Occupational and Environmental Exposures and Cancers in Developing Countries

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ABSTRACT

Background: Over the past few decades, there has been a decline in cancers attributable to environmental and occupational carcinogens of asbestos, arsenic, and indoor and outdoor air pollution in high-income countries. For low- to middle-income countries (LMICs), however, these exposures are likely to increase as industrialization expands and populations grow.

Objective: The aim of this study was to review the evidence on the cancer risks and burdens of selected environmental and occupational exposures in less-developed economies.

Findings: A causal association has been established between asbestos exposure and mesothelioma and lung cancer. For arsenic exposure, there is strong evidence of bladder, skin, lung, liver, and kidney cancer effects. Women are at the highest risk for lung cancer due to indoor air pollution exposure; however, the carcinogenic effect on the risk for cancer in children has not been studied in these countries. Cancer risks associated with ambient air pollution remain the least studied in LMICs, although reported exposures are higher than World Health Organization, European, and US standards. Although some associations between lung cancer and ambient air pollutants have been reported, studies in LMICs are weak or subject to exposure misclassification. For pulmonary cancers, tobacco smoking and respiratory diseases have a positive synergistic effect on cancer risks.

Conclusions: A precise quantification of the burden of human cancer attributable to environmental and occupational exposures in LMICs is uncertain. Although the prevalence of carcinogenic exposures has been reported to be high in many such countries, the effects of the exposures have not been studied due to varying country-specific limitations, some of which include lack of resources and government support.

Key Words: arsenic, asbestos, cancer, developing countries, environmental health, indoor air pollution, occupational health, outdoor air pollution

INTRODUCTION

As more developed countries leave behind a legacy of cancer excess, ill health, and financial strain borne from occupational and environmental exposures of the industrialization process, transitional and growing economies are succeeding these issues in surplus. In addition to nonoccupational factors, such as tobacco smoking, malnutrition, and infectious diseases, less-developed countries face occupational and environmental carcinogens that significantly contribute to cancer incidence and mortality burden. However, empirical studies from these countries on carcinogenic occupational and environmental exposures and their associations with neoplastic outcomes are few and, with few exceptions, are published in low-impact scientific journals.

The aim of this study was to review selected exposures and outcomes related to selected environmental and occupational carcinogens in the context of the unique global health challenges faced by developing countries. The available evidence is evaluated with particular emphasis on large epidemiological studies conducted in these countries and recent global burden assessments. When possible, a recent paper published in the past 15 years from each of the following regions was included: countries of the former Soviet Union (excluding current European Union [EU] member states), Eastern Mediterranean, Western Pacific, South Asia, Africa, and Latin America. Because all carcinogenic exposures and countries were not assessed, this review is not exhaustive and focuses on four major occupational and environmental carcinogens: asbestos, arsenic, indoor air pollution (IAP), and ambient air pollution.

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ASBESTOS

The International Agency for Research on Cancer (IARC) declared sufficient evidence that asbestos and all its commercial forms are human carcinogens in 1973.[1] Despite the multitude of worldwide studies demonstrating strong links between both occupational and nonoccupational asbestos exposure and asbestosis, mesothelioma, lung cancer, and pulmonary function decline,[2-4] it stands that 55 countries have issued a nationwide ban on all forms of asbestos.[5] Other countries still produce, use, import, and export asbestos and asbestos-containing products. Government regulations in these countries have banned certain forms of asbestos, typically exempting chrysotile asbestos, or have imposed permissible limits of 2 fibers/cm^3 asbestos.[6]

Global Estimates of Exposure and Cancer Effects

The Global Burden of Disease (GBD) project estimates that 125 million people are exposed to asbestos globally each year[7] and chrysotile asbestos accounts for more than 95% of all the asbestos used globally (Table 1).[5] Worldwide asbestos production is approximately 2.2 million metric tons per year. Although worldwide asbestos production has decreased since the early 1990s, mass levels have remained at the same magnitude as the 1960s since that time.[8] Urban renewal projects involving mining, manufacturing, and handling asbestos-containing products have been largely responsible for maintaining the asbestos market.[9,10] According to the 2012 Mineral Commodity Summary,[11] five countries accounted for an estimated 99% of the world's asbestos mine production: the Russian Federation (1 million metric tons), the People's Republic of China (PRC; 400,000 metric tons), Brazil (270,000 metric tons), Kazakhstan (210,000 metric tons), and Canada (100,000 metric tons). Since the US Geological Survey 2008 publication, asbestos mine production in metric tons has increased in the Russian Federation, the PRC, and Brazil.[12] A US Geological Survey trend report demonstrated that asbestos consumption also increased in China, India, Kazakhstan, and the Ukraine.[13] In particular, Uzbekistan had an estimated near doubling of asbestos consumption in 2007 compared with 2003.[14]

The magnitude of national asbestos production and consumption is proportional to the number of mesothelioma cases. Since the United States, Great Britain, and Italy have substantially decreased or ceased new asbestos usage, the number of mesothelioma cases are decreasing or are expected to decline.[15-17] Countries that have more recently issued an asbestos ban are anticipating a need in increased social and medical support as mesothelioma incidence has increased and has been predicted to peak over the next few decades.[18,19] For other countries, the burden of asbestos exposure has yet to be predicted. Annual asbestos consumption in China is at 0.5 million tons and nearly 14 million tons of chrysotile have been consumed since 1960, placing an estimated 1 million workers at high risk for mesothelioma and lung cancer. Engineering controls and personal protective equipment use are unenforced and a large proportion of workers exceed the government-imposed occupational exposure limit of 0.8 fibers/mL for an 8-hour time-weighted average.[20] The mortality burden of mesothelioma and other asbestos-related cancers remains unknown for most developing countries that continue to use the product.

After accounting for reported and unreported mesothelioma cases for 56 countries with available data on mesothelioma rates and asbestos use, one study estimated the global burden of mesothelioma to be 213,200 cases for a 15-year cumulative mortality during 1994-2008.[21] This is equivalent to an annual average of approximately 14,200 cases.[21] One mesothelioma case is estimated to be unreported for every four to five cases reported worldwide (38,900 unreported vs 174,300 reported). However, due to underreporting in most developing countries as well as lack of mortality data for other countries, including Uzbekistan, it is likely that these estimates are conservate.[21]

A comparative risk assessment was conducted to identify deaths attributed to independent risk factors.[22] Risk-factor effects were estimated for 21 regions, including parts of sub-Saharan Africa, Asia, and Latin America. Mesothelioma mortality was used as a marker for asbestos exposure. The number of mesothelioma-related deaths had increased almost 1.5-fold from 1990 to 2010 in both sexes. Mesothelioma mortality was used as mortality for asbestos exposure and the estimated number of deaths was higher for men than women in both 1990 and 2010.

The current global burden of asbestos-related cancers has been reflected in asbestos usage in the 20th century. The legacy bequeathed by the North America, the EU, and other countries with long histories of high consumption of asbestos is a large number of asbestos-related deaths and high financial burden of asbestos-related health costs.[23-25] However, given the long mesothelioma latency time and continued asbestos production and consumption, the available mortality data does not allow an analysis of the full consequences of cancer effects. The overall burden of asbestos-related malignancies in developing countries is yet to transpire.

Occupational Asbestos Exposure

In addition to continued asbestos usage, individuals in less-developed countries are at greater risk for asbestos exposure due to lax industrial hygiene, ineffective legislation, and lack of education about asbestos handling in addition to the increased demand for asbestos workers during rapid industrialization. Risk assessments of asbestos workers in China reflect these issues, despite

Table 1. Reported Associations between Carcinogenic Exposures and Cancers in Developing Countries

