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Biomass fuels and lung cancer

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ABSTRACT

It is estimated that about 2.4 billion people around the world, or about 40% of the world's population, depend on biomass fuels (wood, charcoal, dung, crop residue) to meet their energy needs for cooking and heating. The burden is especially high in Asia. Studies suggest that levels of pollutants including particulate matter <10 μm and polycyclic aromatic hydrocarbons indoors in homes where biomass fuels are used far exceed levels recommended as safe. While *in vitro* and *in vivo* studies in animal models suggest that wood smoke emission extracts are mutagenic and carcinogenic, epidemiologic studies have been inconsistent. In this review, we discuss possible carcinogenic mechanisms of action of biomass fuel emissions, summarize the biological evidence for carcinogenesis, and review the epidemiologic evidence in humans of biomass fuel emissions as a risk factor for lung cancer. Finally, we highlight some issues relevant for interpreting the epidemiologic evidence for the relationship between biomass fuel exposure and lung cancer: these include methodologic considerations and recognition of possible effect modification by genetic susceptibility, smoking status, age of exposure and histologic type.

Key words: air pollution, environmental and occupational health and epidemiology, lung cancer.

INTRODUCTION

Biomass fuels refer to the use of biologic materials (both of animal or plant origin) as fuel, and principally refers to wood, crop residues, dung and charcoal. Fuel types used for domestic needs such as cooking and heating can be categorized into nonsolid and solid fuels.[1] Nonsolid fuels include kerosene, liquefied petroleum gas (LPG), natural gas and electricity. Biomass fuels (such as dung, wood, charcoal and crop residues) comprise one of the two main groups of solid fuels, the other being coal. Biomass fuels have been the principal sources of fuel for much of human history. While communities tend to shift away from traditional fuel sources such as wood, dung, charcoal or crop residues to piped gas, kerosene, liquid petroleum gas or electricity for heating and cooking[2] as they become more developed, biomass fuels continue to be important fuel sources in less developed countries and rural areas around the world.

Negative health effects of solid fuels were identified as early as the late 18th century, when coal soot was recognized as a cause of scrotal cancer in chimney sweeps.[3] In the 20th century, both coal and biomass fuels have been subject to intensive investigations into their possible negative health effects. The results of this research suggest that some constituents of biomass smoke emissions have irritant, inflammatory and carcinogenic properties. Smoke emissions have carcinogenic and mutagenic properties in studies conducted on *in vitro* systems, and using animal models. At the population level, there is epidemiological evidence that biomass fuels are associated with respiratory and cardiovascular diseases such as lower respiratory tract infections, chronic obstructive lung disease and coronary heart disease.

The epidemiologic evidence for coal fuel use as a lung carcinogen is convincing, and the International Agency for Research in Cancer has classified indoor emissions from household combustion of coal as carcinogenic.[4] The evidence for biomass fuels however, is less strong. This review focuses on the lung carcinogenic potential of biomass fuel smoke emissions. We consider the extent of exposure to biomass fuels in the world today. We summarize the biological evidence for a role of biomass fuel emissions in carcinogenesis. We then review the epidemiologic evidence for biomass fuel exposure as a risk factor for lung

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cancer in humans, and highlight several issues relevant to the design and conduct of epidemiologic studies aiming to examine this association.

CURRENT EXTENT OF USE OF BIOMASS FUELS

The World Health Organization estimates that about 3 billion people today, or about 50% of the world's population, use solid fuel for their household energy needs. Of these, 600 million use coal, whereas 2.4 billion use wood, charcoal, animal dung and crop wastes.[5] The largest numbers of biomass fuel users come from China and India: 27% of the population in China depend on wood for energy, and in India, about 58% depend on wood and 11% on dung for energy.[5] More than 90% of the population in countries classified as Least Developed Countries (including Asian countries such as Myanmar, Bangladesh and Cambodia) depend on solid fuels (primarily biomass fuels) for their energy needs.[5]

Countries generally move up the 'energy ladder'[2] with economic development, as people shift from using biomass fuels to more modern fuels such as kerosene, LPG and electricity as their economic situation improves. In developed parts of the world, use of biomass fuels is uncommon, at less than 5% of the population. Within each country, biomass fuel use is linked to poverty, with poorer communities reporting higher use levels.[6] Biomass fuel use is also more common in rural areas. Rural areas may not have the infrastructure to allow access to modern fuels. Costs of biomass fuels are also typically very low, and in many rural areas, 'free', as users harvest the necessary fuels themselves. Because exposure to biomass fuels is so prevalent, the population impact (i.e. population attributable risk) of any adverse health effects associated with biomass fuel use is likely to be very large even where the relative risks associated with use is small.

