75th percentile	85.6	49.9
Maximum	88.8	53.8
SD	21.3	4.4

Table 2. PM10 concentrations in the overall population. *See Consonni et al.¹⁶.

Discussion

In a large case-control study with thorough control of major confounders, we did not observe associations between lung cancer risk and air pollution values estimated as annual average for the year 1990, i.e., 12–15 years before diagnosis. Comparable findings were confirmed in the subgroup of never and former smokers. On the other hand, previously reported results in the same population had suggested an increased risk for exposures closer in time to the year of diagnosis (i.e., 2000)¹⁶. We further confirmed this difference not only by comparing the results from the two years but also by considering the two exposures combined, mutually adjusting for one another.

The observed differences might be related to several factors. First, distinct methodologies were used to estimate exposure: FARM chemical transport model was used to estimate PM₁₀ in 1990²¹ while PM₁₀ estimates for the year 2000 were derived from a hybrid spatial-temporal model²⁷. Second, the granularity of 1990 exposure

			A		B*		C			
			1990		2000		1990		2000	
Area	Cases	Controls	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Milan	1,129	1,282	0.94	0.84–1.06	1.51	0.99–2.31	0.87	0.76–1.00	1.87	1.17–3.00
Others	536	526	0.96	0.75–1.24	1.17	0.76–1.82	0.88	0.65–1.19	1.33	0.78–2.27
Total	1,665	1,808	0.94	0.85–1.05	1.28	0.95–1.72	0.89	0.87–1.00	1.49	1.06–2.08

Table 3. Long-term exposure to PM₁₀ and risk of lung cancer per increment of 10 µg/m³ in year 1990 (A), 2000 (B*), and considering both years together (C) (unconditional logistic regression models adjusted for matching variables, education level, smoking variables, occupational exposure to carcinogens and other factors possibly associated with lung cancer). *See Consonni et al.¹⁶.

estimates was coarser than in 2000. For this reason, we rescaled the spatial resolution of exposure estimates in 2000 to a coarser definition (3 × 3 km) and obtained results that were comparable to those from the old analysis. Third, dissimilar levels in pollutant concentrations in the two time periods might also justify the observed difference in air-pollution related lung cancer risk, although the direction of the association is counterintuitive: if we compare PM₁₀ concentration levels, we observe that the average pollutant levels in 1990 were 46% higher than in 2000. This phenomenon is particularly evident in the Milan area, where PM₁₀ levels markedly decrease in the timespan we are considering. Fourth, we might look at our results within the greater framework of tumorigenesis, which was proposed to occur as a two-step process: i.e., the first one inducing mutations in healthy cells, and the second one triggering cancer development³². Our results might thus support a greater relevance of more recent exposures, especially when considering the two exposures combined. To this regard, it is interesting to note that a recent paper by Hill and colleagues provided combined results from a plethora of observational, in vivo, and in vitro studies to support the hypothesis that “*environmental particulate matter measuring ≤ 2.5 µm [...] promotes lung cancer by acting on cells that harbour pre-existing oncogenic mutations in healthy lung tissue*”³³. In addition, in one of the studies they performed on about 250 female lung cancer cases, they observed an association with lung cancer risk when considering 3-year PM_{2.5} cumulative exposure, while this association was not evident after 20-year exposure to the same pollutant.

Several other studies investigated the association between long-term air pollution exposure and lung cancer. Starting from the studies evaluated by the IARC, Hamra et al. conducted a large meta-analysis including 18 studies from different countries in Europe and North America. Data on PM₁₀ were available for nine studies (five in North America, three in Europe and one in New Zealand). Overall, a positive association was observed for PM₁₀ (RR: 1.08; 95% CI: 1.00–1.17), with mean levels ranging from 8.3 to 51 µg/m³¹¹. Looking in more detail at the three studies conducted in Europe,

the Multicenter ESCAPE study investigated the effects of long-term PM₁₀ exposure on lung cancer incidence, using data from 14 cohorts. The enrollment years ranged from 1985 to 2005. Air pollution concentrations at the baseline residential addresses of the study subjects were back-extrapolated using land-use regression models applied to pollution data collected between 2008 and 2011 (i.e., after the study period). Back-extrapolated PM₁₀ levels ranged from about 5 to 90 µg/m³, with the highest levels estimated in Italy and Greece. The pooled analysis showed an association between the risk of lung cancer and increasing PM₁₀ concentrations (HR: 1.22; 95% CI: 1.03–1.45 per 10 µg/m³)³⁴.

