Occupational exposure to dusts and risk of renal cell carcinoma

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BACKGROUND: Occupational exposures to dusts have generally been examined in relation to cancers of the respiratory system and have rarely been examined in relation to other cancers, such as renal cell carcinoma (RCC). Although previous epidemiological studies, though few, have shown certain dusts, such as asbestos, to increase renal cancer risk, the potential for other occupational dust exposures to cause kidney damage and/or cancer may exist. We investigated whether asbestos, as well as 20 other occupational dust exposures, were associated with RCC risk in a large European, multi-center, hospital-based renal case–control study.

METHODS: General occupational histories and job-specific questionnaires were reviewed by occupational hygienists for subject-specific exposure duration and cumulative exposure. No association between RCC risk and asbestos exposure was observed.

RESULTS: Among participants ever exposed to dusts, significant associations were observed for glass fibres (OR: 2.1; 95% CI: 1.1–3.9), mineral wool fibres (OR: 2.5; 95% CI: 1.2–5.1), and brick dust (OR: 1.5; 95% CI: 1.0–2.4). Significant trends were also observed with exposure duration and cumulative exposure. No association between RCC risk and asbestos exposure was observed.

CONCLUSION: Results suggest that increased RCC risk may be associated with occupational exposure to specific types of dusts. Additional studies are needed to replicate and extend findings.

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Occupational dust exposures are generally thought to adversely affect the respiratory system and in some studies have been associated with cancers of the lung, trachea, bronchus, oral cavity, pharynx, and larynx (Maier et al, 1990; Marsh et al, 1990; Alberg et al, 2007). Although the kidney is not in direct contact with dusts through inhalation, increased risk of kidney damage and cancer have been observed in occupational studies of asbestos and crystalline silica exposures (Kolev et al, 1970; Markovic and Arambasic, 1971; Enterline et al, 1987; Smith et al, 1989; Pesch et al, 2000; El-Safty et al, 2003; Steenland, 2005; Pascual and Borque, 2008) and particulates that are primarily inhaled in occupational settings and mainly linked to respiratory cancers (Alberg et al, 2007).

Because kidney cancer and damage has previously been associated with occupational dust exposures (Kolev et al, 1970; Markovic and Arambasic, 1971; Enterline et al, 1987; El-Safty et al, 2003; Steenland, 2005; Pascual and Borque, 2008), we examined this association in the Central and Eastern European Renal Cell Carcinoma (CEERCC) study, where we also were able to extend these findings to dusts other than those studied previously. Here, we investigated whether occupational dust exposures were associated with an increased risk of renal cell carcinoma (RCC) among participants enrolled in a large, multi-centered renal case–control study conducted in Central and Eastern Europe, an area with historically heavy industrial exposures and one of the highest rates of RCC in the world (International Agency for Cancer Research, GLOBCANC, 2011).

MATERIALS AND METHODS

The CEERCC study is a large hospital-based multi-center case–control study of renal cancer conducted across four Central and Eastern European countries (Moscow, Russia; Bucharest, Romania; Lodz, Poland; and Prague, Olomouc, Ceske-Budejovice,
For each subject, exposure metrics for each dust agent that were assessed included the following: (1) ever exposure, (2) duration of exposure expressed as the total number of years subjects worked in a job in which exposure was possible, and (3) cumulative exposure, calculated as the duration of exposure in years for each job multiplied by the midpoint of the frequency category and by the intensity weight of the job, summed across all of the subject’s jobs. To calculate cumulative exposure across jobs with varying frequencies of exposure, frequency weights (0.03, 0.175, and 0.65, respectively) were assigned to the three frequency categories, corresponding to the midpoint of the ranges.

To estimate RCC risk and associations with occupational exposure history, odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated with logistic regression models adjusting for sex, age (continuous), center, smoking status (never, ever), body mass index (BMI) at interview, and self-reported hypertension (no, yes). Occupational co-exposures with a significant \( P < 0.05 \) \( r^2 > 0.50 \), identified using Spearman correlation coefficients, that were shown to modify OR and 95% CI values by at least 10% were also included for adjustment. The strength of associations between co-exposures is presented as a matrix in Supplementary Table 1. The number of women exposed in our study was too small to warrant separate analyses, so both sexes were combined. Subgroup analyses with a 10-year and a 20-year lag period between exposure and diagnosis were conducted to restrict analyses to subjects with a sufficient latency period from occupational exposure to cancer diagnosis. The results of the 10-year lag are not presented because findings are similar to that of the 20-year lag. Subjects were evaluated as never and ever exposed groups. Duration and cumulative exposure categories were divided into level of exposure based on the 50th percentile cut-point among all subjects. All analyses were conducted in STATA 9.0 (STATA Corporation, College Station, TX, USA).