BIOMASS FUEL SMOKE EMISSION AND ITS COMPOSITION

Combustion of any fuel produces emission of complex mixtures containing particles, semi-volatile matter and gases. Modern fuels burn more efficiently, resulting in a greater proportion of the intended end products of carbon dioxide and water (as steam). Biomass fuels are much less efficiently burned, because of the greater difficulty in mixing the fuel with air during burning.[7] Consequently, a larger fraction of the carbon contained in the fuel is not fully combusted to carbon dioxide, and instead forms both particulate matter as well as a variety of organic compounds. Impurities in the fuels also result in the formation of inorganic compounds including carbon monoxide, sulphur dioxide, nitric oxide and ammonia.[4] Hundreds of individual compounds have been detected in wood smoke samples to date, attesting to the complexity of these emissions. Most of these constituents are organic carbon compounds. Alkanes with 1–7 carbons, alkenes with 2–7 carbons, aromatic compounds such as benzene, xylene, toluene and styrene, a variety of polycyclic aromatic hydrocarbons (PAHs) and substituted PAHs, alkanols, carboxylic acids, aldehydes and ketones, alkyl esters and phenolic compounds have all been identified in wood smoke emissions.[4,8] A wide variety of metals including nickel and arsenic have also been identified in wood smoke emissions, reflecting uptake of these elements by trees.[9] Table 1 summarizes constituents that have been identified in biomass fuel emission.

Table 1 Biomass smoke constituents[†]

Class	Constituents
Inorganic compounds	Ammonia
	Carbon monoxide
	Nitric oxide
	Sulphur dioxide
Hydrocarbons	Alkanes and alkenes
	Aromatics including benzene and toluene
	Polycyclic aromatic hydrocarbons
Other organic compounds	Aldehydes and ketones
	Alkanols
	Alkyl esters
	Carboxylic acids
	Coumarins and flavonoids
	Methoxylated phenolic compounds
	Phytosteroids
	Substituted aromatic compounds
	Sugar derivatives
	Terpenoids
Metals	

[†]Data obtained from: International Agency for Research on Cancer.[4]

PAHs are present in both the gas phase as well as the particle phase of emissions, with lower molecular-weight compounds (2–4 aromatic rings) found predominantly in the gaseous phase of emissions, and higher molecular weight PAHs adhered to smoke particles.[10] PAHs can also be found on surfaces of rooms where biomass fuel-powered stoves are used.[11] In addition to the respiratory route, PAHs can therefore also enter the human body through ingestion and via dermal absorption.[12]

CARCINOGENICITY OF BIOMASS FUEL SMOKE EMISSION AND ITS CONSTITUENTS

The key compounds of interest with regard to carcinogenicity in biomass fuel emissions are particulate matter and PAHs. Small particulate matter (particulate matter <10 μm (PM10)) deposit deep within the parenchyma of the lung[13] and clearance depend on phagocytosis and the mucociliary pathway.[14] When

inhaled concentrations of particles are very high, 'lung overloading' with impairment of particle clearance has been observed.[15] Lung overloading causes sustained neutrophilic inflammation. The subsequent release of reactive oxygen species (ROS) directly damages DNA. Cell damage (as well as the pro-cell growth signals from ROS) then promotes cell proliferation and turnover. These chronic pro-inflammatory changes finally result in fibrosis within the lung parenchyma and development of lung tumours.[16] Rat models have clearly shown this sequence of events,[17] although corresponding evidence in humans is poor.

The International Agency for Research on Cancer has classified PAH as a Group 1 carcinogen.[18] Benzo(a)pyrene and larger molecular weight PAHs (4–7 rings) are clearly carcinogenic in both *in vitro* and *in vivo* studies, with a strong dose–effect relationship.[12,18] Activated PAH metabolites can form adducts with DNA, and error-prone repair or a failure to repair these adducts subsequently results in mutations.[4,12] Gene 'hotspots' for adduct formation by activated PAHs include oncogenes such as p53, the K-ras and the H-ras genes.[19,20] PAH-DNA adducts are associated with cancer risk and recurrence of breast and prostate cancers in epidemiologic studies,[21,22] and detectable adducts in leukocytes were also associated with a twofold increased risk of lung cancer.[23]

