Aalborg Universitet

AALBORG UNIVERSITY

Residential Radon and Lung Cancer Incidence in a Danish Cohort

Bräuner, Elvira; Andersen, Claus Erik ; Sørensen , Mette; Andersen , Zorana Jovanovic ; Gravesen , Peter ; Ulbak, Kåre ; Hertel , Ole ; Pedersen, Camilla; Overvad, Kim; Tjønneland , Anne ; Raaschou-Nielsen , Ole

Residential radon and lung cancer incidence in a Danish cohort ☆

Elvira V. Bräuner [a,b,*], Claus E. Andersen [c], Mette Sørensen [a], Zorana Jovanovic Andersen [a,d], Peter Gravesen [e], Kaare Ulbak [f], Ole Hertel [g], Camilla Pedersen [a], Kim Overvad [h], Anne Tjønneland [a], Ole Raaschou-Nielsen [a]

[a] Diet, Genes and Environment, Danish Cancer Society Research Centre, Copenhagen, Denmark
[b] Danish Building Research Institute, Aalborg University, Denmark
[c] Center for Nuclear Technologies, Radiation Research Division, Risø National Laboratory for Sustainable Energy, Technical University of Denmark, Roskilde, Denmark
[d] Center for Epidemiology Screening, Department of Public Health, University of Copenhagen, Denmark
[e] Geological Survey of Denmark and Greenland, Copenhagen, Denmark
[f] National Institute of Radiation Protection, Herlev, Denmark
[g] Department of Environmental Science, Aarhus University, Aarhus, Denmark
[h] Department of Epidemiology, School of Public Health, Aarhus University, Aarhus, Denmark

ARTICLE INFO

ABSTRACT

High-level occupational radon exposure is an established risk factor for lung cancer. We assessed the long-term association between residential radon and lung cancer risk using a prospective Danish cohort using 57,053 persons recruited during 1993–1997. We followed each cohort member for cancer occurrence until 27 June 2006, identifying 589 lung cancer cases. We traced residential addresses from 1 January 1971 until 27 June 2006 and calculated radon at each of these addresses using information from central databases regarding geology and house construction. Cox proportional hazards models were used to estimate incidence rate ratios (IRR) and 95% confidence intervals (CI) for lung cancer risk associated with residential radon exposure with and without adjustment for sex, smoking variables, education, socio-economic status, occupation, body mass index, air pollution and consumption of fruit and alcohol. Potential effect modification by sex, traffic-related air pollution and environmental tobacco smoke was assessed.

Median estimated radon was 35.8 Bq/m^3. The adjusted IRR for lung cancer was 1.04 (95% CI: 0.69–1.56) in association with a 100 Bq/m^3 higher radon concentration and 1.67 (95% CI: 0.69–4.04) among non-smokers. We found no evidence of effect modification.

We find a positive association between radon and lung cancer risk consistent with previous studies but the role of chance cannot be excluded as these associations were not statistically significant. Our results provide valuable information at the low-level radon dose range.

1. Introduction

Radon-222 gas arises from the radioactive decay of radium-226, present throughout the earth's crust and in many building materials. Radon-222 has a 3.8 day half-life, and builds up indoors where most exposure to the general population occurs. Exposure to radon and its radioactive decay products such as the alpha emitters polonium-218 and polonium-214 (Darby et al., 2001), has been classified as a human carcinogen based on epidemiological studies of miners exposed to high levels of radon (International Agency for Research on Cancer (IARC) 1988) and radon exposure is ranked as the second major cause of lung cancer amongst smokers (Darby et al., 2001;International Agency for Research on Cancer (IARC) 2001) and the major cause amongst non-smokers (Samet et al., 2009). The excess risk of lung cancer associated with occupational exposure to radon and progeny was established decades ago (International Agency for Research on Cancer (IARC), 1988) and during the last two decades, more than twenty individual case-control studies have investigated whether lung cancer risk is associated with residential radon. Most of these reported positive associations but only three were significant (Pershagen et al., 1994; Tomasek et al., 2001; Wang et al., 2002). Challenges in these studies included potential for recall bias regarding important confounders

such as smoking, exposure misclassification when reconstructing past residential radon exposures using present 1-year measurements and limited statistical power (Al-Zoughool and Krewski, 2009; Lubin et al., 1995). To overcome power limitations three recent studies combined data from thirteen European (Darby et al., 2005), seven North American (Krewski et al., 2005) and two Chinese (Lubin et al., 2004) studies, resulting in odds ratios (95% CI) of: 1.08 (1.03–1.15), 1.11 (1.00–1.28) and 1.33 (1.01–1.36), respectively, per 100 Bq/m³. These results are compatible with the excess odds ratio predicted by a downward extrapolation of miners data (National Research Council (NRC), 1999) and collectively provide evidence for a link between residential radon and lung cancer risk.

Not much information is available on the association between lung cancer risk and low to medium residential radon levels such as those present in Denmark. Furthermore, participation bias may seriously affect previous studies requiring individual consent, for this reason register based studies making use of predicted doses and avoiding the need for interviews are advantageous (Little et al., 2010). But predicted levels have only been used in one previous study that considered mean county radon levels (Turner et al., 2011). We have now developed and validated a prediction model using register-based input data, which enables estimation of radon in residences in large-scale epidemiological studies (Andersen et al., 2007). We applied this model to the 173,419 residences the cohort members had lived in over a 35 year period and used these predictions to investigate the association between long-term residential radon and risk for lung cancer in Denmark. "Diet, Cancer and Health" is a prospective cohort with detailed information on potential confounders collected at baseline with little potential for recall bias. We used this cohort combined with radon predictions to investigate the association between residential radon and to examine the potential modifying effects of air pollution, environmental tobacco smoke (ETS) and sex.

