

# The Current Understanding Of Asbestos-Induced Epigenetic Changes Associated With Lung Cancer

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**Abstract:** Asbestos is a naturally occurring mineral consisting of extremely fine fibres that can become trapped in the lungs after inhalation. Occupational and environmental exposures to asbestos are linked to development of lung cancer and malignant mesothelioma, a cancer of the lining surrounding the lung. This review discusses the factors that are making asbestos-induced lung cancer a continuing problem, including the extensive historic use of asbestos and decades long latency between exposure and disease development. Genomic mutations of DNA nucleotides and gene rearrangements driving lung cancer are well-studied, with biomarkers and targeted therapies already in clinical use for some of these mutations. The genes involved in these mutation biomarkers and targeted therapies are also involved in epigenetic mechanisms and are discussed in this review as it is hoped that identification of epigenetic aberrations in these genes will enable the same gene biomarkers and targeted therapies to be used. Currently, understanding of how asbestos fibres trapped in the lungs leads to epigenetic changes and lung cancer is incomplete. It has been shown that oxidoreduction reactions on fibre surfaces generate reactive oxygen species (ROS) which in turn damage DNA, leading to genetic and epigenetic alterations that reduce the activity of tumour suppressor genes. Epigenetic DNA methylation changes associated with lung cancer are summarised in this review, and some of these changes will be due to asbestos exposure. So far, little research has been carried out to separate the asbestos driven epigenetic changes from those due to non-asbestos causes of lung cancer. Asbestos-associated lung cancers exhibit less methylation variability than lung cancers in general, and in a large proportion of samples variability has been found to be restricted to promoter regions. Epigenetic aberrations in cancer are proving to be promising biomarkers for diagnosing cancers. It is hoped that further understanding of epigenetic changes in lung cancer can result in useful asbestos-associated lung cancer biomarkers to guide treatment. Research is ongoing into the detection of lung cancer epigenetic alterations using non-invasive samples of blood and sputum. These efforts hold the promise of non-invasive cancer diagnosis in the future. Efforts to reverse epigenetic aberrations in lung cancer by epigenetic therapies are ongoing but have not yet yielded success.

**Keywords:** lung cancer, epigenetic biomarkers, microRNA, DNA methylation, immunohistochemistry, IHC, fluorescence in situ hybridization, FISH

## Asbestos And Lung Cancer

Asbestos is a group of naturally occurring fibrous silicate minerals with multiple commercial applications. Asbestos material is resistant to heat and corrosion. Its natural fibrous nature enables it to be woven into cloth, incorporated into cement materials, ceiling tiles, break and clutch linings, flooring, resins, polymers, and filter papers. In the 19th and 20th centuries, asbestos was used in a large number of industries with minimal control of exposure. From 1950 to 1985, it was extensively

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used in construction and ship building for insulation and fire protection, and as material for anti-friction and filtering. It is estimated that one in every three houses in Australia built before 1990 contains asbestos,<sup>1</sup> putting Australians at risk of exposure.

Lung cancers are aggressive respiratory tumours with poor survival.<sup>2</sup> While tobacco smoking remains the principal cause for lung cancers, exposure to asbestos is the most important occupational risk factor for these cancers.<sup>3</sup> Asbestos exposure causes 6 to 23% of all male lung cancers (estimates depend on the exposure and population),<sup>4,5</sup> and >107,000 deaths annually in Europe from asbestos-related diseases. In 2018, there were 12,741 reported lung cancer deaths in Australia, which is equivalent to 500 deaths for every one million people, placing lung cancer in the top five deadly cancers.<sup>6</sup> All forms of asbestos are carcinogenic to humans.<sup>4</sup> It is estimated that asbestos exposure causes six times more lung cancer than malignant mesothelioma,<sup>7</sup> and mesothelioma deaths are estimated to be 38,400 per year worldwide.<sup>8</sup> Research has linked asbestos exposures to development of lung cancer and malignant mesothelioma,<sup>9</sup> and has shown the potential for asbestos to induce formation of reactive oxygen species (ROS) that cause damage of DNA and alterations that reduce the activity of tumour suppressor genes.<sup>10</sup> Given that the latency of cancer development may be as long as 30–40 years after asbestos exposure and the fact that demolition of asbestos-containing buildings is common, asbestos exposure will continue to inflict substantial disease morbidity and mortality in future years.<sup>4,11</sup> Although the link between asbestos and lung cancer risk is well-established, asbestos-associated neoplasms have proven difficult to diagnose early and treat successfully. As with other cancers, most asbestos-related lung cancers are diagnosed at late stages of disease, underscoring the need for better understanding of the molecular mechanisms of these diseases, and for identification of critical gene targets for new diagnostic biomarkers and therapies.