The English study followed up a national cohort from 2003 to 2007 and observed positive associations for an interquartile range (IQR) increase in PM₁₀ (HR: 1.03; 95% CI: 0.98–1.08), using exposure data in 2002 (1–5 years before death) and adjusting for smoking status, cigarettes/day and income³⁵. PM₁₀, estimated from emission-based models, ranged from 12.6 to 29.8 µg/m³.

The mortality of a small cohort of women enrolled between 1985 and 1994 was examined through 2008 in Germany. PM₁₀ in the years 1985–1994 was derived from total suspended particles (TSP, applying a coefficient of 0.71) measured by fixed monitoring sites. An increase of 7 µg/m³ in PM₁₀ was associated with an increased HR of 1.84 (95%CI: 1.23–2.74), in models adjusted for education and smoking status³⁶.

Among the five US studies included in the meta-analysis by Hamra and colleagues, the Adventist Health Study on Smog (ASHMOG) followed up for cancer incidence (1977–1992) a large cohort of 6,338 non-smoking Californian adults. PM₁₀ levels were derived from TSP from 1972 to 1987 and subsequently directly measured through fixed-site monitoring stations. PM₁₀ ranged from 0 to 85 µg/m³ with mean values of 51.0 µg/m³. Incident lung cancer in males was positively associated with an IQR increase (24 µg/m³) in PM₁₀ mean concentrations (RR: 5.21, 95%CI: 1.94–13.99, adjusted by cigarette pack-years, education, and alcohol)³⁷.

A cohort study performed by the American Cancer Society within the Cancer Prevention Study (ACS-CPS-II) examined the association between air pollution and mortality among over 400,000 people enrolled in 1982–1998. Mean PM₁₀ concentration derived from fixed monitoring stations in the enrollment period was 28.8 µg/m³. Unfortunately, numerical results for PM₁₀ were not available, and a relative risk slightly greater than 1.00 in the period 1987–1996 (with 95%CI including the null value) could be derived only by looking at one of the paper figures³⁸.

The association between PM₁₀ exposure and cancer mortality (1985–2000) was investigated in about 40,000 workers employed in the U.S. trucking industry. PM₁₀ annual average exposures were determined for 1985 through 2000 from a model using spatial smoothing and geographical information system-based covariates. The average exposure during the study period was 26.8 µg/m³. A HR for lung cancer of 1.08 (95%CI: 0.91–1.30) was estimated per 10 µg/m³. No data on smoking were available³⁹.

The California teachers Study (TCS) involved a large cohort of women followed up for mortality (1997–2005)⁴⁰. Monthly average PM₁₀ concentrations were calculated from fixed-site monitors for the period 1996–2005. PM₁₀ estimates ranged from 9.19 to 82.64 µg/m³ (mean: 29.21). The HR per 10 µg/m³, adjusted for smoking status, pack-years, body mass index, alcohol, passive smoking, dietary fat, fiber and calories, was 0.93 (95%CI: 0.81–1.07).

The relationship between lung cancer incidence and long-term residential exposure to PM₁₀ was also evaluated within the Nurses' Health Study, another large cohort of women followed up from 1994 to 2010⁴¹. PM₁₀ ranged from 3.17 to 74.79 µg/m³. Exposure was defined as the time-varying cumulative PM₁₀ average experienced in the previous 72-months. The HR per 10 µg/m³, adjusted for income, (active and passive) smoking and dietary variables, was 1.04 (95%CI: 0.95–1.14).

Finally, in the New Zealand Census-Mortality study, records from the 1996 national census were probabilistically linked to mortality data (1996–1999)⁴². Average PM₁₀ exposure at 1996 census were estimated using land use regression models and ranged from 0 to 30 µg/m³. The OR per 10 µg/m³ of PM₁₀, adjusted for ethnicity, social deprivation, income, education, and smoking status was 1.14 (95%CI: 1.05–1.23) among subjects who had not changed residence since 1991.

In summary, the abovementioned studies return a heterogeneous picture, where different time windows of exposure are investigated, concentration levels cover a quite wide range of values, and results are often characterized by some uncertainty, notwithstanding the overall interpretation of the findings that point towards an increasing trend in risk.

Following the IARC evaluation other studies were published.