2. Material and methods

2.1. Design and study participants

Between December 1993 and May 1997, 57,053 persons aged 50–64 years were enrolled in the prospective study "Diet, Cancer and Health". The participants had to be born in Denmark, live in Copenhagen or Aarhus, and cancer free at the time of inclusion (Tjønneland et al., 2007). The baseline examination included a self-administered questionnaire on diet, smoking habits (status, intensity and duration), occupational history, length of school attendance and a number of other health-related items. We calculated smoking intensity by equating a cigarette to 1 g, a cheroot or a pipe to 3 g, and a cigar to 4.5 g of tobacco.

We followed each cohort member for occurrence of any cancer from enrolment until 27 June 2006 in the Danish Cancer Registry (Storm et al., 1997) and the Danish Pathology Data Bank by use of the personal identification number, which is unique for each Danish citizen. We traced the date of death, emigration or disappearance of cohort members in the Central Population Registry by use of the personal identification number. We retrieved the addresses of each participant from 1 January 1971 until 27 June 2006 from the same registry, thus including 35 years of address history dating back to when these cohort persons were in their 20–40s. We noted the dates of moving in and leaving each address, and linked the addresses to the Danish address database to obtain geographical coordinates (denoted in the following as 'geocodes'), which were obtained for 94% of the addresses. Relevant Danish ethical committees and data protection agencies approved the study, and written informed consent was obtained from all participants.

2.2. Exposure assessment

Residential radon concentrations for each address occupied by a participant were predicted with a validated regression model (Andersen et al., 2007). The model uses nine explanatory variables, including geographic location, soil type and dwelling characteristics such as residential type, floor level, basement and building materials. The National Survey and Cadastre identified geographical coordinates for all houses, and the Geological Survey of Denmark and Greenland subsequently identified the local soil from digital soil maps. House construction data were obtained from the Building and Dwelling Register. Model predictions

were corrected for seasonal variation. The model has been successfully validated and previously described in detail (Andersen et al., 2007) as well as applied in two previous studies (Bräuner et al., 2010; Raaschou-Nielsen, 2008). The model predicts low residential radon concentrations with great certainty and detected differences in groups well (Fig. 1) (Andersen et al., 2007).

Information on traffic has previously been collected for the entire study population (Raaschou-Nielsen et al., 2011b). The average concentrations of nitrogen oxides (NO_x) at the front door of each dwelling during the period that the participants occupied the address were assessed by use of the Danish air pollution dispersion modelling system (AirGIS), with high temporal and spatial resolution (Jensen et al., 2001) and including the state-of-the-art urban street pollution model, currently used in more than 17 countries around the world (Kakosimos et al., 2010). AirGIS has been successfully validated (Berkowicz et al., 2007) and applied (Andersen et al., 2011; Raaschou-Nielsen et al., 2011a). We focused on the concentration of NO_x as an indicator for particular matter (PM) from traffic because NO_x correlates strongly with ultrafine particles in Danish streets (Hertel et al., 2001; Ketzel et al., 2003).
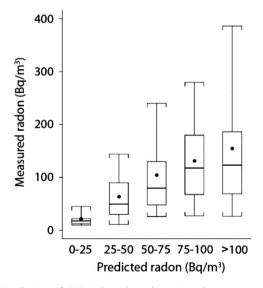
We calculated the time-weighted average radon and NO_x concentrations at each cohort member's residential addresses from 1 January 1971 onwards. These concentrations were entered into the statistical cancer risk model as time-dependent variables.

If radon or air pollution variables could not be calculated because of the failed geocoding of an address, we imputed the concentration calculated at the preceding address. If the concentration was missing for the first address, we imputed the value at the subsequent address. We included only participants for which we imputed radon or air pollution for less than 20% of time from 1 January 1971 until diagnosis or censoring.

2.3. Statistical methods

The end-point for the risk analyses was primary lung cancer. IRRs were estimated by a Cox proportional hazards model with age as the underlying time scale (Thiebaut and Benichou, 2004). We calculated two-sided 95% CIs on the basis of the Wald test statistic for regression parameters in Cox regression models with the PHREG procedure in SAS (version 9.1; SAS Institute, Cary, NC). Analyses were corrected for delayed entry at the time of enrolment, so that persons were considered under risk from time of enrolment into the cohort. People diagnosed with another previous cancer were excluded from the analyses. Censoring occurred at the time of death, emigration or disappearance, the time of a cancer diagnosis, or 27 June 2006 (end of follow-up), whichever came first.

