*European Journal of Epidemiology* **19**: 49–54, 2004.


CANCER

# Case–control study on cancer risk associated to residence in the neighbourhood of a petrochemical plant

S. Belli[1], M. Benedetti[1], P. Comba[1], D. Lagravinese[2], V. Martucci[2], M. Martuzzi[3], D. Morleo[2], S. Trinca[1] & G. Viviano[1]

[1]*Istituto Superiore di Sanità;* [2]*Local Health Authority, Brindisi;* [3]*WHO, European Center for Environment and Health, Rome, Italy*

Accepted in revised form 11 July 2003

**Abstract.** The aim of the present study is to investigate cancer mortality and residence in the neighbourhood of the petrochemical plant located in Brindisi, South-eastern Italy. Cases were all subjects resident in Brindisi and in three neighbouring municipalities who died in the study area in 1996–1997 from lung cancer, pleural neoplasm, bladder cancer and lymphohematopoietic malignancies. Controls were subjects resident in the same area and deceased in 1996–1997 for any cause except those listed for the cases. Next of kin's of all study subjects were visited by an interviewer who collected anamnestic information. The main residence of each subject, defined as the longest held residence with exclusion of the last 10 years, was reported on a digitalized map of the study area (MapInfo). The study included 144 cases and 176 controls; response rate was 98%. Residence within 2 km from the centre of the petrochemical plant was associated with a 3 fold increase of the Odds ratios (OR) for lung cancer, which did not reach statistical significance. Living close to the petrochemical plant was associated with moderate increases of OR for bladder cancer and lymphohematopoietic neoplasms which did not reach statistical significance. In conclusion the present study has shown moderate increases in risk for lung, bladder and lymphohematopoietic neoplasms in the population resident within 2 km from the centre of the petrochemical plant in Brindisi. These figures were confirmed after adjusting for smoking habit, occupation and school level. Random misclassification may have somehow resulted in risk underestimation.

**Key words:** Bladder cancer, Environmental exposure, Lung cancer, Lymphohematopoietic neoplasms, Petrochemical plants

## Introduction

The association between air pollution and cancer, especially lung cancer, has been studied by various authors and is the object of several reviews of the literature [1–4]. In the last years both ecological and case–control studies have provided increasing support to the hypothesis of an etiological role of the association between air pollution and lung cancer. In this frame a specific issue addressed by some authors is lung cancer risk associated to residence in the neighbourhood of an industrial site emitting volatile compounds and particulate matters. Some authors reported an association between lung cancer and residence in the neighbourhood of smelters [5, 6], complex industrial sites [7–9] and other point sources of air and soil pollution [10–12]. Pleural mesothelioma cases associated with residential proximity to plants where asbestos products were manufactured, or asbestos was employed in large quantities for insulation, have been repeatedly reported in the literature; a recent European case–control study has provided estimates of the relationship between Odds ratio (OR) and distance of residence from the plant [13]. A lower number of studies have shown an increased risk for lymphohematopoietic neoplasms [14, 15]. A study from Taiwan has associated bladder cancer with residence near a petrochemical site [16].

The aim of the present study is to investigate mortality from lung, pleural, bladder and lymphohematopoietic neoplasms and residence in the neighbourhood of the petrochemical plant located in Brindisi, South-eastern Italy. Potential confounding variables (namely age, sex, school level, occupational exposures and smoking habits) have been allowed for.

## Methods

Cases were all subjects resident in Brindisi and in three neighbouring municipalities (Carovigno, Torchiarolo and San Pietro Vernotico) who died in the study area in 1996–1997 from lung cancer (ICD IX revision 162.0–162.9), pleural neoplasm (163.0–163.9), bladder cancer (188.0–188.9) and lymphohematopoietic malignancies (200.0–208.9). These subjects constitute

84% of the total number of death for the above mentioned causes; another 16% died from these causes out of the Brindisi area, and their information is not available in the local population registries.

Controls were a random sample of the subjects resident in the same area and deceased in 1996–1997 for any cause except those listed for the cases. The distribution of age and sex among controls was made similar to the corresponding distribution among cases by frequency matching. The distribution of controls according to residence thus reflects the distribution of the population resident in the study area. The case–control ratio ranged between 1:2 for lung cancer to about 1:6 for lymphohematopoietic neoplasms and 1:13 for bladder cancer.