In addition, active PAH metabolites such as catechols can undergo repeated redox cycles, generating ROS as a by-product.[24] PAH metabolites also increase cell proliferation through interaction with the insulin-like growth factor signalling pathway,[25] and through disruptions in calcium ion movement between intra and extracellular spaces, with the consequent activation of the protein kinase C pathway.[26] Interactions with other important cell signalling pathways have been described including the epidermal growth factor receptor pathway and the serine-threonine kinase Akt pathway.[27] The epidermal growth factor receptor signalling pathway in particular is known to be important in the carcinogenesis of lung adenocarcinomas.[28]

In vitro studies indicate that wood smoke emission extracts cause DNA damage[29–32] and are mutagenic[33,34] in *Salmonella* reverse-mutation assays. A substantial portion of the metabolically activated mutagenic activity can be attributed to PAHs, although there are other compounds such as aromatic ketones, phenols, aromatic amines and nitroarenes[33,34] that exhibit mutagenic activity. In animal model studies, dermal applications of wood smoke extracts have shown increased papilloma but not carcinoma formation,[35] whereas inhalation exposure to wood smoke increased lung adenocarcinomas in mice but not rats.[36] A study in 1993 reported higher levels of DNA adducts in Xuan Wei women who used wood for cooking, compared with Beijing women who used natural gas.[37] Further, higher levels of P53 and MDM2 proteins have been reported in lung cancer patients who reported exposure to wood smoke, compared with smokers with chronic obstructive pulmonary disorders and healthy persons who did not report exposure.[38] This is consistent with *in vitro* data showing that PAH-DNA adduct formation occurs preferentially on promoter regions of the p53 gene.

There are other studies that indirectly support a relationship between biomass fuel emissions and lung cancer, by showing evidence of *in vivo* changes such as urinary metabolite excretion, DNA damage and cytogenetic abnormalities in humans associated with wood smoke exposure. An Indian study comparing women who reported using biomass fuels for cooking compared with women who used LPG showed that women exposed to biomass fuels had higher levels of cytogenetic changes such as chromosomal aberrations and micronucleus formation in peripheral lymphocytes.[39] Data from an occupational study in Brazil reported higher levels of excretion of organic carbon metabolites in the urine (e.g. 2-napthol, 1-pyrenol) in kiln-tenders exposed to eucalyptus wood smoke compared with tree cutters in a charcoal production facility.[40] The International Agency for Research on Cancer classifies biomass (primarily wood) fuel emissions as probable human carcinogens (group 2A).[4]

HUMAN EXPOSURE TO BIOMASS FUEL SMOKE EMISSIONS

The amount of smoke emission produced depends on the nature of the fuel and the type of stove used.[4] In addition, house characteristics such as the size of the room, the quality and extent of ventilation, and the use of room partitions (for example separation of cooking areas from living or sleeping areas) affect the intensity and concentration of emissions encountered.[4] Over time, concentrations of emissions equilibrate between indoor and outdoor air, and so community factors such as the number of neighbours, the extent to which biomass fuels are used by the neighbours and the closeness of houses also are important.

Studies have generally focused on a limited number of pollutants—total suspended particles, PM10 (particles of size 10 μm or smaller), PM4 (particles of size 4 μm or smaller), benzo(a)pyrene and total PAHs. In general, reported ranges of exposure of 24-h indoor levels of PM10 and PM4 are in the hundreds of $\mu g/m^3$ range, significantly above the level considered healthy in most guidelines for indoor air standards.[4,41,42] Studies that have monitored benzo(a)pyrene have reported widely varying estimates, over four orders of magnitude. Nevertheless, use of traditional wood stoves in China resulted in emissions of benzo(a)pyrene that were higher than households where coal was used in improved stoves,[43] and South Asian households using biomass fuels (dung, wood and charcoal) had exposure to benzo(a)pyrene in the high hundreds or thousands of nanograms per cubic metre.[44] As comparison, the World Health Organization guidelines for indoor air pollution note that a lifetime exposure equivalent to 1.2 ng/m^3 results in an excess lifetime cancer risk of

1 in 10000, and report that induction of DNA damage was observed with as low an exposure as 1 ng/m^3 of benzo(a)pyrene.[12]

EPIDEMIOLOGIC STUDIES OF BIOMASS FUEL USE AND LUNG CANCER

We have been able to identify twenty studies that have reported on the association between solid fuels or biomass fuels and lung cancer.[45–64] In addition, there is 1 pooled analysis using data from seven studies in the International Lung Cancer Consortium.[65] Table 2 summarizes results of these 21 studies, all of which were case–control studies, using either interviews or medical records to obtain self-reported biomass fuel use as the exposure variable.