When a person inhales airborne asbestos particles, the asbestos fibres can become lodged in their lung tissue.<sup>12,13</sup> Exposure to asbestos puts people at risk of developing cancers in the lungs (lung cancer),<sup>12–15</sup> pleural and peritoneal lining (pleural and peritoneal mesothelioma),<sup>12,14–16</sup> larynx,<sup>17</sup> and ovaries.<sup>18</sup> All four major histological types of lung cancers (squamous, adeno, large-cell, and small cell) can be caused by asbestos exposure.<sup>14</sup> Almost all mesotheliomas are caused by asbestos exposure.<sup>16</sup> Over many years, asbestos fibres can cause genetic, epigenetic,

and cellular damage, causing lung cells to become malignant. For these cancers, there is a long latency period between exposure and development of symptoms. Lung cancer caused by asbestos is different from pleural malignant mesothelioma, with the former developing inside the lung and the latter in the outer lining of the lung.

## Biomarkers Used In Lung Cancers To Choose Treatment (Table 1)

The identification of genetic alterations in lung cancers allows clinicians to select optimal treatments tailored to an individual's pathology. Replacing the generalised approach, the use of agents targeting specific driver gene mutations or overexpression has served to increase therapeutic effect and overall survival, often with a more tolerable side effect profile than traditional chemotherapy.

Genes frequently mutated in lung cancer and thus used as biomarkers are summarised in Table 1. Amongst these biomarkers, alterations in EGFR, ALK, ROS1 and BRAF genes are currently the most relevant in clinical practice with clinically effective specific targeted treatments available.<sup>19</sup>

EGFR mutations for example, present in approximately 15% of patients with adenocarcinoma in Western countries and over 50% in some Asian populations,<sup>20</sup> have been managed with first generation EGFR tyrosine kinase inhibitors (TKIs) (e.g. gefinitib or erlotinib) with demonstrable superiority over systemic first line chemotherapy.<sup>21</sup> These agents traditionally proved ineffective in tumours with T790M EGFR mutations, though third generation agents (e.g. osimertinib) have proven capable of not only overcoming the development of this resistance mutation, but offer improved progression free survival over first generation agents in treatment naïve EGFR mutation positive populations, with or without a T790M mutation.

Additional driver mutations are currently under investigation with preliminary evidence of treatment efficacy when targeted therapies are utilised, including HER2 mutations, MET14 mutation or amplification, and RET rearrangements, whilst RAS and PIK3CA mutations may confer worse prognosis and response to other therapies (e.g. EGFR TKIs in EGFR-mutant non-small cell lung cancer (NSCLC)).

Table 2 summaries other relevant treatment options indicated by biomarker alterations. Most of these biomarkers are nucleotide mutations and gene rearrangements rather than epigenetic alterations. It is hoped that future characterisation of epigenetic alterations will increase the