The source of cases and controls was the death register available in each municipality, integrated by the archive of causes of death held by the Local Health Authority. Feasibility constraints related to the entity of work required for information retrieval and quality control, led to a restriction of the study period to 1996–1997 biennium. Notwithstanding predictable low statistical power, the study was regarded as being potentially informative because of the lack of previous investigations in this highly industrialized area.

Next of kin's of all study subjects were identified through Registry Offices and, subsequent to obtaining their informed consent, were visited by an interviewer who was not aware of the caseness of their relatives. The interviewer collected information on residential history, occupation, school level, smoking habits and alcohol consumption of the study subject.

The main residence of each subject, defined as the longest held residence with exclusion of the last ten years, was reported on a digitalized map of the study area (MapInfo). Distance between the central point of the petrochemical plant was computed for each study subject.

OR's were estimated by logistic regression by use of the STATA package. Estimates were adjusted by age, sex, smoking habits and school level (none, primary, secondary, bachelor, universitary degree).

## Results

The study included 144 cases (121 men, 23 women) and 176 controls (127 men, 49 women); mean age at death for cases and controls was 66.87 (±0.93) and 66.97 (±0.87) respectively. Six relatives of controls either were not retrieved or refused to be interviewed. Response rate was thus 98%.

Table 1 shows the distribution of cases and controls by occupation. Some branches of occupation (metal industry, chemical industry, mining, construction and road works) were identified *a priori* as potential sources of exposure to carcinogens, on the basis of information retrieved by the Local Health Authority. It was also decided to have an *ad hoc* category including farmers, breeders and fishermen, given the remarkable proportion of subjects active in these occupation in the province of Brindisi.

### *Lung cancer*

Residence within 2 km from the centre of the petrochemical plant was associated with a 3 fold increase of the OR, which did not reach statistical significance (Table 2). The proportion of smokers and former smokers among cases and controls was 90.4 and 62.4% respectively. This corresponds to an OR of 5.7 (95% confidence interval [CI] = 2.7–11).

Alcohol consumption was also associated to lung cancer (OR = 2.9; CI = 1.4–5.9), but statistical significance was not achieved when smoking habits (notably associated with alcohol consumption) were introduced in the model (OR = 1.8; CI = 0.80–3.9).

**Table 1.** Distribution of cases and controls by occupation, both sexes combined

| | Cases | | | | | |
|---|---|---|---|---|---|---|
| | Cancer site | | | | | |
| Job title | Lung[a] | Pleura[b] | Bladder[c] | Lympho-hematopoietic[d] | Controls | Total |
| Farmers, fishermen, breeders | 24 | 0 | 5 | 5 | 47 | 81 |
| Metal foundry, iron and steel industry workers | 5 | 1 | 1 | 0 | 4 | 11 |
| Chemical and petroleum plants workers | 11 | 0 | 1 | 2 | 10 | 24 |
| Building trade workers, miners, road-workers | 16 | 0 | 0 | 2 | 14 | 32 |
| Other jobs | 39 | 4 | 6 | 22 | 95 | 166 |
| Total | 95 | 5 | 13 | 31 | 170 | 314 |

[a] ICD code (IX revision) = 162.0–162.9.
[b] ICD code (IX revision) = 163.0–163.9.
[c] ICD code (IX revision) = 188.0–188.9.
[d] ICD code (IX revision) = 200.0–208.9.

**Table 2.** Crude and adjusted OR for lung cancer, and distance from the petrochemical plant

| Distance from the source (km) | Cases | Controls | Crude OR (95% CI[a]) | Adjusted OR[b] (95% CI[a]) |
|---|---|---|---|---|
| ⩽2 | 10 | 5 | 3.2 (1.1–9.9) | 3.1 (0.83–12) |
| 2–3 | 11 | 41 | 0.43 (0.20–0.95) | 0.34 (0.14–0.87) |
| 3–4 | 27 | 44 | 0.99 (0.52–1.9) | 1.0 (0.47–2.2) |
| 4–5 | 13 | 25 | 0.84 (0.38–1.9) | 0.70 (0.26–1.9) |
| >5[c] | 34 | 55 | 1 | 1 |

[a] CI = Confidence interval.
[b] OR adjusted for: Age, sex, smoking and education.
[c] Reference category.