In understanding the current evidence regarding the effect of biomass fuel use on lung cancer, some limitations affect our interpretation of the findings from the full list of studies cited in Table 2. Chief among these is the inability to separate the effect of biomass fuel use from coal use in many of the studies, because exposure was measured in terms of solid fuel (often stated as 'wood or coal') use,[45–52] which in many cases would be mixed and predominantly coal rather than biomass. The reference group was also not uniformly 'non-users'—for example, one study compared the effect of wood use with a reference group of coal users.[54]

Of the 12 studies that specifically examined biomass use (most commonly wood, charcoal, grass or straw), several early reports originated from Chinese populations in Asia. Studies in the 1980s[53–55] in Hong Kong and China did not find an elevated risk with wood use in these populations, However, a positive association was reported with wood or charcoal use at a young age among women in Taiwan[56,57] and in never-smoker women in Japan.[58]Two European multicentre studies reported significantly elevated risks with wood use.[59,62] One of these was a large study that used a common standardized questionnaire in all centres, and collected detailed information of fuel use as well as other covariates, and achieved very high response rates. This study[62] reported odds ratios for wood fuel use for cooking of 1.23 (95% confidence interval (CI): 1.00–1.52) and for heating of 1.31 (95% CI: 1.06–1.61).

Notably, recent results from a pooled analysis of 4181 cases and 5125 controls[65] found an increased risk with wood smoke exposure odds ratio (OR) 1.21, 95% CI: 1.06–1.38 among individuals from Europe and North America who reported predominant use of wood fuels in the house. No effect of wood use was seen in never-smokers (OR 1.01, 95% CI: 0.74–1.37), although wood use was risk-conferring in ever-smokers (OR 1.22, 95% CI: 1.05–1.42). No estimates could be made for the effect of wood use in Asia because of the small number of exposed cases from the studies represented—in contrast, coal use was associated with an almost fivefold increased risk in these populations.

Evaluating the evidence

Methodologic issues

Overall, the epidemiologic evidence is suggestive but not strong. All the studies to date have been case–control in design, and methodological limitations of case–control studies are well known.[66] The risk of selection bias is higher in hospital- or clinic-based studies, especially when controls are picked from limited patient groups,[45,47,50,61] such as patients attending respiratory clinics.[50,61] Because some respiratory conditions may be exacerbated or caused by biomass fuel emissions, the risk of biomass fuel use on lung cancer might be under-estimated in these studies.

Most studies have elicited information on historical exposure type of fuel and the type of stove most commonly used in the household as a proxy for exposure to fumes emitted from these fuels. This is reasonable given that environmental sampling and individual monitoring or biomarker measurement would not have been feasible. Liu *et al*.[54] showed that household characteristics such as having a separate kitchen, self-reported quality of ventilation, and size of ventilation openings in living areas and kitchens were associated with lung cancer risk, and this data may be important in providing a more accurate measurement of true exposure. The use of historical reporting also acknowledges that the relevant period of exposure could have been 20–30 years prior to diagnosis. However, it is particularly susceptible to recall bias that may lead to both differential and non-differential misclassification. Almost all studies have necessarily dichomotized exposure into use/no use or into very broad categories. All these factors may contribute to the fact that none of the studies to date have demonstrated a convincing dose–response relationship, which would have strengthened the evidence considerably.

Most of the studies were able to control for confounding to a reasonable extent. However, while all studies took into account smoking status, either by restricting the study population to non-smokers, or through adjustment,[48,54,60,64] fewer considered the potential confounding effect of socioeconomic status and adjusted for this.[49,56,57,61,64] A strong inverse association between socioeconomic factors such as income and wealth and lung cancer has been detected.[67] Although it is not yet clear what drives this association, it is possible that income and wealth may affect downstream factors such as nutrition that finally result in differences in risk. Fuel use similarly exhibits a strong socioeconomic gradient, with biomass fuel use usually confined to people in the lowest socioeconomic groups of that community.

Effect of smoking history

Relative to smoking, solid fuel emissions are low-risk agents for lung carcinogenesis and their effects may be masked when studied in populations with a high prevalence of active smokers; adjustment for smoking will also not allow detection of the true effects. This

