Case-Control Study on Radon Exposure and Lung Cancer in an Italian Region: Preliminary Results

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INTRODUCTION

The risk of lung cancer has been quantitatively estimated using exposure-response relations derived from the epidemiological investigations of uranium and other underground miners. Based on extrapolations from miners, it has been postulated that indoor radon poses a substantial lung cancer risk, accounting for a significant fraction of the total lung cancer cases in a population (1). In all, nine case-control studies on lung cancer and radon exposure in dwellings have been published so far that have included at least 200 subjects with lung cancer and measured radon concentration in at least one residence for most residents. Lubin and Boice (2) have reviewed eight of these studies and have conducted a metanalysis based on a total of 4263 cases and 6612 controls. There was a moderate but slightly significant overall increase in lung cancer risk due to radon exposure in dwellings, with an estimated relative risk of 1.14 (95% confidence interval: 1.01–1.30) at 150 Bq m^{-3}. Subsequently, a large case-control study has been conducted in South-West England and included 982 cases and 3185 controls with radon measurement of all the dwellings lived by the study subjects in the 5-35 year period before the date of the enrollment (3). Increased (but not statistically significant) relative risks have been observed in the category of subjects who had a time-weighted radon concentration of 200-399 Bq m^{-3} (RR=1.24), and among those in the highest exposure group, 400+ Bq m^{-3} (RR=1.79). The excess relative risk per 100 Bq m^{-3} was estimated 8% (95%CI = -3–20%), which is consistent with the meta-analysis estimate.

The bulk of epidemiologic studies available so far suggests a role of indoor radon exposure for lung cancer. Several aspects are uncertain, however, especially because reliable estimates of past exposure are difficult to obtain. Unsolved questions include the form of the exposure-response relationship, the histologic type(s) of lung cancer potentially involved, the modifying effect of active and passive smoking. It is has been indicated that the findings from individual studies provide only small pieces of the whole information which is needed (4). In view of this problem, pooling of the findings of the individual studies in Europe and in the North-America has been planned.

The present study is a part of the foreseen European pooling of case-control studies on radon and lung cancer; it has been conducted to evaluate the degree of association between residential exposure to radon and lung cancer in an Italian region (Lazio) while considering the potential confounding role of several determinants of the disease.

METHODS

Area of the study

Lazio encompasses about five million inhabitants, including the metropolitan area of Rome (with about three million inhabitants). Some of the areas of the Lazio region have a relatively high indoor radon level due to particular geologic features (volcanic geology) and building material used. In particular, local tuff ("tufo"), which has a high exhalation of radon and thoron (5,6), has been widely used as the main building material in the region. A national survey on radon concentration in dwellings showed that the Lazio region has high residential radon concentration (average = 120 Bq m^{-3}, GSD = 2.0) with a relatively wide radon distribution (7,8).

Subjects and study design

A hospital based case-control study on lung cancer has been conducted in one of the main hospitals of the metropolitan area of Rome (Forlanini-S.Camillo Hospital). The study has been conducted within the IARC (International Agency for Research on Cancer) collaborative initiative to investigate the role of Environmental Tobacco Smoke (9), active smoking, and markers of DNA damage and genetic *susceptibility* (10) on lung cancer.

The eligible cases consisted of all Caucasian subjects aged 35 years or more, residents in the Lazio Region, admitted to the hospital during the period November 1993–June 1996 for a suspected lung cancer to be further evaluated through a diagnostic bronchoscopy. Eligible cases were asked a consent for an interview to be performed, if possible, before the diagnostic bronchoscopy.

Controls were selected among patients admitted to the same hospital during the study period, with the same residence and age restrictions, from the following hospital wards: General Surgery, Orthopaedics, ENT, and General Medicine. Subjects admitted to the hospital because of conditions that are somehow related to either smoking or dietary habits, such as most cancers, respiratory diseases, diabetes, cardiovascular, digestive and renal diseases, were not included in the control series. A balance between different diagnoses was kept when sampling controls in order to minimize potential bias if one disease turns out to be related to dietary habits. The control subjects had to be frequency matched to the cases by gender (1:1 for males, and 1:2 for females) and age (in 5-year age strata).

Table 1 shows the outcome of the selection process of the subjects under study. In all, 679 patients (74.1% of 918 originally identified as suspected lung cancer cases) and 443 controls (74.0% of the subjects approached) were interviewed by two trained assistants using a structured questionnaire regarding demographic data, active smoking, occupational exposure to carcinogens, and environmental tobacco smoke. The Italian version of the EPIC food-frequency questionnaire (a self-administrated questionnaire designed and used in the ongoing European Study of Diet and Cancer) (11) was used to assess dietary habits.