The Nation-wide Dutch Environmental Longitudinal Study (DUELS) examined the mortality (2004–2011) of a cohort of more than 7 million subjects⁴³. Applying land-used regression models, annual mean PM₁₀ concentrations in 2001 were derived. The median PM₁₀ concentrations was 29 µg/m³. The HR, adjusted for age, sex, marital status, region of origin, household income, per 10 µg/m³ increase in PM₁₀ was 1.26 (95%CI: 1.21–1.30). No information on smoking and diet was available.

In a multi-cohort Swedish study, high-resolution dispersion models were used to estimate annual mean concentrations of PM₁₀ at individual address during each year of follow-up (1990–2011), and moving averages were calculated for the time-windows 1–5 years and 6–10 years preceding the outcomes of interest (i.e., natural and cause-specific deaths). No associations were observed between PM₁₀ exposure (range: 6.3–41.9 µg/m³) and lung cancer mortality, in models adjusted for sex, calendar year, sub-cohort, smoking status, alcohol consumption, physical activity, marital status, socioeconomic status, educational level, and occupation⁴⁴.

Moving to lung cancer incidence, several studies were conducted in South Korea. A large cohort study included more than 6.5 million subjects from the Korean National Health Insurance Service (NHIS) database for 2006–2007, who were linked to Korea Central Cancer Registry data to confirm lung cancer incidence for 2006–2013. Individual exposure to PM₁₀ was assessed as five-year average concentrations predicted at subjects' district-specific home addresses for 2002–2007 via a geo-statistical model (mean: 55.8 µg/m³). An increased risk in lung cancer incidence (comparing the upper vs. the lower quartile of exposure) was estimated only for adenocarcinoma in current male smokers (HR: 1.14, 95%CI: 1.03–1.25, in models adjusted for age, gender, income, BMI, pack-year, history of COPD, interstitial lung disease, lung disease due to external factor, physical activity and alcohol consumption)⁴⁵. Another NHIS-based study was conducted in the Seoul metropolitan area, where about 83,000 people were followed up for 2007–2015. PM₁₀ exposure was estimated predicting district-specific annual-average concentrations (mean: 56.2 µg/m³). HRs for lung cancer incidence ranged from 1.05 (95%CI: 0.81–1.36) to 1.14 (95%CI: 0.84–1.54) considering either a 1-year or 5-year exposure average, respectively⁴⁶. A further update of this study was provided, taking also advantage of improved exposure assessment: about 2 million people without history of lung cancer in 2002–2006 were selected from the NHIS database. Lung cancer incident cases were identified up to 2016, and PM₁₀ concentration levels were estimated as 5-year averages at subjects' residential addresses geocoded on a 100-m grid through a prediction model. PM₁₀ levels ranged from 28.6 to 100.7 µg/m³ and were not associated with increased lung cancer risk, regardless of the various adjustments applied, which included both individual and areal covariates⁴⁷.

The potential of the UK Biobank was exploited to investigate whether air pollution and genetic factors could jointly contribute to incident lung cancer. Almost 460,000 participants aged 40–69 years, recruited between 2006 and 2010, and without previous cancer at baseline, were included. PM₁₀ concentrations at residential address were estimated applying land-use regression models: estimates were available for years 2007 and 2010, and the average of these sets of values was used as mean exposure of the study participants (19.3 µg/m³). In the fully adjusted model (i.e., including age, sex, BMI, household income, education level, smoking status, and pack-years of smoking), a 10 µg/m³ increase in PM₁₀ concentration was associated with an HR of 1.53 (95%CI: 1.20–1.96). Interestingly, subjects with a high “genetic risk” (based on gene polymorphisms) had a higher risk of incident lung cancer (HR: 1.77, 95%CI: 1.50–2.10)⁴⁸. Another analysis on a smaller population selected from the UK biobank (*N* ≈ 367,000) tried to consider also the effect of lifestyle factors, and the association between PM₁₀ exposure and lung cancer risk was smaller and slightly more uncertain (HR: 1.05, 95%CI: 0.99–1.10 per IQR increase in PM₁₀, in models adjusted for age, sex, race, educational level, household income, region, BMI, alcohol status, smoking status, physical activity, and diet)⁴⁹.

The role of PM₁₀ exposure on both mortality and hospitalization for lung cancer was investigated in a recent cohort study conducted in Guangzhou, China, where about 650,000 participants were recruited between 2009 and 2015, and followed up for an average of 8.2 years. Annual mean concentration of PM₁₀ (58.8 µg/m³) was estimated using a satellite-based random forest algorithm. Applying a causal inference model, for every 1 µg/m³ increase in PM₁₀ concentration the HR for mortality due to lung cancer was 1.032 (95%CI: 1.024–1.041), and that for hospitalization was 1.067 (95%CI: 1.020–1.115)⁵⁰.