Table 2 Lung cancer risk and exposure to biomass fuel emissions

	Authors	Type and location of study	Year of study	Exposure classification	Number of subjects	Key findings Odds ratios (ORs) (95% confidence interval (CI))	Remarks
				Studies reporting risk estimates for solid fuels			
1	Chen *et al.*[45]	Hospital case–control, Taipei, Taiwan		Ever use of various fuel types	323 cases, 617 eye patients as controls	Coal or wood versus charcoal, gas or electricity: Epidermoid cancer 0.85 (NS) Small-cell 1.08 (NS) Adenocarcinoma 1.02 (NS)	Adjusted for age and gender
2	Shen *et al.*[46]	Population case–control, Nanjing China	1986–1993	Type of fuel used in home (solid fuels vs non-solid fuels) over last 20 years	263 cases 263 unmatched controls	Solid fuel versus no solid fuel use Squamous carcinomas 4.97 (0.80–30.88) Adenocarcinomas: Not significant (OR not reported)	Multivariate conditional logistic regression performed; 14 variables in the model including smoking, passive smoking, occupational cooking fume exposure, coal stove use, cooking index, among others.
3	Mzileni *et al.*[47]	Hospital case–control, Northern province, South Africa	1993–1995	Current wood or coal use at home	348 cases, 380 other cancers not related to smoking	Wood or coal use at home compared with no use Men: 1.9 (0.9–2.3) Women 1.4 (0.6–3.2) Combined: 2.0 (1.1–3.6)	Adjusted for smoking,'dusty' jobs, household asbestos exposure.
4	Pisani *et al.*[48]	Population & Hospital case–control, Lampang province, Thailand	1993–1995	Type of fuel used at home for heating and cooking, and the duration of exposure. Variables combined to create index of total time spent using coal or wood; years of exposure halved if cooking outdoors Index: <9 years 9–14 years 15–20 years >20 years	211 cases 202 population and 211 hospital controls, age- and gender-matched	Exposure to fumes from coal or wood at home (an index created taking into account whether cooking was indoors or outdoors) <9 years reference group 9–14 years 1.3 (0.7–2.2) 15–20 years 0.8 (0.4–1.4) >20 years 0.8 (0.5–1.5)	Adjusted for age, gender and smoking
5	Ramanakumar *et al.*[49]	Population case–control, Montreal, Canada	1996–2001	Ever lived full-time in a house or apartment where cooking done on gas or wood stove (traditional cooking), and where heating was by stove or fireplace located in the living quarters (traditional heating); stratified by 2 time windows: up to 20 years of age, and after 20 years of age; duration of exposure elicited in 2 categories: 1–9 years and 10 or more years	1205 cases 1541 controls age- and gender-matched	In women: Traditional heating (wood or coal stove) versus no exposure 2.0 (1.4–2.8) Traditional cooking (wood or gas stove) for cooking versus no exposure: 1.6 (1.1–2.3) In men: Traditional heating (wood or coal stove) versus no exposure 0.8 (0.6–1.1) Traditional cooking (wood or gas stove) for cooking versus no exposure: 0.7 (0.5–1.0) No effect modification by age at exposure (<20 years vs 20 or more)	Adjusted for age, ethnic group, family income, smoking, place of birth, type of interview, years of schooling, and exposure to asbestos, silica, chromium compounds and environmental tobacco smoke (ETS) exposure;