RESULTS

Selected characteristics of the study population by case–control status are shown in Table 1. Participants were similar with respect to age. Cases, however, were more likely to be female and to have excess BMI and hypertension. Cases were less likely to smoke after adjustment for sex, age, study center, BMI, and self-reported hypertension the inverse association with smoking, as previously reported, was no longer significant (van der Hel et al, 2008).

Renal cancer risk associations by occupational dust exposure are provided in Table 2. Increased ORs were observed among subjects ever occupationally exposed to glass fibres (OR: 2.1; 95% CI: 1.1–3.9), mineral wool fibres (OR: 2.5; 95% CI: 1.2–5.1), and brick dust (OR: 1.5; 95% CI: 1.0–2.4). Results by duration and cumulative exposure are shown in Table 3 for agents for which a significant association was found in the analysis of ever exposure, duration of exposure, or cumulative exposure. Duration of exposure in years revealed a two- to three-fold increase in cancer risk for occupational exposures to glass fibres (P-trend = 0.03), mineral wool fibres (P-trend = 0.02), and brick dust (P-trend = 0.01). Similar findings were also shown for cumulative exposure to these dust agents. RCC risk was lower among individuals exposed to graphite dust by duration in years (P-trend = 0.02) and cumulative exposure (P-trend = 0.049), though ever exposure to graphite dust was not associated with risk. Exposure to asbestos and other dust agents listed in Table 2 were not associated with RCC risk by duration or cumulative exposure (data not shown).

The relationship between renal cancer risk and these occupational dust exposures was also examined allowing for a 20-year lag between exposure and diagnosis (Supplementary Table 2). Similar associations between RCC risk and exposure were observed;
mineral fibre workers, a lack of association between kidney cancer mortality risk and exposure to airborne fibre concentrations among mineral wool and fibreglass plant workers was reported by Marsh et al (1990). No relationship between kidney cancer risk and exposure to wool or mineral wool was observed in a Montreal multi-cancer case–control study of 100 kidney cancer patients (Siemiatycki et al, 1986) or in a cohort of mineral wool production workers in Denmark (Olsen and Jensen, 1984). The lack of supporting evidence from cohort studies, therefore, reduces the plausibility of an association between RCC risk and exposure to both glass and mineral wool fibres. Among workers suspected of brick dust exposure, a nonsignificant elevation in RCC risk was observed among bricklayers in a small population-based case–control study in Europe (Mellmengaard et al, 1994) and elevated kidney cancer mortality risk was seen among concrete/terrazzo finishers in a surveillance study of construction workers across the United States (Robinson et al, 1995). On the other hand, using occupational mortality surveillance data, the National Institute for Occupational Safety and Health reported a significant increase in kidney cancer risk among female workers employed in the pottery industry, where silica exposure occurs (Burnett and Dosemeci, 1994). Possible explanations for the lack of consistent findings across studies include insufficient power due to limited number of cases or exposed subjects, exposure misclassification, or co-existing occupational/environmental exposures that were not accounted for; therefore, additional sufficiently powered and well-conducted studies are needed to determine if these associations are real.