Exposure	Sources of Exposure	Global Population/y Exposed[5,40,72,117]	Association Measurement	Magnitude of Association	Cancer Site	95% Confidence Interval	Country	Source
Asbestos	Shipwrecking, mining, manufacturing	125 million	MR	3.3	Lung	1.6-6.9	China	Wang X et al.[27]
			SMR	12.2	Gastrointestinal	8.7-17.1	China	Lin S et al.[29]
			SMR	4.9	lung cancer for >10 y of work	2.9-8.4	China	Wang X,Yano et al.[30]
			SIR	2	Oral cavity	1.6-2.5	Taiwan (China)	Wu et al.[28]
				1.4	Trachea, bronchus, and lung	1.0-1.8		
	Geological		OR	1.7	Mesothelioma, men	1.4-2.0	Turkey	Bayram et al.[37]
			OR	2.2	Mesothelioma, women	1.7-2.7		
			SIR	13	Mesothelioma	10.2-16.6	New Caledonia	Baumann et al.[39]
Arsenic	Drinking water, diet, ore mining	200 million	OR	2.5	Bladder	1.1-5.5	Argentina	Bates et al.[48]
			RR	2.3	Lung	1.4-3.6	Taiwan	Chen et al.[49]
			RR	10.6	Liver, children	2.9-39.2	Chile	Liaw et al.[50]
			MR	6.1	Lung	3.5-9.9	Chile	Smith AH et al.[51]
			OR	5.7	Renal pelvis and ureter	1.7-19.8	Chile	Ferreccio et al.[52]
			MR	3.1	Kidney, age 40+	2.7-3.6	Chile	Yuan et al.[53]
			MR	7.1	Kidney, age 30-39	3.1-14.0		
Indoor air pollution	Coal	3 billion	OR	2.6	Lung	1.6-4.1	China	Luo et al.[89]
			OR	2.4	Lung	1.6-3.6	China	Zhao et al.[90]
			HR	1.5	Lung	1.2-2.0	China	Kim et al.[91]
			OR	3.8	Lung	1.6-8.6	India	Sapkota et al.[97]
			OR	1.9	Hypopharynx	0.7-5.5		
			OR	3.8	Larynx	1.6-8.6		
	Biomass		OR	3.59	Lung	1.1-12.0	India	Behera et al.[94]
			OR	2.7	Oral	1.8-4.7	Brazil	Pintos et al.[98]
			OR	3.8	Pharyngeal	2.0-7.4		
			OR	2.3	Laryngeal	1.2-4.7		
Ambient air pollution	$PM_{2.5}$	3.22 million attributable deaths	RR	1.2	Lung, for every >10 μg/m^3	1.1-1.3	Taiwan (China)	Chiang et al.[127]
			OR	2.15	Lung, age >30	1.3-3.5	India	Rumana et al.[132]
	SO_2		MR	4.3	Lung	2.3-6.2	China	Cao et al.[131]

HR, hazard ratio; MR, mortality ratio; OR, overall response; PM, particulate matter; RR, risk ratio; SIR, standardized incidence ratio; SMR, standardized mortality ratio; SO_2 , sulfur dioxide.

Chinese national standard regulations on asbestos usage.[26]

A 37-year prospective cohort study in China studied 577 asbestos-manufacturing factory workers and 435 control workers from other cohorts.[27] All workers were followed from 1972 to 2008 with a follow-up rate of 99% and 73%, respectively. Age and smoking-adjusted all-cause mortality hazard ratios (HRs) were 2.05 (95% confidence interval [CI], 1.56-2.68) in asbestos workers and 1.89 (95% CI, 1.25-2.87) in controls. The risk for lung cancer death in the asbestos workers was more than threefold that in controls (HR, 3.31; 95% CI, 1.60-6.87). There was a clear exposure-response trend with asbestos exposure level and lung cancer mortality in both smokers and nonsmokers.

A retrospective study was conducted with 4155 male shipwrecking employees from Kaohsiung Shipbreaking Workers Union database from 1985. This cohort was linked to the Taiwan Cancer Registry from 1985 to 2008 to determine cancer incidence due to asbestos exposure.[28] After a 5-year latency period, an elevated incidence of overall cancer were found among male shipbreaking employees (N = 368; standardized incidence ratio [SIR], 1.13; 95% CI, 1.01-1.25), oral cavity cancer (N = 83; SIR, 1.99; 95% CI, 1.58-2.46), and trachea, bronchus, and lung cancers (N = 53; SIR, 1.36; 95% CI, 1.02-1.78) compared with the general population of Taiwan from 1985 to 2008. Mesothelioma cases were found in flame cutters, who had the highest intensity of asbestos exposure via inhalation of asbestos-containing smoke in welding processes. Additionally, an increased SIR for both overall cancer and oral cancer was associated with the high asbestos exposure group for both a 5- or 10-year latency period.

One study followed a cohort of 1539 Chinese chrysotile asbestos miners for 26 years and collected information on vital status and death causes from personnel records and hospitals.[29] Cancer causes of death were determined by combination of clinical manifestations and pathological confirmation. Standardized mortality ratios (SMR) were calculated based on Chinese national data and stratified by exposure (levels 1-3, from low to high determined by partitioning the cumulative intensity and duration exposure measurements of the deaths from each cancer type into tertiles). Fifty-one deaths from digestive cancers were identified in the cohort (SMR, 1.45; 95% CI, 1.10-1.90). A dose-response relationship was found between asbestos dust exposure and stomach cancer mortality at exposure levels 2 (SMR, 2.39; 95% CI, 1.02-5.60) and 3 (SMR, 6.49; 95% CI, 2.77-15.20). In the multivariate analysis, workers at the highest exposure level had an HR of 12.23 (95% CI, 8.74-17.12). Excess mortality from esophageal and liver cancers was also observed at high exposure levels.

A study was conducted with the same 1539 Chinese chrysotile asbestos miner cohort and also found positive relationship for SMR and lung cancer, gastrointestinal (GI) cancer, and all cancers with employment years at entry to the study ($P_{trend} < 0.001$).[30] Lung cancer mortality increased by 3.5-fold in 10 years or more of asbestos work (SMR, 4.92; 95% CI, 2.88-8.43) and 5.3-fold in at least 20 years (SMR, 7.46; 95% CI, 5.41-10.28) compared with less than 10 years. A clear gradient was also demonstrated for GI cancer mortality when age and smoking were adjusted for (SMR, 1.90; 95% CI, 1.22-2.97) at 10 years or more and (SMR, 1.74; 95% CI, 1.17-2.56) in 20 years or more compared with less than10 years.

In Brazil, asbestos is widely used in cement-fiber products. The Brazilian mesothelioma mortality trend 1980-2003 was reported[31] using records from the national System of Mortality Information of DATASUS, including all deaths with IX International Disease Classification (ICD-9) codes 163.n—pleura cancer during the period 1980-1995; and ICD10 codes c45.n—mesotheliomas and c38.4—pleura cancer for the years 1996-2003. In Brazil, mesothelioma mortality rates (MRs) increased over the period studied, from 0.56 to 1.01 deaths per 1 million habitants. The total number of mesothelioma deaths nationwide in the period studied was 2414. Fifty-nine percent (1415) of the mesothelioma deaths occurred in the Southeast region, where many cement factories are located.

National trends of mesothelioma mortalities due to asbestos exposure also have been conducted. After the 2001 asbestos extraction and production ban in Argentina, a positive trend was reported in the number of mesothelioma deaths from 1990 to 2010.[32] A total of 1734 of mesothelioma deaths were reported, varying widely, from 99 in 1995 to 16 in 1997. There was an increasing (44%) trend of deaths over time. The proportionate mesothelioma mortality in 1990 was 0.3 per 1000 and showed a linear declining trend to 0.01 per 1000 in 2010. In the Ukraine, 2645 cases of malignant mesothelioma were registered from 2001 to 2011.[33] Occupational mesothelioma totaled three diagnosed cases from 1992 to 2011 and two cases of these were related to occupational asbestos exposure. It was estimated that one case of malignant mesothelioma occurred per 457.4 tons of industry asbestos consumed.

There remains a disproportion in the number of asbestos-related cancer reports to the magnitude of asbestos consumption in certain countries. For the eight countries that accounted for 80% of the world's asbestos consumption according to the latest US Geological Survey trend report from Russia, China, India, Kazakhstan, Ukraine, Thailand, Brazil, and Iran,[34] scant public health reports or epidemiological studies have been made public in scientific literature compared with other countries with asbestos consumption history. This leads to the conclusion that the health consequences of asbestos exposure are being underestimated and underreported for various social, economic, and political domestic reasons.

In order to provide the framework for effective education and legislation, risk assessment of asbestos sites and inventory are necessary. There is currently a retrospective cohort study in progress funded by the Ministry of Health of the Russian Federation that aims to measure occupational exposures and follow up 30,000 workers of JSC Uralasbest mine employed between 1975 and 2010. Because this is one of the largest chrysotile mines in the world and produces 20% of the world's asbestos, conclusions of this study would contribute substantially toward estimating the magnitude of cancer risk and national burden secondary to occupational asbestos exposure.[35]

Environmental Asbestos Exposures

Due to close proximity to naturally occurring asbestos, asbestos presents a health threat to individuals living in certain countries bordering the Mediterranean Sea regardless of direct occupational exposure. The geological uplifting of water-submerged oceanic plates beyond sea level bring in serpentine (including chrysotiles) asbestos, providing asbestos-containing rock and soil (ophiolites).[36] Environmental sources of asbestos exposure as well as traditional asbestos usage are additional challenges facing certain regions.

