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BRIEF REPORT

Is there any interaction between domestic radon exposure and air pollution from traffic in relation to childhood leukemia risk?

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Abstract
Background In a recent population-based case–control study using 2,400 cases of childhood cancer, we found a statistically significant association between residential radon and acute lymphoblastic leukemia risk.
Hypothesis Traffic exhaust in the air enhances the risk association between radon and childhood leukemia.
Methods We included 985 cases of childhood leukemia and 1,969 control children. We used validated models to calculate residential radon and street NO_x concentrations for each home. Conditional logistic regression analyses were used to analyze the effect of radon on childhood leukemia risk within different strata of air pollution and traffic density.
Results The relative risk for childhood leukemia in association with a 10^3 Bq/m^3-years increase in radon was 1.77 (1.11, 2.82) among those exposed to high levels of NO_x and 1.23 (0.79, 1.91) for those exposed to low levels of NO_x ($p_{interaction,}$ 0.17). Analyses for different morphological subtypes of leukemia and within different strata of traffic density showed a non-significant pattern of stronger associations between radon and childhood leukemia within strata of higher traffic density at the street address.
Interpretation Air pollution from traffic may enhance the effect of radon on the risk of childhood leukemia. The observed tendency may also be attributed to chance.

Keywords Air pollution · Radon · Interaction · Case–control · Childhood leukemia

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Introduction

Geographical correlations between residential radon and childhood leukemia have been shown in several studies [1, 2]. We have previously reported that domestic radon exposure is significantly associated with the risk of childhood acute lymphoblastic leukemia [3]. So far, it has been assumed that the primary mechanism by which radon gas may damage stem cells for acute lymphoblastic leukemia is by dissolution of radon gas in fatty tissues leading to exposure of the red bone marrow [4]. However, as recently proposed, an alternative pathway may exist where inhaled radon decay products provide a high dose to lymphocyte stem cells circulating through the bronchial mucosa [5].

Radon decay products easily attach to particulate matter in the air such as dust, smoke, and traffic exhaust particles [6, 7]. The evidence of traffic exhaust being a risk factor for childhood cancer on its own is inconclusive [8], but radon and traffic exhaust particles might operate together to enhance risk. 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 [9]. Attachment furthermore significantly influences the deposition pattern in the lungs due to the altered size distribution of the radon decay products [10]. Although the presence of aerosols in the air will inevitably affect the dose of radon decay products to the lung, it is difficult to predict the effect from theoretical dosimetric models. However, the demonstrated interaction between smoking and indoor radon with respect to risk for lung cancer [11] suggests that the presence of aerosols in the air could enhance the effect of radon decay products on cancer risk. Populations in industrialized countries spend 85–90% of their time in indoor environments [12], and recent studies have demonstrated that up to 60–70% of outdoor fine particles (<2.5 μm) penetrate indoors [13].

We test the novel hypothesis that traffic exhaust that penetrate indoors at locations with high traffic density results in a stronger risk association between radon and childhood leukemia. We use NO_x and traffic density as proxy variables for traffic exhaust, because these variables are highly correlated with particle concentrations in streets. To our knowledge, this has never been studied.

Methods

The case–control study design has previously been described in detail [1]. In the present study, we included children (below age 15 years) registered in the Danish Cancer Registry [14] from 1968 to 1994 with a diagnosis of leukemia, and two control children matched individually by sex and birthday. Control children were randomly selected from the files of the Danish Central Population Registry, covering the entire Danish population. Eligible controls for a case were all Danish children of the same sex and without a cancer diagnosis and under risk at the age where the case received the diagnosis.

Residential radon concentrations for each child address from birth to diagnosis (and a similar time period for the individually matched control children) were predicted using a validated regression model using input data from Danish registries on geographical location, soil type and dwelling characteristics such as house type, floor, basement, and building materials. Model predictions were corrected for seasonal variation [15]. We calculated cumulative radon exposure as the product of exposure level and time occupied at each address during childhood.

Traffic density has previously been collected, and nitrogen oxide gasses (NO_x ($NO + NO_2$)) calculated for each address of cases and control children [16]. The average concentrations of NO_x at the front door of each dwelling during the period that the families occupied the address were assessed by use of the Operational Street Pollution Model [17]. Briefly, the model can be used to calculate air pollution levels from information on the exact configuration of the street in front of the address (the width of the street, the height of the buildings and their distance from the street, and street sections with no buildings), the traffic density on the street (vehicles per day), the proportion of heavy vehicles, and the average traffic speed (km/h) in combination with information on emission factors (g/km) for the Danish car fleet, meteorological variables (wind speed, temperature, and solar radiation), and background levels of air pollution [16]. NO_x is highly correlated with particle number concentration in Danish streets [18, 19], and both NO_x and traffic density were used as proxy measures for traffic exhaust particles in the present study.

The relative risk and 95% confidence intervals (CIs) were estimated from conditional logistic regression models with the PHREG procedure of SAS (version 9.1; SAS Institute, Cary, NC), respecting the matched design. Possible associations between radon and risk of leukemia and its morphological subtypes were investigated using the continuous values by increments of 10^3 Bq/m^3-years in a log-linear model [3, 16]. The possible interaction between exposure to traffic particles and radon was analyzed by comparing the respective effect estimate for radon from the model above in different strata of NO_x concentration and traffic density at the addresses. The cut-off point for NO_x was equivalent to the median value among all the case and control children, and the cut-off points for traffic density were adapted from previous studies [16, 20].