6	Behera & Balamugesh[50]	Hospital case–control, Chandigarh, India	1999–2002	Exposure to various types of cooking fuels	67 female cases, 46 non-cancer respiratory diseases	Biomass fuel use versus LPG fuel use 3.6 (1.1–12.0) In never-smokers: 5.3 (1.7–16.7) In smokers: 3.0 (1.1–8.3).	Adjusted for smoking, ETS Biomass fuels defined as coal, wood, cow dung cake, crop waste
7	Xu *et al.*[51]	Population-based case–control, Shenyang, China	1985–1987	Burning Kang (coal, wood, grass or other fuels burned directly under the bed for heating), and duration of use	1249 cases, 1345 population-based controls	Males 1–19 years of use: 1.7 ($P < 0.05$) 20+ years of use: 2.1 ($P < 0.05$) Females 1–19 years of use: 1.3 ($P > 0.05$) 20+ years of use: 2.3 ($P < 0.05$) Reference group: 0 years of use	Adjusted for age, smoking and education
8	Wu-Williams *et al.*[52]	Population-based case–control, Harbin and Shenyang	1985–1987	Burning Kang (brick beds heated by stoves underneath) and duration of use	965 female cases, 959 controls	1–20 years: 1.2 (0.9–1.7) 21+ years: 1.5 (1.1–2.0) Reference group: 0 years of use	Adjusted for age, education, personal smoking and study area Includes female participants from study reported by Xu *et al.*
				Studies reporting risk estimates for biomass fuels			
9	Koo *et al.*[53]	Community case–control, Hong Kong	1981–1983	Ever/never exposed to Wood/grass Charcoal Kerosene LPG	200 female cases 200 controls (matched on age, housing, district	Wood/grass fuel use 0.74 (NS) Charcoal use 0.96 (NS)	Adjustment not done Reference category unclear
10	Liu *et al.*[54]	Hospital case–control, Guangzhou China	1983–1984	Type of fuel used during 3 periods: 1949–1957, 1958–1976, 1977 to interview	316 cases, 316 hospital controls matched on gender, age, residential district	Wood use compared with coal use during 1977–date of interview Men 0.57 (0.11–3.0) Women 0.67 (0.04–11.7) —very few wood users: 17 men and 7 women used wood	Adjusted for education, occupation and occupational exposure, history of tuberculosis and chronic bronchitis, family history of cancer, smoking, size of living area and ETS Very little variation in fuel usage among participants, with wood and charcoal use before 1958, coal use 1958–1976 and gas only after 1976; variation seen only in last period
11	Gao *et al.*[55]	Population case–control, Shanghai, China	1984–1986	Type of fuel used for cooking, duration of use	672 cases and 735 controls, all women	Wood use for cooking: 1.0 (0.6–1.8) (No data presented for duration of use)	Adjustment variables and reference group not mentioned
12	Ko *et al.*[56]	Hospital case–control, Kaohsiung Taiwan	1992–1993	No cooking or use of gas for cooking; Coal or anthracite for cooking; Wood or charcoal for cooking Participants asked about exposure during 3 age –stages -<20 years, 20–40 years, >40 years of age;	117 cases 117 controls matched on age (105 matched pairs were never-smokers), all women	Wood or charcoal versus gas or none in non-smokers; age of exposure: <20 years old 2.5 (1.3–5.1) 20–40 years 2.5 (1.1–5.7) >40 1.0 (0.2–3.9) 20–40 years 2.7 (0.9–8.9) after further adjustment for use of fume extractor, history of tuberculosis, vegetable consumption and living near industrial district	Adjusted for socioeconomic status education, residential area Use of fume extractor in the kitchen is protective: No use of fume extractor at age 20–40 OR 8.3 (95% CI: 3.1–22.7) after adjustment, with use of fume extractor as reference group

Table 2 *Continued*

	Authors	Type and location of study	Year of study	Exposure classification	Number of subjects	Key findings Odds ratios (ORs) (95% confidence interval (CI))	Remarks
13	Lee *et al.*[57]	Hospital case–control, Kaohsiung, Taiwan	1993–1999	No cooking or gas as cooking fuel; Coal or anthracite; Wood or charcoal Data collected during participant's main period in life when she cooked (20–40 years of age)	527 cases 805 controls without tobacco related illness. Age-gender matched	Women: Wood or charcoal use for cooking versus gas or none Small-cell carcinoma 3.1 (1.0–9.2) Adenocarcinoma 3.0 (1.4–6.4)	Adjusted for smoking, residential area, socioeconomic status and education. Only 7% of men reported cooking
14	Sobue *et al.*[58]	Hospital case–control, Osaka Japan	1986–1998	Use of wood or straw as cooking fuel at age 15, age 30 and at time of interview	144 never-smoker women. 731 unmatched never smokers	Straw or wood for cooking at age 30 1.77 (1.08–2.91)	Adjusted for age, ETS exposure, maternal smoking in childhood
15	Malats *et al.*[59]	Case–control in 8 countries: Brazil, France, Germany. Italy. Poland, Romania. Russia, Sweden	Not mentioned	Use of wood or coal for cooking or heating, and duration of exposure	122 never-smoker cases 121 never-smoker hospital controls or, in Sweden and Germany, population controls	Indoor pollution from wood fuel >20 years versus no use 2.5 (1.0–6.2)	Adjusted for age, gender, centre
16	Gupta *et al.*[60]	Hospital case–control, Chandigarh, India	1995–1997	Wood fuel use, and duration of exposure	265 cases 525 controls matched by age and gender	Wood fuel for cooking Men 1–45 years 0.94 (0.58–1.54) >45 years 0.87 (0.58–1.30) Females 1–45 years 0.74 (0.20–2.65) >45 years 1.11 (0.34–3.60) Wood fuel for heating Men 1–45 years 2.62 (0.47–14.5) >45 years 0.97 (0.65–1.43) Women 1–45 years not calculated as no cases exposed >45 years 2.78 (0.97–7.98)	Adjusted for age, education, smoking, gender
17	Hernandez-Garduño *et al.*[61]	Hospital case–control, Mexico City, Mexico	1986–1994	Ever cooked using wood fuel, and duration of exposure in years	113 never-smoker female cases (adenocarcinomas), 273 never-smoker female controls from National Institute of Respiratory Disease	Years of cooking with wood versus no use of wood fuel 1–20 years 0.6 (0.3–1.2) 21–50 years 0.6 (0.3–1.3) >50 years 1.9 (1.1–3.5)	Adjusted for age, ETS exposure, socioeconomic status and education