In a case—control analysis in Turkey, a risk for malignant mesothelioma was found in individuals born significantly closer to ophiolites than matched controls.[37] Odds ratios (ORs) were 1.68 (95% CI, 1.39-2.04) for men and 2.15 (95% CI, 1.69-2.74) for women for every 5 km decrease in the distance of birthplace to ophiolites. Two rural towns with a tradition of using asbestos-containing white soil to whitewash houses in Malatya Province, Turkey were studied.[38] Lung cancer incidences in Hekimhan in this province were nearly 1.3-fold higher than the general population of Turkey and fourfold higher in Arguvan. None of the subject revealed occupational exposure to asbestos.

In a New Caledonia population, an ecological study was conducted to investigate the associations of naturally occurring asbestos and malignant mesothelioma.[39] Between 1984 and 2008, 109 mesothelioma cases were recorded in the Cancer Registry of New Caledonia. The ecological analysis involved 100 tribes over a large area and associations with naturally occurring asbestos were assessed using logistic and Poisson regression. The highest mesothelioma incidence was observed in the Houaïlou area (SIR, 128.7; 95% CI, 70.41-137.84) standardized to the world population. The ecological analyses identified serpentinite-type asbestos on roads as the greatest environmental risk factor (OR, 495.0; 95% CI, 46.2-4679.7; multivariate incidence rate ratio, 13; 95% CI, 10.2-16.6). The risk for mesothelioma increased with serpentinite surface, proximity to serpentinite quarries, and distance to the peridotite mountain mass. Living on a slope and close to dense vegetation was protective against mesothelioma.

The observed disparities in global mesothelioma trends between more developed and less-developed countries are likely related to country-to-country disparities in asbestos use trends. There is a public health concern that the decline in asbestos usage by more developed countries is being offset by less-developed countries that are continuing to use asbestos. Less-developed countries lack the technical and social infrastructure to provide the population protection and education against asbestos environmental or ergonomic hazards. For countries with existing or naturally occurring asbestos, strict management for asbestos removal and standard respiratory protection must be imposed.[25] The experience of many countries suggest that attempts to reduce asbestos exposure without a concurrent reduction or ban in overall use are insufficient to control risk. To reduce the future mortality and financial burden, a ban on the mining, manufacture, and general use of asbestos is imperative.

ARSENIC

Drinking Water Contamination

Chronic inorganic arsenic exposure in drinking water has long been recognized as a detriment to global health, with more than 200 million individuals worldwide estimated to be exposed and concentrations above the World Health Organization (WHO) safety standard of 10 μg/L.[40] The WHO and Australia set and confirmed a guideline level of 10 μg/L for inorganic arsenic in drinking water in 2008 and 2011, respectively.[40,41] However, in many developing countries, a higher concentration of arsenic in drinking water is accepted. Countries that have had difficulties providing alternative drinking water to the population, such as Bangladesh, have adopted a guideline of 50 μg/L.[40]

In certain areas of Bangladesh, naturally occurring arsenic in drinking water is attributable to 5% to 10% of all cancer deaths.[42,43] Signs and symptoms of arsenic poisoning include metallic taste, skin pigmentation changes, palmer and plantar hyperkeratosis, GI symptoms, anemia due to bone marrow depression, and no cirrhotic portal hypertension.[44] Arsenic-related carcinogenesis due to chronic exposure has a latency period of 30 to 50 years.[45] Numerous epidemiological studies have found associations of chronic arsenic exposure with skin, bladder, lung, prostate, and liver cancers.[46,47]

One study[48] assessed the relationship between arsenic water concentration less than 100 μg/L and bladder cancer in two Córdoba Province counties in Argentina. The case-control study recruited 114 case-control pairs, matched on age, sex, and county, form 1996 to 2000. When well-water consumption was used as the exposure measure, time-window analyses suggested that use of well water more than 50 years before interview was associated with increased risk for bladder

cancer. The association was limited to ever smokers (OR, 2.5, 95% CI, 1.1-5.5) for 51 to 70 years before interview. However, lack of high magnitude of association for general arsenic exposure and bladder cancer may have been due to exposure misclassification.

A prospective analysis of 6888 individuals in northeastern Taiwan measured well-water arsenic concentration exposure for 11 years.[49] A total of 178 lung cancers were ascertained through linkage with the national cancer registry profiles in Taiwan. A significant dose-response trend ($P = 0.001$) of lung cancer risk was associated with increasing arsenic concentration. Lung cancer risk was associated with arsenic exposure of at least 300 μg/L compared with arsenic exposure less than 10 μg/L (RR, 2.25; 95% CI, 1.43-3.55). Significant dose-response trends and the synergistic effect of arsenic exposure and cigarette smoking were found for squamous ($P = 0.004$) and small cell carcinomas ($P=0.02$) of the lung, but not in adenocarcinoma ($P = 0.67$). When duration was accounted for, all levels of exposure including low concentration were in the direction of increased risk for lung cancer.

The carcinogenic effects of arsenic extend to developmental exposures in children. In region II of Chile, which had a period of elevated arsenic levels in drinking water from 1958 to 1970, the effects of early-life arsenic exposure in drinking water on childhood mortality were investigated.[50] The study compared cancer MRs of individuals under the age of 20 in region II during 1950 to 2000 with those of unexposed region V, dividing participants into those born before, during, or after the peak exposure period. Mortality from the most common childhood cancers, leukemia, and brain cancer was not increased in the exposed population. However, the researchers found that childhood liver cancer mortality occurred at higher rates than expected. For those exposed as young children (<10 years), the liver cancer RR for males born during this period was 8.9 (95% CI, 1.7-45.8); for females, the RR was 14.1 (95% CI, 1.6-12.6); and for males and females pooled, the RR was 10.6 (95% CI, 2.9-39.2).

A cohort study was conducted in Antofagasta, the second largest city in Chile, which had a period of high arsenic exposure between 1958 to 1971, when an arsenic removal plant was installed.[51] The study focused on individuals who were born during or just before the peak exposure period and who were 30 to 49 years old at the time of death. After comparing MRs in Antofagasta in the period 1989 to 2000 with those of the rest of Chile, for the birth cohort born just before the high-exposure period (1950-1957) and exposed in early childhood, the SMR for lung cancer was 7 (95% CI, 5.4-8.9). For those born during the high-exposure period (1958-1970) with probable exposure in utero and early childhood, the corresponding SMRs were 6.1 (95% CI, 3.5-9.9; $P < 0.001$) for lung cancer. These findings suggest that exposure to arsenic in drinking water during early childhood or in utero has pronounced pulmonary effects, greatly increasing subsequent mortality in young adults from both malignant and nonmalignant lung disease.

Another study from northern Chile[52] included a case-control study of 122 kidney cancer cases and 640 population-based controls from 2007 to 2010 with individual data on exposure and potential confounders. Cases included 76 renal cell, 24 transitional cell renal pelvis and ureter, and 22 other kidney cancers. For renal pelvis and ureter cancers, the adjusted OR by average arsenic intakes of 400 to 1000, and more than 1,000 μg per day compared with less than 400 μg per day were OR, 5.71 (95% CI, 1.65-19.82), and 11.09 (95% CI, 3.60-34.16; $P_{trend} < 0.001$), respectively. Odds ratios were not elevated for renal cell cancer. A subsequent analysis of the same northern Chilean region found that after a 10-year period, kidney cancer risks for the exposed region compared with the unexposed started to increase.[53] The peak kidney cancer mortality rate was 3.4 (95% CI, 2.2-5.1) for men in 1981-1985, with subsequent declines to 1.6 (95% CI, 1.2-2.1) by 1996-2000. MRs among women were lower (MR, 2.9; 95% CI, 1.8-4.7) in 1981-1985 but remained high longer than for men, increasing further to a MR, 4.4 (95% CI, 3.0-6.4) after another 10 years. The investigators also found that early-life arsenic exposure was associated with a kidney cancer MR of 7.1 (95% CI, 3.1-14) for young adults aged 30 to 39 years, born just before or during the high exposure period.