Data were analysed with and without adjustment for sex, body mass index (linear, BMI, kg/m²), length of school attendance (< 8, 8–10 and > 10 years), socio-economic status (SES, low, medium, high and very high) based on work market affiliation, income and education standards for the municipal lived in, smoking status (never, former, present), smoking intensity (lifetime average, linear variable allowing for different slopes below and above 19 g/day), smoking duration (linear, years), ETS (a dichotomous variable indicating no/low versus high exposure: 'no

Fig. 1. Distribution of 758 independent domestic radon measurements for 5 groups of concentrations predicted by the exposure assessment method used in the study. The solid points and the thick horizontal lines mark mean and median values, respectively. The inner boxes mark the 25%–75% quartiles, and the umbrellas mark the 5% and 95% percentiles. Within the 5 groups, the following maximum values were measured: 130, 290, 700, 620, and 1800 Bq/m³. (Reprinted with permission from Radiat. Prot. Dosim. (Andersen et al., 2007)).

smoker in the home and ETS at work for less than 4 h/day' versus 'high'), dietary intake of fruit (linear, g/day) and alcohol (linear, g/day), a dichotomous variable indicating employment for at least one year in an industry or job associated with risk for lung cancer (mining, electroplating, shoe/leather product manufacture, metal processing, steel rolling mill, shipyard, glass/china/pottery industry, roof construction, asphalt/demolition, truck/bus/taxi chauffeur, cement manufacture, asbestos manufacture/insulation, butcher, painter, welder, auto mechanic, waiter or cook), residence type (a dichotomous variable indicating single family home versus apartment) and NO_x at residencies since 1971 (linear, $\mu g/m^3$). We excluded cohort members that had a missing value in any covariate, thus the persons included in the crude and the adjusted analyses are identical. All information on the covariates, with the exception of NO_x was collected at enrolment. We also conducted a sub-analysis including only those persons living in single detached homes at enrolment as radon levels are generally higher and with more variation compared to apartments (Andersen et al., 2001) and because these persons form a more homogeneous group with respect to SES and lifestyle, reducing the potential for confounding.

The assumption of linearity for the continuous variables (residential radon, NO_x, fruit and alcohol consumption, smoking duration, smoking intensity and BMI) in relation to lung cancer was evaluated graphically using linear splines with boundaries placed at the nine deciles among all participants as well as by a numerical test using the likelihood ratio test statistic to compare the model assuming linearity with the linear spline model. Smoking intensity and BMI deviated from linearity, the intensity was, thus, included as a linear variable allowing for different slopes above and below 19 g tobacco/day, whilst BMI was included as a linear variable along with BMI squared.

We formed four intervals for exposure to residential radon using the 25th, 50th and 75th percentiles for all participants as the cut-off points and estimated the IRR for lung cancer for the higher exposure ranges compared with the lowest exposure range. We also estimated the IRRs as linear trends per 100 Bq/m^3 increment in residential radon concentration. PM in ambient air penetrates homes and contributes significantly to indoor PM (Schneider et al., 2004) as does ETS (International Agency for Research on Cancer (IARC), 2004). Presence of indoor PM may modify the association between residential radon and lung cancer because radon decay products easily attach to PM in the air (Tokonami, 2000; Yu et al., 2001) which might modify exposure and airway deposition (Bair, 1995). Also, for women spend more time indoors than men so the apparent association may be greater for them. The possible effect modification by traffic-related air pollution, ETS and sex were analysed by comparing the respective estimate for radon within different strata of the variable. These interactions were tested amongst all participants as well as for smokers and non-smokers separately.

3. Results

Among the 57,053 cohort members, we excluded 571 due to a cancer diagnosis before enrolment, 2 because of uncertain date of cancer diagnosis, 960 for which their address history was not available in the Central Population Registry or their baseline address could not be geocoded, 1365 because of missing data in potential confounders, and 1463 because radon or NO_x exposure was assessed for less than 80% of the time from 1 January 1971 until diagnosis or censoring. The 52,692 included cohort members had lived in a total of 173,419 addresses and were followed up for cancer for an average of 9.6 years (total person years at risk was 506,492). We identified 589 lung cancer cases, corresponding to an overall incidence rate of 116 per 100,000 person years. The crude lung cancer incidence rate was 270 and 30 per 100,000 person years amongst smokers than non-smokers, respectively.

Table 1 shows the characteristics of the cohort members and the lung cancer cases. Sex distribution, alcohol consumption and BMI were similar among cases and cohort members. The proportion of participants living in single detached homes was lower amongst cases than amongst cohort members whilst all smoking variables showed higher exposure among cases. The proportion of participants with a short length of school attendance, low SES and low fruit consumption was higher among cases than among the cohort members and a higher proportion of cases had been employed in an industry or job associated with a higher risk for lung cancer. The median predicted radon concentration was 24 and 39.5 Bq/m^3 for cases and the cohort, respectively, whilst NO_x levels were higher among cases. Table 1 also shows that those living at addresses with high radon tended to live in single-

detached homes, have longer school attendance, have higher SES, be less likely to smoke, be less exposed to ETS, have a higher fruit intake, be less likely to have been employed in an industry or job associated with higher risk for lung cancer and be exposed to lower NO_x levels.

Overall the adjusted IRR associated with 100 Bq/m^3 radon levels was 1.04 (95% CI: 0.69; 1.56) for all participants and 1.14 (95% CI: 0.69; 1.90) when restricting data to participants living in single detached family homes at enrolment (Table 2). Among non-smokers, the IRR was 1.67 (95% CI: 0.69; 4.04) and the IRR was dose-dependently higher over the four radon exposure quartiles (Table 2). The unadjusted results for all participants showed substantially and significantly lower risk of lung cancer in association with higher radon levels and smoking was by far the most important co-variate for the change in the estimated association between radon and lung cancer in model 2 versus model 1 (Table 2). The IRRs for lung cancer in association with a 100 Bq/m^3 higher radon level were slightly higher among those living in single detached homes. There was no evidence that the association between radon and risk of lung cancer was modified by sex, traffic-related air pollution or ETS (Table 3).