18	Lissowska *et al.*[62]	Hospital and population case–control, Czech Republic, Hungary, Poland, Romania, Russia, Slovenia, United Kingdom	1998–2002	Principal fuels used in each residence of more than 1 year for cooking and for heating	Multicentre study from seven European countries, 2861 cases from 15 hospitals, 3118 hospital and population controls matched by age, gender and area	Ever used wood for cooking compared with no solid fuel use: 1.23 (1.00–1.52) Ever used wood for heating compared with no solid fuel use: 1.31 (1.06–1.61)	Adjusted for age, gender, education, smoking and centre
19	Tang *et al.*[63]	Hospital based case–control, Singapore	1996–1998, 2005–2008	Frequency of wood-stove use at period 25 years prior to diagnosis	703 female cases, 1578 controls	Never-smokers: 0.81 (0.56–1.17) Smokers: 1.25 (0.74–2.12) (ref group in both cases: <daily wood stove use)	Adjusted for age, education, housing type, second-hand smoke exposure, history of cancer in the first-degree relative, duration of smoking (for smokers), fruit and vegetable intake, and study set
20	Sapkota *et al.*[64]	Multicentre case–control, Ahmedabad, Bhopal, Kolkata, Chennai	2001–2004	Wood fuel use and duration of exposure	799 cases, 718 controls (19% hospital controls, 81% visitors to hospitalized patients)	Always wood use: All individuals 1.06 (0.77–1.47) Never-smokers 0.75 (0.45–1.24) Duration of wood use (all individuals): >0–30 years: 0.49 (0.29–0.83) >30–50 years: 1.27 (0.87–1.85) >50 years: 0.95 (0.65–1.37) *P* for trend 0.86 (always modern fuels as reference)	Adjusted for centre, age gender, education, family income, crowdedness and cumulative tobacco consumption
21	Hosgood III *et al.*[65]	Pooled study of seven case–control studies in the International Lung Cancer Consortium (5105 cases and 6535 controls)	Range of dates: 1985–2008	Predominant fuels used in one study, fuel used as an adult (three other studies) Participants characterized as predominant wood fuel users, predominant coal users, predominant non-solid fuel users	4184 cases and 5125 controls from North American and Europe studies	Pooled OR 1.21 (1.06–1.38) for predominant wood-users (Reference group: predominant non-solid fuel users)	Adj for age, gender, education, ethnicity, study centre and smoking, and product terms of covariates and studies

may explain why some of the studies reviewed here did not demonstrate a positive association overall.[48,54,60] On the other hand, of the six studies that restricted or stratified their study populations to low-risk individuals, either non-smokers[56,64] or non-smoking women in particular,[50,58,59,61,63] all but two[63,64] reported positive associations with odds ratios in the range of 1.8 or higher. Unfortunately, most of these studies did not include smokers, with whom a direct comparison could be made. One study that did was conducted in India with 67 cases and 46 controls of non-cancer patients in a respiratory clinic[50] and reported higher risks for non-smokers (OR 5.3 95% CI: 1.7–16.7) than smokers (OR 3.0, 95% CI: 1.1–8.4).

Recent evidence suggests the possibility of a different pattern of risk in relation to smoking – that of a synergistic effect between smoking and other indoor air pollutants.[63] This scenario is not implausible, given that both tobacco smoke and biomass fuel smoke share similar carcinogenic constituents such as PAH, and if it were to apply we would expect to see a stronger association among smokers than non-smokers. In the pooled analysis by Hosgood *et al.*,[65] a risk-conferring effect was observed for wood use in ever-smokers (OR 1.22, 95% CI: 1.05–1.42) and a null effect in never-smokers (OR 1.01, 95% CI: 0.74–1.37). In a study conducted in Singapore,[63] the risk associated with daily (vs <daily) woodstove use in the past was 1.25 (0.74–2.12) among smokers and 0.81 (0.56–1.17) among non-smokers (*P* for interaction 0.06). It was postulated that risks associated with inhalant exposure may be present only in a background of chronic inflammation and cellular damage induced by tobacco use.

Differences by histological type

Just as the effect of smoking-related carcinogens on lung cancer differs by histological type, with stronger associations for squamous cell and small-cell carcinomas than for adenocarcinomas,[68] it is plausible that similar differences in risk exist for biomass fuel emissions exposure. Two studies[45,57] in Table 2 reported results by histological type, and in both cases there was no suggestion of material differences in the risk estimates between squamous/epidermoid and adenocarcinomas.