Food Contamination

Although water consumption provides the majority of human exposure, millions of individuals worldwide are significantly exposed to arsenic through grains, vegetables, meats, and fish, as well as through food processed or grown in water containing arsenic. Arsenic in food may occur in both organic and inorganic forms depending on the food.[54] Due to the method in which rice is grown, as well as the high absorption capacity, rice absorbs arsenic more readily than other grains. The FDA as well as the European Food and Safety Authority (EFSA) have stated that rice, organic rice syrups, fruits, juices, and other grains can contain significant amounts of arsenic.[55,56] Special attention toward pediatric health must be considered. Due to their high consumption of rice products and their developing organ systems, children younger than 3 years old are estimated to have the greatest dietary arsenic exposures and are particularly vulnerable to harmful effects of arsenic.[51,57] However, studies from developing countries on the association of arsenic exposure and cancer in children have been conducted for drinking water exposure only and not diet.

One study[58] estimated the global burdens of disease for bladder, lung, and skin cancers attributable to inorganic arsenic in food. The researchers used WHO estimates of food consumption in 13 country clusters, in conjunction with reported measurements of total and

inorganic arsenic in different foods. The study estimated slope factors for arsenic-related bladder and lung cancers, and used the US Environmental Protection Agency (EPA) skin cancer slope factor, to calculate the annual risk for cancer incidence in men and women within each country cluster. Each year 9129 to 119,176 additional cases of bladder cancer, 11,844 to 121,442 of lung cancer, and 10,729 to 110,015 of skin cancer worldwide are attributable to inorganic arsenic in food. A mean total arsenic concentration in Bangladesh for 46 rice samples of 358 μg/kg (range 46-1110 μg/kg dry weight) and 333 μg/kg (range 19-2334 μg/kg dry weight) in 39 vegetable samples have been reported.[59] Total arsenic in water ranged from 200 to 500 μg/L.

A study of 901 polished white grain samples originating from 10 countries and 4 continents[60] estimated cancer risks by multiplying daily arsenic intakes by the slope of internal cancer risk proposed by the EPA. For a fixed consumption of 100 g per day of rice, median excess internal cancer risks were 7 in 10,000 for India, 15 in 10,000 for China, and 22 in 10,000 for Bangladesh.

Considering that vegetables and cooked rice are cuisine staples for rural populations Asia, South America, and parts of Africa, they are substantial exposure pathways for inorganic arsenic exposure and intervention strategies must consider dietary arsenic sources. Although the FDA and the EFSA have advised individuals to consume a wide variety of foods while limiting rice products to a smaller percentage of all food intake, accomplishing this is less feasible in areas where rice may be the only calorie source available.

Occupational Arsenic Exposures

Work-related arsenic exposure can occur by inhalation and skin contact with arsenical compounds in diverse industrial or agricultural settings, including mining or smelting metal ores, manufacturing or using pesticides (e.g., insecticides, herbicides, fungicides), producing or using wood preservatives (i.e., chromated copper arsenate), manufacturing or working with paints and pigments, manufacturing glass and ceramics, and producing or working with lead-arsenic alloys and electronics (e.g., semiconductors).[61] In one study, 618 incident cases of nonmelanoma skin cancer and 527 hospital-based controls aged 30 to 79 years from Hungary, Romania, and Slovakia on the cusp of EU membership between 2003 and 2004 were reviewed.[46] The lifetime prevalence of exposure to occupational arsenic was 23.9% for cases and 15.5% for controls. Of 229 participants ever exposed to work-related arsenic, 141(62%) were exposed through dust mostly from ore mines, 74 (32%) through both dust and fumes, and 14 (6.1%) only through fumes. An increased OR was observed for participants with higher cumulative lifetime workplace exposure to arsenic in dust and fumes compared with controls (OR, 1.94; 95% CI, 0.76-4.95). However, epidemiological evidence in less-developed countries remains limited.

These epidemiological studies have demonstrated strong evidence for an association of inorganic and organic arsenic exposure and lung, kidney, liver, and skin cancers in developing countries. Both high and low concentrations of arsenic, whether by inhalation, ingestion, or dermal contact exposure routes, have been demonstrated to act as human carcinogens. However, the manifested health and carcinogenic effects after arsenic exposure are broad and there are several variables including exposure route, sex, genetic susceptibility, and presence of ionizing radiation, smoking, and malnourishment, which may modulate or confound the relationship between arsenic and cancer.[45]

The challenge for developing countries is to implement preventive public health measures against arsenic exposure while still maintaining a sufficient water and food supply to an increasing population. Malnutrition may exacerbate cancer vulnerability to arsenic exposure. Nutritional studies both in vivo[62,63] and epidemiological studies[64,65] provide convincing evidence that nutritional intervention is a pragmatic approach to mitigate the health effects of arsenic exposure in developing countries.[47] Particularly, selenium,[66] vitamin A, and vitamin E nutrients[67] have been shown to alleviate arsenic toxicity. A case-control study of tin miners in Yunnan Province, China demonstrated that a diet high in tomatoes and yellow and green vegetables, which are antioxidant sources, are associated with a lower likelihood of lung cancer than miners who had reduced intake of these vegetables.[65] An improved diet with a nutritional profile that includes antioxidants may be a preventive host defense and reduce the financial and mortality burden of averse arsenic health effects, including carcinogenesis.

Reducing tobacco smoking could mitigate lung cancer mortality caused by concurrent arsenic exposure. There has been much evidence to demonstrate that the positive dose-response trend between arsenic and lung cancer is more prominent among tobacco smokers.[68] Considering that tobacco smoking has a higher prevalence and rising rates among populations in low- and middle-income countries,[69] prioritizing public health programs to reduce tobacco smoking offers another route of reducing arsenic-exposure cancer burden.

Drinking water is still the largest source of exposure to arsenic in the world. The economic burden of a delay in removing arsenic from drinking water has been estimated to be greater than the economic losses of removing it. In Comilla district, Bangladesh, which is heavily affected by arsenic-contaminated drinking water, a cost analysis for productivity was performed. If a steady economic growth and an average loss of 10 years of productivity per arsenic-attributable death were assumed, losses ranged from $0.5 to $1.67 billion over 20 years for an arsenic exposure of more than 10 μg/L. These losses

are at least 10 times the cost of providing safe drinking water coverage for the exposed population.[70] Although setting stringent drinking water standards might help to solve the problem of arsenic exposures, it might impede short-term solutions such as shallow-dug wells. Developing countries with large populations exposed to arsenic in water might reasonably be advised to keep their arsenic drinking water standards at 50 μg/L.[71]

Reducing nutrient deficiencies, tobacco smoking, and arsenic exposure are interwoven and all directly related to meeting the domestic, industrial, and agricultural needs of populations in less-developed countries. As the life expectancy of developing and transitional economies increases, the economic burdens of chronic arsenic exposure are expected to increase. The WHO estimates that if exposure to arsenic concentrations greater than 50 μg/L had been eliminated by 2010, only 1.1% of eventual deaths in the 2000 to 2030 cohorts would be attributable to arsenic. If the same arsenic exposure is eliminated by 2030 in Comilla district, 2.4% of children's future deaths (between 1 million and 5 million children) would be attributable to arsenic.[42] However, large populations continue to be exposed to inorganic arsenic through geologically contaminated drinking water, particularly in developing countries.

INDOOR AIR POLLUTION

According to the WHO, more than 3 billion people worldwide depend on biomass fuels and coal for cooking and heating.[72] IAP is ubiquitous in developing countries, particularly in rural areas where households use cheap, inefficient, and locally available fuels sources such as crop waste, dung, wood, and leaves. Gases such as ozone (O_3), nitrogen dioxide (NO_2), carbon monoxide, and sulfur dioxide (SO_2) from coal; microbial and chemical volatile organic compounds; passive smoke; and outdoor ambient air are the most common types of air pollutants encountered indoors. Particulate matter less than 10 μm in aerodynamic diameter (PM_{10}), and particularly particulate matter less than 2.5 μm in diameter ($PM_{2.5}$), can penetrate deeply into the lungs and have the greatest potential for damaging health.[72] The WHO estimates that IAP is responsible for 2.7% of the loss of disability-adjusted life years (DALYs) worldwide and 3.7% in high-mortality developing countries.[73] Worldwide exposure to solid fuel smoke results in 1.6 million deaths yearly, 693,000 due to chronic obstructive pulmonary disease (COPD), and 910,000 due to acute lower respiratory infections (ALRI), as well as 38.5 million DALYs, most due to ALRI, being the eighth overall cause of DALYs in the world and the eleventh cause of death.[74]

