Arsenic, asbestos and radon: emerging players in lung tumorigenesis

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Abstract
The cause of lung cancer is generally attributed to tobacco smoking. However lung cancer in never smokers accounts for 10 to 25% of all lung cancer cases. Arsenic, asbestos and radon are three prominent non-tobacco carcinogens strongly associated with lung cancer. Exposure to these agents can lead to genetic and epigenetic alterations in tumor genomes, impacting genes and pathways involved in lung cancer development. Moreover, these agents not only exhibit unique mechanisms in causing genomic alterations, but also exert deleterious effects through common mechanisms, such as oxidative stress, commonly associated with carcinogenesis. This article provides a comprehensive review of arsenic, asbestos, and radon induced molecular mechanisms responsible for the generation of genetic and epigenetic alterations in lung cancer. A better understanding of the mode of action of these carcinogens will facilitate the prevention and management of lung cancer related to such environmental hazards.

Background
Lung cancer is commonly associated with tobacco smoke exposure. However, lung cancer in never smokers accounts for 10 to 25% of all cases, ranking as the 7th most common cause of cancer-related death [1,2]. As lung cancer in never smokers is thought to develop through molecular pathways different from those induced by tobacco, the study of non-tobacco related carcinogens is fundamental to better understand the biology of lung tumors arising in never smokers [1-5].

Arsenic, asbestos and radon are well known human carcinogens, based on evidence derived from human and animal studies [6,7]. These three agents have been strongly linked to lung cancer development, both in smoker and never smokers [5,8-19]. Due to its wide distribution on a global scale (Figure 1), chronic exposure to these agents poses a significant public health problem. Millions of people, including those who never smoke, are at risk of developing lung cancer induced by arsenic, asbestos and radon.

The carcinogenic effects due to exposure to these elements are well documented [5,8,9]. Table 1 summarizes different sources that provide scientific information linking exposure to these agents with lung cancer and other diseases. These lung carcinogens can induce a wide range of molecular alterations, including genetic (from specific point mutations to genome-wide aberrations) and epigenetic (including alterations in DNA methylation, and microRNA expression) [25]. Considering the relevance of this issue to public health, this article highlights the specific molecular events associated with exposure to arsenic, asbestos and radon as environmental carcinogens driving lung cancer.

Environmental evidence for lung carcinogenesis induced by arsenic, asbestos and radon

Arsenic
Arsenic, a naturally occurring metalloid in earth's crust, is a well-established human carcinogen [7]. Exposure occurs mainly through drinking water, but also via air and food [22,26]. Arsenic contamination has been considered the largest mass poisoning in mankind's history, since ~160 million people live in regions with naturally elevated levels of arsenic in drinking water [27]. Health effects, including lung cancer, have been documented with chronic exposure at levels below the currently accepted threshold of 10μg/L [3,27-29] – and at such dosage several hundred million individuals would be affected.

Although skin cancer is the most common form of malignancy associated with arsenic exposure, lung, as
well as bladder, liver, and kidneys, are other main targets of arsenic carcinogenesis [2,30]. Lung cancer is in fact the main cause of death following chronic arsenic ingestion, and this metalloid is considered as a risk factor for lung cancer in never smokers [2,5,26,31]. Augmented levels of arsenic in drinking water have been associated with an increase in the incidence of lung cancer. In the United States alone, an estimated 5,297 arsenic-related lung cancer cases per year are associated with arsenic exposure [32]. Moreover, arsenic exposure contributes synergistically with other risks factors such as tobacco smoke and history of lung disease [29,33]. The most frequent histological subtypes observed in arsenic-induced lung tumors are squamous cell carcinomas (SqCC) and small cell carcinomas (SCC), which are unusual in tumors arising in never smokers [29,34-37]. Lung SqCC associated with arsenic exposure exhibit unique patterns of genomic alterations, raising the possibility of arsenic-specific oncogenic pathways [37].

**Asbestos**  
Asbestos are mineral fibers found naturally in rocks and widely used by industry. Exposure to asbestos fibers, such as chrysotile, amosite, anthophyllite and mixed fibers containing crocidolite, has resulted in a high incidence of lung cancer [6]. Like arsenic, asbestos can act independently or synergistically with tobacco smoke to induce lung cancer [6,38].

Asbestos fibers, with the exception of crocidolite, cause at least twice as many lung cancer deaths than asbestos-related mesothelioma, and these two malignancies combined are responsible for nearly 10,000 deaths per year in the United States [39,40]. The relative risk for developing lung cancer among individuals exposed to asbestos was more than 3 times higher than for non-exposed individuals after controlling for smoking, among other variables [41]. Asbestos-induced effects in the lungs are dose-dependent and are related to the type of fiber inhaled and its composition, such as iron-rich fibers, which are more redox reactive [38,42-45]. Other fibers, such as libby amphibole transition fibers and erionite, although not classified in the asbestos mineral group, have also been implicated in asbestos-associated diseases, suggesting that other thin mineral fibers may have carcinogenic properties similar to those found in asbestos [42]. Even though the current use and management of asbestos is under strict control in most countries, the high latency between exposure and asbestos-related disease development poses a significant public health threat [46].

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**Figure 1** Worldwide occurrence of asbestos, arsenic and radon. Regions known to be affected by contamination with asbestos are colored coded in yellow (production >100,000 tons in 2010), blue (consumption >10,000 tons in 1970) and purple (consumption >10,000 tons in 2010). The five largest producers of asbestos (yellow) in 2010 were Russia (1 million tons), China (0.35 million tons), Brazil (0.27 million tons), Kazakhstan (0.23 million tons) and Canada (0.1 million tons). *Zimbabwe produced 0.15 million tons in 2003 but its production was banned in 2004, however, a controversial production revival plan is expected. Countries with current high consumption of asbestos (purple) are distinguished from countries that had previously high consumption prior to the last decades (blue). Grey indicates consumption of less than 10,000 tons per year. Asbestos production and consumption trends (from 1900 through 2003 and for 2010) are provided by the US Geological Survey (USGS) [20,21]. Areas with known occurrence of arsenic in ground water at >50 μg/L (red circles) are estimated using information retrieved from the International Groundwater Resources Assessment Centre (USGS) [22]. Areas reported (non-exhaustive) to have high radon levels are depicted by green circles. Radon occurrence was based on 238U detected in soil and country radon levels (UNSCEAR, WHO, USGS) [23,24]. Circle placement was determined by approximation; for detailed information, see references as information availability differed from country to country.
Radon is a radioactive gas formed naturally by the breakdown of uranium from soils and rocks. Exposure to this gas is estimated to be associated with more than 20,000 lung cancer deaths per year in the United States [47-49]. Radon accounts for more than 50% of the annual effective dose of natural radioactivity exposure [50], affecting not only miners but also the general population as a ubiquitous contaminant of water and indoor environments [50,51].