Table 1 Genes Frequently Possessing Alterations In Lung Cancer

Lung Tumour Types (WHO Classification <sup>27</sup> )	TP53	EGRF	RBI	KEAP1	NOTCHI	BRAF	MET	ERBB2	RET	KRAS NFI STK11 MAP2K1 NRAS HRAS ROSI ALK	CDKN2A PTEN PIK3CA MLL2 HLA- A NFE2L2	KIAA1211 COL22A1 RGS7 FPR1 CREBBP FMN2	TMEM41B DEFB127 WDYHVI TBPL1
<b>Epithelial tumours</b>													
Adenocarcinoma <sup>23-25</sup>	X	X	X	X	X	X	X	X	X	X	X		
Squamous cell carcinoma <sup>24,26</sup>	X		X	X	X	X	X	X	X				
<b>Neuroendocrine tumours</b>													
Small cell carcinoma <sup>27</sup>	X		X		X							X	
Large cell neuroendocrine carcinoma <sup>28</sup>	X		X										
Carcinoid tumours <sup>29</sup>	X		X										
Sarcomatoid carcinoma <sup>30</sup>	X	X				X	X	X	X				X

number of targetable individual cancers for which a potentially beneficial treatment can be identified.

### Asbestos-Induced Epigenetic Changes (Figure 1)

How asbestos induces epigenetic changes is not fully understood. Several studies have shown both clastogenic and cytotoxic responses of cells to asbestos fibres.<sup>32,33</sup> Phagocytosis of fibres by macrophages and oxidoreduction reactions on fibre surfaces are known to generate genotoxic ROS that result in DNA damage and oxidative stress, leading to genetic alterations in the cells.<sup>34-36</sup> When asbestos interacts with human cells, asbestos silicates attract and bind cations, and in the lungs, asbestos fibres will both retain the ions on the fibre surface and leach them into the cellular milieu.<sup>37</sup> These processes can generate reactive oxygen species and free radicals that initiate the processes of cellular and DNA damage and genotoxicity.<sup>38,39</sup> The high iron content of some asbestos fibres, as well as the propensity for asbestos to adsorb iron in vivo, have led to the suggestion that iron-induced Fenton reactions also contribute to increased ROS, inflammation, and carcinogenesis.<sup>40</sup> Chrysotile and crocidolite types of asbestos were shown to induce oxidative stress and induce local inflammatory mediators (cytokines and growth factors), leading to a reactive microenvironment of inflammation and proliferation of cells.<sup>41,42</sup> Exposure of cells to asbestos induces extensive alterations in expression of genes involved in integrin-mediated signalling, DNA damage repair, and cell cycle regulation pathways.<sup>43,44</sup> The chronic inflammation caused by exposure of serosal surfaces to asbestos fibres is likely to represent a central factor in the carcinogenesis and is likely to be mediated through epigenetic changes.<sup>45</sup>

Many studies have investigated microRNAs associated with asbestos induced epigenetic alteration in mesothelioma (a highly specific cancer induced by asbestos exposure).<sup>46-48</sup> However, there has been only limited exploration in asbestos-related lung cancers, including adenocarcinoma, adenosquamous carcinoma, small cell lung cancer and large cell lung cancer.<sup>49</sup> Although these demonstrated effects show the potential of asbestos to induce epigenetic alterations, it is nonetheless unclear how these factors contribute to cell toxicity and the transformation to a malignant state.

### Epigenetic Biomarkers In Cancer

DNA methylation is a fundamental epigenetic mechanism for regulating gene expression. Dysregulation of epigenetic transcriptional control, particularly aberrant promoter DNA