A disproportionate number of individuals depending on solid fuel smoke reside in Africa and Asia. Health risks from IAP are likely to be greatest in cities in developing countries, especially where risks associated with solid fuel combustion coincide with the air pollution risk associated with modern industrial factory buildings.[75] Additionally, the range of particulate matter concentrations in kitchens increase during cooking on simple stoves and combustion is incomplete, with fuel carbon leaving 10% to 38% products of incomplete combustion.[76] The biomass fuel smoke possesses the majority of the toxins found in tobacco smoke.[77] Due in part to spending more time indoors, women and children are at greater risk than men for adverse health effects from chronic low levels of IAP exposure. Chronic IAP exposure has been associated with acute respiratory infection in children,[78] which is a cause of 59% of deaths among children younger than 5 years in developing countries,[74] childhood cancer, and lung cancer in women.[79] There is evidence that IAP exposure and tuberculosis, which also has a high incidence in low- to middle- income countries (LMICs), increases the likelihood of lung cancer.[72]

Risk Factors of IAP Exposures

Survey and recorded PM_{10} concentrations ($\mu g/m^3$) from 236 households (4612 individuals), including urban, peri-urban, and rural, were analyzed to estimate IAP exposure in seven regions in Bangladesh.[80] The highest concentration of PM_{10} exposure occurred from 6 to 10 PM and occurred in the cooking area compared with the living room. During peak cooking periods, daily 1-hour PM_{10} concentrations rose to 845 $\mu g/m^3$ in the cooking area and 683 $\mu g/m^3$ in the living areas. For males ages 6 and older, men had at least 50% of the PM_{10} exposure of women, whereas women had exposure concentrations that were similar to children and adolescents ($P < 0.01$). Regression models across households demonstrated that PM_{10} concentrations were significantly affected by choices of cooking fuel, cooking locations, construction materials, and ventilation practices ($P < 0.01$). These choices are also significantly affected by family income and adult education level ($P < 0.01$). For young children (aged <5 years), monitored PM_{10} concentrations were particularly high at least 192 $\mu g/m^3$. In this study, young children spent an average of 3 hours per day outdoors.

Major challenges in accurately assessing IAP exposure include reducing exposure misclassification, selection biases, and confounders that may or may not be unique to the study population. The RESPIRE (Randomized Exposure Study of Pollution Indoors and Respiratory Effects) study attempted to accurately measure the effect of IAP on health by designing a household randomized trial in rural highland Guatemala. A study of 504 Mayan woman aged 15 to 50 years who had been using traditional indoor open fires randomized the women to either receive a chimney woodstove (plancha) or to continue using traditional open fire.[81] Personal exposure to carbon monoxide was measured for 48 hours using passive diffusion tubes

at baseline and every 6 months for 18 months in addition to respiratory symptoms lung function. Use of plancha in households significantly reduced carbon monoxide exposure (1.63 vs 4.24 ppm, respectively) by 61.6% ($P < 0.001$). During follow-up, reductions in respiratory symptom risk were observed in the plancha group for wheezing (RR, 0.42; 95% CI, 0.25-0.70) as well as the number of respiratory symptoms reported at each follow-up (OR, 0.7; 95% CI, 0.50-0.97). However, the follow-up time period was too brief to observe a significant relationship with lung function.[82]

To determine the effect of stove improvement, one study[83] assessed whether lung cancer incidence decreased after residents in rural Xuanwei County, China switched from open fire pits to chimney stoves. A cohort of 21,232 farmers, born from 1917 to 1951, was followed retrospectively from 1976 to 1992. All farmers were users of smoky coal who had been born into homes with unvented fire pits. During their lifetime, 17,184 of the participants (80.9%) changed permanently to stoves with chimneys. A hospital record search detected 1384 cases of lung cancer (6.5%) during follow-up. In 1995, indoor concentrations of airborne particles and benzo[a] pyrene were compared in Xuanwei homes during smoky coal burning in stoves with chimneys and in unvented stoves or fire pits. A long-term reduction in lung cancer incidence was noted after stove improvement. After use of chimney stoves, RRs for lung cancer were 0.59 (95% CI, 0.49-0.71) in men and 0.54 (95% CI, 0.44-0.65) in women. Incidence reduction became unequivocal about 10 years after stove improvement. Levels of IAP during burning with chimneys were less than 35% of levels during unvented burning.

IAP in China

Nearly all of China's rural residents and few urban residents use solid fuels (biomass and coal) for household cooking and/or heating.[84] IAP has been listed as the sixth largest risk contributing to burden of disease in China.[85] Household air pollution from solid fuel use has become a major public health problem and has been estimated to be one of the top five major risk factors for global disease in 2010 (4.3%; 95% CI, 3.4%-5.3% of global DALYs), after tobacco smoking,[22] accounting for 3.9 million premature deaths.[86] Approximately 4.3 million deaths and 17% of adult premature lung cancer deaths were attributed to household air pollution in 2012.[87]

One study[88] characterized IAP exposure related to solid fuel use and ventilation patterns in 163 nonsmoking female heads of households enrolled from 30 villages. The study was conducted in Xuanwei and Fuyuan, two neighboring rural counties with high incidence of lung cancer due to the burning of bituminous coal. Personal and indoor 24-h $PM_{2.5}$ samples were collected over 2 consecutive days in each household, with approximately one-third of measurements retaken in a second season. Personal $PM_{2.5}$ was moderately highly correlated with indoor $PM_{2.5}$ (Spearman $r = 0.70$; $P < 0.001$). Burning wood or plant materials resulted in the highest personal $PM_{2.5}$ concentrations (geometric mean [GM], 289 and 225 $\mu g/m^3$, respectively), followed by smoky coal, and smokeless coal (GM, 148 and 115 $\mu g/m^3$, respectively). $PM_{2.5}$ levels of vented stoves were 34% to 80% lower than unvented stoves and fire pits across fuel types. Mixed-effect models indicated that fuel type, ventilation, number of windows, season, and burning time per stove were the main factors related to personal $PM_{2.5}$ exposure.

A case-control study was conducted with 102 patients with primary lung cancer cases (78 men and 24 women) in urban Fuzhou in southern China.[89] A total of 306 population-based controls were obtained from the general population by random, stratified sampling and consisted of noncancer cases matched for sex, ethnicity, and age. Trained professionals used a standardized questionnaire to interview cases and controls. Information was obtained on smoking habits, living conditions, history of respiratory diseases that influence lung cancer development, air pollution, and other variables. They were later evaluated by conditional logistic regression analysis. The OR estimate for women was 1.94 (95% CI, 1.09-3.47) after adjustment for smoking and chronic respiratory disease. For men, the OR estimate was 1.5 (95% CI, 0.97-2.46) after adjustment for smoking and chronic airway disease. The overall OR estimate for men and women combined, with the same adjustments, was 2.55 (95% CI, 1.58-4.10). Major risk factors for lung cancer in Fuzhou were burning coal indoors, smoking, exposure to environmental tobacco smoke before 20 years of age, chronic bronchitis, and high economic income.

A meta-analysis confirmed the association for IAP due to coal burning and lung cancer in China.[90] For indoor exposure to coal dust, the estimated pooled OR was 2.52 (95% CI, 1.94-3.28) for women and 2.42 (95% CI, 1.62-3.63) for both sexes. For exposure to cooking oil vapor, estimated pooled ORs were 2.12 (95% CI, 1.81-2.47) for nonsmoking women, 1.78 (95% CI, 1.50-2.12) for women overall, and 6.20 (95% CI, 2.88-13.32) for both sexes. For exposure to environmental tobacco smoke, the pooled ORs were 1.70 (95% CI, 1.32-2.18) and 1.64 (95% CI, 1.29-2.07) for nonsmoking women and both sexes, respectively.

An association between cooking conditions, fuel use, oil use, and risk for lung cancer has been reported in a developed urban population in a prospective cohort of women in Shanghai.[91] A total of 71,320 never-smoking women were followed from 1996 to 2009 and 429 incident lung cancer cases were identified. Questionnaires collected information on household living and cooking practices, use of cooking fuel and oil, and ventilation conditions for the three most recent residencies. Cox proportional hazards regression estimated that poor kitchen

ventilation was associated with a 49% increase in lung cancer risk (HR, 1.49; 95% CI, 1.15-1.95) compared with never poor ventilation. Kitchen ventilation status is subject to exposure misclassification because self-assessment was made based on questionnaires. However, ever coal use with poor ventilation (HR, 1.69; 95% CI, 1.22-2.35) and 20 or more years of using coal with poor ventilation (HR, 2.03; 95% CI, 1.35-3.05) was significantly associated compared with no exposure to coal or poor ventilation.