The relationship between radon and lung cancer has mainly been established from epidemiologic studies of underground miners [52]. Specifically, non-smoking uranium miners in the southwestern United States experienced an increased incidence of lung cancer [53,54]. Further analysis established that up to 70% of lung cancer deaths among uranium miners can be attributed to radon exposure, and the risk of lung cancer among non-smoking miners was up to 3 times higher than in other occupations [48,50,55]. It has been estimated that up to 30% of lung cancer deaths among non-occupationally exposed never-smokers might be linked to indoor radon [48]. The maximum accepted level in most countries is currently 200 Bq/m³; however, studies have established an elevated lung cancer risk at radon levels as low as 100 Bq/m³ [56,57].

Carcinogenic mechanisms induced by exposure to arsenic, asbestos, and radon

Arsenic
Carcinogenesis of arsenic is related to its biotransformation process. When arsenic enters the body, it induces a series of reduction, oxidation, and methylation reactions (Figure 2) [63]. Pentavalent arsenical species (AsV or arsenate) are reduced to trivalent species (As III or arsenite) in a glutathione (GSH)-dependent reaction [64], followed by oxidative methylation resulting in monomethylarsonous acid (MMAIII), methylarsonate (MMAV) or dimethylarsenate (DMAV) [65-67]. Some of the methylated metabolites generated in the detoxification process may in fact be more potent carcinogens than inorganic non-methylated species [58-60].

Arsenate interferes with phosphorylation reactions and competes with phosphate transport, while arsenite can react with the sulphydryl groups of proteins, resulting in inhibition of many biochemical pathways [68]. It is also well established that free radicals are generated during the process of arsenic metabolism [69-73]. By interfering with enzymes that control redox status and glutathione production, arsenic compounds, especially trivalent species, inhibit the protection of cells against oxidative damage [74]. Moreover, arsenic induces a rapid

| Name | Website | Description |
|------|---------|-------------|
| The IARC Monographs, International Agency for Research on Cancer (IARC) | http://monographs.iarc.fr/ | Compilation of reports about environmental factors that can increase the risk of human cancer: chemicals, complex mixtures, occupational exposures, physical agents, biological agents, and lifestyle factors |
| Carcinogens, American Cancer Society (ACS) | http://www.cancer.org/Cancer/CancerCauses/OtherCarcinogens/index | Information about environmental carcinogens that can be found at home, work, pollution, medical tests and treatments |
| Understanding Cancer Series, National Cancer Institute (NCI) | http://www.cancer.gov/cancertopics/understandingcancer/environment | Compilation of slides on environment and its association with cancer |
| Chemicals of Public Health Concern, World Health Organization (WHO) | http://www.who.int/ippcs/assessment/public_health/chemicals_phc/en/index.html | Information on the 10 chemicals or groups of chemicals of major public health concern |
| Report on Carcinogens, National Toxicology Program (NTP) | http://ntp.niehs.nih.gov/?objectid=72016262-BDB7-CEBA-FA60E92B18C2540 | Congressionally mandated, science-based, public health reports that identify agents, substances, mixtures, or exposures in the environment that may potentially put people in the United States at increased risk for cancer |
| Science and Technology: Health, Environmental Protection Agency (EPA) | http://www.epa.gov/gateway/science/humanhealth.html | Information on human health impacts associated with environmental exposures |
| Work-Related Lung Disease (WoRLD) Surveillance System, National Institute for Occupational Safety and Health (NIOSH) | http://www2.cdc.gov/drds/WorldReportData/ | Contents on occupationally-related respiratory disease surveillance data. |
| U.S. Geological Survey (USGS) | http://www.usgs.gov/ | Organization that provides impartial information on the health of U.S. environment and the natural hazards |
| CARcinogen EXposure Canadian Surveillance Project (CAREX) | http://www.carexcanada.ca | Multi-institution research project that combines academic expertise and government resources to generate an evidence-based carcinogen surveillance program for Canada |
depolarization of the mitochondrial membrane, together with mtDNA deletions and depletions which contribute to carcinogenicity in humans [75,76]. Under these conditions, mitochondria is considered to be the primary site of superoxide anion (\( \bullet O_2^- \)) formation [69]. After formation of \( \bullet O_2^- \) in arsenic-induced oxidative stress, a cascade of secondary reactive oxygen species (ROS), such as hydrogen peroxide (\( H_2O_2 \)) and hydroxyl radical (\( \bullet OH \)) is generated [70]. The hydroxyl radical is one of the most impactful ROS and reacts with DNA to produce 8-Hydroxy-2'-deoxyguanosine, a major ROS-induced DNA base-modified product [71,77]. Furthermore, glutathione depletion induced by arsenic may increase its toxicity via ROS-related damage [71,78].

Figure 2 Arsenic biotransformation drives carcinogenesis. Arsenic biotransformation occurs through a series of reduction, oxidation, and methylation reactions. Pentavalent arsenic (As\(^V\)) is reduced to arsenite (As\(^{III}\)), using glutathione (GSH) and thioredoxin (TRX) as electron donors. In the excretion process of this compound, As\(^{III}\) is methylated using S-Adenosyl methionine (SAM) as a source of methyl groups; however, this result in generation of arsenic species with higher carcinogenic potential [58-62]. Carcinogenic effects are mostly generated due to this biotransformation process, having effects at genetic and epigenetic levels. Genetic alterations are largely due to generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), partially derived from arsenic-induced mitochondrial dysfunction. Epigenetic effects, such as changes in DNA methylation patterns have been linked to deprivation of SAM. Changes in miRNA expression and histone modifications have also been reported.
Asbestos

Inhaled asbestos fibers longer than 5μm are not efficiently eliminated by phagocytosis. This can induce a cascade of molecular events that lead to fibrosis, inflammation and carcinogenesis [79,80]. On the other hand, fully phagocytized fibers can interfere with mitosis, leading to chromosomal missegregation [81] (Figure 3). The induction of reactive oxygen and nitrogen species upon incomplete phagocytosis of fibers plays an important role in DNA damage [84]. Asbestos induces the release of ROS, including $\cdot\text{O}_2^-$ and $\text{H}_2\text{O}_2$ [79]. Such reactions can be catalyzed on the asbestos fiber surface, and asbestos fibers with high iron content, such as crocidolite and amosite, are capable of generating higher levels of ROS [85]. Similar to arsenic, asbestos also affects mitochondrial DNA and functional electron transport resulting in mitochondrial-derived ROS, which has been shown to induce base oxidation, single-strand breaks, micronuclei, and apoptosis in lung alveolar epithelial cells, [86,87]. Therefore, asbestos carcinogenesis is suspected to occur through creation of an environment of chronic inflammation, and especially through the induction of oxidative stress, a well-known inducer of DNA damage [88]. Lesions at sites of fiber deposition and

Figure 3 Mechanisms of asbestos-induced carcinogenesis. Inhaled asbestos fibers can either be cleared by mucociliary movements and translocations, or undergo phagocytosis [44,82,83]. Fibers not efficiently eliminated by phagocytosis can generate reactive oxygen and nitrogen species (ROS and RNS, respectively) which can lead to generation of DNA single-strand breaks (SSBs) and cell signalling alterations, among other effects. Epigenetic changes, such as alterations in miRNA expression and DNA methylation are also a consequence of incomplete clearance of asbestos fibers. Alternately, fully phagocytized fibers can physically interfere with the mitotic process by interacting directly with microtubules or anchoring to mitotic structures.
alterations in gene expression are other relevant mechanisms in asbestos-induced neoplasia in lungs and other target organs [89]. Direct asbestos mutagenicity has also been proposed as a mode of action for asbestos, although this theory requires further study [89,90].