4. Discussion

When considering all participants we only found slight evidence supporting an association between residential radon and lung cancer risk and the estimated IRRs were heavily affected by adjustment for smoking. Among non-smokers, we found an insignificantly higher risk for lung cancer in association with residential radon with evidence of a dose-response pattern. We found no effect modification by sources of indoor PM (ETS and indoor PM) or sex. Power constraints played an integral role in the ability of this study to detect significant effects as well as detect effect modifications.

In this study we use a prospective cohort where information on potential confounding factors was collected at enrolment with little potential for recall bias. Complete follow-up for cancer, vital status as well as address history from 1971 onwards was ensured by use of reliable population-based Danish registries.

The use of a newly developed prediction model facilitated estimation of residential radon in as many as 173,419 homes. Validation of the model against independent radon measurements has been reported previously and showed that the model detected differences in groups well (Fig. 1) (Andersen et al., 2007). However, such model-based estimation of radon is inevitably associated with uncertainty, resulting in less precise risk estimates (Andersen et al., 2007). It is clear that measurements in homes would provide a more accurate measure for radon than model-based predictions, but use of measurements in epidemiological studies may also imply disadvantages such as differential participation among cases and controls, a limited number of measurements due to economy constraints and exposure misclassification when reconstructing past residential radon exposures using present 1-year measurements. The main advantage of our novel model-based approach to estimate domestic radon levels is that potential participation bias is avoided and our model allows for a larger study predicting levels in all historical residencies of cohort participants from 1971 onwards at reasonable costs.

In the present study, a number of risk factors for lung cancer were less prevalent among participants living at the higher radon concentrations, including low educational level, low SES, being a smoker, smoking intensity, low fruit intake, risk occupation and traffic-related air pollution. This would result in an underestimation of the association between radon and lung cancer risk in our study.

Table 1
Characteristics of all study participants, cases and those with low and high levels of radon at the residences.

Characteristic	Cohort		Cases		Radon[a] < 66.1 Bq/m³		Radon[a] ≥ 66.1 Bq/m³	
	No. (%)	Median (5–95 percentile)	No. (%)	Median (5–95 percentile)	No. (%)	Median (5–95 percentile)	No. (%)	Median (5–95 percentile)
All participants	52,692 (100)		589 (100)		39,507 (75.0)		13,185 (25.0)	
Age at enrolment		56.1 (50.7–64.1)		59.1 (51.1–64.7)		56.1 (50.7–64.1)		56.2 (50.8–64.1)
Sex								
Male	25,036 (47.5)		298 (50.6)		18,331 (46.4)		6705 (50.8)	
Female	27,656 (52.5)		291 (49.4)		21,176 (53.6)		6480 (49.2)	
Home type at enrolment	30,570 (58.0)		230 (39.0)		20,921 (50.9)		9649 (83.4)	
Single detached home								
Apartment	22,122 (42.0)		359 (61.0)		20,195 (49.1)		1927 (16.7)	
Body Mass Index (kg/m²)		25.3 (20.4–33.3)		25.0 (19.5–32.8)		25.6 (20.4–33.6)		25.3 (20.5–32.4)
School attendance (years)								
< 8	17,382 (33.0)		295 (50.1)		13,425 (34.0)		3957 (30.0)	
≥ 8	35,310 (67.0)		294 (49.9)		26,082 (66.0)		9228 (70.0)	
Socio-economic status[b]								
Low	9007 (17.1)		170 (28.9)		8067 (19.6)		940 (8.1)	
Medium	23,891 (45.3)		238 (40.4)		17,429 (42.4)		6462 (55.8)	
High	8502 (16.2)		95 (16.1)		7366 (17.9)		1136 (9.8)	
Very High	11,292 (21.4)		86 (14.6)		8254 (20.1)		3038 (26.2)	
Smoking								
Non-smoker	33,555 (63.7)		99 (16.8)		26,233 (61.3)		9322 (70.7)	
Present smoker	19,137 (36.3)		490 (83.2)		15 274 (38.7)		3863 (29.3)	
Intensity (g/day)[c]		15.1 (5.0–32.1)		18.2 (9.7–35.4)		15.3 (5.1–32.1)		14.4 (4.5–32.2)
Duration (years)[c]		37.0 (22.0–48.0)		41.0 (31.0–49.0)		37.0 (22.0–48.0)		37.0 (22.0–47.0)
ETS								
No/low	18,827 (35.7)		51 (8.7)		13,360 (33.8)		5467 (41.5)	
High	33,865 (64.3)		538 (91.3)		26,147 (66.2)		7718 (58.5)	
Fruit intake (g/day)								
< 100	17,836 (33.8)		283 (48.0)		13,783 (34.9)		4053 (30.7)	
≥ 100	34,856 (66.2)		306 (52.0)		25,724 (65.1)		9132 (69.3)	
Alcohol								
No	1203 (2.3)		22 (3.7)		1011 (2.5)		192 (1.7)	
Yes	51,489 (97.7)		567 (96.3)		40,105 (97.5)		11,384 (98.3)	
Consumption (g/day)[d]		12.9 (0.71–64.4)		16.3 (1.13–86.3)		15.0 (0.20–86.3)		16.0 (0.71–86.1)
Risk occupation[e]								
No	37,979 (72.0)		354 (60.1)		28,103 (71.1)		9876 (74.9)	
Yes	14,713 (28.0)		235 (39.9)		11,404 (28.9)		3309 (25.1)	
Radon at the address (Bq/m³)		39.5 (9.2–98.6)		24.0 (8.8–92.1)				
NOx at front door[f] (µg/m³)		21.8 (14.8–68.9)		23.9 (15.2–76.5)		23.4 (15.3–77.7)		17.4 (14.4–30.1)