Although it is questionable whether inhaled dust particles can reach the kidney, the relationship between renal cancer and the dust exposures observed in our study is plausible as they contain silica; however, the relationship is less plausible for the fibres as the silica is bound. In 1996, the International Agency for Cancer Research classified crystalline silica as a group 1 human carcinogen based on epidemiological and laboratory animal studies that demonstrated silica exposure was associated with increased lung cancer (IARC, 1997). Furthermore, growing scientific evidence over the past few decades suggests that chronic silica exposure can induce nephrotoxicity and cause fibrosis, glomerulonephritis, and degenerative changes in tubular epithelium (Kolev et al, 1970; Markovic and Arambasic, 1971; IARC, 1997; El-Safty et al, 2003; Steenland, 2005). In a recently published review of occupational epidemiological studies, Steenland (2005) reported excess risk of end stage renal disease among silica-exposed workers. Excess kidney cancer risk has also been reported among silica-exposed workers in two earlier cohort studies (Cooper et al, 1992; Hobbesland et al, 1999). In our case–control study, however, no association between occupational respirable free crystalline silica exposure and RCC risk was observed. Animal studies have demonstrated that silica exposure may affect DNA replication, gene expression, and repair (Ding et al, 2002; Fabini and Hubbard, 2003). Animal studies have also shown silica to interfere with mitotic spindle formation and the segregation of chromosomes, which could eventually induce aneuploidy (Ding et al, 2002; Fabini and Hubbard, 2003; Vodicka et al, 2010). Because the exact mechanism involved in the carcinogenicity of silica remains unclear and it is questionable whether silica from fibres is available for bioactivity, until additional epidemiological studies are conducted, the possible association between renal carcinoma and silica exposure remains uncertain.

In our study a large proportion of subjects who were occupationally exposed to glass (57% of cases and 42% of
controls) or mineral wool (86% of cases and 64% of controls) fibres were also occupationally exposed to asbestos. The relationship between RCC risk and glass and mineral wool fibres in our study may also be explained by the asbestos-like properties shared by these fibres (Kamp, 2009; Agency for Toxic Substances and Diseases Registry, http://www.atsdr.cdc.gov/toxprofiles/tp161.pdf). Similar to asbestos, inhaled mineral wool and glass fibre particulates are capable of depositing deep within the lungs, due to their needle-like dimensions, reaching the alveoli, and provoking phagocytes to attack (Agency for Toxic Substances and Diseases Registry, http://www.atsdr.cdc.gov/toxprofiles/tp161.pdf). The ingested particles produce an inflammatory response where fibroblasts deposit, produce, and proliferate tissue leading to the development of cancer (Agency for Toxic Substances and Diseases Registry, http://www.atsdr.cdc.gov/toxprofiles/tp61.pdf and http://www.atsdr.cdc.gov/toxprofiles/tp161.pdf). Evidence of asbestos inhalation associated with kidney cancer in studies of workers has been inconsistent (Partanen et al, 1991; Sali and Boffetta, 2000; Agency for Toxic Substances and Diseases Registry, http://www.atsdr.cdc.gov/toxprofiles/tp161.pdf). In our study, no association between RCC risk and occupational exposure to asbestos was shown. Moreover, a meta-analysis of 37 cohort studies conducted on workers suspected of asbestos exposure revealed limited evidence of an association between kidney cancer risk and asbestos exposure. Standardised mortality ratios/standardised incidence ratios (SMR/SIR) across the studies ranged from 0.22 to 5.00 and pooled analyses revealed no significant findings for chrysotile or amphibole asbestos exposures (Sali and Boffetta, 2000). Thus, it is unclear whether our findings of an association with glass and mineral wool fibres are real.

The inverse association between graphite dust exposure and RCC risk in our study was unexpected. Results are suspected to be chance related, due to the small number of exposed participants (cases N = 12, controls N = 32) and limited power to conclude

### Table 2 (Continued)

| High confidence exposures | Case | Control |
|---------------------------|------|---------|
|                            | N    | %      | N    | %   | OR   | 95% CI |
| Wood dust                 |      |        |      |     |      |        |
| Unexposed                 | 742  | 89.9   | 1082 | 91.5| 1.0  |        |
| Exposed                   | 83   | 10.1   | 101  | 8.5 | 1.2  | 0.9 – 1.7|
| Hard wood dust\(^1\)      |      |        |      |     |      |        |
| Unexposed                 | 798  | 96.6   | 1141 | 96.4| 1.0  |        |
| Exposed                   | 28   | 3.4    | 43   | 3.6 | 0.7  | 0.4 – 1.3|
| Soft wood dust\(^1\)      |      |        |      |     |      |        |
| Unexposed                 | 760  | 92.0   | 1095 | 92.4| 1.0  |        |
| Exposed                   | 66   | 8.0    | 90   | 7.6 | 1.3  | 0.8 – 2.0|
| Ash                       |      |        |      |     |      |        |
| Unexposed                 | 808  | 97.8   | 1152 | 97.2| 1.0  |        |
| Exposed                   | 18   | 2.2    | 33   | 2.8 | 0.6  | 0.4 – 1.2|