**Table 2** Gene alteration and drug approval status in NSCLC

Gene	Alteration	Drug Approval Status	Frequency In NSCLC	Ref
<i>AKT1</i>	Mutation	Drugs approved in NSCLC.	0.6–2%	[101]
<i>ALK</i>	Rearrangement	Drugs approved in NSCLC.	1–5%	[102]
<i>BRAF</i>	Mutation	Drugs approved in other cancer.	2–4%	[103, 104]
<i>DDR2</i>	Mutation	Drugs approved in other cancer.	2–4%	[105, 106]
<i>EGFR</i>	Mutation	Drugs approved in NSCLC.	4–40%	[107, 108]
<i>FGFR1</i>	Amplification	Drugs in clinical development.	8.7–21%	[109–112]
<i>HER2</i>	Mutation	Drugs approved in other cancer.	1–4%	[113–115]
<i>KRAS</i>	Mutation	Drugs in clinical development.	15–25%	[116]
<i>MEK1</i>	Mutation	Drugs approved in other cancer.	~1%	[117]
<i>MET<math>\alpha</math></i>	Amplification	Drugs approved in NSCLC but for other molecular subtype.	1%	[118]
<i>NRAS</i>	Mutation	Drugs in clinical development.	1%	[116]
<i>PIK3CA</i>	Mutation	Drugs in clinical development.	3.7%	[119]
<i>PTEN</i>	Mutation	Drugs in clinical development.	4.5%	[120]
<i>RET</i>	Rearrangement	Drugs in clinical development.	1–2%	[121]
<i>ROS1<math>\alpha</math></i>	Rearrangement	Drugs approved in NSCLC.	1–2%	[122, 123]

**Key:**

Drugs approved in NSCLC.

Drugs approved in NSCLC but for other molecular subtype.

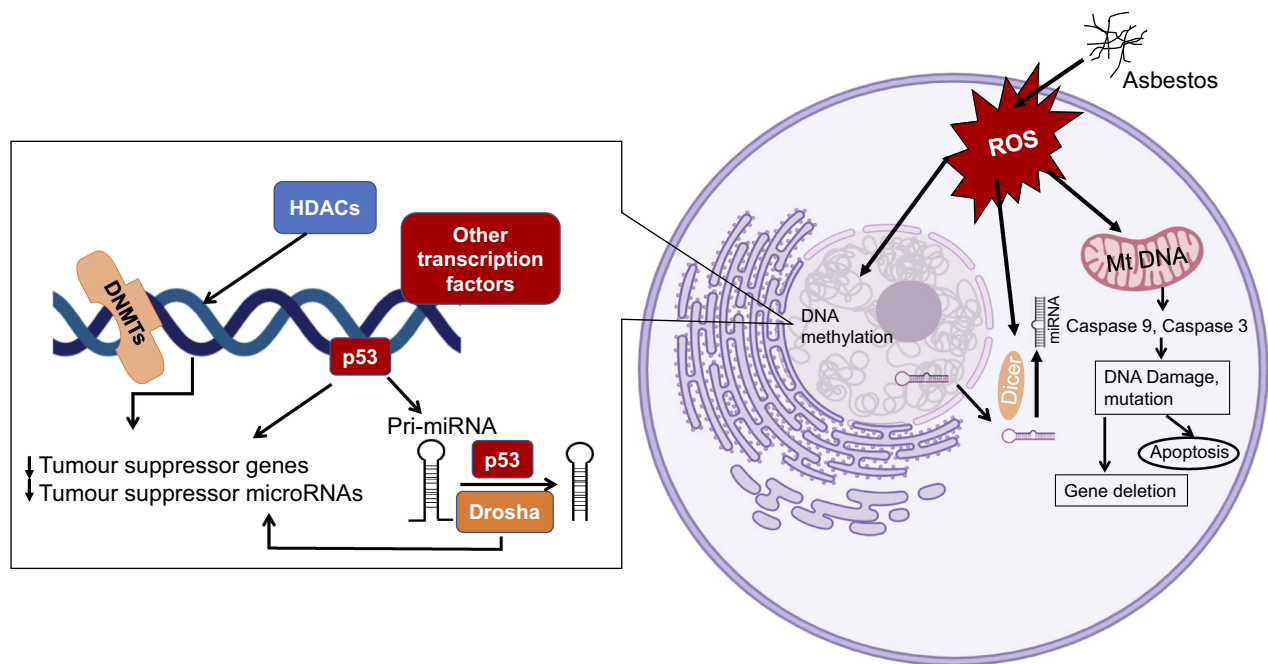
Drugs approved in other cancer.