**Table 3.** Adjusted OR for lung cancer by job title

| Job title | Cases | OR[a] (95% CI[b]) | OR[c] (95% CI[b]) |
|---|---|---|---|
| Farmers, fishermen, breeders | 24 | 0.99 (0.52–1.9) | 1.0 (0.48–2.1) |
| Metal foundry, and iron and steel industry workers | 5 | 2.0 (0.50–7.9) | 2.3 (0.54–9.8) |
| Chemical and petroleum plants workers | 11 | 1.9 (0.73–5.1) | 1.9 (0.67–5.1) |
| Building trade workers, miners, road-workers | 16 | 1.9 (0.83–4.4) | 1.9 (0.77–4.7) |
| Other jobs | 39 | 1 | 1 |

[a] OR adjusted for: Age and sex.
[b] CI = Confidence Interval.
[c] OR adjusted for: Age, sex, smoking and education.

**Table 4.** Crude and adjusted OR for bladder cancer, and distance from the petrochemical plant

| Distance from the source (km) | Cases | Controls | Crude OR (95% CI[a]) | Adjusted OR[b] (95% CI[a]) |
|---|---|---|---|---|
| ⩽2 | 2 | 5 | 5.5 (0.93–32) | 3.9 (0.33–47) |
| 2–3 | 1 | 41 | 0.34 (0.04–2.9) | 0.30 (0.02–3.9) |
| 3–4 | 6 | 44 | 1.9 (0.50–7.0) | 2.8 (0.52–15) |
| 4–5 | 0 | 25 | – | – |
| >5[c] | 4 | 55 | 1 | 1 |

[a] CI = Confidence interval.
[b] OR adjusted for: Age, sex, smoking and education.
[c] Reference category.

School level was not associated to lung cancer ($p = 0.955$). Risk estimates associated with occupation are reported in Table 3. A doubling of risk was detected for metal workers, chemical workers and building trade workers, but confidence intervals were rather wide because of the limited size of the study population.

*Pleural neoplasms*

Five cases were observed (two men and three women), all of them resident in Brindisi. Only one subject lived at less than 2 km from the centre of the petrochemical plant. Occupational exposure to asbestos was regarded as probable for the pipe fitter, while it could not be evaluated for the other subjects.

*Bladder cancer*

The proportion of smokers and former smokers among cases and controls was 92.3 and 62.4% respectively, resulting in an OR of 7.2 (CI = 1.2–4.3). Allowing for smoking habits, alcohol consumption was not significantly associated with bladder cancer (OR = 2.5; 95% CI = 0.3–21).

Table 4 shows an increase of OR corresponding to residence within 2 km of the centre of the petrochemical plant, which does not reach significance because of the low number of cases.

School level was not associated with bladder cancer ($p = 0.407$). OR's associated with occupational branches are shown in Table 5; sparse numbers do not allow to draw conclusions.

*Lymphohematopoietic neoplasms*

The diseases entities included in this paper were leukaemia (13 cases), non-Hodgkin lymphomas (10 cases), multiple mieloma (7 cases) and Hodgkin's disease (1 case). Living close to the petrochemical plant was associated with an increase of OR for

**Table 5.** Adjusted OR for bladder cancer, by job title

| Job title | Cases | OR 1[a] (95% CI[b]) | OR 2[c] (95% CI[b]) |
|---|---|---|---|
| Farmers, fishermen, breeders | 5 | 1.6 (0.43–5.7) | 1.3 (0.29–5.6) |
| Metal foundry, and iron and steel industry workers | 1 | 3.0 (0.26–33) | 1.6 (0.12–23) |
| Chemical and petroleum plants workers | 1 | 1.5 (0.14–14) | 1.5 (0.13–17) |
| Building trade workers, miners, road-workers | 0 | – | – |
| Other jobs | 6 | 1 | 1 |

[a] OR adjusted for: Age and sex.
[b] CI = Confidence interval.
[c] OR adjusted for: Age, sex, smoking and education.

**Table 6.** Crude and adjusted OR for lymphohematopoietic malignancies, and distance from the petrochemical plant

| Distance from the source (km) | Cases | Controls | Crude OR (95% CI[a]) | Adjusted OR[b] (95% CI [a]) |
|---|---|---|---|---|
| ⩽2 | 4 | 5 | 4.4 (1.1–18) | 2.7 (0.45–17) |
| 2–3 | 7 | 41 | 0.94 (0.33–2.7) | 0.39 (0.10–1.6) |
| 3–4 | 5 | 44 | 0.63 (0.20–2.0) | 0.26 (0.06–1.1) |
| 4–5 | 5 | 25 | 1.1 (0.34–3.6) | 0.57 (0.14–2.4) |
| >5[c] | 10 | 55 | 1 | 1 |

[a] CI = Confidence interval.
[b] OR adjusted for: Age, sex, smoking and education.
[c] Reference category.