[a] Cut-off based on the 75th percentile for radon concentrations.
[b] Based on work market affiliation, income and education standards for the municipal each person lived in at enrolment.
[c] Based on all ever-smokers.
[d] Based on persons that consume alcohol.
[e] Ever employed in an industry or job associated with higher risk for lung cancer employed for at least 1 year (see Methods Section for specification).
[f] Time-weighted average for the period 1 January 1971 to censoring date.

Indeed, our crude IRRs were much lower than 1.00, indicating an apparent protective association between radon on lung cancer and we observed a substantial effect of adjustment such that this apparent protective association disappeared. However, such strong confounding in the crude model implies the risk for residual confounding in the adjusted model if the most influential confounders are not perfectly adjusted for. Tobacco smoking is by far the most important lung cancer risk factor (Williams and Sandler, 2001); in the present study, smokers had a 9 times higher crude lung cancer incidence rate than non-smokers. To address the risk for residual confounding from smoking, we repeated the analyses for non-smokers, and found an insignificant association between radon and risk for lung cancer with an associated convincing dose-response pattern over the four quartiles of radon exposure. The lack of significant linear response amongst non-smokers was surprising, but only 99 non-smokers developed lung cancer and power constraints may explain this. In light of the findings amongst non-smokers, the lack of association between radon and risk for lung cancer among all study participants might be due to residual confounding from smoking. Furthermore, the higher relative risk estimates for lung cancer in association with radon among non-smokers than smokers should be interpreted along with the above

Table 2

Incidence rate ratios for lung cancer associated with the concentration of radon at the residence.

Radon (Bq/m³)[a]	All residencies[b] IRR (95% CI)			Single detached homes[c] IRR (95% CI)	
	Cases, *n*	Model 1[d]	Model 2 [d,e]	Cases, *n*	Model 3 [f]
All persons					
< 17.6	228	1.00	1.00	63	[g]
17.6–39.5	151	0.74 (0.61–0.91)	0.98 (0.78–1.22)	46	[g]
39.5–66.1	112	0.56 (0.45–0.71)	1.02 (0.77–1.37)	45	[g]
> 66.1	98	0.48 (0.38–0.60)	0.98 (0.70–1.36)	76	[g]
Linear trend per 100 Bq/m³	*589*	*0.39 (0.29–0.52)*	*1.04 (0.69–1.56)*	*230*	*1.14 (0.69–1.90)*
Smoker					
< 17.6	201	1.00	1.00	54	[g]
17.6–39.5	127	0.82 (0.66–1.02)	0.95 (0.75–1.21)	33	[g]
39.5–66.1	90	0.73 (0.57–0.93)	1.00 (0.72–1.37)	31	[g]
> 66.1	72	0.61 (0.46–0.80)	0.90 (0.62–1.30)	61	[g]
Linear trend per 100 Bq/m³	*490*	*0.54 (0.39–0.75)*	*0.92 (0.58–1.46)*	*179*	*1.03 (0.58–1.84)*
Non-smoker					
< 17.6	27	1.00	1.00	9	[g]
17.6–39.5	24	0.91 (0.52–1.58)	1.16 (0.63–2.13)	13	[g]
39.5–66.1	22	0.78 (0.44–1.37)	1.25 (0.60–2.59)	14	[g]
> 66.1	26	0.85 (0.49–1.45)	1.48 (0.68–3.20)	15	[g]
Linear trend per 100 Bq/m³	*99*	*0.82 (0.43–1.56)*	*1.67 (0.69–4.04)*	*51*	*1.71 (0.60–4.92)*

[a] Time-weighted average concentration of radon at residences from 1 January 1971 until censoring. The cut-off points between exposure groups were the 25th, 50th and 75th percentiles for all participants.

[b] Analyses based on 52,692 cohort members, 589 lung cancers and 506,492 person-years at risk.

[c] Analyses based on 30,570 cohort members, 230 lung cancers and 289,831 person-years at risk.

[d] Adjusted for age by using it as time scale in the Cox model.

[e] Adjusted for sex, BMI, length of school attendance, socio-economic status, smoking status (intensity and duration), environmental tobacco smoke, fruit intake, alcohol, residence type, employment in an industry or job associated with higher risk for lung cancer and traffic (time weighted average NO_x exposure). See Methods Section for specifications. Due to exclusion of cohort members with missing value in any covariate, the number of persons is identical in the crude and the adjusted analyses.

[f] As for model 2, but data restricted to persons living in single-detached home at enrolment.