Drugs in clinical development.

methylation and histone modifications, is a fundamental feature of human malignancies.<sup>10</sup> Many cancers present with a global DNA hypomethylation of non-coding regions, and site-specific hypermethylation of CpG islands (CGI) in tumour suppressor regions.<sup>50</sup> To what extent epigenetic changes cause carcinogenesis is currently being investigated.<sup>51</sup> Complicated epigenetics mechanisms, including CGI shores' and gene body methylation may contribute to the carcinogenesis process.<sup>51,52</sup> Genomic regions having different DNA methylation status in cancer versus non-cancer are referred to as differentially methylated regions (DMRs). The most widely studied epigenetic alterations are DNA methylation at CpG dinucleotides. These are highly concentrated in CpG islands within promoter regions or near the first exon of genes. Their state of methylation controls gene expression.<sup>53</sup> Differences in DNA methylation status lead to various levels of gene silencing in cancer. Promoter hypermethylation has been linked to the silencing of tumour suppressor genes and oncogenesis.<sup>54–56</sup> DNA methylation heterogeneity and variability are observed at distinctive genomic regions in cancer tissue.<sup>57,58</sup> These differentially methylated CpGs (DMCs) are consistently methylated in

a non-cancer group, and variably methylated in cancer groups, with the highly variable CpGs hypothesised to contribute to tumour heterogeneity.<sup>59</sup> Studies have identified differentially variable and differentially methylated CpGs (DVMCs) using algorithms that identify regions of differential variability and rank or filter them by the statistical significance of their differential methylation.<sup>59</sup> There are a number of epigenetic biomarkers that show potential for the early detection of cancers due to their involvement in the initiation of carcinogenic pathways.<sup>60,61</sup> Epigenetic biomarkers have high potential and wide scope to be implemented as early diagnostic biomarkers.

Amongst all epigenetic alterations in cancer, aberrant DNA hypermethylation is more studied than aberrant hypomethylation, and diagnostic tests being developed also tend to look for hypermethylated regions rather than hypomethylated ones.<sup>62</sup> The reason for the focus on hypermethylation instead of hypomethylation is technical. Methylation assays produce a signal for methylated DNA, and a lack of signal signifies a lack of methylated DNA due to either hypomethylation of the DNA present or due to absence of the targeted DNA in the assay. Thus, molecular tests to identify



**Figure 1** Potential molecular responses of affected cells to the presence of asbestos. When cells are exposed to asbestos, the generation of reactive oxygen species (ROS) will lead to alteration of DNA methylation and microRNA (miRNA) expression/processing, resulting in cell apoptosis or epigenetic alterations that allow cells to progress to diseased states.

methylated DNA are carried out more often than tests for hypomethylation. On the other hand, hypomethylation of genes leads to overexpression of their protein. Thus, immunohistochemistry (IHC) to measure protein expression is a common tool in the diagnostic setting.

## DNA Methylation In Lung Cancers

There are a number of genes that have been reported as aberrantly hypermethylated in human lung cancers (Table 3). Studies have shown that epigenetic alterations (Figure 1), especially DNA methylation, can be used to identify patients

at risk of developing lung cancer.<sup>44</sup> The relationship between promoter DNA hypermethylation and inflammation has been documented in many forms of cancer, including asbestos-related lung cancer.<sup>76</sup> It is hypothesised that asbestos exposure contributes to lung cancer formation through this relationship.<sup>45</sup> Genomic investigations have shown DNA copy number alterations, changes in miRNA profiles, and deregulation of expression of certain genes in asbestos-related lung cancer.<sup>49,51,77,78</sup> However, little is known about how asbestos fibres directly or indirectly interact with cells at the molecular level.<sup>78</sup>