The only case-control study that we know of specifically investigating PM₁₀ exposure and lung cancer was performed in South Korea⁵¹. Nine hundred and eight incident lung cancer cases were matched to population controls by sex, smoking status and age. PM₁₀ exposure assessment was done using land-use regression models in a 20-year period preceding subjects' enrollment and complete residential histories since 1995. PM₁₀ levels ranged from 18.25 to 95.58 µg/m³. The OR adjusted for education, smoking status, education, exposure to occupational carcinogens, and fruit intake was 1.09 (95%CI: 0.96–1.23) per 10 µg/m³ of PM₁₀. Compared to the EAGLE study, this investigation is limited by the poor characterization of information regarding smoking habits (i.e., only smoking status was available).

In summary, the evidence trying to link PM₁₀ and lung cancer risk has been steadily growing and points towards the carcinogenic effects of this air pollutant. Nonetheless, uncertainties characterizing the various investigations must be acknowledged, probably related to the variability of the confounders considered in the analyses, the different methods applied for the exposure assessment, the wide range of the pollutant concentration values, and the different time windows investigated (very often close to the health event of interest).

To this regard, the role of exposure to air pollution 10 years before lung cancer diagnosis has been recently examined in a large Southern Californian cohort study including more than 45,000 participants aged 50+ years at enrollment. Lung cancer risk was estimated considering 5-year moving averages of ultrafine particles (UFP) exposure, lagged 10 years⁵². Interestingly, the authors found only a modest association between UFP exposure and lung cancer risk when considering the entire cohort (HR: 1.03, 95%CI: 0.99–1.08), while an increased risk was observed for adenocarcinoma when comparing most exposed vs. least exposed males (HR: 1.39, 95%CI: 1.05–1.85), and also in male participants who were oldest at the time of enrollment (HR: 1.13, 95%CI: 1.02–1.26). Notwithstanding the far smaller sample size of our study population and the difference in the considered pollutants (although combustion-derived ultrafine particles are numerous in urban PM₁₀⁵³), we tried to replicate the analyses by Jones and colleagues: however, no positive associations were observed neither when looking at adenocarcinoma in males, nor when further restricting our analysis to the same histological subtype among males aged 60 years or more at enrollment (results not shown). Possible explanations of these partially contrasting findings (apart from the obvious difference in sample size and pollutants considered among the two studies) might be the finer spatial resolution of exposure levels in the California study (LUR models to predict average levels at participant residential addresses) but also, on the other hand, the lack of control for important confounders such as occupational exposures, for which indeed we were able to control for.

Our study has several strengths. First, EAGLE is a population-based case-control study with a large number of enrolled subjects¹⁸. Many variables regarding residential history, smoking habits, and several others factors relevant for lung cancer were collected. This makes us confident of the quality of our data and allowed us to control for many potential confounders or risk factors that could bias the effect of air pollution in the analysis. Second, we assessed a past exposure to air pollution temporally located 12–15 years before the enrollment which, as far as we know, has rarely been evaluated. Third, we are dealing with exceptionally high values of air pollution concentrations: the mean PM₁₀ estimate of exposure of our study population in 1990 was 68 µg/m³, i.e., more than four times the air quality guideline level recommended by the World Health Organization (15 µg/m³)⁵⁴. Notably, we also had estimates of PM_{2.5} values in 1990. We did not focus our analyses on PM_{2.5} because our main aim was to make a comparison with our previous results regarding the year 2000, where only PM₁₀ estimates were available. However, PM_{2.5} levels represented about 96% of PM₁₀ values in our dataset. As such, the annual average PM_{2.5} level in our study population would roughly be 65 µg/m³, i.e., more than three times higher than the mean of the highest quartile of exposure in the study by Jones and colleagues (21.8 µg/m³). In any case, we replicated our main analysis considering PM_{2.5} exposure and found comparable results (Table S9). Fourth, by comparing exposures in two time points, we tried to address the insidious topic of temporality in cancer development.

