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Coal combustion and lung cancer risk in XuanWei: a possible role of silica?

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Key words
PAHs; silica; lung cancer

Summary
Background: *XuanWei County, Yunnan province, has the highest lung cancer mortality rates among men and women in China. The high mortality has been linked to the use of smoky (bituminous) coal for heating and cooking. Research to date has suggested that exposure to polycyclic aromatic hydrocarbons (PAHs) is one of the main contributors to the observed risk. More recently exposure to crystalline silica has been suggested as another contributing factor.* **Methods:** *We used data of indoor benzo[a]pyrene (BaP) and silica level and lung cancer mortality at the communal level from previous reports to discuss etiological hypotheses on the lung cancer epidemics in XuanWei County.* **Results:** *We estimated that PAH exposure as measured by benzo[a]pyrene (BaP) can explain a significant part of the excess risk but not fully (Odd Ratio (OR) ~ 3 as compared to an observed OR=8 for smoky coal users versus smokeless coal users). This leaves open the possibility of other contributing exposures. Exposure to crystalline silica however would likely only result in an increased risk (OR) of less than 1.5 and as such silica seems not to be the main exposure of interest. However, this does not exclude that risks are present because of the specific physic-chemical characteristics of the silica in smoky coal or that there is an interaction between silica and PAH exposures.* **Conclusion:** *More detailed exposure assessment of indoor air pollution due to the use of smoky coal and subsequent linkage on an individual level to ongoing epidemiological studies should provide more insight in the etiology of lung cancer in this region.*

Riassunto
«Combustione di carbone e rischio di tumore polmonare in XuanWei: un possibile ruolo della silice?». *La contea di XuanWei, nella provincia di Yunnan, presenta i tassi di mortalità per tumore polmonare più elevati nella Repubblica Popolare Cinese, sia nella popolazione maschile che in quella femminile. Questo aumento della mortalità è stato associate all'uso di carboni bituminosi come combustibile sia per cucinare che a scopo di riscaldamento. Gli studi finora condotti hanno suggerito che uno dei maggiori contributi eziologici provenga dall'emissione di idrocarburi aromatici policiclici (IPA). Più recentemente, è stato suggerito che l'esposizione a silice cristallina possa costituire un ulteriore co-fattore. Abbiamo utilizzato dati sulle concentrazioni indoor di benzo[a]pirene (BaP) e silice e sui tassi di mortalità per tumore polmonare, disponibili a livello comunale da precedenti pubblicazioni, allo scopo di discutere ipotesi eziologiche sull'epidemia di neoplasie polmonari nella contea di XuanWei. In questo lavoro, abbiamo*

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stimato che l'esposizione a IPA, misurata come concentrazione di BaP, potrebbe solo in parte spiegare l'eccesso di rischio (Odds Ratio (OR) ~ 3 a confronto di OR=8 osservato negli utilizzatori di carboni bituminosi in riferimento ai non utilizzatori di tali carboni). Ciò lascia spazio alla possibilità di un contributo da parte di altri possibili fattori. Tra questi, l'esposizione a silice potrebbe dar luogo ad un aumento del rischio uguale o inferiore a 1,5 volte; pertanto, la silice come tale non sembra costituire il principale fattore di rischio cancerogeno per il polmone nella contea di Xuan Wei. Tuttavia, ciò non esclude che un ruolo eziologicamente rilevante sia da attribuirsi alle specifiche caratteristiche fisico-chimiche dei particolati silicei emessi dai carboni bituminosi e la loro interazione con gli IPA. Misurazioni dettagliate della contaminazione indoor associata all'utilizzo dei carboni bituminosi ed il loro collegamento all'esposizione individuale in studi epidemiologici attualmente in corso potrebbero contribuire a fare maggiore chiarezza sull'eziologia del tumore polmonare in questa contea della Cina.

Introduction

Lung cancer rates in XuanWei, Yunnan Province, China have been among the highest in China for both males and females. Previous epidemiological studies carried out in this region have suggested that the observed excess risk could be attributed mainly to burning smoky coal (bituminous coal) indoors for heating and cooking without adequate ventilation (15).