**Table 3** Genes Found To Have Hypermethylated DNA In Human Lung Cancer

Gene	% (And Number) Of Lung Cancers Exhibiting Hypermethylation	Year Reported	Reference
CDKN2A	44% (9/22)/25%(27/107)/47% (8/17)/25.9%(22/85)/34%(22/99)/14%(3/21)	1999/2001/2005/2007/2007/2009	63/64/65/66/67/68
MGMT	27% (6/22)/21% (22/107)	1999/2001	63/64
RAR beta	59%(178/301)/44.6%(41/92)/31%(19/61)	2000/2007/2004	69/66/70
CYGB	48%/(25/52)	2006	71
RASSF1	33%/(30/90)/36%(64/178)/39%(28/72)/	2007/2012	66/68/70
APC	31%(28/91)/48%(48/99)	2007/2007	66/67
DAPK	26%(24/92)	2007	66
FHIT	34%(34/99)/48%(21/44)/42.6%(23/54)	2007/2004/2009	67/70,72
DOK1	81%(68/84)	2012	68
TCF21	81%(85/105)	2011	73
BRMS1	35%(14/40)/44%(58/132)	2010/2011	74,75

Lung cancer cases with no documented occupational exposure to asbestos have been found to have larger methylation variability and a higher proportion of hypomethylated DVMCs than asbestos-exposed subjects.<sup>76</sup> A large proportion of DVMCs in lung tumours of the asbestos-exposed subjects have been found within 1 kilobasepair (kb) of promoter regions.<sup>76</sup> The genes *NPTN*, *NRG2*, and *TRPC3* exhibit significant asbestos-related DVMCs.<sup>76</sup> *NRG2* has a cell proliferation role and thus its DVMC in asbestos-related lung cancers may be playing a role in the cancer.<sup>76</sup> Little is known about the role of *NPTN* (neuroplastin), and it may potentially be involved in modulating intracellular  $Ca^{2+}$  as a result of its interaction with *FGFR*.<sup>79</sup> This may result in stimulating the  $Ca^{2+}$  sensing receptor that promotes the expression of *TRPC3*, a member of the canonical transient receptor potential channels, leading to perturbation in  $Ca^{2+}$  homeostasis.<sup>80</sup> Hypermethylation of *TRPC3* was observed in lung cancer cases that were not associated with asbestos exposure. In asbestos-associated tumours, *TRPC3* methylation remained at the same level as in peripheral normal lung tissue.<sup>81</sup>

In asbestos-associated lung cancers, DMRs were identified in genes *RARB*, *GPR135*, *MYT1L*, *TPO*, and *RPTOR*.<sup>76</sup> Hypomethylation of *TPO* was observed in asbestos-associated lung tumours.<sup>76</sup> *TPO* is a thyroid peroxidase that is responsible for oxidative metabolic reactions and was mostly studied in thyroid cells.<sup>82</sup> The carcinogenesis mechanism of asbestos is hypothesised to involve reactive oxygen species (ROS).<sup>39</sup> An increase in expression of *TPO* has been observed in tumour and lung tissue of adenocarcinoma patients with high intakes of red

meat and the increased expression was attributed to a gene product linked to heme-iron toxicity and oxidative stress.<sup>83</sup> Iron-related toxicity mechanisms have also been proposed for asbestos.<sup>4</sup> Importantly, *TPO* expression was not found to be associated with smoking in lung adenocarcinoma.<sup>83</sup>

## Epigenetic Biomarkers Detectable In Lung Cancer Using Minimally Invasive Biopsy Samples

Of all the known types of epigenetic alterations, DNA methylation is the most widely studied in cancer due to the stability of DNA and it being readily detectable in blood circulation. To definitively diagnose lung cancer, a tissue biopsy needs to be obtained from the patient based upon the initial clinical and radiological findings. The lesion is often detected by an initial thoracic screening for respiratory lesions performed by computed tomography (CT). This method is considered highly sensitive for lung cancer. However, it has a high false positive rate as a proportion of the lesions are benign tumours.<sup>84,85</sup> There are several tissue and circulating epigenetic biomarkers for lung cancers, including EGF-like and two follistatin domains (TMEFF2),<sup>86</sup> that are detectable in the blood of lung cancer patients as tumours shed tumour DNA into the blood. TMEFF2 is inactivated through hypermethylation in many cancers including NSCLC and is common in non-EGFR mutated patients who have never smoked.<sup>86</sup> RASFF1A hypermethylation was detected in 33.8% of NSCLC patients and not in healthy control benign pulmonary disease.<sup>54</sup> Confirmation by tissue or other biopsy is currently still required for definitive diagnosis.<sup>87</sup> In NSCLC, sputum represents a good source for biomarker