Coal and biomass fuels are just two sources of the indoor air contaminants in China. Ambient air pollution in areas located near industrial factories also may affect individuals indoors. One study examined 16 air pollutants (formaldehyde, acetaldehyde, 1,3-butadiene, 1,4-dichlorobenzene, benzene, carbon tetrachloride, chloroform, ethylbenzene, styrene, tetrachloroethene, trichloroethene, toluene, m,p-xylene, o-xylene, and 1,2,4-trimethylbenzene) in three urban areas responsible for 40% of the country's gross domestic product.[92] Monte Carlo simulation demonstrated that an additional 2.27 additional cancers per 10,000 urban working women and 2.93 additional cancers per 10,000 urban working men. An average 70% of the exposure risk occurred in homes as opposed to outdoors, in office, or commuting. The largest mean contributing pollutants to median cancer risk estimates were formaldehyde (33%), 1,4-dichlorobenzene (24%), and benzene (21%).

IAP in Brazil, India, and Africa

In India, more than 75% of the population use solid fuels for cooking.[93] IAP is a major contributor to the national cancer burden and is the third largest risk contributing to the burden of diseases.[85,94] However, few quantitative exposure estimates are available for India and other less-developed countries.

Daily average concentrations of respirable particulates in 412 rural homes were quantified from January to May 2001 selected through stratified random sampling from three districts of Andhra Pradesh, India.[95] Time activity and recorded time activity data were collected from 1400 individuals to reconstruct 24-hour average exposures. The mean 24-hour average concentrations ranged from 73 to 732 $\mu g/m^3$ in gas-versus-solid fuel-using households, respectively, and were significantly correlated with fuel type, kitchen type, and fuel quantity. Among solid fuel users, the mean 24-hour average exposures were the highest for women cooks and were significantly different from men and children.

Indoor $PM_{2.5}$ exposure in 617 rural households from four states in India were analyzed[96] between 2004 and 2005. $PM_{2.5}$ concentrations 24-hour households were monitored. Log-linear regression models were fitted to predict household concentrations as a function of multiple, independent household-level variables available in national household surveys and estimates using the 2005 Indian National Family and Health Survey. The mean 24-hour concentration of $PM_{2.5}$ in solid fuel-using households ranged from 163 $\mu g/m^3$ in the living area to 609 to 472 $\mu g/m^3$ in the cooking area. Fuel type, kitchen type, ventilation, geographical location, and cooking duration were significant predictors of $PM_{2.5}$ concentrations. The relationships of these exposures to cancer were not explored in these studies and there is little recent evidence linking IAP exposures to cancer in India.

A case-control study in India[94] analyzed data from 67 women with lung cancer and 46 women with nonmalignant respiratory disease as the control group. All women were asked about exposure to various cooking fuels using a questionnaire. After adjustment for active and passive smoking, biomass fuel exposure was still significant with an OR of 3.59 (95% CI, 1.07-11.97).

A multicenter case-control study in India[97] examined the relationship between aerodigestive cancers and IAP. Cases included 1042 hypopharyngeal/laryngeal cancers and 635 lung cancers and were matched with 718 controls. Coal-fuel users had ORs of 1.92 (95% CI, 0.67-5.54) for the hypopharynx cancer, 2.42 (95% CI, 0.94-6.25) for the larynx, and 3.76 (95% CI, 1.64-8.63) for lung cancer after adjusting for tobacco smoking and other factors. Among never smokers, the risk for lung cancer was 7.46 (95% CI, 2.15-25.94; based on 11 cases). The risk increased with years of coal usage for cancers of the hypopharynx ($P_{trend} = 0.06$), larynx ($P_{trend} = 0.05$), and lung ($P_{trend} < 0.01$).

In Brazil, wood is the primary source of cooking fuel. A case-control study found that oral cancer was associated with IAP from wood stoves in Brazil.[98] After adjusting for smoking, alcohol, diet, and socioeconomic factors, the estimated OR was 2.68 (95% CI, 2.2-3.3) for oral, pharyngeal, and laryngeal cancer cases (n = 784) and noncancer controls (n = 1568) for exposure to wood smoke compared with cleaner fuels. Increased risks also were seen in site-specific analyses for oral (OR, 2.73; 95% CI, 1.8-4.2), pharyngeal (OR, 3.82; 95% CI, 2.0-7.4), and laryngeal carcinomas (OR, 2.34; 95% CI, 1.2-4.7).

To our knowledge, no studies of IAP and its association with cancer have been conducted in sub-Saharan Africa, although indoor combustion of biomass is a major fuel source. An estimated 75% of sub-Saharan African households burn solid fuels, with lowest percentages in Southern Africa (<50%), and highest percentages (>95%) in Central and Western Africa. Surveys of mean respirable dust levels have demonstrated that all homes exceed WHO maximum safe limits of 25 $\mu g/m^3$, with half of rural homes having levels above 250 $\mu g/m^3$ for at least 1 hour per day, during burning.[99] In a Johannesburg South Africa hospital inpatients, 30% currently use nonelectric domestic cooking fuel.[99]

In Ethiopia where an estimated 95% of the population of Ethiopia uses traditional biomass fuels, $PM_{2.5}$

was measured in 59 households. The geometric mean of 24-hour indoor $PM_{2.5}$ concentration was approximately 818 $\mu g/m^3$ (SD 3.61).[100] A survey was conducted in Upper River Njoro Watershed, Kenya, an area with long periods of rain from March to June.[101] Questionnaires were collected from 350 rural households on household characteristics, type of primary building in homestead, number of rooms, type of ventilation present, and type of fuel used to identify household IAP risk factors. All households used wood fuel for cooking. Of those interviewed, 52.6% were living in mud-walled houses with iron sheet roofs and 91% lived in either single- or two-roomed houses. Ventilation was provided by small windows and space left between the wall and roof. No windows were present in 37% of houses. This study demonstrates the influence of harsh weather conditions on air ventilation in addition to providing a basis the amount of households exposed to IAP in this area.

Women and children are the highest exposed demographics to IAP globally, partly due to women's societal role in food preparation, childrearing, and consequent time spent near the household cooking area. Additionally, females of all ages, including infants, have stronger IAP exposures[80] and associations between IAP and lung cancer or other health effects. It remains unclear whether this is due to social or physiological etiologies, or a combination of both.

Seventeen percent of annual premature lung cancer deaths in adults are attributable to exposure to carcinogens from household air pollution caused by cooking with solid fuels like wood, charcoal, or coal.[102] Improving indoor air quality in households using solid fuel should be an urgent and high-priority task on the public health agenda of developing countries. Mortality and morbidity effects in infants and young children younger than 5 years are high in households using biomass and coal fuels.[80] Pollution exposure can be decreased by increasing children's outdoor time and concentrating outdoor time during peak cooking periods.[103]

Another consideration in public health interventions of developing countries is control and prevention of lower respiratory diseases. A history of previous lower respiratory tract disease attributable to tuberculosis, other lung infections, emphysema, and others could contribute to lung cancer development with chronic exposure to IAP.[89] COPD has been demonstrated to be associated with an increase in cancer risk, even after adjustment for age, sex, occupation, and smoking.[104] Research on IAP health effects in relation to tuberculosis and acute lower respiratory infections also have been studied to incorporate a systematic approach to the development and evaluation of interventions with clearer recognition of the interrelationships between poverty and dependence on polluting fuels.[72]

Replacing open fires with chimneys is another intervention. After installing more than 180 million stoves in rural households in the early 1980s as part of the Chinese National Improved Stoves Program, a 2004 retrospective cohort study demonstrated that the incidence of both lung cancer and COPD had decreased over time.[105,106] Despite the stove improvement, indoor air quality remained below Chinese national standards due to multiple fuels for cooking and space heating and lack of flue use to divert harmful air pollutants.[107] A similar stove improvement initiative was started in India in 1983 as part of the Indian National Program of Improved Cook Stoves. However, despite a wide distribution encompassing 35 million stove replacements, a follow-up review found that the stoves were not being used or maintained safely.[108] Substituting cleaner and more efficient fuels, education on stove usage with flues, reducing fuel demand, and raising overall welfare levels have been cited as avenues for reducing adverse effects of indoor air pollution.[107] Strategies toward reducing IAP must improve the source of pollution including the fuel itself, living environment including air ventilation, and user behaviors including education, in addition to providing households with new stoves.[108-110]

In low-income countries, development and adoption of improved cooking stoves for the population and education in stove usage would be the most feasible priorities rather than complete elimination of biomass fuel usage. Indeed, less-expensive modern fuels including natural gas and liquefied petroleum gas need to be accessible and economical.[111] These interventions are only viable with coordinated support from the government and the commercial sector.[112]