Traditionally, fuel was burned in an unvented firepit in the floor of the living area. Such burning generates high indoor concentrations of airborne particulate matter, polycyclic aromatic hydrocarbons (PAHs) and other organic compounds (22). In a recent study, significant variation was observed in the lung cancer risk by smoky coal subtype (11). The leading hypothesis has been that the increased risks and heterogeneity in risk can be attributed to high concentrations and variability in volatile organic compounds such as PAHs. Indeed, exposure levels to PAHs as measured by benzo[a]pyrene (BaP) have been exceptionally high reaching levels that have been experienced by coke oven production workers (8). Moreover, two ecological studies found a strong correlation (Spearman Rho >0.9) between BaP air concentration levels and lung cancer mortality and risk at the commune level in XuanWei (8, 11). However, it has been noted that the PAH-hypothesis potentially does not fully explain why this coal, which seems similar to other bituminous coals that are used elsewhere in China for cooking and heating, so carcinogenic (14). Such a comparison however is hampered by the fact that no good quantitative exposure studies have been published to date from different areas in China, including XuanWei, using bituminous coal.

In search of possible other constituents present in smoky coal combustion emissions that might be responsible for at least part of the observed increase in lung cancer risk, crystalline silica has been proposed. This is in part based on the observation of ultra and nanoparticulate crystalline silica being present in smoky coal (21). A recent study focussing more in depth on the silica hypothesis indeed found that coal in XuanWei had exceptionally high levels of authigenic quartz, which was mostly smaller than 10 μm (14). A subsequent ecological analyses showed that the quartz contents of coal was correlated to lung cancer mortality at the commune level while the measured volatile contents of which an unknown part are PAHs was not. Interestingly, analyses with a measure of the potential for silica-volatile interaction (PSVI), which is a multiplication of the free silica and volatile contents of the coal standardised for energy potential of the coal, showed a stronger correlation with lung cancer mortality than free silica alone (Spearman Rho 0.66 versus 0.53, respectively). This possible interaction is of interest as an interaction between silica and PAH exposure also has been observed in an occupational study in Chinese mines and pottery factories (6).

In this short paper we focus on the two leading hypothesis (i.e. PAHs and quartz) being responsible for the observed increased lung cancer risk in XuanWei.

The Polycyclic Aromatic Hydrocarbon hypothesis

Polycyclic aromatic hydrocarbons (PAHs) are a class of chemicals. Characterized by the presence of two or more benzene rings, which derive mainly from the incomplete combustion of organic material. These include hundreds of compounds, among which the best known is BaP, often used as a marker of exposure to (particle bound) PAHs. Recently, the IARC classified BaP as carcinogenic to humans (Group 1) as well as several industries where workers are exposed to PAHs based on sufficient evidence for an increased risk of lung cancer (3, 19). The highest (historical) occupational exposures to PAHs occur in coke oven production workers where levels up to a few $\mu g/m^3$ have been reported (20). A recent meta-analyses reported a summary relative risk (RR) of 1.58 (95%CI 1.47-1.69) for lung cancer among coke production workers with the highest individual study risk estimate of around 3.(2) Armstrong and Gibbs (1) derived a dose-response curve for BaP exposure and lung cancer among coke oven workers, which predicted a relative risk of 2.68 at 100 $\mu g/m^3$ BaP years using a power risk-curve. Assuming that exposures in XuanWei were around 0.5 $\mu g/m^3$ (median BaP exposure concentration in XuanWei; figure 1 panel A), and that subjects are exposed for 55 years, 24 hrs a day instead of 8 hrs, and year round instead of 220 working days, we would predict a cumulative exposure of 140 $\mu g/m^3$ BaP years. This estimate of cumulative exposure using the power risk function from the coke oven workers would predict a relative risk of around 2.8. This calculated risk is lower than what has been observed in epidemiological studies in XuanWei where the relative risk of smoky coal use was estimated to be around 8 as compared to subjects using smokeless coal (11). However, it is questionable if the risk function of coke oven workers can be used as the mixture of PAHs will have been different in coke oven production operations as to combustion of smoky coal indoors. Furthermore, the timing of exposure is different with exposure in occupational settings starting for most individuals after the age of 18 while exposure in XuanWei due to indoor air pollution starts in utero. It has been suggested that timing of exposure can have an influence on the observed risk later in life. For instance, it has been hypothesised that exposure to PAHs in early life confers an increased risk of breast cancer compared with adult exposure to PAHs (4). Similar observations have been made for exposure to ionizing radiation (13). As such it might be that exposure to PAHs in utero or in early life when lungs are still developing confers a different risk than when exposed in adulthood as would be the case for coke oven workers.