Abbreviations: BMI = body mass index; CI = confidence interval; OR = odds ratio. Adjusted for age, sex, centre, BMI, self-reported hypertension, and smoking status (ever, never). High confidence exposures include only those exposures assessed with a confidence of probable (40 – 90%) or definite (>90%). Occupational exposures to ceramic fibres (cases N = 1; controls N = 1) and charcoal dust (cases N = 1; controls N = 1) are not shown due to small number of exposed. Model also adjusted for occupational: \(^1\)Asbestos exposure. \(^2\)Inorganic insulation dust exposure. \(^3\)Amphibole asbestos exposure. \(^4\)Chrysotile asbestos exposure. \(^5\)Brick dust exposure. \(^6\)Concrete dust exposure. \(^7\)Sand exposure. \(^8\)Coke combustion fume exposure. \(^9\)Hard wood dust exposure. \(^10\)Soft wood dust exposure.

### Table 2

Table 2. Ever occupationally exposed to dusts and risk of renal cell carcinoma.

| High confidence exposures | Case | Control |
|---------------------------|------|---------|
|                            | N    | %      | N    | %   | OR   | 95% CI |
| Inorganic insulation dust\(^a\) |      |        |      |     |      |        |
| Unexposed                 | 750  | 91.9   | 1100 | 93.5| 1.0  |        |
| Exposed                   | 66   | 8.1    | 77   | 6.5 | 1.3  | 0.9 – 2.1|
| Asbestos\(^b\)            |      |        |      |     |      |        |
| Unexposed                 | 738  | 90.3   | 1062 | 90.5| 1.0  |        |
| Exposed                   | 79   | 9.7    | 112  | 9.5 | 0.8  | 0.5 – 1.2|
| Chrysotile asbestos\(^c\) |      |        |      |     |      |        |
| Unexposed                 | 778  | 94.8   | 1107 | 93.7| 1.0  |        |
| Exposed                   | 43   | 5.2    | 75   | 6.3 | 0.7  | 0.4 – 1.2|
| Amphibole asbestos\(^d\) |      |        |      |     |      |        |
| Unexposed                 | 800  | 97.1   | 1151 | 97.3| 1.0  |        |
| Exposed                   | 24   | 2.9    | 32   | 2.7 | 1.4  | 0.6 – 3.1|
| Graphite dust\(^e\)       |      |        |      |     |      |        |
| Unexposed                 | 669  | 81.6   | 947  | 80.1| 1.0  |        |
| Exposed                   | 151  | 18.4   | 236  | 19.9| 0.9  | 0.7 – 1.2|
| Sand                      |      |        |      |     |      |        |
| Unexposed                 | 657  | 79.6   | 881  | 74.8| 1.0  |        |
| Exposed                   | 168  | 20.4   | 297  | 25.2| 0.9  | 0.7 – 1.1|
| Respirable free crystalline silica |       |        |      |     |      |        |
| Unexposed                 | 774  | 93.9   | 1117 | 94.3| 1.0  |        |
| Exposed                   | 50   | 6.1    | 67   | 5.7 | 1.0  | 0.7 – 1.5|
| Concrete dust\(^f\)       |      |        |      |     |      |        |
| Unexposed                 | 726  | 87.9   | 1028 | 87.0| 1.0  |        |
| Exposed                   | 100  | 12.1   | 154  | 13.0| 0.8  | 0.6 – 1.1|
| Cement dust\(^g\)         |      |        |      |     |      |        |
| Unexposed                 | 718  | 86.9   | 1020 | 86.1| 1.0  |        |
| Exposed                   | 108  | 13.1   | 164  | 13.9| 1.3  | 0.8 – 2.0|
| Brick dust\(^h\)          |      |        |      |     |      |        |
| Unexposed                 | 753  | 91.3   | 1103 | 93.2| 1.0  |        |
| Exposed                   | 72   | 8.7    | 80   | 6.8 | 1.5  | 1.0 – 2.4|
| Coal dust\(^i\)           |      |        |      |     |      |        |
| Unexposed                 | 783  | 94.8   | 1121 | 94.5| 1.0  |        |
| Exposed                   | 43   | 5.2    | 65   | 5.5 | 0.9  | 0.6 – 1.4|
| Carbon black              |      |        |      |     |      |        |
| Unexposed                 | 819  | 99.3   | 1167 | 98.5| 1.0  |        |
| Exposed                   | 6    | 0.7    | 18   | 1.5 | 0.5  | 0.2 – 1.2|
| Soot                      |      |        |      |     |      |        |
| Unexposed                 | 784  | 95.1   | 1119 | 94.7| 1.0  |        |
| Exposed                   | 40   | 4.9    | 43   | 5.3 | 0.9  | 0.6 – 1.3|
| Coke dust\(^j\)           |      |        |      |     |      |        |
| Unexposed                 | 814  | 98.5   | 1164 | 98.1| 1.0  |        |
| Exposed                   | 12   | 1.5    | 22   | 1.9 | 0.7  | 0.3 – 1.6|
| Graphite dust\(^k\)       |      |        |      |     |      |        |
| Unexposed                 | 813  | 98.5   | 1153 | 97.3| 1.0  |        |
| Exposed                   | 12   | 1.5    | 32   | 2.7 | 0.5  | 0.3 – 1.0|
A statistically meaningful result for ever exposure (47%) or for trend analysis for cumulative exposure (58%). Furthermore, the only study to examine cancer risk in graphite electric workers reported a nonsignificant 1.8-fold increased SMR for kidney cancer (Merlo et al., 2004).