**Table 7.** Adjusted OR for lymphohematopoietic malignancies, by job title

| Job title | Cases | OR 1[a] (95% CI[b]) | OR 2[c] (95% CI[b]) |
|---|---|---|---|
| Farmers, fishermen, breeders | 5 | 0.62 (0.21–1.9) | 0.62 (0.21–1.9) |
| Metal foundry, and iron and steel industry workers | 0 | – | – |
| Chemical and petroleum plants workers | 2 | 1.2 (0.23–6.7) | 1.2 (0.23–6.7) |
| Building trade workers, miners, road-workers | 2 | 1.0 (0.20–5.4) | 1.0 (0.20–5.4) |
| Other jobs | 22 | 1 | 1 |

[a] OR adjusted for: Age and sex.
[b] CI = Confidence interval.
[c] OR adjusted for: Age, sex, smoking and education.

lymphohematopoietic neoplasms which did not reach statistical significance (Table 6).

Smoking habits were negatively associated with these diseases (OR = 0.38; 95% CI = 0.18–0.82), while no association was observed with alcohol consumption (OR = 0.98; 95% CI = 0.42–2.3).

No association was detected with school level ($p = 0.101$). OR's relative to occupation were not informative because of the low number of cases (Table 7).

## Discussion

The present study was based on mortality data, which implies the probability of introducing both false positive and false negative. The detection of cancer cases from death certificates may imply an underestimation of the number of cases, especially among older subjects and, for lung cancer, among non-smokers [17, 18]. The erroneous inclusion of some cases among controls may have contributed to underestimation of risk because of random misclassification. Furthermore, it should be noted that 43% of controls were affected by cancer of all sites, except those of the case series, or respiratory diseases. Since these outcomes might be to some extent associated with emissions from the petrochemical plant, this finding suggests a possible underestimation, rather than overestimation, of risk. On the other hand, there is no evidence to hypothesise selective misclassification of cause of death associated with residence, thus resulting in a systematic error.

Information on risk factors and potential confounders was retrieved by interviewers to next of kin's of deceased subjects. This procedure implies some loss of information which can be particularly relevant for remote events and for quantitative variables [19, 20]. This effect is less likely for dichotomous variables (e.g. smokers, non-smokers) or question related to easily definable variables, like main occupation. In the present study, all interviews concerned relatives of

deceased subject, and were performed blindly with respect to caseness. It is likely that only random misclassification may have been introduced, thus further contributing to underestimating the risk.

Environmental exposure to emission from the petrochemical plant was indirectly estimated by means of distance. This criterion is largely used in ecological studies, in which health data are disaggregated at the individual level, while environmental and socio-economic data are aggregated at group level [21–23]. In case–control studies the use of distance as a proxy of exposure is generally associated with a better definition of residence (main residence rather than last residence), furthermore it is possible to allow for confounding variables. The use of main residence, defined as the longest held residence with exclusion of the last 10 years, requires a comment. The case-entities at study are characterized, among else, by different median latency times, ranging from over 30 years for mesothelioma to 10–20 years, for lymphohematopoietic malignancies and bladder cancer. In this frame, the search for a common time window aimed at taking into account latency might have been somehow arbitrary, while the adoption of different time windows for the various case entities might have implied comparability problems.

In the present study, OR's relative to environmental exposure were adjusted for age, sex, smoking, occupation and school level, regarded as an indirect indicator of socio-economic level.

Notwithstanding low statistical power due to limited sample size, the present study has shown a moderate increase of cancer mortality associated with residence near the petrochemical plant. On the other side, the study did not provide evidence supporting the presence of a trend in the distribution of cases and the finding of a significantly decreased mortality from lung cancer in 2–3 km ring remains unexplained.

In conclusion the present study has shown moderate increases in risk for lung, bladder and lymphohematopoietic neoplasms in the population resident within 2 km from the center of the petrochemical plant in Brindisi. These figures were confirmed after adjusting for smoking habit, occupation and school level. No major bias has been suggested, while random misclassification may have somehow resulted in risk underestimation.