Further evidence of the role of PAHs in the observed lung cancer risk in XuanWei can be found in the fact that key genes involved in the metabolism of PAHs have been found to be associated with increased risks in this area (10, 12). Furthermore, mutation spectra of lung tumours from patients in this area have shown a distinct mutation pattern, which is consisted with PAH exposure (7). These observations strengthen the fact that there is a distinct PAH effect in the observed increased risk in XuanWei. However, given the difference between the observed and predicted lung cancer risks based on estimated BaP exposure levels in XuanWei there might be other biological processes or exposures that play a role as well. One of these possible factors is the presence of nanosized silica particles in smoky coal of this region.

The Silica hypothesis

In 1997 the International Agency for Research on Cancer (IARC) classified inhaled crystalline silica as a human carcinogen, but acknowledged limitations in the epidemiologic data, including inconsistencies across studies and the lack of extensive exposure-response data (9). It has been hypothesised that these inconsistencies could be due to differences in host factors, physico-chemical characteristics of the surface of silica particles, exposure circumstances (e.g. concurrent exposures), and the mineral ore composition (5). Steenland et al. (18), conducted a pooled exposure analyses among 10 cohorts of silica-exposed workers and found a significant linear dose-response association with an

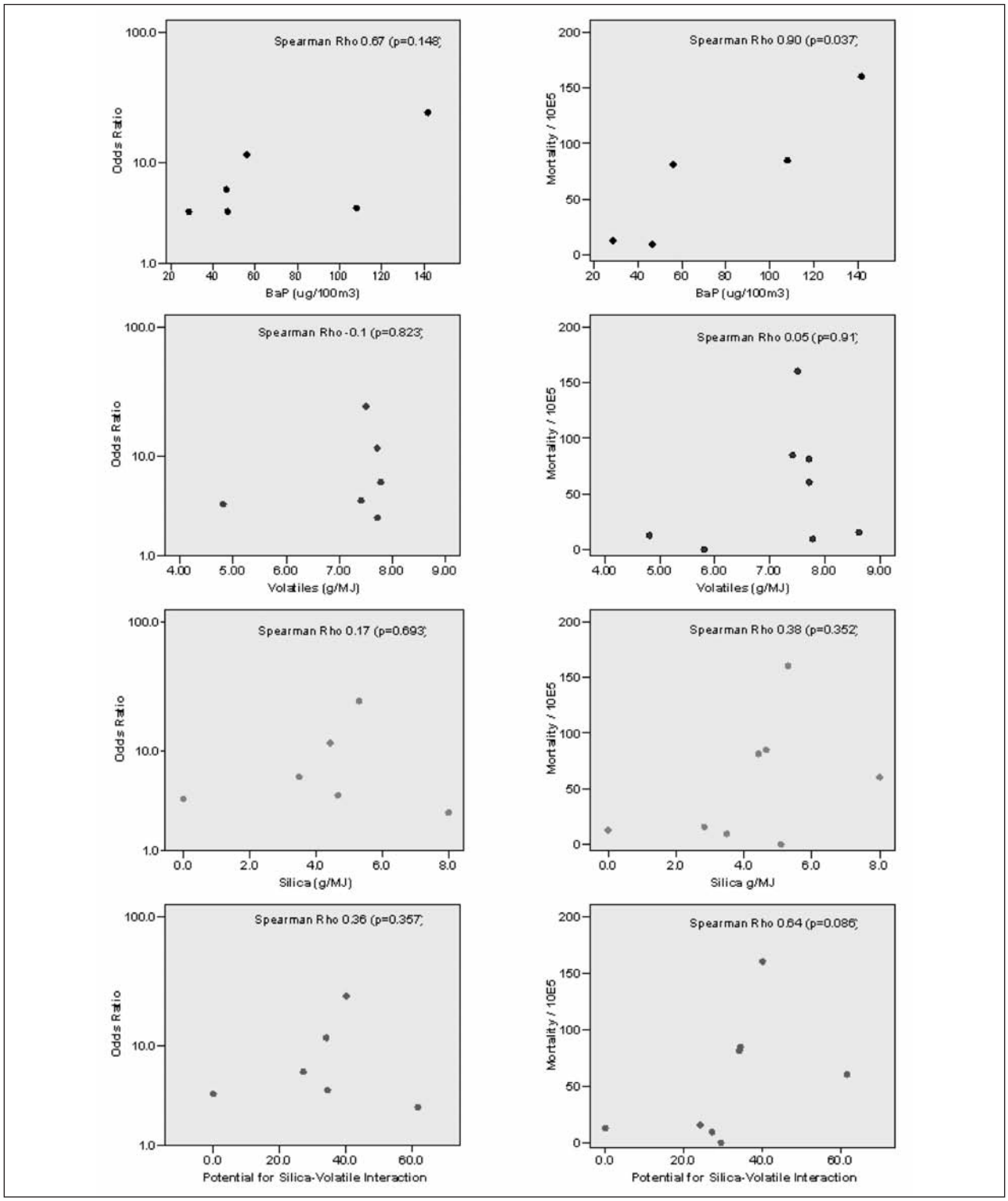

Figure 1 - Risk of lung cancer and lung cancer mortality by BaP, volatiles, silica, and potential for silica-volatile interaction by commune in XuanWei. Figures have been adapted from Lan et al, He et al, and Large et al. (8,11,14). Results differ from original publications due to standardisation of communes [communes: Laibin (Chenguan, Rongcheng, Laibin); Longtan; Baoshan; Longchang, Yagchang (Haidai, Banqiao); Wenxing (Puli); TangTang; Tianba; Yangliu]

odds ratio of 1.5 for subjects exposed between 5.4 and 12.8 mg/m^3 years.

Recently, it was shown that coal from XuanWei might have an unusual high concentration of quartz (13.5 wt%) of which 35-55% occurs at <10 μm grains.(14) No quantitative data is available to date on quartz exposure in the air due to combustion of coal or discharge of the ashes. Data is however available for particulate exposure (PM10) which can be around 1.6 mg/m^3 for unvented stoves (22). If we assume that 13.5% of the weight of the airborne particulates is quartz, which is likely a significant overestimation given the low volatility of silica as compared to many of the other compounds, and if we further assume that about 50% of the silica is less than 10 μm in diameter than we can estimate that the exposures (PM10) to quartz at a maximum can be around 0.1 mg/m^3. These levels are similar to exposure levels encountered by miners (18) and as indicated are likely a severe overestimation of the airborne quartz exposure in households burning coal with a high quartz contents. However, even with these unrealistic high