[g] We did not estimate IRRs because of too few cases.

Table 3

Adjusted[a] incidence rate ratios for lung cancer in association with a 100 Bq/m³ increase in domestic radon[b] within strata of sex, NO_x at the residential address, and ETS.

Interaction variable	Cases, *n*	Cohort IRR (95% CI)	P [d]	Cases, *n*	Non-smokers IRR (95% CI)	P	Cases, *n*	Smokers IRR (95% CI)	P
Sex									
Men	298	1.01 (0.62–1.64)	0.86	46	1.35 (0.44–4.11)	0.52	252	0.95 (0.55–1.63)	0.84
Women	291	1.06 (0.64–1.77)		53	2.02 (0.70–5.76)		238	0.89 (0.49–1.61)	
NO_x at front door (μg/m³)									
< 21.8	359	1.23 (0.76–1.99)	0.26	48	1.80 (0.60–5.42)	0.92	311	1.14 (0.67–1.96)	0.17
≥ 21.8	230	0.85 (0.49–1.50)		51	1.68 (0.54–5.23)		179	0.69 (0.36–1.33)	
ETS									
No	–	–	–	34	1.19 (0.34–4.20)	0.45	–	–	–
Yes	–	–	–	65	1.99 (0.74–5.33)		–	–	–

[c]Time weighted average for NO_x.

[a] We adjusted the analyses for sex, age (age used as time scale), BMI, length of school attendance, socio-economic status, smoking status (intensity and duration), environmental tobacco smoke, fruit intake, alcohol, residence type, employment in an industry or job associated with higher risk for lung cancer and traffic (time weighted average NOx exposure), see Methods Section for specifications. However, with no adjustment for the stratification variable.

[b] Radon exposure was entered as a continuous variable in all models of the time-weighted average concentration at residences from 1 January 1971 until censoring.

[d] Test of the null hypothesis that the linear trends are identical, for Wald test for interaction.

mentioned nine times higher crude rates amongst smokers. If radon causes an equal absolute number of lung cases among smokers and non-smokers, the relative risk estimates would appear higher among non-smokers due to the lower crude cancer rates.

The IRR of 1.67 (95% CI: 0.69–4.04) per 100 Bq/m³ radon among non-smokers in the present study is in corroboration with results of several other studies that report highest odds ratios amongst non-smokers when compared to smokers (Darby et al., 1998; Field et al., 2000; Pershagen et al., 1992). Also the IRR of 1.04 (95% CI: 0.69–1.56) for all participants in the present study is in line with the results of combined studies in Europe (Darby

et al., 2005), Northern America (Krewski et al., 2005) and China (Lubin et al., 2004) which report odds ratios (95% CI) of 1.08 (95% CI: 1.03–1.15), 1.11 (95% CI: 1.00–1.28) and 1.33 (95% CI: 1.01–1.36) per 100 Bq/m³ respectively. Thus, the results from Denmark, with lower residential radon concentrations than in most of the other study areas, show results which are generally in line with previous studies of residential radon and risk for lung cancer.

Sample size needs for individual studies of indoor radon and lung cancer under realistic scenarios have indicated that thousands of cases would be required to determine whether exposure to indoor radon posed either no risk or a risk substantially

different from the risk projected on the basis of epidemiological studies of underground miners (Lubin, 1994; Lubin et al., 1995). Our study included 52,692 persons of which 589 developed lung cancer and power constraints may explain the lack of significant effect estimates as well as affect the ability of detecting effect modification.

Radon decay products easily attach to PM in the air (Tokonami, 2000; Yu et al., 2001) and the attachment of radon decay products to aerosols in the air reduces the fraction of the so-called unattached radon decay products and increases the airborne concentration of attached radon decay products due to a significant reduction in the plate out on indoor surfaces (Abu-Jarad, 1997). Attachment furthermore significantly influences the deposition pattern in the lungs due to the altered size distribution of the radon decay products (Bair, 1995). Radon and indoor particles might, operate together and influence risk and we have previously reported a non-significant pattern of stronger associations between radon and leukaemia among children living at streets with high traffic density (Bräuner et al., 2010). We, therefore, hypothesised that the presence of indoor PM modifies the association between residential radon and risk of lung cancer and tested the hypothesis using outdoor traffic-related air pollution at the residence which penetrates indoors (Schneider et al., 2004) and ETS (among non-smokers) as markers of indoor PM. Our results do not support this theory, but power constraints made it difficult to detect such modifications in the present study. No previous study has reported on a possible interaction between residential radon and traffic-related air pollution at the residence and one previous study reports an insignificantly higher relative risk for lung cancer in association with residential radon for those exposed to ETS (Lagarde et al., 2001). More work is needed to elucidate whether such an interaction between indoor radon and PM exists.

5. Conclusion

Despite weak statistical evidence arising from power constraints the results of the present prospective cohort study are fully compatible with an association between residential radon and risk for lung cancer as detected in three previous meta analyses and provide important evidence at the low end of the low end of the residential dose curve.

Acknowledgment

References

Abu-Jarad, F., 1997. Indoor cigarette smoking: Uranium contents and carrier of indoor radon products. Radiat. Meas. 28, 579–584.

Al-Zoughool, M., Krewski, D., 2009. Health effects of radon: a review of the literature. Int. J. Radiat. Biol. 85, 57–69.