Table 1. Outcome of the selection process of the subjects under study.

OUTCOME	SUSPECTED LUNG CANCER CASES		CONTROLS	
	N	%	N	%
Patients approached for the study	918	100.0	599	100.0
Interviewed	679	74.1	443	70.6
Lung cancer not confirmed *	247	26.9	-	
Residential history not available	19	2.1	13	2.2
Residence in the study area below 25 years	5	0.5	7	1.2
Subjects included	408	44.4	423	70.6

* For a total of 247 subjects, the broncoscopy did not confirm a lung cancer but lung fibrosis, tubercolosis, or pulmonary disease attributable to smoking was diagnosed.

Few weeks after the enrollment and the interview of the suspected lung cancer cases, all the relevant findings from bronchoscopy, thoracic surgery, pathology, and other medical records from the hospitals were examined for a confirmation of the suspected lung cancer diagnosis. Histological or cytological confirmation of a primary lung cancer was searched. A lung cancer diagnosis was not confirmed for 247 subjects, who had another respiratory disease mainly associated with smoking, and they were then excluded from the study.

In order to select the individuals for the present investigation on radon exposure, the residential history (dates and complete addresses) of all the study subjects during the 35 years preceding the enrolment (the period of exposure to indoor radon that we assumed as relevant to the risk of lung cancer) was collected from the Municipal Registers of the last residence. For each dwelling occupied for more than a year, the precise address and the relevant dates were collected. We excluded 19 cases and 13 controls because no residential history was available, and 5 cases and 7 controls who had lived in the Lazio region for less than 25 years. We finally selected for the present study a total of 829 subjects, 408 cases and 423 controls (Table 1).

Table 2 shows the main demographic characteristics of cases and controls, the frequency distribution of the histological types of lung cancer, and the diagnosis of the hospital controls. There were some difficulties in finding controls among older males because they had to be hospitalized because of diseases unrelated to both smoking and diet; therefore, the older age classes are less represented among male controls. Most cases (79.4%) and controls (90.5%) were residents in Rome or in the Rome district outside the city at the time of the interview. A histological or a cytological confirmation of the lung cancer diagnosis was available for 368 cases (89.2%) while there was no microscopic evidence for 44 cases (10.8%), and the diagnosis was based on clinical evidence only. The diseases more frequent among the controls were conditions of the sense organs (19.1%) (hospitalized in the ENT ward), musculoskeletal diseases (10.7%), and injury and poisoning hospitalized in the Orthopaedics ward (16.3%).

Table 2. Demographic characteristics of the subjecty included in the study, histological type of lung cancer, and diagnosis of hospital controls.

VARIABLE	CASES (N=408)		CONTROLS (N=423)	
	N	%	N	%
Sex				
male	341	83.6	309	73.0
female	67	16.4	114	27.0
Age (y)				
35-44	7	1.7	23	5.4
45-54	41	10.0	61	14.4
55-64	134	32.8	155	36.6
65-74	177	43.5	135	31.9
75-84	47	11.5	46	10.9
85-90	2	0.5	3	0.7
Residence at interview				
city of Rome	264	64.7	336	79.4
districts of Rome	60	14.7	47	11.1
other places of the Lazio Region	84	20.6	40	9.5
Hystological type				
epidermoid	185	45.3	-	-
small cell	47	11.5	-	-
adenocarcinoma	72	17.7	-	-
large cell	13	3.2	-	-
other	47	11.5	-	-
clinical diagnosis only, no microscopic evidence	44	10.8	-	-
Other diagnosis				
infectious diseases	-	-	20	4.7
other cancers	-	-	7	1.7
diseases of the endocrinous system	-	-	4	0.9
diseases of the blood	-	-	2	0.5
diseases of central nervous system and sense organs	-	-	81	19.1
circulatory diseases	-	-	24	5.7
other respiratory diseases			27	6.4
diseases of the digestive system	-	-	50	11.8
diseases of the genitourinary system	-	-	6	1.4
diseases of the skin	-	-	4	0.9
musculoskeletal diseases	-	-	83	19.7
ill-defined diseases	-	-	46	10.9
injury and poisoning	-	-	69	16.3

Residential histories

To supplement the available residential histories obtained from the Municipal Registers, a short questionnaire was administered (through mail or telephone) to cases and controls (or to the next-of-kin) regarding the addresses and the relevant dates. In some cases, there were inconsistencies between the residential histories derived from the short questionnaire and those derived from the Municipal Registers. Therefore, to reduce the possibility of errors, it was planned that the information regarding the individual residential history had to be confirmed from the subjects (or the next-of-kin) during the home visit for the placement of the radon dosemeters (see below). The subjects (or the next-of-kin) had to be interviewed regarding the possible inconsistencies between the registry data and their previous report on the short questionnaire.