**Radon**

Although chemically inert, radon decays into active progenies that are electrically charged and can be inhaled when attached to natural aerosols, eventually reaching lung epithelial cells. Once in the lung tissue, deposited radon progeny decays to generate alpha-particles, which damage DNA both directly and through generation of free radicals (Figure 4) [51]. Decay of alpha-particles results in the ejection of electrons from water, generating several reactive species leading to cellular damage by hydroxyl radical attack [92,93]. Cellular damage can also occur in nearby, non-irradiated bystander cells through the release of chemical byproducts by irradiated cells [94]. This 'bystander' effect can result in non-linear dose–response damage and underestimation of radon exposure risks [95]. In fact, it has been proposed that lung tissue cellular injury from alpha particles is predominantly due to chromosomal damage in neighboring non-irradiated cells [96]. Moreover, after exposure to alpha-particle radiation, observable levels of cytokines are detected in the supernatants of exposed cells, implying a possible effect of cytokines in radon-induced carcinogenesis [97].

![Figure 4 Radon induces reactive oxygen species through emission of alpha-particles.](image)

Radon decays to radioactive progenies ($^{218}$Po and $^{214}$Po) that can be inhaled when attached to natural particles in aerosol [50,91]. Once inside the lungs, radon progenies emit alpha-particles that can lead to generation of reactive oxygen species (ROS), eventually resulting in DNA damage not only in the irradiated cell itself, but also affecting neighboring non-irradiated cells [51]. Additionally, changes in DNA methylation are also observed in radon-induced lung tumors.
Genetic and epigenetic consequences in lung tumor genomes due to arsenic, asbestos and radon exposure

The mechanisms discussed above lead to specific genetic alterations including mutations and chromosomal rearrangements, as well as epigenetic changes, meaning mechanisms of gene expression disruption that do not modify the DNA sequence itself, such as DNA methylation, histone modifications and microRNA (miRNA) regulation [98]. Although there have been several reports of specific genetic alterations in lung cancer in never smokers, only a few studies have directly linked such alterations with specific environmental carcinogens.

Molecular and genetic alterations

**Arsenic**

Moderate levels of arsenic activate the EGFR pathway in human lungs and other target organs of arsenic-carcinogenesis, such as the liver [68,99]. Moreover, arsenic-induced ROS activate the Wnt/β-catenin signaling pathway (which has been shown to promote lung cancer), and stimulate angiogenesis through AKT and ERK1/2 [100-102]. In murine lung tissue, arsenic interferes with expression and protein levels of components of DNA repair machinery, such as APE1, LIG1, OGG1, PARP1 [103].

DMA\(^\text{V}\) has been able to induce lung-specific DNA strand breaks by arsenic-mediated production of ROS in mice [104]. Arsenic has been shown to increase the frequency of micronuclei in cultivated cells from human small airways [105]. Compared to tumors of non-exposed individuals, DNA losses at chromosomal locus 1q21.1 and gains at 19q13.31 and 19q13.33 have been observed lung squamous cell carcinoma (SqCC) in arsenic exposed never smokers [37]. In human small airway epithelial cells arsenic increases expression of cancer related genes and protein levels, such as C-MYC, C-HA-RAS, and C-FOS and decreases β4 integrin protein expression compared with non-exposed cells [105].

**Asbestos**

In lung epithelial cells, asbestos-induced glutathione depletion results in phosphorylation and activation of EGFR, overexpression of different AP-1 proto-oncogenes, and AP-1 transactivation [106]. In human epithelial bronchial cell lines (Beas-2B), asbestos exposure induces a range of gene expression alterations, affecting MAP4K3, CEBPZ, QCPT, FANCG, IGFBP1L1, CCL19, MELK, FANCN, and CDDK1 [107]. Asbestos inhalation also causes up-regulation of mRNA levels of matrix metalloproteinase family members in rat lungs, suggesting induction of extracellular matrix remodeling [108]. Mutations in the KRAS and TP53 genes have been detected in animal models human tumors linked to asbestos exposure, although these alterations have not been conclusively associated with asbestos exposure Nelson, 1999 #387, [109,110].

A higher frequency of deletions affecting the P16/CDKN2A locus has been identified in asbestos-exposed non-small cell lung cancer cases compared to unexposed cases, which represent a main gene inactivation mechanism, although no differences were reported linked to smoking status [111]. Changes at chromosomes 5, 8 and 19 have been detected in HBECs transformed by chrysotile asbestos [112]. Additionally, asbestos interferes with chromosomal segregation by interacting directly with microtubules and chromosomes [113-116].

**Radon**

Inhaled particles of radon generate alpha-emissions that cause DNA damage primarily through double-strand breaks and large chromosomal aberrations, mainly deletions and, to a lesser extent, point mutations [117,118]. Specific mutational events have been described in radon-induced lung cancer. Vahakangas et al detected both P53 mutations and deletions in lung tumors from uranium miners. Although the contribution of tobacco smoke cannot be completely ruled out, the most frequent base substitutions associated with tobacco smoking (G:C to T:A transversions), were not identified in that study [119].

Table 2 summarizes the most known genetic alterations observed in lung cancer associated with exposure to these three carcinogens. Specific genetic alterations

| CNA* at Locus | Carcinogen | References |
|---------------|------------|------------|
| 1q21.1        | Arsenic    | [37]       |
| 2p21-p16      | Asbestos   | [110] S, [121,122] |
| Ch.5          | Asbestos   | [112] CL  |
| 5q35          | Asbestos   | [110] S, [122] |
| Ch.8          | Asbestos   | [112] CL  |
| 9p21.3 (CDKN2A)| Radon, Asbestos | [113] R, [111] |
| 12p12.1 (KRAS**) | Asbestos | [114] |
| 16p13.3       | Asbestos   | [112]      |
| 17p13.1 (TP53**) | Asbestos | [110] S |
| Ch.19         | Asbestos   | [112] CL  |
| 19p13.3-13.1  | Asbestos   | [120] S, [122] |
| 19q13.31      | Arsenic    | [37]       |
| 19q13.33 (SPIB, NR1H2, POLD1) | Asbestos | [37] |
| 22q12.3-q13.1 | Asbestos   | [112]      |
| Xq28          | Asbestos   | [120]      |

* CNA = copy number alteration.
** Sequence mutation.
References include both smokers and non smokers except if indicated (S: smokers only, CL: Cell Lines, R: rat).
appear to be prevalent to the exposure to a given carcinogen, for example, DNA losses at chromosomal locus 1q21.1 and gains at 19q13.31 and 19q13.33 are associated with arsenic exposure in never smokers [37].