## References


1. Cohen AJ, Pope III CA. Lung cancer and air pollution. Environ Health Perspect 1995; 103(Suppl 8): S219–S224.
2. Katsouyanni K, Pershagen G. Ambient air pollution exposure and cancer. Cancer Causes Control 1997; 8: 284–291.
3. Pershagen G, Lung cancer. In: Bertollini R, Lebowitz MD, Saracci R, Savitz D (eds), Environmental epidemiology, exposure and disease. Boca Raton: Lewis Publisher, 1993; 147–159.
4. Speizer FE, Samet J. Air pollution and lung cancer. In: Samet JM (ed), Epidemiology of lung cancer. New York, Basel, Hong Kong: Marcel Dekker, Inc., 1994; 131–150.
5. Pershagen G. Lung cancer mortality among men living near an arsenic emitting smelter. Am J Epidemiol 1985; 122: 684–694.
6. Xu ZY, Blot WJ, Li Xu G, et al. Environmental determination of lung cancer in Sheniang China. In: O'Neill IK, Chen J, Bartsch H (eds), 'Relevance to human cancer in N-Nitroso compounds, tobacco smoke and mycotoxins' IARC. Lyon: IARC Scientific Publications, 1991; 105: 460–465.
7. Barbone F, Bovenzi M, Cavallieri F, Stanta G. Air pollution and lung cancer in Trieste. Am J Epidemiol 1995; 41: 1161–1169.
8. Minerba L, Scarpa B, Contu A. Studio di mortalità tra i residenti in un'area ad elevato rischio di crisi ambientale. Ann Igiene 2001; 13: 339–350.
9. Shear CL, Seale DB, Gottlieb MS. Evidence for space-time clustering of lung cancer deaths. Arch Environ Health 1980; 35: 335–343.
10. Jedrychowski W, Becher H, Waherendorf J, Basa-Cierpialek Z. A case–control study of lung cancer with special reference to air pollution in Poland. J Epidemiol Community Health 1989; 44: 114–120.
11. Morris Brown L, Pottern LM, Blot WJ. Lung cancer in relation to environmental pollutants emitted from industrial sources. Environ Res 1984; 34: 250–261.
12. Vena JE. Air pollution as a risk factor in lung cancer. Am J Epidemiol 1982; 116: 42–56.
13. Magnani C, Agudo A, González CA, et al. Multicentric study on malignant pleural mesothelioma and non-occupational exposure to asbestos. Br J Cancer 2000; 83; 104–111.
14. Linos A, Blair A, Gibson RW, et al. Leukemia and non-Hodgkin's lymphoma and residential proximity to industrial plants. Arch Environ Health 1991; 46: 70–74.
15. Shore DL, Sandler DP, Davey FR, McIntyre OR, Bloomfield CR. Acute leukemia and residential proximity to potential sources of environmental pollutants. Arch Environ Health 1993; 48: 414–420.
16. Pan BJ, Hong YJ, Chang GC, et al. Excess cancer mortality among children and adolescents in residential districts polluted by petrochemical manufacturing plants in Taiwan. J Toxicol Environ Health 1994; 43: 117–129.
17. Bruno C, Comba P, Maiozzi P, Vetrugno T. Accuracy of death certification of pleural mesothelioma in Italy. Eur J Epidemiol 1996; 12: 421–423.
18. Ridgon RH. Problems in a statistical study of disease based on death certificates. South Medical J 1981; 74: 1104–1111.
19. Debanne SM, Petot GJ, Li J, et al. On the use of surrogate respondents for controls in a case–control study of Alzheimer's disease. J Am Ger Soc 2001; 49: 980–984.
20. Williams Pickle L, Morris Brown L, Blot WJ. Information available from surrogate respondents in case–control interview studies. Am J Epidemiol 1983; 118: 99–198.

21. Diggle P, Elliott P. Disease risk near point sources: Statistical issues for analyses using individual or spatially aggregated data. J Epidemiol Community Health 1995; 49(Suppl 2): S20–S27.
22. Dolk H, Mertens B, Kleinschmidt I, Walls P, Shaddick G, Elliot PA. Standardisation approach to the control of socioeconomic confounding in small area studies of environment and health. J Epidemiol Community Health 1995; 49(Suppl 2): S9–S14.
23. Elliott P, Martuzzi M, Shaddick G. Spatial statistical methods in environmental epidemiology: A critique. Stat Meth Med Res 1995; 4: 137–159.

*Address for correspondence*: Pietro Comba, Istituto Superiore di Sanità, Viale Regina Elena, 299, 00161 Rome, Italy
Phone: +39-6-49902249; Fax: +39-6-49387083
E-mail: comba@iss.it