Results and discussion

We identified 1,153 cases of childhood leukemia and 2,306 controls. Air quality and radon data were available for 985 (85%) cases and 1,969 (85%) controls, and this subset formed the basis for all analyses. Cases had slightly higher radon concentrations and slightly lower NO_x and traffic values than the control children (Table 1).

Table 2 confirms our previous finding of a significant association between radon exposure and childhood acute lymphoblastic leukemia. Further, the table shows a consistent pattern of higher relative risk estimates for all leukemia combined within the strata for higher NO_x

Table 1 Exposure of the study population to radon, NO_x, and traffic[a]

	Cases ($n = 985$) (5th pct; 50th pct; mean; 95th pct)	Controls ($n = 1{,}969$) (5th pct; 50th pct; mean; 95th pct)
Cumulated radon exposure at the residencies during childhood (Bq/m^3 years)	19; 204; 300; 939	16; 192; 282; 878
Time-weighted NO_x at residencies (ppb)	4.23; 8.62; 10.50; 23.48	4.18; 8.78; 11.20; 26.93
Time-weighted traffic density at the street address (vehicles/street/day)	20; 259; 947; 3731	20; 282; 1,058; 4,610

[a] We identified 1,153 cases of childhood leukemia and 2,306 controls, but air quality and radon data were available for 85% of these resulting in 985 cases and 1,969 controls, which formed basis for all analyses

Table 2 Risk for childhood leukemia in association with a 10^3 Bq/m^3-years increase in domestic radon exposure[a] within different strata of NO_x concentration and traffic density at residential addresses'

Interaction	All leukemias			Morphologic subtype[b]								
				Acute lymphoblastic			Acute non-lymphoblastic			Other unknown subtypes		
Variable	$N_{cases/control}$	Relative risk (95% CI[e])	p^f	$N_{cases/control}$	Relative risk (95% CI[e])	p^f	$N_{cases/control}$	Relative risk (95% CI[e])	p^f	$N_{cases/control}$	Relative risk (95% CI[e])	p^f
None	985/1,969	1.48 (1.03, 2.13)		731/1,461	1.78 (1.16, 2.75)		127/254	0.61 (0.25, 1.46)		127/254	1.84 (0.63, 5.38)	
$NO_x^c < 8.71$	506/971	1.23 (0.79, 1.91)	0.17	382/719	1.52 (0.89, 2.57)	0.38	54/118	0.70 (0.24, 2.04)	0.78	70/134	0.93 (0.25, 3.44)	0.04
$NO_x^c \geq 8.71$	479/998	1.77 (1.11, 2.82)		349/742	2.01 (1.15, 3.51)		73/136	0.57 (0.18, 1.78)		57/120	4.49 (1.06, 19.12)	
$TD^d < 500$	642/1223	1.32 (0.88, 1.98)	0.37	479/918	1.78 (1.10, 2.89)	0.83	78/168	0.47 (0.17, 1.27)	0.07	85/137	1.26 (0.37, 4.24)	0.79
$TD^d \geq 500$	343/746	1.72 (0.98, 3.02)		252/543	1.64 (0.83, 3.24)		49/86	1.76 (0.43, 7.21)		42/117	1.55 (0.33, 7.23)	
$TD^d < 5000$	943/1877	1.47 (1.02, 2.11)	0.37	701/1394	1.77 (1.14, 2.74)	0.50	122/244	–		120/239	–	
$TD^d \geq 5000$	42/92	3.31 (0.54, 20.20)		30/67	4.38 (0.45, 42.82)		5/10	–		7/15	–	

[a] Radon exposure was entered as a continuous variable in all models

[b] Based on the international classification of diseases for oncology (ICD-O; 1976 version)

[c] Time-weighted average for total nitrogen oxides ($NO_2 + NO$): ppb

[d] *TD* Traffic density, time-weighted average: vehicles/day

[e] *CI* confidence interval

[f] *p* value for interaction

concentration and higher traffic density, although no significant interaction was found. The relative risk estimates for acute lymphoblastic leukemia and "other/unknown" leukemia (of which a vast majority is expected to be acute lymphoblastic leukemia) showed a similar pattern of insignificantly higher risk estimates within the stratum of higher traffic pollution, except for the strata separated at 500 vehicles per day, which showed similar effects of radon on acute lymphoblastic leukemia within both strata. The relative risk estimates for acute non-lymphoblastic leukemia in association with radon exposure were similarly highest within the stratum of highest traffic density. The relative risk estimates were below 1.0 within both strata of NO_x indicating a protective effect, but the small number of cases and the wide confidence intervals indicate that this might be a chance finding. Adjustment of the analyses for birth order, mother's age [16], and electromagnetic fields from 50 Hz high-voltage facilities [21] only changed the effect estimates marginally (results not shown).

Overall, the results indicate that high levels of traffic pollution at the residence might enhance an association between residential radon and childhood leukemia. The underlying mechanism may be complementary mutations caused by traffic-related air pollution and radon or may relate to modification in the radiation dose, because radon progeny attaches to aerosols [22]. This novel hypothesis could be further tested by studying possible interactions between radon and environmental tobacco smoke.

We did not have air quality data and/or radon data for fifteen percent of cases and an equal percentage of controls due to problems in obtaining or geocoding addresses. The residential movement pattern, and thereby the radon concentration, might be different for this 15% of children, leaving the remaining 85% with a slightly different radon level than that of the whole study population. Although this 15% "non-participation" depends on objective factors unrelated to the child, the family, or the disease, we cannot rule out the possibility for selection bias.

Conclusion

This study suggests that high levels of air pollution from traffic at the residence might enhance a risk association between radon and childhood leukemia. However, no statistically significant interaction was demonstrated, and the observed tendency may be attributable to chance.

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