Epigenetic alterations
Specific alterations at the epigenetic level, such as modifications in DNA methylation and microRNA (miRNA) expression patterns, have been associated with arsenic, asbestos and radon exposure. Aberrant methylation of CpG islands in the promoter region of tumor suppressor genes (TSGs) are linked to gene silencing, while deregulation of miRNAs – small, noncoding RNAs species that regulate gene expression – is implicated in diverse human pathologies, including lung cancer (reviewed in [125-128]).

Arsenic
Arsenic induces promoter hypermethylation and subsequent transcriptional silencing of tumor suppressors genes, such as P53, CDKN2A and RASSF1A in animal models [129,130]. Chronic arsenic exposure depleted miR-200 levels in human bronchial epithelial cells (HBECs) through increased promoter methylation, and interestingly, re-established expression of miR-200b alone was capable of entirely reversing and preventing arsenic-induced EMT and malignant transformation [131].

Asbestos
Epigenetic inactivation of tumor-suppressor genes, such as RASSF1A and CDKN2A (p16) has been observed in lung cancer patients exposed to asbestos [132]. Interestingly, p16 has been found to be inactivated in NSCLC tumors from nonsmokers only through promoter hypermethylation [133]. A recent study has identified an asbestos-associated miRNA signature in lung cancer, where miR-148b, miR-374a, miR-24-1*, let-7d, Let-7e, miR-199b-5p, miR-331-3p, and miR-96, were found to be over-expressed, while miR-939, miR-671-5p, miR-605, miR-1224-5p and miR-202 were under-expressed [134].

Radon
Long-term radon exposure has been associated with increased CDKN2A and MGMT promoter methylation among Chinese miners [135]. The locus containing the CDKN2A gene is in fact frequently affected by DNA losses in radon-induced lung tumors in rats [123]. Interestingly, exposure to plutonium, which similar to radon exerts its effects through alpha particles, can induce CDKN2A gene inactivation by promoter methylation [136].

Table 3 summarizes epigenetic changes observed in lung tumors associated with exposure to these three agents.

### Table 3 Epigenetic alterations occurring in environmentally induced lung cancer

| Type of alteration | Carcinogen | Gene References |
|--------------------|------------|----------------|
| Hypermethylation   | Radon, Asbestos | CDKN2A [132,135,136] |
| Hypermethylation   | Arsenic | TP53 [129,137] |
| Hypermethylation   | Arsenic, Asbestos | RASSF1A [130] |
| Histone Methylation | Arsenic | H3K4, H3K9, H3K27 [138-140] |
| Histone Hypoacetylation | Arsenic | H4K16 [138,140,141] |
| Global DNA Hypomethylation | Arsenic | N.A. [137,142] |
| miR Downregulation | Arsenic | miR-200 [131] CL |
| miR Overexpression  | Asbestos | miR-148b, miR-374a, miR-24-1*, Let-7d, Let-7e, miR-199b-5p, miR-331-3p, miR-96, miR-17-92 [134] S |
| miR Downregulation | Asbestos | miR-939, miR-671-5p, miR-605, miR-1224-5p, miR-202 [134] S |

Studies concern both smokers and non-smokers except if indicated (S: smokers only, CL: Cell Lines).

Management strategies for radon, arsenic and asbestos exposure
Geological carcinogen mapping plays an essential role in risk management. Examples of geological maps for radon and arsenic can be found on websites from U.S. Environmental Protection Agency as well as from the U.S. Geological Survey (Table 1). Similar maps for Canada are available from the CAREX (CARcinogen EXposure) Canadian surveillance project website (www.carexcanada.ca). Mapping these carcinogens will help to determine occurrence of co-exposure its health consequences, and the urgency for specific management strategies.

Methods for arsenic removal from water include oxidation, precipitation, coagulation, adsorption, nanofiltration, reverse osmosis, and even bioremediation [143]. A cost-effective technique is based on Arsenic Removal Using Bottom Ash (ARUBA) whereby particles of coal bottom ash (a waste material from coal fired power plants), coated with iron hydroxide react with and immobilize arsenic by adsorption and/or co-precipitation. In Bangladesh, ARUBA has been shown to reduce arsenic concentrations in contaminated groundwater to below the Bangladesh safety threshold [144]. Non-viable fungal bio-masses of Aspergillus niger coated with iron oxide have also been shown to remove approximately 95% of As(V) and 75% of As(III) from aqueous solutions [145].

The issue of asbestos is more amendable to control since the release of asbestos into the environment originates from human activity. Most developed countries
have well documented and regulated management strategies, such as the Italian directives for the remediation of asbestos-cement roofs to be treated prior to disposal on landfill [146]. Some processes are able to eliminate the hazard of these wastes in order to recycle mineral components in new building materials [147,148]. Asbestos-cement wastes are milled in a cyclic process leading to mineralogical and morphological transformations of asbestos while keeping interesting physical properties for building use. On the other hand, two million metric tons of asbestos were consumed in developing countries in 2007, illustrating the need for regulating the use of this carcinogen in developing nations [149].

Strategies against radon rely on radiation detectors and implementation of radon-resistant features; for example, houses in potentially high exposure zones should be equipped with pipes to vent radon gas generated in the ground, and sealed with plastic sheeting and caulking. Ideally, active mitigation techniques involving physical alterations such as sub-slab depressurization should be instigated, as these methods are more effective [150].

Conclusions
In the next decades, an increasing proportion of lung cancer cases will arise in former or never smokers. While the reduction of environmental carcinogenic exposure is certainly a very important cancer prevention issue, understanding the mechanisms of carcinogenesis will facilitate targeted treatment design.

Although tobacco smoke is the major cause of lung cancer, environmental carcinogens, such as arsenic, asbestos and radon play an increasingly important role in this disease, either independently or through additive or multiplicative effects [151,152]. While the number of individuals exposed to these carcinogens is significant, the difficulty to associate tumor cases directly with exposure to these agents (mainly due to the long latency period between exposure and disease onset) may be highly underestimated.

The growing interest in non-tobacco induced causes of lung cancer is reflected in the increasing number of reports describing molecular alterations correlated with exposure to these carcinogens. In this article, we have collected evidence of the involvement of specific molecular mechanisms that can lead to genetic and epigenetic aberrations in lung tumor genomes as a result of exposure to these agents. While sharing a few carcinogenic mechanisms, each agent may induce specific sets of alterations which might affect tumor biology and define tumor behavior, presenting therefore a unique opportunity for developing diagnostic and treatment options. Future research, including the integration of different genetic and epigenetic dimensions, will further the characterization of these etiologically distinct tumors and identify actionable candidates for therapeutic targets.