Andersen, C.E., Ulbak, K., Damkjaer, A., Gravesen, P., 2001. [Radon i danske boliger: Kortlægning af lands-, amts- og kommuneværdier].: Sundhedsstyrelsen, Statens Institut for Strålehygiejne.

Andersen, C.E., Raaschou-Nielsen, O., Andersen, H.P., Lind, M., Gravesen, P., Thomsen, B.L., Ulbak, K., 2007. Prediction of ^{222}Rn in Danish dwellings using geology and house construction information from central databases. Radiat. Prot. Dosim. 123, 83–94.

Andersen, Z.J., Hvidberg, M., Jensen, S.S., Ketzel, M., Loft, S., Sørensen, M., Tjønne-land, A., Vervad, K., Aaschou-Nielsen, O., 2011. Chronic obstructive pulmonary disease and long-term exposure to traffic-related air pollution: a cohort study. Am. J. Respir. Crit. Care Med. 183, 455–461.

Bair, W.J., 1995. The ICRP human respiratory tract model for radiological protection. Radiat. Prot. Dosim. 60, 307–310.

Berkowicz, R., Ketzel, M., Jensen, S.S., Hvidberg, M., Raaschou-Nielsen, O., 2007. Evaluation and application of OPSM for traffic pollution assessment for a large number of street locations. Environ. Modell. Softw.

Bräuner, E.V., Andersen, C.E., Andersen, H.P., Gravesen, P., Lind, M., Ulbak, K., Hertel, O., Schüz, J., Raaschou-Nielsen, O., 2010. Is there any interaction between domestic radon exposure and air pollution from traffic in relation to childhood leukemia risk? Cancer Causes Control 21, 1961–1964.

Darby, S., Hill, D., Doll, R., 2001. Radon: a likely carcinogen at all exposures. Ann. Oncol. 12, 1341–1351.

Darby, S., Whitley, E., Silcocks, P., Thakrar, B., Green, M., Lomas, P., Miles, J., Reeves, G., Fearn, T., Doll, R., 1998. Risk of lung cancer associated with residential radon exposure in south-west England: a case-control study. Br. J. Cancer 78, 394–408.

Darby, S., Hill, D., Auvinen, A., Barros-Dios, J.M., Baysson, H., Bochicchio, F., Deo, H., Falk, R., Forastiere, F., Hakama, M., Heid, I., Kreienbrock, L., Kreuzer, M., Lagarde, F., Makelainen, I., Muirhead, C., Oberaigner, W., Pershagen, G., Ruano-Ravina, A., Ruosteenoja, E., Rosario, A.S., Tirmarche, M., Tomasek, L., Whitley, E., Wichmann, H.E., Doll, R., 2005. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ 330, 223.

Field, R.W., Steck, D.J., Smith, B.J., Brus, C.P., Fisher, E.L., Neuberger, J.S., Platz, C.E., Robinson, R.A., Woolson, R.F., Lynch, C.F., 2000. Residential radon gas exposure and lung cancer: the Iowa radon lung cancer study. Am. J. Epidemiol. 151, 1091–1102.

Hertel, O., Jensen, S.S., Andersen, H.V., Palmgren, F., Wåhlin, P., Skov, H., Nielsen, I.V., Sørensen, M., Loft, S., Raaschou-Nielsen, O., 2001. Human exposure to traffic pollution. Experience from Danish studies. Pure Appl. Chem. 73, 137–145.

International Agency for Research on Cancer (IARC), 1988. Monographs on the evaluation of carcinogenic risks to humans. Man-Made Mineral Fibres and Radon, vol. 43. International Agency for Research on Cancer 1988, Lyon France.

International Agency for Research on Cancer (IARC), 2001. Monographs on the evaluation of carcinogenic risks to humans. Ionizing Radiation Part 2. Some Internally Deposited Radionuclides, vol. 78. International Agency for Research on Cancer 2001, Lyon France.

International Agency for Research on Cancer (IARC), 2004. Monographs on the evaluation of carcinogenic risks to humans, Tobacco Smoke and Involuntary Smoking. International Agency for Research on Cancer 2004, Lyon France.

Jensen, S.S., Berkowicz, R., Hansen, H.S., Hertel, O., 2001. A Danish decision-support GIS tool for management of urban air quality and human exposures. Transp. Res. D: Transp. Environ. 6, 229–241.

Kakosimos, K.E., Hertel, O., Ketzel, M., Berkowicz, R., 2010. Operational street pollution model (OSPM) GÇô a review of performed application and validation studies, and future prospects. Environ. Chem. 7, 485–503.

Ketzel, M., Wåhlin, P., Berkowicz, R., Palmgren, F., 2003. Particle and trace gas emission factors under urban driving conditions in Copenhagen based on street and roof-level observations. Atmos. Environ. 37, 2735–2749.

Krewski, D., Lubin, J.H., Zielinski, J.M., Alavanja, M., Catalan, V.S., Field, R.W., Klotz, J.B., Letourneau, E.G., Lynch, C.F., Lyon, J.I., Sandler, D.P., Schoenberg, J.B., Steck, D.J., Stolwijk, J.A., Weinberg, C., Wilcox, H.B., 2005. Residential radon and risk of lung cancer: a combined analysis of 7 North American case-control studies. Epidemiology 16, 137–145.