To tackle the problem of IAP, additional research is necessary for associations between cancers and IAP risk factors, exposure assessment, and public health intervention outcomes.[113] Additional outcomes of IAP need evaluation. Although associations between IAP exposure and lung cancer and aerodigestive cancers have been studied in developing countries, links between IAP and other cancers such as bladder, skin, and kidney in these countries remain unknown. Women have among the highest exposures to IAP and studies on the relationship of IAP and female reproductive cancers would add beneficially to the knowledge base. Although there are studies on childhood respiratory illness resulting from IAP exposures,[114] there are no studies on subsequential development of childhood or adult cancers. For exposure assessments, there is much to be studied. Coal and wood sources of exposure have been the most commonly studied, but there is limited evidence of other biomass fuel source exposures (dung, waste, crops) and their detrimental effects on public health. IAP exposure assessments are also needed for countries in Africa, South America, Asia, and the former Soviet Union that include longitudinal studies on carcinogenic effects. Other opportunities for research include studies of genetic factors or epigenetic changes that modify cancer susceptibility

after chronic IAP exposure.[115] Finally, domestic viewpoints on stove improvement initiatives, cultural, or environmental barriers toward switching to efficient fuel sources can provide guidance for effective preventive intitiatives.[77]

AMBIENT AIR POLLUTION

In 2013, the IARC declared sufficient evidence for carcinogenicity of ambient air pollution to humans (IARC group 1 category) based on numerous animal experimental and epidemiological studies.[116] IARC defines outdoor air pollution as a complex mixture of pollutants originating from anthropogenic activity. A few sources of outdoor air pollution that have been extensively monitored include PM_{10}, $PM_{2.5}$, NO_2, SO_2, and O_3.[116] Common chemical constituents of PM include sulfates, nitrates, ammonium, other inorganic ions such as ions of sodium, potassium, calcium, magnesium and chloride, organic and elemental carbon, crustal material, particle-bound water, metals (including cadmium, copper, nickel, vanadium and zinc) and polycyclic aromatic hydrocarbons (PAH). Although most PM contains eroded mineral, areas of urban development produce metals and metalloids where there are contributions from waste incineration, vehicle traffic, mining activities, and incomplete fuel combustion due to biomass or oil fuel usage.[117] These metals and transition metals produce reactive oxygen species and initiate inflammatory response, increasing likelihood of genetic damage, including cytogenetic abnormalities, mutations in both somatic and germ cells, and altered gene expression, which have been linked to increased cancer risk in humans.[116]

Air pollution has been recognized as the third leading cause of DALYs due to chronic respiratory disease globally. Exposure to $PM_{2.5}$ was recently estimated to have contributed to 3.2 million premature deaths worldwide in 2010, due largely to cardiovascular disease, and 223,000 deaths from lung cancer.[118] Worldwide, it has been estimated that 6% of all lung cancer deaths are attributable to ambient air pollution.[119] More than half of the lung cancer deaths attributable to ambient $PM_{2.5}$ were estimated to have been in China and other Asian countries. The GBD collaboration estimated that approximately 3.22 million deaths were caused by exposure to air pollution in 2010, an increase from 2.91 million deaths attributed to air pollution in 1990.[22] On a global scale, half of the burden of disease attributable to air pollution is borne by individuals in developing countries. Cities with annual mean PM_{10} concentrations above the European Commission annual standard of 40 $\mu g/m^3$ for the years 2008 to 2013 are distinctly clustered in South America, Asia, Africa, and Eastern Europe.[120] Additionally, cities with an annual mean PM_{10} concentrations of more than 150 $\mu g/m^3$ for the same time interval are clustered exclusively in South and East Asia.[121]

Recent studies in developed countries have shown a significant positive relationship between IAP exposure and mortality.[122,123] Outdoor air pollution in urban areas have been associated in developed countries with lung cancer,[124] cardiovascular disease,[125] and COPD.[126] By 2050, outdoor air pollution exposure is expected to become the top environmental cause of premature mortality worldwide.[127]

Ambient Air Pollution Exposures and Cancer

Concentrations and patterns of outdoor air pollution in developing countries have altered dramatically with the rapid economic development and urbanization over the past 2 decades. However, few studies have investigated the association of outdoor air pollution with cancer incidence or mortality, especially in the high pollution ranges. The following studies have attempted to classify ambient air exposures for statistical models in order to assess its carcinogenic associations and effects.

Daily $PM_{2.5}$ concentrations were collected from 73 air-monitoring stations throughout Taiwan and extrapolated to 290 townships using geographic information system data.[128] The average annual $PM_{2.5}$ concentration in Taiwan was 35.6 ± 0.4 $\mu g/m^3$. Lung cancer mortality has a mean estimated increase of 16% for each 10 $\mu g/m^3$ $PM_{2.5}$ concentration (RR, 1.16; 95% CI, 1.06-1.25) and one of nine female lung cancer deaths (11%) in Taiwan was estimated to be attributed to $PM_{2.5}$ exposures.

In a study of 345 never-smoking lung cancer cases and 828 community referents,[129] participants were interviewed on exposures to radon, exhaust appliances, and mosquito coil burning, as well as occupational exposures (nickel, chromium, diesel exhaust, welding fumes, etc) before receiving lung cancer diagnoses. A collective environmental exposure index was developed by assigning a value of 1 to individuals at high risk for environmental risk factors and 0 otherwise, and then summed using weights equivalent to the excess OR. Additive and multiplicative interactions between environmental exposure index and family cancer history were examined. Compared with "low environmental exposure and without family cancer history," the OR was 6.80 (95% CI, 3.31-13.98) for men who had high environmental exposures but without family cancer history. For men with both high exposure and family cancer history, OR was 30.61 (95% CI, 9.38-99.87). The corresponding associations were weaker in never-smoking females. No multiplicative interaction was observed for either sex and an additive interaction was restricted among men. Because the environmental exposure index included sources of IAP and outdoor air pollution, conclusions

cannot be made on the effects of specific exposures. However, the study demonstrates that the ambient environmental exposures collectively lead to an increased likelihood of lung cancer.

An atmospheric transport model (Canadian Model for Environmental Transport of Organochlorine Pesticides) was used to estimate PAH ambient air concentrations at ground level in China and then associate PAH exposure with lung cancer in the Chinese population.[130] Taking into consideration the variation in exposure concentration, respiration rate, and susceptibility, the overall population attributable fraction (PAF) for lung cancer caused by inhalation exposure to PAHs was 1.6% (interquartile range ≈0.91-2.6%), corresponding to an excess annual lung cancer incidence rate of 0.65×10^{-5}. The lung cancer risk in eastern China was higher than in western China, and populations in major cities had a higher risk for lung cancer than those living in rural areas. A PAF greater than 44% was estimated in isolated locations near small-scale coke oven operations.

In one study, gas and particulate-phase PAH were collected from passive air samples in Taiyuan, China between 2009 and 2010.[131] The annual average concentrations of its byproduct, benzo[a]pyrene (BaP), in background, rural, and urban areas were 2.90 ± 0.29, 23.2 ± 30.8, and 27.4 ± 28.1 ng/m^3, respectively, with higher concentration in the winter than in other seasons. The median BaP equivalent concentrations of annual inhalation exposure were estimated to be in the range of 103 to 347 ng per day for all population groups in rural as well as in urban areas. The median values of incremental lifetime cancer risk (ILCR) induced by whole-year inhalation exposure for all groups were higher than 10^{-6}, with higher values in winter than in other seasons and in urban than in rural area. In the same season and area, the ILCR of adults was larger than other age groups and that of women was a little higher than men.

Another Chinese study analyzed data collected on 70,947 Chinese adults (mean age = 55.8 years) as part of the China National Hypertension Survey.[132] Data on air pollution exposure was collected from government monitoring sites and included total suspended particles (TSP), SO_2, and nitrogen oxides. The study group found an increase in lung cancer MR (4.3; 95% CI: 2.3-6.2) for every 10 μg/m^3 increase in SO_2 after adjustment for age, sex, body mass index, physical activity, education, smoking status, age at starting to smoke, years smoked, cigarettes per day, alcohol intake, and hypertension. Associations between lung cancer mortality and TSP or nitrogen oxides were not statistically significant. However, this study had limitations that included lack of specific PM monitoring. Although TSP measurement includes $PM_{2.5}$ concentrations, it is a nonspecific PM indicator that also includes dust and other coarse particles. Another major limitation of the study was a short latency period for observation of lung cancer effects. Air pollution concentrations were collected between 1991 and 2000 and follow-up evaluation was conducted in 1999 and 2000.