Abbreviations
ARUBA: Arsenic removal using bottom ash; Bq: Becquerel; CAREX: Carcinogen exposure canadian surveillance project; DMA²⁺: Dimethylarseniate; GSH: Glutathione; H₂O₂: Hydrogen peroxide; HBEC: Human bronchial epithelial cell line; MMA²⁺: Monomethylarsenous acid; MMA³⁻: Methylarsonate; mtDNA: Mitochondrial DNA; RNS: Reactive nitrogen species; ROS: Reactive oxygen species; SAM: S-adenosylmethionine; SCC: Lung small cell carcinoma; SqcCC: Lung squamous cell carcinoma.

Competing interests
The authors declared they have no competing interests.

Authors’ contributions
RH, DDB, KSSE and VDM designed and collected information for this review. RH and DDB drafted the manuscript. SL and WLL are principal investigators of related projects. All authors have been involved in revision and approved the final manuscript.

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References
1. Parkin DM, Bray F, Ferlay J, Pisani P: Global cancer statistics, 2002. CA Cancer J Clin 2005, 55(2):74–108.
2. Sun S, Schiller JH, Gazdar AF: Lung cancer in never smokers—a different disease, Nat Rev Cancer 2007, 7(10):778–790.
3. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM: Estimates of worldwide burden of cancer in 2008. GLOBOCAN 2008. Int J Cancer 2010, 127(2):2893–2917.
4. Bédar F, Mezeria F, Khokhar RA, Ali FA, Irfan N, Kamran S, Shahid N, Mahmood S: Characteristics of lung cancer patients—the shaukat khanum memorial experience. Asian Pac J Cancer Prev 2006, 7(2):245–248.
5. Subramanian J, Govindan R: Lung cancer in never smokers: a review. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 2007, 25(5):551–570.
6. IARC: IARC monographs on the evaluation of carcinogenic risks to humans. Lyon, France: International Agency for Research on Cancer; 1987.
7. IARC: Some drinking-water disinfectedants and contaminants, including arsenic. Monographs on chloramine, chloral and chloral hydrate, dichloroacetic acid, trichloroacetic acid and 3-chloro-4-(dichloromethyl)-5-hydroxy-2(5H)-furanone. IARC Monogr Eval Carcinog Risks Hum 2004, 84:469–477.
8. Alberg AJ, Brock NW, Samet JM: Epidemiology of lung cancer: looking to the future. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 2005, 23(14):3175–3185.
9. Boffetta P: Human cancer from environmental pollutants: the epidemiological evidence. Mutat Res 2006, 608(2):157–162.
10. Boffetta P, Nyberg F: Contribution of environmental factors to cancer risk. Br Med Bull 2003, 68:71–94.
11. De Matteis S, Consolini D, Lubin JH, Tucker M, Peters S, Vermeulen RC, Kromhout H, Bertazzi PA, Caporaso NE, Pesatori AC, et al: Impact of occupational carcinogens on lung cancer risk in a general population. Int J Epidemiol 2012, 41(3):711–721.
12. Harley NH, Harley JH: Potential lung cancer risk from indoor radon exposure. CA Cancer J Clin 1990, 40(5):265–275.
13. Lepeule J, Laden F, Dockery D, Schwartz J: Chronic exposure to fine particles and mortality: an extended follow-Up of the Harvard Six cities study from 1974 to 2009. Environ Health Perspect 2012, 120(7):965–970.
14. Martinez VD, Becker-Santos DO, Vucic EA, Lam S, Lam WL: Induction of human squamous cell-type carcinomas by arsenic. J Skin Cancer 2011, 2011:454157.
15. Martinez VD, Vucic EA, Becker-Santos DO, Gil L, Lam WL: Arsenic exposure and the induction of human cancers. J Toxicol 2011, 2011:431287.

16. Sethi TK, El-Ghamry MN, Kloecker GH: Radon and lung cancer. Clin Adv Hematol Oncol 2012, 10(3):157–164.

17. Turner MC, Kreviski D, Pope Iii CA, Chen Y, Gapstur SM, Thun MJ: Long-term ambient fine particulate matter Air pollution and lung cancer in a large cohort of never smokers. Am J Respir Crit Care Med 2012, 84(12):1374–1381.

18. Veloso B, Nogueira JR, Cardoso MF: Lung cancer and indoor radon exposure in the north of Portugal—an ecological study. Cancer Epidemiol 2012, 36(1):26–32.

19. Yang M: A current global view of environmental and occupational cancers. J Environ Health 2010, 72(1):23–29.

20. Vreta BL: Worldwide asbestos supply and consumption trends from 1900 through 2003. Reston, Virginia: U.S. Geological Survey; 2006:80.

21. U.S. Geological Survey. Mineral commodity summaries 2011. Reston, Virginia: U.S. Geological Survey; 2011:198. http://minerals.usgs.gov/minerals/pubs/mcs/2011/mcs111pdf.

22. Brunt RL, Vaslik L, Gillfien J: Arsenic in groundwater worldwide: probability of occurrence of excessive concentration on global scale. International groundwater resources assessment centre. Utrecht; 2004:15.

23. United Nations Scientific Committee on the Effects of Atomic Radiation. United Nations Scientific Committee on the Effects of Atomic Radiation 2000 Report. Sources and effects of ionizing radiation. Volume 1: UNSCEAR 2000. http://www.unscear.org/unscear/publications/2000_1.html.

24. Mclaughlin Centre. World Map of national residential radon levels. http://www.mclaughlincentre.ca/research/map.shtml.

25. Loeb LA, Harris CC: Advances in chemical carcinogenesis: a historical review and prospective. Cancer Res 2008, 68(7):6863–6872.

26. WHO: Evaluation of certain contaminants in food, World health organ tech Rep Ser. 59th edition. India; 2011:1–105. 115p. [http://www.who.int/foodsafety/dietaryguidelines/nutrients/en/]

27. Smith AH, Lingas EO, Mahfuzar R: Drinking water and lung cancer: a review of epidemiological evidence. J Environ Health 2010, 72(11):717–1723.

28. Heck JE, Andrew AS, Onega T, Rigas JR, Jackson BP, Karagas MR, Duell EJ: Lung cancer in a U.S. Population with low to moderate arsenic exposure. Environ Health Perspect 2009, 117(11):1718–1723.

29. Sapio T, Grosche B: Arsenic in the aetiology of cancer. Mutat Res 2006, 612(2):215–246.

30. NRC (National Research Council): Arsenic in drinking water: 2001 update. Washington DC: The National Academies Press; 2001.

31. NRC (National Research Council): Worldwide asbestos supply and consumption trends from 1900 through 2003. Reston, Virginia: U.S. Geological Survey; 2006:80.

32. Putila JJ, Guo NL: Association of arsenic exposure with lung cancer incidence rates in the united states. PLoS One 2011, 16(10):e25886.