Effect of age at exposure

Diagnosis of lung cancer among cases in these studies took place, on average, at around 60 years of age. Studies vary in the reference period for which exposure to these emissions was measured. Very few considered age of the participants at exposure. Sobue *et al.*[58] reported significantly elevated risk for use at age 30 (OR 1.89, 95% CI: 1.16–3.06), but not at age 15 (OR 1.24, 95% CI: 0.86–1.81). This may reflect non-differential misclassification due to difficulty remembering exposures in the past, resulting in shifts towards the null, or may represent a true effect of the age at exposure on lung cancer risk. Ko *et al.*,[56] in contrast, reported a significant effect of wood fuel exposure for women reporting exposure at age <20, and at age 20–40 years, but no effect at age >40 years, although this was based on very small numbers. Lung development in humans is not complete at birth, and postnatal development of the lung, including cellular proliferation and lung growth and expansion continues until the end of adolescence.[69] Children exhibit greater susceptibility to air pollution, and particulate matter and tobacco smoke exposure have been associated with respiratory manifestations in children and adolescents such as asthma exacerbation, increased incidence of respiratory infections, bronchitis and chronic cough.[69] The greater susceptibility of the growing lung to environmental pollutants may extend to biomass fuel exposure as well. Studies should therefore consider the age of exposure separately from the latent period, and, in particular, obtain information about childhood and adolescence exposure.

Modification by host susceptibility

The effect of genetic susceptibility on the risks conferred by biomass fuel emission may also be informative. Most studies of such gene-environment interactions have focused on gene polymorphisms in Phase 2 enzymes such as the glutathione-S-transferase (GST) family (of which GSTM1 and GSTT1 are the most common subtypes studied), as these enzymes play central roles in the deactivation and excretion of activated organic compounds. Persons with GST null genotypes would therefore less readily excrete these compounds. These individuals would be expected to have higher circulating levels when exposed to PAH and other similar compounds, relative to those with GST non-null genotypes. Smith and Ebrahim[70] have suggested that stratifying individuals according to their genotype of functionally significant gene polymorphisms that can serve as an indicator of the exposure can effectively 'randomize' these individuals in a way that controls for confounders. If the associations observed on stratified analyses are congruent with the biological actions of the enzyme and the environmental exposure, then this could be considered supportive of a probable aetiologic role. This approach is limited by our understanding of the putative biologic pathways involved and our ability to identify relevant genes and polymorphisms, but may form one of several contributing lines of evidence for a particular exposure-disease relationship. For example, smoky coal use, another known source of PAH, was observed to confer a significantly increased risk of lung cancer in Xuanwei when combined with the GSTM1 null genotype.[71]

In their study of Caucasian non-smokers from eight countries, Malats *et al.*[59] reported that among those with GSTM1-null status, exposure to wood smoke for 20 years or more was associated with a significantly increased risk of lung cancer (OR 6.2, 95 % CI 1.5–25.0) whereas among GSTM1 positive subjects, no such association was seen (OR 1.8, 95% CI 0.5–7.1).

However, for GSTT1, the association was only present with non-null genotypes and the small number of subjects in this study (122 cases and 121 controls) was a limiting factor.

Evaluation of interventions

China and India have both implemented wood stove improvement programmes in which modified stoves that result in more complete burning and lower levels of emissions have been given or sold at subsidized rates to poor communities.[72,73] Programme evaluation of these initiatives has focused on the uptake and use of the improved stoves, and changes in indoor air pollution levels after programme implementation. Extending the evaluation to look at biomarkers of exposure or DNA damage, as well as long-term outcomes such as development of lung cancer, in programmes where good uptake and sustained use of the new stoves have been documented, and using an appropriate control group will help establish if this intervention has succeeded in mitigating exposure to these putative environmental carcinogens.

CONCLUSIONS

The data thus far relating biomass fuel emissions to lung cancer is highly suggestive but not yet conclusive. There is good evidence that the constituents of biomass fuels are carcinogenic in *in vitro* models, and emission extracts are clearly mutagenic and cause cell damage in *in vitro* studies. However, the evidence in animal models is not as convincing, and the epidemiologic evidence in humans, particularly that of a dose–response relationship is incomplete. Given that many households combine coal with biomass fuels use, establishing a causal association using epidemiologic methods is challenging. Large well-designed studies with comprehensive exposure ascertainment, careful control for confounders, conducted in study populations with sufficient variation in type of fuel used for energy needs, combined with a consideration of genetic factors that influence susceptibility, will be needed in order to place this on a more solid footing.

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