This study has also limitations. First, the spatial distribution of exposure estimates in 1990 is very different from that in 2000. This is particularly evident in Milan, which has much higher PM₁₀ values as compared with other areas. A second limitation regards the low spatial resolution of our exposure data. The model applied to estimate 1990 PM₁₀ concentration levels used a 3 × 3 km grid, thus implying that all subjects localized within the same cell were assigned the exact same exposure value, possibly introducing a nondifferential misclassification of exposure. To this regard, we must also consider that about 70% of our study population was resident within the metropolitan city of Milan. These subjects all fall within four cells only: as such, in our analysis for the year 1990 most subjects share the same exposure. However, the sensitivity analysis where we rescaled exposure estimates for the year 2000 to the 3 × 3 km grid basically reconfirmed previous results obtained with exposure estimates at a much finer spatial resolution, suggesting that exposure granularity is not the main driver of the different findings. Finally, as already discussed, we are comparing different methodologies to estimate exposures in the two time points, which could affect results with their own uncertainties⁵⁵.

Conclusions

In conclusion, in a large case-control study characterized by a vast set of information on individual confounders and conducted in a very polluted area of northern Italy, we did not observe an increased lung cancer risk when considering air pollution exposures 12–15 years before diagnosis. On the other hand, the positive association suggested for exposures to air pollution in a time point closer to diagnosis were confirmed (and strengthened) by analyses that were able to consider both past and more recent exposures at the same time. Our results thus might contribute to the intriguing hypothesis that air pollution could act as a promoter of cancer development, and stimulate further research aimed to deepen our knowledge on the biological role that air pollution could play in the carcinogenic process. Further research is required to verify this hypothesis: nonetheless, should it be confirmed, it would have groundbreaking public health implications, as interventions to reduce air pollution levels could have beneficial and relevant effects in a relatively short period of time (e.g., a few years).

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Received: 10 January 2025; Accepted: 21 August 2025

Published online: 27 August 2025

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Acknowledgements

This work is part of L. Fedrizzi's dissertation project for the Epidemiology Master Program, University of Turin, Italy. We thank Mikhail Sofiev and the Finnish Meteorological Institute for providing results of their long-term re-analysis of atmospheric composition and air quality at continental scale.

Author contributions

According to the CRediT author statement- L.F.: conceptualization, data curation, formal analysis, methodology, writing – original draft, writing – review & editing. - M.C.: conceptualization, methodology, supervision, writing – original draft, writing – review & editing. - D.C.: conceptualization, data curation, methodology, supervision, writing – review & editing. - C.S.: data curation, formal analysis, methodology, writing – review & editing. - S.F.: data curation, formal analysis, methodology, writing – review & editing. - P.R.: data curation, formal analysis, methodology, writing – review & editing. - A.C.P.: conceptualization, funding acquisition, methodology, supervision, writing – review & editing. - M.T.L.: conceptualization, funding acquisition, supervision, writing – review & editing. All authors read and approved the final manuscript.

Funding

This work was partially supported by: the Intramural Research Program of the National Institutes of Health, the National Cancer Institute, Division of Cancer Epidemiology and Genetics, Bethesda, Maryland, USA; the Lombardy Regional Government (research grant “Regione Lombardia Ricerca Indipendente 2012: ESSIA - Effetti Sulla Salute degli Inquinanti Aerodispersi in Regione Lombardia”), Milan, Italy.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval

The study was approved by the institutional review boards (IRBs) of the following institutions: USA: National Cancer Institute, Bethesda, MD; Italy: Università degli Studi di Milano, Milan; Istituti Clinici di Perfezionamento, Milan and Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena, Milan (now Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan); Ospedale Niguarda, Milan; Istituto Clinico Humanitas, Rozzano; Istituto Scientifico Universitario Ospedale San Raffaele, Milan; Ospedale Luigi Sacco, Milan; AO San Paolo, Milan; AO Ospedale San Carlo Borromeo, Milan; Ospedale Fatebenefratelli e Oftalmico, Milan; Ospedale San Giuseppe, Milan; Ospedale San Gerardo, Monza; Spedali Civili, Brescia; Fondazione IRCCS Policlinico San Matteo, Pavia; Ospedale di Circolo e Fondazione Macchi, Varese. The original IRB number was 02-C-N211. However, since the National Cancer Institute only received de-identified samples and data from collaborating centers, had no direct contact or interaction with the study participants, and did not use or generate identifiable private information, EAGLE has been later determined to constitute “Not Human Subject Research (NHSR)” based on the federal Common Rule (45 CFR 46; <https://www.ecfr.gov/current/title-45/subtitle-A/subchapter-A/part-46>).

Additional information

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1038/s41598-025-17159-y>

[0.1038/s41598-025-17159-y](https://doi.org/10.1038/s41598-025-17159-y).

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