33. Chen CL, HSu U, Chou HY, Hsuie YM, Chen SY, Wu MM, Chen CJ: Ingested arsenic, cigarette smoking, and lung cancer risk: a follow-up study in arseniasis-endemic areas in taiwan. JAMA 2004, 292(4):2984–2990.

34. Toh CK, Gao F, Lim WT, Leong SS, Fong KW, Yap SP, HSu AA, Eng P, Koong HH, Thirumalnagam A, et al: Never-smokers with lung cancer: epidemiologic evidence of a distinct disease entity. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 2006, 24(15):2245–2251.

35. Toh CK, Lim WT: Lung cancer in never-smokers. J Clin Pathol 2007, 60(4):337–340.

36. Chen CL, Chou HY, HSu U, Hsuie YM, Wu MM, Chen CJ: Ingested arsenic, characteristics of well water consumption and risk of different histological types of lung cancer in northeastern taiwan. Environ Res 2010, 110(3):455–462.

37. Martinez VD, Buys TP, Adornis M, Benitez H, Gallegos I, Lam S, Lam WL, Gil L: Arsenic-related DNA copy-number alterations in lung squamous cell carcinomas. Br J Cancer 2010, 103(8):1277–1283.

38. Carbonne H, Kratika RA, Testa JR: The pathogenesis of mesothelioma. Semin Oncol 2002, 29(4):12–17.

39. McCormack V, Petro J, Byrnes G, Straf K, Boffetta P: Estimating the asbestos-related lung cancer burden from mesothelioma mortality. Br J Cancer 2012, 106(5):575–584.

40. Zervos MD, Bezekis C, Pass HI: Malignant mesothelioma 2008. Curr Opin Pulm Med 2008, 14(4):305–309.
Toxicological sciences: an official journal of the Society of Toxicology 2010, 117(2):270–281.

65. Dobroza Z, Styblo M, Thomas DJ: Purification of arsenic (+3 oxidation state) methyltransferase from rat liver cytosol. Curr Protoc Toxicol 2009, 42(2):141–13.

66. Rossman TG: Mechanism of arsenic carcinogenesis: an integrated approach. Mutat Res 2003, 533(1–2):7–66.

67. Rossman TG, Klein CB: Genetic and epigenetic effects of environmental arsenicals. Metallomics 2011, 3(11):1335–141.

68. Sung TL, Wang YL, Chen CY, Hung TL, Guo HR: Increased serum level of epidermal growth factor receptor in liver cancer patients and its association with exposure to arsenic. Sci Total Environ 2012, 424:74–78.

69. Jomova K, Jenisova Z, Feszterova M, Baros S, Liska J, Hudcove D, Rhodes CJ, Valko M: Arsenic: oxidative stress and human disease. J Appl Toxicol 2011, 31(9):95–107.

70. Shi H, Shi X, Liu KJ: Oxidative mechanism of arsenic toxicity and carcinogenesis. Mol Cell Biochem 2004, 255(1–2):267–78.

71. Valko M, Rhodes CJ, Moncol J, Jakubovska M, Mazur M: Free radicals, metals and antioxidants in oxidative stress-induced cancer. Chem Biol Interact 2006, 160(1–2):1–40.

72. Kitchin KT, Ahmad S: Oxidative stress as a possible mode of action for arsenic toxicity. Toxicol Lett 2003, 137:1–21–3.

73. Kessel M, Liu SX, Xu A, Santella R, Hei TK: Arsenic induces DNA damage in mammalian cells. Mol Cell Biochem 2002, 234–235:291–308.

74. Miller WH Jr, Schipper HM, Lee JS, Singer J, Waxman S: Mechanisms of action of arsenic trioxide. Cancer Res 2002, 62(1):3933–3930.

75. Partridge MA, Huang SX, Hernandez-Rosa E, Davidson MM, Hei TK: Arsenic induced mitochondrial DNA damage and altered mitochondrial oxidative function: implications for genotoxic mechanisms in mammalian cells. Cancer Res 2007, 67(15):5239–5247.

76. Ruiz-Ramos R, Lopez-Carrillo L, Rios-Perez AD, De Vizcaya-Ruiz A, Cebrian M: Sodium arsenite induces ROS generation, DNA oxidative damage, HO-1 and c-Myc proteins, NF-kappaB activation and cell proliferation in human breast cancer MCF-7 cells. Mutat Res 2009, 674(1–2):109–115.

77. Matsui M, Nishigori C, Toyokuni S, Takada J, Akaboshi M, Ishikawa M, Imamura S, Miyachi Y: The role of oxidative DNA damage in human arsenic carcinogenesis: detection of 8-hydroxy-2'-deoxyguanosine in arsenic-related Bowen's disease. J Invest Dermatol 1999, 113(3):26–31.

78. Cohen SM, Arnold LL, Eldan M, Lewis AS, Beck BD: Arsenic-related Bowen's disease: A case-control study. J Lab Clin Med 1999, 133(5):408–415.

79. Husgafvel-Pursiainen K, Karjalainen A, Kannio A, Anttila S, Partanen T, Nymark P, Lindholm PM, Korpela MV, Lahti L, Ruosaari S, Kaski S, Hollmen J, et al: Purification of arsenic (+3 oxidation state) methyltransferase from rat liver cytosol. Curr Protoc Toxicol 2009, 42(2):141–13.

80. Jiang BH, Liu LZ, Jiang Y, Carpenter RL, Jing Y, Peiper SC, Jing R: Down-regulation of Mcl-1 through GSK-3beta activation contributes to arsenic trioxide-induced apoptosis in acute myeloid leukemia cells. Leukemia 2012, 26(3):339–344.

81. Sharma S, Kelly TK, Jones PA: Epigenetics in cancer. Carcinogenesis 2010, 31(7):37–36.

82. Aujla AK, Mason RA, Memoli V, Duell EJ: Arsenic activates EGFR pathway signaling in the lung. Toxicological sciences: an official journal of the Society of Toxicology 2009, 109(2):350–357.

83. Liu LZ, Jiang Y, Carpenter RL, Jing Y, Peiper SC, Jiang BH: Role and mechanism of arsenic in regulating angiogenesis. J Clin Invest 2011, 121(6):2817–2826.

84. Wang X, Xia L, Gabrielove J, Waxman S, Jing Y: DNA methylation and histone acetylation of tumor suppressor genes in human lung adenocarcinoma cells following arsenic exposure. Cancer Lett 2008, 266(1):128–136.

85. Wang Y, Cheng S, Sun L, Son YQ, Yao H, Li W, Budhrajha A, Li L, Shelton BJ, et al: Reactive oxygen species mediated arsenic induced cellular transformation and tumorigenesis through Wnt/beta-catenin pathway in human colorectal adenocarcinoma DLD1 cells. Toxicol Appl Pharmacol 2011, 256(2):114–121.

86. Ormond MJ, Kunz BA, Snow ET: Age and exposure to arsenic alter base excision repair transcript levels in mice. Mutagenesis 2010, 25(5):57–52.