Lagarde, F., Axelsson, G., Damber, L., Mellander, H., Nyberg, F., Pershagen, G., 2001. Residential radon and lung cancer among never-smokers in Sweden. Epidemiology 12, 396–404.

Little, M.P., Wakeford, R., Lubin, J.H., Kendall, G.M., 2010. The statistical power of epidemiological studies analyzing the relationship between exposure to ionizing radiation and natural background radiation, with special reference to childhood leukemia and natural background radiation. Radiat. Res. 174, 387–402.

Lubin, J.H., 1994. Invited commentary: lung cancer and exposure to residential radon. Am. J. Epidemiol. 140, 323–332.

Lubin, J.H., Boice Jr., J.D., Samet, J.M., 1995. Errors in exposure assessment, statistical power and the interpretation of residential radon studies. Radiat. Res. 144, 329–341.

Lubin, J.H., Wang, Z.Y., Boice Jr., J.D., Xu, Z.Y., Blot, W.J., De, W.L., Kleinerman, R.A., 2004. Risk of lung cancer and residential radon in China: pooled results of two studies. Int. J. Cancer 109, 132–137.

National Research Council (NRC), 1999. Health effects of exposure to radon. Committee on the Biological Effects of Ionizing Radiations.

Pershagen, G., Akerblom, G., Axelson, O., Clavensjo, B., Damber, L., Desai, G., Enflo, A., Lagarde, F., Mellander, H., Svartengren, M., 1994. Residential radon exposure and lung cancer in Sweden. N. Engl. J. Med. 330, 159–164.

Pershagen, G., Liang, Z.H., Hrubec, Z., Svensson, C., Boice Jr., J.D., 1992. Residential radon exposure and lung cancer in Swedish women. Health Phys. 63, 179–186.

Raaschou-Nielsen, O., 2008. Indoor radon and childhood leukaemia. Radiat. Prot. Dosim. 132, 175–181.

Raaschou-Nielsen, O., Andersen, Z.J., Hvidberg, M., Jensen, S.S., Ketzel, M., Sorensen, M., Hansen, J., Loft, S., Overvad, K., Tjonneland, A., 2011a. Air pollution from traffic and cancer incidence: a Danish cohort study. Environ. Health 10, 67.

Raaschou-Nielsen, O., Andersen, Z.J., Hvidberg, M., Jensen, S.S., Ketzel, M., Sorensen, M., Loft, S., Overvad, K., Tjonneland, A., 2011b. Lung cancer incidence

and long-term exposure to air pollution from traffic. Environ. Health Perspect. 119, 860–865.

Samet, J.M., vila-Tang, E., Boffetta, P., Hannan, L.M., Olivo-Marston, S., Thun, M.J., Rudin, C.M., 2009. Lung cancer in never smokers: clinical epidemiology and environmental risk factors. Clin. Cancer Res. 15, 5626–5645.

Schneider, T., Jensen, K.A., Clausen, P.A., Afshari, A., Gunnarsen, L., Wåhlin, P., Palmgren, F., Nielsen, O.J., Fogh, C.L., 2004. Prediction of indoor concentration of 0.5-4mm particles of outdoor origin in an uninhabited apartment. Atmos. Environ. 38, 6349–6359.

Storm, H.H., Michelsen, E.V., Clemmensen, I.H., Pihl, J., 1997. The Danish Cancer Registry–history, content, quality and use. Dan. Med. Bull. 44, 535–539.

Thiebaut, A.C., Benichou, J., 2004. Choice of time-scale in Cox's model analysis of epidemiologic cohort data: a simulation study. Stat. Med. 23, 3803–3820.

Tjønneland, A., Olsen, A., Boll, K., Stripp, C., Christensen, J., Engholm, G., Overvad, K., 2007. Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and Health: a population-based prospective cohort study of 57,053 men and women in Denmark. Scand. J. Public Health 35, 432–441.

Tokonami, S., 2000. Experimental verification of the attachment theory of radon progeny onto ambient aerosols. Health Phys. 78, 74–79.

Tomasek, L., Kunz, E., Muller, T., Hulka, J., Heribanova, A., Matzner, J., Placek, V., Burian, I., Holecek, J., 2001. Radon exposure and lung cancer risk—Czech cohort study on residential radon. Sci. Total Environ. 272, 43–51.

Turner, M.C., Krewski, D., Chen, Y., Pope III, C.A., Gapstur, S., Thun, M.J., 2011. Radon and lung cancer in the American cancer society cohort. Cancer. Epidemiol. Biomarkers Prev. 20, 438–448.

Wang, Z., Lubin, J.H., Wang, L., Zhang, S., Boice Jr., J.D., Cui, H., Zhang, S., Conrath, S., Xia, Y., Shang, B., Brenner, A., Lei, S., Metayer, C., Cao, J., Chen, K.W., Lei, S., Kleinerman, R.A., 2002. Residential radon and lung cancer risk in a high-exposure area of Gansu Province, China. Am. J. Epidemiol. 155, 554–564.

Williams, M.D., Sandler, A.B., 2001. The epidemiology of lung cancer. Cancer Treat. Res. 105, 31–52.

Yu, K.N., Wong, B.T.Y., Lau, B.M.F., Nikezic, D., 2001. Indoor dose conversion coefficients for radon progeny for different ambient environments. Environ. Sci. Technol. 35, 2136–2140.