In addition to those questionnaires used during the hospital recruitment phase, two specific questionnaires were designed to be used during the home visit: i) a *subject's questionnaire*, to be administered to each subject (or next-of-kin), included a detailed ascertainment and verification of the residential history, data on the relevant characteristics of the dwellings in which the subject had lived, and on some residential habits (e.g., sleeping with windows open, etc.); ii) a *dwelling questionnaire*, to be filled out for each dwelling where a radon measurement had to be performed, included a detailed description on the characteristics of the dwelling (from the entire building structure to the single rooms where the dosemeters were placed) and on the residential habits of whoever lived in that particular dwelling.

Contact with the subject under study (or with next-of-kin) was first searched by mail and phone call, then a home visit followed. The confirmed residential history was obtained for 681 subjects (81.9%) (342 cases). Therefore, the Municipal Registers and the short questionnaire were the sources of information for 86 subjects (10.3%) (34 cases) (in case of discrepancies, the results from the short questionnaire were chosen), and the Municipal Registers was the only available source for 65 (7.8%) individuals (32 cases). The subject's questionnaire was completed for 658 subjects (330 cases, 328 controls).

Table 3 shows the distribution of the residential addresses occupied by cases and controls for more than a year in the 35-year period before enrollment: 19.4% of the cases and 20% of the controls had lived all the preceding 35 years always in the same dwelling, whereas only a minority (1.7%) changed seven addresses or more. The mean number of dwellings was similar between cases (2.82) and controls (2.86). It is to note that two controls (for whom the residential history was confirmed after an interview with next-of-kin) had actually been homeless and mobile within Lazio in the relevant time period and therefore they were excluded from the subsequent analysis.

Table 3. Frequency distribution of the number dwellings occupied by cases and controls for more then one year in the 35 year period before enrollment.

VARIABLE	CASES (N=408)		CONTROLS* (N=421)		TOTAL (N=829)	
	N	%	N	%	N	%
Number of residential periods						
1	79	19.4	84	20.0	163	19.7
2	121	29.7	113	26.8	234	28.2
3	85	20.8	95	22.6	180	21.7
4	71	17.4	71	16.9	142	17.1
5	32	7.8	31	7.4	63	7.6
6	13	3.2	20	4.8	33	4.0
7	5	1.2	6	1.4	11	1.3
8	1	0.2	1	0.2	2	0.2
9	1	0.2	-		1	0.1
Mean number of residential periods (st.dev.)	2.82	(1.47)	2.86	(1.49)	2.84	(1.48)

* 2 controls were found to be homeless for all the relevant study period and were excluded form the analysis.

Radon and gamma measurements

We placeed radon dosemeters for two consecutive six-month periods in both the main bedroom and the living room of each dwelling occupied by the study subjects in the relevant 35-year period before enrollment. This choice allows to obtain information on seasonal variation of radon concentration and to take into account of it. Moreover, it reduces the effect of detector saturation and losses.

It was planned that, in case of a refusal of the present occupant of the dwelling to be monitored, a proxy dwelling in the same building could be measured. Such a proxy had to be preferably on the same floor of the index dwelling, otherwise the closest dwelling above or below could be selected. In the latter cases, it was planned that two dwellings (above and below the index) had to be preferably chosen. In few cases there was no information on the exact location of the index dwelling in the building: in such cases two dwelling chosen from the lowest and the highest lived floor had to be selected for radon measurement.

Radon was measured by a solid-state nuclear track detector, LR115 type II (produced by Kodak), which is formed by a ~12 µm thick film of cellulose nitrate deposited on a 100 µm polyester support. Each dosemeter contained two radon detectors, so that 8 detectors (2 dosemeters * 2 rooms * 2 six-month periods) were used in each dwelling, thus reducing at minimum the losses of radon exposure due to detector losses, and improving the precision of measurements. The dosemeters are closed-type ones, being enclosed in a heat-sealed 35 µm low density (0.92 g cm^{-3}) polyethylene bag, which blocks radon decay products and thoron, and has a relatively low permeability to water vapour.

The LR115 detectors are chemically etched in a 10% NaOH solution at 60°C for 110 min. After washing in running water for 30 min and rinsing in distilled water for 15 min, the film is separated from the support and dried. The tracks are spark counted and corrected for the residual detector thickness, which is measured by means of a high precision mechanical system (this measurement is necessary because the number of tracks increases linearly as the residual thickness decreases).