87. Yarnakal K, Okada S: Induction of lung-specific DNA damage by metabolically methylated arsenic(III) through the production of free radicals. Environ Health Perspect 1994, 102:Suppl(3):37–40.

88. Wen G, Calaf GM, Partridge MA, Echiburu-Chau C, Zhao Y, Huang S, Chai Y, Li B, Hu B, Hei TK: Neoplastic transformation of human small airway epithelial cells induced by arsenic. Mol Med 2008, 14(1):22–10.

89. Shukla A, Flanders T, Lounsbury KM, Mossman BT: The gamma-glutamylcysteine synthetase and glutathione regulate asbestos-induced expression of activator protein-1 family members and activity. Cancer Res 2004, 64(21):7778–7785.

90. Nymark P, Lindholm PA, Korpeila MV, Lahl T, Ruosaari S, Kadi S, Holmnen J, Anttila S, Kunala V, Knutula S, Gene expression profiles in asbestos-exposed epididymal and mesothelial lung cell lines, BMC Genomics 2007, 8:62.

91. Shukla A, Barrett TF, Nakayama R, Nakayama K, Mossman BT, Lounsbury KM: Transcriptional up-regulation of MMP12 and MMP13 by asbestos occurs via a PKCdelta-dependent pathway in murine lung. FASEB J 2006, 20(7):997–999.

92. Husaifel-Pursiainen K, Karjalainen A, Kannio A, Anttila S, Partanen T, Ruosaari S, Kaski S, Hollmen J, et al: Recognition of arsenic-induced cell transformation and tumorigenesis through Wnt/beta-catenin pathway in human colorectal adenocarcinoma DLD1 cells. Toxicol Appl Pharmacol 2011, 256(2):114–121.

93. Ormond MJ, Kunz BA, Snow ET: Age and exposure to arsenic alter base excision repair transcript levels in mice. Mutagenesis 2010, 25(5):57–52.

94. Yarnakal K, Okada S: Induction of lung-specific DNA damage by metabolically methylated arsenic(III) through the production of free radicals. Environ Health Perspect 1994, 102:Suppl(3):37–40.

95. Wen G, Calaf GM, Partridge MA, Echiburu-Chau C, Zhao Y, Huang S, Chai Y, Li B, Hu B, Hei TK: Neoplastic transformation of human small airway epithelial cells induced by arsenic. Mol Med 2008, 14(1):22–10.

96. Shukla A, Flanders T, Lounsbury KM, Mossman BT: The gamma-glutamylcysteine synthetase and glutathione regulate asbestos-induced expression of activator protein-1 family members and activity. Cancer Res 2004, 64(21):7778–7785.

97. Nymark P, Lindholm PA, Korpeila MV, Lahl T, Ruosaari S, Kadi S, Holmnen J, Anttila S, Kunala V, Knutula S, Gene expression profiles in asbestos-exposed epididymal and mesothelial lung cell lines, BMC Genomics 2007, 8:62.

98. Shukla A, Barrett TF, Nakayama R, Nakayama K, Mossman BT, Lounsbury KM: Transcriptional up-regulation of MMP12 and MMP13 by asbestos occurs via a PKCdelta-dependent pathway in murine lung. FASEB J 2006, 20(7):997–999.

99. Husaifel-Pursiainen K, Karjalainen A, Kannio A, Anttila S, Partanen T, Ojarvair A, Vainio H: Lung cancer and past occupational exposure to asbestos. Role of p53 and K-ras mutations. Am J Respir Cell Mol Biol 1999, 20(4):667–674.

100. Wang X, Christiani DC, Wiencze JK, Fischer BN, Xu X, Cheng TJ, Mark E, Wain JC, Kelsey KT: Mutations in the p53 gene in lung cancer are associated with cigarette smoking and asbestos exposure. Cancer Epidemiol Biomarkers Prev 1995, 4(5):543–548.

101. Andujar P, Wang J, Deschafia A, Galateau-Salle F, Abd-alsamad I, Billon-Galland MA, Bions H, Clin B, Daniel C, Houzet S, et al: p16INK4A...
Inactivation mechanisms in non-small-cell lung cancer patients occupationally exposed to asbestos. Lung Cancer 2010, 67(1):23–30.

Suzuki M, Piao CQ, Zhao YL, Hei TK: Karyotype analysis of tumorigenic human bronchial epithelial cells transformed by chrysotile asbestos using chemically induced premature chromosome condensation technique. Int J Med Sci 2007, 4(3):47.

Olsonk K, Mark J: Specificity of asbestos-induced chromosomal aberrations in short-term cultured human mesothelial cells. Cancer Genet Cytogenet 1989, 41(133–39).

Barrett JC, Lamb PW, Wiseman RW: Multiple mechanisms for the carcinogenic effects of asbestos and other mineral fibers. Environ Health Perspect 1989, 81:81–89.

Yegles M, Janson X, Dong HY, Renier A, Jauroand MC: Role of fibre characteristics on cytotoxicity and induction of anaphase/telophase aberrations in rat pleural mesothelial cells in vitro: correlations with in vivo animal findings. Carcinogenesis 1995, 16(1):271–2758.

Hesterberg TW, Barrett JC: Induction of fibrosarcoma by asbestos ofer abnormalities: mechanism for anapleoinduction and possibly carcinogenicity. Carcinogenesis 1985, 6(3):473–475.

Prise KM, Pinto M, Newman HC, Michael ED: A review of studies of ionizing radiation-induced double-strand break clustering. Radiat Res 2001, 156(5 Pt 2):2572–2576.

McDonald JW, Taylor JA, Watson MA, Saccomanno G, Devereux TR: p53 And K-ras in radon-associated lung adenocarcinoma. Canc Epiderm Biol Markers Prev 1995, 4(7):791–799.

Vahakangas KH, S suspect JM, Marsal RA, Welsh JA, Bennett WP, Lane DP, Harris CC: Mutations of p53 and ras genes in radon-associated lung cancer from uranium miners. Cancer 1992, 339(8):376–380.

Nymark P, Wilkman H, Ruosaari S, Hollmen J, Vanhala E, Karjalainen A, Anttila S, Knuttila S: Identification of specific gene copy number changes in asbestos-related lung cancer. Cancer Res 2006, 66(11):5737–5743.

Kettunen E, Aavikko M, Nymark P, Ruosaari S, Wilkman H, Vanhala E, Salmenkivi K, Pirinen P, Karjalainen A, Ruddan E, et al: DNA copy number loss and allelism of imbalance at 2p16 in lung cancer associated with asbestos exposure. Br J Cancer 2009, 100(8):1336–1342.

Wilkman H, Ruosaari S, Nymark P, Sarhadi VK, Saharinen J, Vanhala E, Karjalainen A, Hollmen J, Knuttila S: Gene expression and copy number profiling suggests the importance of allelic imbalance in 19p in asbestos-associated lung cancer. Oncogene 2007, 26(32):4730–4737.