In Jodhpur, India, a retrospective study was conducted with a sample population of 10,000 to estimate magnitude of $PM_{2.5}$ pollutant and human health risks, including lung cancer.[133] Annual mean $PM_{2.5}$ exposures were 71.4 μg/m^3 at industrial sites, 143.8 μg/m^3 at traffic intersections, and 54.3 μg/m^3 at residential sites. The odd ratio estimate for lung cancer and $PM_{2.5}$ exposure was 2.15 (95% CI, 1.33-3.5) for those older than 30 years when fitted to a log-linear model.

There were no other comparable studies of ambient air pollution exposure and cancer in other less-developed countries. Paradoxically, countries that have the highest ambient air pollution also have limited empirical information. Limitations include lack of prioritization of environmental pollutant studies, analytical expertise, and standardized methods for monitoring air pollution.[134] Most other studies characterize exposure concentrations in developing countries. Between 2012 and 2013, air sample were collected in Bamako, Mali, one of the fastest growing cities in the world.[135] Mean $PM_{2.5}$ and PM_{10} concentration estimates and SDs for an individual in Bamko were 43 ± 21 and 210 ± 93 μg/m^3, respectively. This was 1.2- to 4.5-fold greater than existing limits by the WHO, EPA, and EU.[135]

Challenges of Ambient Air Pollution in Less-Developed Countries

These studies contain information for assessing air pollutant exposures in developing countries and many studies have been conducted on exposures and respiratory outcomes. However, there is a need for studies with a specific focus on cancer in developing countries where large populations are exposed to relatively high concentrations of outdoor air pollution. The WHO reports annual mean $PM_{2.5}$ measurements for 70 cities and PM_{10} measurements for 512 cities, from which $PM_{2.5}$ estimates can be derived.[136] Many direct combustion sources, predominantly diesel and gasoline engine exhaust, stationary power plants, and IAP have been identified as predominant contributors to outdoor air pollution.[118] Exact composition of PM varies depending on its source and more research is needed, particularly in developing countries, on the background concentrations of metals, dust, ammonia, in addition to gaseous precursors SO_2, nitrogen oxides, O_3, and carbon monoxide.[118] There is also a need for identification and evaluation of the carcinogenic outcomes of outdoor air pollution, which include lung, bladder,[137] aerodigestive cancers,[138,139] and other cancers[140-142] that have an increasing incidence in developing countries.

Current estimates of lung cancer burden in developing countries, in particular, may be underestimated as a result of synergistic interactions between the effects of

tobacco smoking and IAP, which are already contributing substantially to disease burden in LMICs.[22] The effect modification of cancer risk by smoking status has also been observed in other air pollution studies whereby tobacco smoking acts synergistically with air pollution to increase individual lung cancer risk.[143-145] Estimates for the effect of smoking and air pollutants are particularly important for many developing countries because a high proportion of populations in LMICs smoke tobacco. In particular, China, India, and Russia have quit rates less than 20%.[69] Studies from Africa, Asia, and South America are particularly needed to discern the joint effect estimates of tobacco smoking and air pollution on lung cancer.

Although $PM_{2.5}$ and O_3 concentrations in western Europe and North America have generally declined since the late 20th century, they are increasing in industrializing areas, notably Russia, Asia, and Africa where WHO and national air quality guidelines for $PM_{2.5}$ and other pollutants are exceeded.[116,146] Although cancer incidence is lower in India than high-income countries, relative MRs in India are higher and result in a substantial contribution to global cancer deaths because of the country's growing and aging population.[147] In China, the increase in cancer rates has been strongly linked to environmental pollutants in rural areas.[148] The proportion of Chinese persons aged over 60 years is 13.3% according to data from the sixth national census in 2010,[148] which will increase the burden of cancer on the country. This consists of 178 million people and the number is estimated to increase by 5 million every year, potentially increasing the cancer incidence and mortality burden.[149] However, China has a short history in cancer incidence and mortality data collection and data collection often is incomplete, neglecting those living in rural areas (48% of the Chinese population) and ethnic minorities.[150]

Similarly, indigenous minorities in Russia often live amid areas of natural resources that are subject to exploitation and deforestation, leading to subsequent environmental pollution and contaminated soil.[147,151] Disenfranchised individuals in Siberia and far eastern Russia have higher MRs than western Russia and limited access to sites of cancer care.[152] Research has already demonstrated that minorities often are the largest bearers of air pollution exposure,[153] therefore forthcoming research must take into account disadvantaged populations in developing countries as well in order to discern accurate estimations and allocation of resources. Although pollution concentrations are monitored in many Russian cities,[154] there are no studies on outdoor air pollution exposure and its health effects in Russia or eastern Russia, where air pollution is increasing due to limited resources. A similar social and economic situation exists in areas of South Asia, the Eastern Mediterranean, and Africa. Research of ambient air pollution exposures in these areas are also lacking and are necessary in recognizing and streamlining the burden of cancers caused by air pollution.

Fortunately, pollution is a modifiable cancer risk factor. The lesson learned from other countries is that air pollution can indeed be reduced with adoption of renewable sources of energy, primary regulation, and sustained intervention.[155-157] Efforts toward environmental risk assessment and control have been developed in some countries, including future research efforts,[158] cancer screening programs, and education.[159] However, more research contributions from developing regions faced with high cancer rates and air pollution exposures are necessary to provide the basis for policy change and reduction in cancer burden.

CONCLUSION

A number of modifiable environmental and occupational exposures have been associated with increased cancer risk and this has been reflected in several empirical studies using various analytical methods. In addition to the exposures mentioned in this review, there are several other exposures that carry a heavy risk for cancer outcomes, including silica, heavy metals, benzene, and diesel engine exhaust. Although not exhaustive, this article serves as a compilation of studies conducted in less-developed countries that highlight exposures to environmental and occupational carcinogens.

Individuals at risk for asbestos, arsenic, indoor and outdoor air pollution exposures vary widely depending on the population, location, and exposure source. When all carcinogenic exposure sources are taken under consideration, however, no groups of people are exempt. Men, women, children, elderly, minority populations, urban dwellers, rural residents, and those who work outdoors in polluted cities, such as traffic police, drivers, and street vendors, are exposed to environmental and occupational carcinogens.

Challenges for asbestos use facing developing countries are low resources, poor industrial regulation, and lack of systemic methods to record occupational-related diseases.[160] An example is the lack of data on mesothelioma in India's cancer registries.[161] This has been related to insufficient resources for primary reporting, collecting, classifying, and publishing occupational health data. Of the 300 medical schools in India, only 1 has a training program in occupational health.[162] There are only a few hundred occupational health physicians are available in the country out of an estimated requirement of 8000.[161] Thus, an insufficiency of occupational health education and training may increase the likelihood of occupational exposure diseases misclassification in the case of mesothelioma and other occupational cancers.

There are examples of improved outcomes following public education and effective, reformed regulations. This has been observed in findings from Dublin, Ireland once a ban on coal sales had been implemented.[163] and resulted in decreases in local atmospheric concentrations of PM and SO_2.[156] Smoky air pollution declined by 70% and respiratory-related deaths decreased by 15.5% 6 years after the ban.[164] Likewise, the number of deaths attributable to both household and ambient air pollution in LMICs of the western Pacific and southeast Asia is more than twice the number of other world regions.[165] Therefore, it is possible that a reduction in inefficient combustible fuel sources IAP would result in improvement of overall air pollution as well as a reduction in mortalities attributed to environmental air pollution.

Although there has been a trend in the improvement of environmental and occupational carcinogen exposures in high-income countries, hazardous industry exposures have been partly transferred to less-developed countries as part of the rapid industrialization process in the 20th century.[164] Due to large and increasing populations, these countries are currently in danger of experiencing a magnified reproduction of the detrimental health effects experienced faced by high-income countries. Although many publications report that exposure concentrations exceed regulatory standards in the United States and Europe, many do not provide evidence on associations with cancer outcomes. There remains a gap in knowledge of the cancer risks due to these modifiable exposures in LMICs, particularly for indoor and outdoor air pollutants. Currently, developing countries contribute 5% to the collection of literature on pollutants[166] and this proportion must increase in order to curb the increasing demand of cancer burden on a global scale. Additional steps that must be taken include a reduction in tobacco use, control of infectious respiratory diseases, and replacement of inefficient fuel sources with renewable energy sources. The need for additional research from less-developed countries is essential as each country faces unique challenges integral to its cultural, political, and economic context.

This review provided context and quantitative information for guiding risk assessment in particular areas and underscored a need for better understanding of the cancer effects of carcinogenic environmental and occupational exposures. The trend toward improvement in high-income countries demonstrates that countries that once experienced high carcinogen exposures and cancer burdens can reduce them through interventions.

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