In the second six-month period, two thermoluminescent dosemeters (TLD) were also placed in each monitored room to measure gamma radiation emitted from the building materials, in order to evaluate more comprehensively the exposure of population to natural radioactivity, and to estimate the correlation of gamma radiation with the measured radon concentration. Such measurements are quite interesting because the average dose rate due to gamma radiation in dwellings of Lazio region was the highest amost the Italian regions (12). All TLDs used for this study come from the same batch in order to reduce sensitivity variability; moreover, the relative sensitivity (i.e. the sensitivity relative to the average sensitivity of all the TLD) was measured for each TLD, in order to adjust the result obtained by each TLD using the average calibration factor.

The radon dosemeters were first placed between September 1997 and June 1998. The first six-month period of dosemeter exposure was completed in December 1998, whereas the second six-month period ended in June 1999. Table 4 shows the results of the radon measurement program. Out of a total of 2355 dwellings to be assessed (1148 for cases and 1207 for controls), a measurement in the index dwelling has been performed in 1311 (55.7%) cases and in most instances (1251) for the entire one-year period. In 485 (20.6 %) a proxy dwelling has been measured (in 451 for the entire one-year period). The proxy dwellings were on the same floor in most of the cases. Multiple refusals in the building, houses not used as residence, building demolished, houses not located, dwellings not inhabited and proxy dwelling not available, were all reasons for not having a dwelling monitored. In addition, we decided not to proceed further in 152 dwellings for which the present occupant had refuted and the residential period of the study subject in that specific house had been short (few years). Finally, dwellings outside the Lazio region were not searched. There were no major differences in the results of the radon measurement program between cases and controls. In all, we have measured 1796 addresses (76.3% of the target).

Table 4. Outcomes of the radon measurement program in residential addresses occupied by study subjects for at least one year.

VARIABLE	CASES		CONTROLS		TOTAL	
	N	%	N	%	N	%
Total number of dwellings to be monitored	1148	100.0	1207	100.0	2355	100.0
Measurement obtained						
direct measurement						
both six-month periods	611	53.2	640	53.0	1251	53.1
first six-month period only	28	2.4	32	2.7	60	2.5
measurement in a proxy dwelling						
both six-month periods	217	18.9	234	19.4	451	19.2
first six-month period only	17	1.5	17	1.4	34	1.4
Measurement not obtained						
refusals	36	3.1	30	2.5	66	2.8
not used as residence	25	2.2	26	2.2	51	2.2
demolished	38	3.3	42	3.5	80	3.4
not located	25	2.2	31	2.6	56	2.4
not inhabited	17	1.5	18	1.5	35	1.5
excluded (residential period too short)	79	6.9	73	6.0	152	6.5
dwellings outside Lazio Region	55	4.8	64	5.3	119	5.1

Data analysis

The complete results of all the radon and of the gamma measurements are not available yet, and the quality control on such measurements are still on-going. A preliminary analysis of the association between radon exposure in dwellings and lung cancer has been conducted using the results of the radon measurement regarding the latest house inhabited by cases and controls. For this analysis, we used the radon measurements of one out of the two detectors present in each dosemeter and averaged the results from the living room and the bedroom.

Logistic regression analysis was used to build the core model to be used in evaluating the effect of indoor radon. Odds ratios (ORs) and 95% Confidence Intervals (95%CI) were derived from logistic models.

Gender and age (in 5-year classes) were considered by design as confounders; since the age distribution of cases and controls was slightly different in males, an interaction term (gender*age) was also introduced in the models. Moreover, as the referral pattern of cases and controls could have been different for residents in Rome compared to residents in other places of Lazio, adjustment was made for area of residence. The following variables were considered as confounders: active smoking, years of education, occupational exposure to carcinogens, consumption of citrus fruit, consumption of tomatoes, consumption of salad. Finally, since we used six-month data, we adjusted also for month of start of the radon measurement by using dummy variables in the logistic model (however, the distributions of month of start of the radon measurement for cases and controls were very similar).

In order to evaluate the effect of smoking, the reference category included lifelong nonsmokers, namely individuals who had smoked less than a total of 400 cigarettes; ex-smokers were individuals who had stopped smoking at least one year before the date of the enrollment. Active smoking was a strong risk factor for lung cancer, and gender was an important effect modifier. Higher risk estimates for smoking were found in males in comparison with females, and the highest OR was detected among males currently smoking 25+ cigarettes/day (OR=20.7, 95% CI=7.9-53.9), whereas the risk estimate for the corresponding category in females was lower (OR=5.8, 95% CI=1.5-22.5). In all the models, the interaction term gender*smoking was always considered.