Bartrde K, Guilly MN, Beraind JF, Joubert C, Lecard B, Levalois C, Malfoy B, Chevillard S: Molecular analysis of the In4a/In1-Arf/Tp53 pathways in radon-induced rat lung tumors. Lung Cancer 2009, 63(3):348–353.

Nelson NH, Christani DC, Winkoe JK, Mark EL, Wain JC, Kelsey KT: k-mutation and occupational asbestos exposure in lung adenocarcinoma: asbestos-related cancer without asbestos. Cancer Res 1999, 59(18):4570–4575.

Filippowicz W, Bhattacharyya SN, Sonenberg N: Mechanisms of post-transcriptional regulation by microRNAs: are the answers in sight? Nat Rev Genet 2008, 9(2):102–114.

Iorio MV Croce CM: mRNA involvement in human cancer. Carcinogenesis 2012, 33(6):1126–1133.

Nair VS, Meada LS, Loanm6 JP: Clinical outcome prediction by microRNAs in human cancer: a systematic review. J Natl Cancer Inst 2012, 104(7):529–540.

Calin GA, Croce CM: MicroRNA signatures in human cancer. Nat Rev Cancer 2006, 6(11):857–866.

Mass MJ, Wang L: Arsenic alters cytinosine methylation patterns of the promoter of the tumor suppressor gene p53 in human lung cells: a model for mechanism of carcinogenesis. Mutat Res 1997, 386(3):263–277.

Cui X, Waki T, Shira Y, Hatakeyama K, Hitono S: Chronic oral exposure to inorganic arsenate interferes with methylation status of p16Ink4a and RASSF1A and induces lung cancer in A/J mice. Toxicological sciences: an official journal of the Society of Toxicology 2006, 91(2):372–381.

Wang Z, Zhao Y, Smith E, Goodall GJ, Drew PA, Brabetz T, Yang C: Reversal and prevention of arsenic-induced human bronchial epithelial cell malignant transformation by microRNA-200b. Toxicological sciences: an official journal of the Society of Toxicology 2011, 121(1):102–122.

Dammann R, Strunnikova M, Schagdarsurengin U, Rastetter M, Papritz M, Hattenhorst UE, Hofmann HS, Silber RE, Burdach S, Hansen G: GpG island methylation and expression of tumour-associated genes in lung carcinoma. Eur J Cancer 2005, 41(8):1223–1236.

Sanchez-Cespedes M, Ahrendt SA, Piantadosi S, Rosell R, Monzo M, Wu L, Westra WH, Yang SC, Jen J, Sidransky D: Chromosomal alterations in lung adenocarcinoma from smokers and nonsmokers. Cancer Res 2001, 61(4):1309–1313.

Nymark P, Guled M, Borze I, Faisal A, Lahti L, Salmenkivi K, Kettunen E, Anttila S, Knuttila S: Integrative analysis of microRNA, miRNA and aCGH data reveals asbestos- and histology-related changes in lung cancer. Genes Chromosomes Cancer 2011, 50(9):585–597.

Su S, Jin Y, Zhang W, Yang L, Shen Y, Cao Y, Tong J: Abramer promoter methylation of p16/INK4a and O(6)-methylguanine-DNA methyltransferase genes in workers at a chinese uranium mine. J Occup Health 2006, 48(4):261–266.

Belinsky SA, Xing E, Lichtry CK, March TH, Kang T, Gilliland FD, Satrinic N, Adamova G, Rusinova G, Telnov V: Platinum targets the p16 gene for inactivation by promoter hypermethylation in human lung adenocarcinoma. Carcinogenesis 2004, 25(6):1063–1067.

Intarasunanont P, Navasumrit P, Worraraprasit S, Chaisatra K, Suk WA, Mahdol C, Rhuchrawat M: Effects of arsenic exposure on DNA methylation in cord blood samples from newborn babies and in a human lymphoblast cell line. Environmental health: a global access science source 2012, 11(3):1.

Jensen TJ, Novak P, Eblin RJ, Fandell AJ, Futscher BW: Epigenetic remodeling during arsenical-induced malignant transformation. Carcinogenesis 2008, 29(8):1500–1508.

Jensen TJ, Wozniak RJ, Eblin KE, Wnek SM, Gandolfi AJ, Futscher BW: Epigenetic mediated transcriptional activation of WNTSIA participates in arsenical-associated malignant transformation. Toxicol Appl Pharmacol 2009, 235(3):349–406.

Zhou X, Sun H, Ellis TP, Chen H, Costa M: Arsenite alters global histone H3 methylation. Carcinogenesis 2008, 29(9):1831–1836.

Jo WI, Ren X, Chu F, Aleshin M, Wintz H, Burlingame A, Smith MT, Vulpe CD, Zhang L: Acetylated H4K16 by MYST1 promotes UROtsa cells from arsenic toxicity and is decreased following chronic arsenic exposure. Toxicol Appl Pharmacol 2009, 241(3):294–302.

Zhao QG, Young MR, Dixian BA, Coopan TP, Waalke MP: Association of arsenic-induced malignant transformation with DNA hypomethylation and aberrant gene expression. Proc Natl Acad Sci USA 1997, 94(20):10907–10912.

Mohan D, Pittman CU: Arsenic removal from water/wastewater using adsorbents--a critical review. J Hazard Mater 2007, 142(1–2):51–53.

Mattew JL, Gadgil AJ, Addy SE, Kowolik K, Mathieu JL, Gadgil AJ, Addy SE, Kowolik K: Arsenic remediation of drinking water using iron-oxide coated carbon bottom ash. J Environ Sci Health, Part A: Toxicol Subj Environ Eng 2010, 45(11):1446–1460.

Pokhrel D, Viraraghavan T: Arsenic removal from an aqueous solution by a modified fungal biomass. Water Res 2006, 40(3):549–552.

Paglietti W, Malinconico S, Molletta JD, Gianguioso M: Guidelines for arsenic remediation at Italian superfund sites. J Environ Sci Health, Part C: Environ Carcinog Ecotox Rev 2012, 30(2):253–265.

Colangelo F, Cioffi R, Lavorgna M, Verdoliti L, De Stefano L: Treatment and recycling of asbestos-cement containing waste. J Hazard Mater 2011, 195:391–397.

Guaitieri AF, Giacobbe C, Sardisco L, Saraceno M, Gualtieri ML, Lusvardi G, Gualtieri AF, Giacobbe C, Sardisco L, Saraceno M, Gualtieri ML, Lusvardi G: Environmental Health: A review of studies of asbestos remediation at Italian superfund sites. J Environ Sci Health, Part C: Environ Carcinog Ecotox Rev 2012, 30(2):253–265.

Tamin BP: Environmental exposure measurement in cancer epidemiology. Mutagenes 2009, 24(2):117–125.

Boffetta P, McLaughlin JK, La Vecchia C, Autier P, Boyle P: Environment: In cancer causation and etiological fraction: limitations and ambiguities. Carcinogenesis 2007, 28(5):93–915.