estimated quartz exposure levels an increase of at maximum 50% in lung cancer risk would be predicted based on the dose-response association published by Steenland et al. (18). It seems therefore unlikely that silica in itself would be a major contributor to the observed lung cancer risk in XuanWei. Of course, as has been observed in occupational studies the lung cancer potential of quartz depends for part on its physico-chemical characteristics. Quartz in the XuanWei area has been characterized as being of nanosize.

Recent studies on mono dispersed amorphous silica nanoparticles have shown that cytotoxicity of silica nanoparticles is strongly related to its particle size (i.e. surface area) (17). It is unclear if these observations can be equated to crystalline silica (16) but it strongly suggest that it would be of importance, as in occupational studies, to consider silica particle size distribution in future studies in XuanWei to better understand the contribution of quartz in the observed increased lung cancer risk in this area.

Discussion

Lung cancer rates in XuanWei have been among the highest in China for both males and females. Previous epidemiological studies carried out in this region have suggested that the observed excess risk could be attributed mainly to burning smoky coal (bituminous coal) indoors for heating and cooking without adequate ventilation (16). More recently, a contribution of quartz has been hypothesised. These hypotheses are mainly driven by the presence of these exposures and ecological analyses linking these exposures to the observed lung cancer risk. In figure 1 we present the risk estimates as published by Lan et al. (11) and lung cancer mortality figures as published by Large et al. (14) by published exposure concentrations of BaP, volatiles, silica and the potential for silica-Volatile Interaction on a commune level (8, 11, 14). These figures differ from the original publications because of standardisation of the data at the commune level. However, these results confirm that moderate to strong correlations are observed between BaP concentration and lung cancer risk on a commune level. Correlations with silica tended to be slightly weaker. However, results are relatively uncertain given the limited number of observations. Moreover, while BaP are based on measured air concentrations the other measures are estimated based on coal characteristics adding to the uncertainty in exposure estimation. It remains therefore to be researched if indeed silica has an etiological role in the observed cancer risk in XuanWei and if indeed interactions between silica and PAHs exist.

Conclusion

Ecological studies have shown that PAH and possibly quartz play a role in the observed lung cancer risk in XuanWei. Further investigation of these exposures and lung cancer risk is warranted. Etiological observations of this environmental study might also provide information relevant for occupational settings where PAH and silica exposure might occur concurrent.

NO POTENTIAL CONFLICT OF INTEREST RELEVANT TO THIS ARTICLE WAS REPORTED

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