RESULTS

On the basis of a preliminary analysis of the measurements made on about 7000 dosemeters exposed for six-month periods, we estimate a mean radon concentration of 111 Bq m^{-3} (median = 78 Bq m^{-3}, geometric mean = 83 Bq m^{-3}, geometric standard deviation = 2.1); the percentage of results above 200 Bq m^{-3} and 400 Bq m^{-3} were 12% and 2.6 %, respectively. As regards measurements of indoor gamma radiation, the preliminary results of dose rate in air in 3488 rooms are the following: average = 264 nGy h^{-1}, median = 264 nGy h^{-1}, standard deviation = 80 nGy h^{-1}. These values actually include a contribution due to cosmic-rays, which is ~32 nGy h^{-1} and has to be subtracted in order to obtain the dose rate due to gamma radiation from building materials. All these preliminary results confirm the presence of a significant radon and gamma radiation exposure in Lazio.

Table 5 reports the results of a preliminary analysis of the association between lung cancer and radon concentration that consider only subjects having lived in the latest house for at least 15 years. The odds ratios are adjusted for all the variables in the core model. A slightly increased risk is present only in the category of 400+ Bq m^{-3} (OR=1.26) although with wide 95% confidence intervals.

Table 5. Association between lung cancer and radon gas concentration in the last dwellings (lived at least 15 years before the study date).

VARIABLE	CASES (N=263)		CONTROLS (N=265)		O.R.*	(95% C.I.)
	N	%	N	%		
Radon gas concentration (Bq m^{-3})						
<99	163	61.5	178	67.7	1.00	
100-199	72	27.2	64	24.3	0.90	(0.55-1.48)
200-399	23	8.7	20	7.6	1.02	(0.46-2.26)
400+	5	1.9	3	1.1	1:26	(0.20-7.89)

* adjusted for sex, age, sex*age, smoking habit, sex*smoking habit, residence, month at the start of the radon measurement.

The analysis has been repeated for those subjects who had lived in the last dwelling for at least 25 years before the study date (Table 6) and again an increased risk was observed only in the highest radon category (OR=2.26).

Table 6. Association between lung cancer and radon gas concentration in the last dwellings (lived at least 25 years before the study date).

VARIABLE	CASES (N=173)		CONTROLS (N=187)		O.R.*	(95% C.I.)
	N	%	N	%		
Radon gas concentration (Bq m^{-3})						
<99	105	60.7	124	66.3	1.00	
100-199	49	28.3	44	23.5	0.86	(0.47-1.59)
200-399	15	8.7	17	9.1	0.81	(0.31-2.11)
400+	4	2.3	2	1.1	2.26	(0.29-17.40)

* adjusted for sex, age, sex*age, smoking habit, sex*smoking habit, residence, month at the start of the radon measurement.

DISCUSSION

A case control on lung cancer and radon exposure has been conducted in Lazio, an area with relatively high indoor radon concentration levels. Although the complete results of the study are not available yet, there are preliminary indications that the radon risk in this area is compatible with the risk estimates from the available meta-analysis (2). This study will contribute to the European pooling, especially in the region of medium-high exposure categories.

There are several strengths in the present study that should be underlined. We have data on a large set of potential risk factors for lung cancer that were collected from alive incident subjects and alive controls. We put extra efforts to check the residential histories in order to avoid possible misclassifications. The population studied is relatively stable in comparison with subjects investigated in other countries, especially in North America. The radon measurements lasted one year and were based on multiple radon detectors to reduce errors. We had a satisfactory coverage of the relevant time period of exposure that reduce the uncertainties due to imputation of missing values. We inquired on several factors regarding the dwelling that could help in refining the exposure profile.

There limitations of the study as well. The sample size is not large, although comparable with some earlier investigations. We had to rely on proxy dwellings in a large percentage of the cases thus introducing an error in the exposure estimate. However, our parallel survey in the index and in the proxy houses does not indicate that a large difference exists, provided that the houses at the ground floor are not used as proxies for dwellings at high floors. Most of the subjects in our study were urban dwellers and the time that they spent in the house is probably lower than other populations.

An aspect that may be relevant in Italy as well in other countries, like for example Sweden, is that there might be considerable exposure to gamma radiation associated with radon exposure. This aspect is relevant when radioactive building material contributes to indoor radon levels as well as gamma radiation (blue lightweight concrete in Sweden and tuff of volcanic origin in Italy). Observations in another Italian study suggest that there might be a DNA-damaging effect from particularly the indoor gamma radiation (13). Hence, several questions on the respective role of radon and gamma radiation in cancer causation are still open, and they may be addressed with the present and similar studies.

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