**Table 4** Epigenetic Biomarkers In Lung Cancer Using Minimally Invasive Biospecimens

Lung Cancer Subtypes	Gene	DNA Source	Ref	miRNA Source	microRNA	Ref
NSCLC	CDKN2A	cfDNA	90	cfmiRNAs	Up: miR-21, miR-210, miR-182, miR-31, miR-200b, miR-205, miR-183; Down: miR-21, miR-210, miR-182, miR-31, miR-200b, miR-205 and miR-183	91
NSCLC	RARB2	cfDNA	92			
LCLC/SCLC/SCLC	RASSF1A	cfDNA	93	cfmiRNAs	Up: miR-20a, miR-24, miR-25, miR-199a-5p, miR-221, miR-222, miR-223; Down: mir-145, miR-152, miR-320	94
NSCLC	SOX17	cfDNA	95			
NSCLC	TMEFF2	serum	86			
NSCLC	MGMT	Bronchial wash	96			

detection, as cancer cells shed tumour DNA from the lung into the sputum.<sup>54,88</sup> Various studies utilised sputum as a minimally invasive biospecimen and identified DNA methylation biomarkers including *p16*, *DAPK*, *PAX5b*, *GATA5*,<sup>88</sup> *RASSF1A*, *PRDM14*, and *3OST2*<sup>36</sup> for early detection of lung cancer in stage I of the disease. *MGMT* has been shown to be capable of identifying squamous cell lung carcinoma three years before clinical diagnosis.<sup>89</sup> Table 4 summarises the most useful of the promising epigenetic biomarkers detected using minimally invasive lung cancer biospecimens.

## Epigenetic Alterations As Treatment Options For Lung Cancer

Unlike gene mutations, epigenetic dysregulation can be reversed by selectively targeted treatment. Studies suggest that epigenetic dysregulation may contribute to drug-resistance in subpopulations of cells within the heterogeneous tumour population.<sup>97</sup> Single-agent demethylation drugs such as azacytidine have been investigated for treating NSCLC solid tumours. A comparison of outcomes for 103 patients treated between 1972 and 1977 indicated that single epigenetic agents have limited efficacy in NSCLC, with an objective response rate of only 8%.<sup>98</sup> A study of more than 200 NSCLC patients enrolled in a single epigenetic-agent trial produced disappointing initial findings.<sup>98</sup> Given these initial findings for single epigenetic agents in treating solid tumours, researchers are investigating combination therapies on the basis that the ineffectiveness of single-agent epigenetic therapies may be due to complications associated with DNMT inhibitors at cytotoxic doses.<sup>99</sup> The results of a phase I/II study of azacytidine and etinostat combination therapy in 45 heavily pre-treated advanced NSCLC patients indicate that combinations with low-dose epigenetic therapy may be beneficial for treating solid tumours.<sup>99</sup> More combination clinical trials are needed to confirm the efficacy of epigenetic therapy, and such trials are in progress.<sup>100</sup>

## Conclusion

In summary, DNA methylation and microRNA alterations are key epigenetic alteration features in asbestos-related lung cancers. There are a number of epigenetic biomarkers (*CDKN2A*, *RARB2*, *RASSF1A*, *SOX17*, *TMEFF2* and *MGMT*) that are potentially useful for identifying asbestos-related lung cancers. However, further studies are needed to clarify the direct link

between asbestos and these biomarkers. Development of new treatments is needed for better outcomes in asbestos-related lung cancers. Currently, despite their promise, no epigenetic therapies have been implemented clinically. Therefore, further characterisation and development in utilising epigenetic biomarkers for drug treatment discovery is warranted.

## Disclosure

The authors report no conflicts of interest in this work.

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