High participation rates, a large sample size, inclusion of only newly diagnosed and histologically confirmed cancers, use of job-specific questionnaire modules to collect individual-specific exposure information, and expert-based exposure assessment teams were some of the strengths of our study. Sufficient statistical power to detect relatively small associations between RCC risk and exposure (ever vs never) to occupational dust was possible due to the large sample size of the study; however, power for some of the exposure–response relationships was limited due to the small number of exposed subjects. Other limitations of our study included the possibility of inaccurate or incomplete recall of all occupational histories and the use of hospital-based controls, which may not be representative of the general non-diseased reference population, even though we attempted to address this issue by recruiting controls with a wide range of disease diagnoses. Moreover, lack of data regarding personal protective equipment, ventilation at specific jobs, working conditions, and possible environmental exposures to dust (i.e., pollution), may have increased the likelihood of exposure misclassification and possibly confounded results. Although exposure misclassification is always of concern, the result of any misclassification would likely diminish the elevated risks and significant trends towards the null if the misclassification were non-differential. In our study, the prevalence of occupational exposures to certain dusts (e.g., asbestos silica, chrysotile asbestos, and amphibole asbestos) were compatible to the prevalence of exposure reported in other recently published case–control studies in Central and Eastern Europe (Krstev et al., 2005; Zeka et al., 2006; Carel et al., 2007), which strengthens our exposure assessment confidence. Even so, assessment of jobs and exposures obtained through interview should be critically evaluated, as the likelihood of exposure misclassification is higher than for studies with actual exposure measurements. For this reason, analysis of dust exposures was evaluated among jobs with only high confidence exposures, which were assessed by raters blinded to disease status. Restricting the analyses to these subjects generally increased the risks slightly. Additionally, although we were able to control for known RCC risk factors, such as self-reported hypertension, smoking, and BMI, other potential risk modifiers (i.e., other occupational exposures, genetics, diet, environmental exposures, working conditions) were not considered and may have biased our results due to uncontrolled confounding. Self-reported hypertension status was unconfirmed and was a potential source of misclassification. Finally, 63 tests were preformed of which 11 were chance findings due to multiple comparison tests is probable. However for some agents, such as brick dust, this is unlikely as the association with RCC risk became stronger with increasing years and cumulative exposure and restriction of jobs with high confidence.

In summary, the results of our study found a possible association between RCC risk and workers in Central and Eastern Europe exposed to glass fibre, mineral wool fibre, and brick dust. When analyses were restricted to high-confidence exposures, the association between these dust agents and RCC risk became stronger and statistically significant. Additionally, exposure–response relationships for these agents showed both a significant and linear increase in RCC risk by cumulative exposure and duration (except for glass fibres) of exposure. Similar associations were also observed when analyses were examined allowing for a 20-year lag between exposure and diagnosis. The lack of association between RCC and occupational exposures to silica and asbestos in our study, however, justifies the need for further investigation. Our observed associations also require replication before meaningful inferences can be concluded.

Supplementary Information accompanies the paper on British Journal of Cancer website (http://www.nature.com/bjc)
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