Occupational exposures and genetic susceptibility to lung cancer and pleural mesothelioma: a systematic review

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ABSTRACT

Background: The risk of occupationally related lung cancer, as well as pleural mesothelioma, in association with genetic polymorphisms, has been investigated with contradictory results. This systematic review aims to summarize the current knowledge on the relationship between genetic polymorphisms, occupational exposures, and lung cancer and pleural mesothelioma.

Methods: We searched MEDLINE, ISI Web of science, and SCOPUS online databases for all articles published in English language up to September 2016. Studies were considered eligible if they had assessed the association between occupational exposures and lung cancer/pleural mesothelioma in relation to genetic polymorphisms.

Results: Sixteen studies were included, of which eleven on lung cancer and six on mesothelioma, of which one was in common. NAT2 slow acetylator genotype confers an increased risk of pleural mesothelioma in subjects exposed to asbestos (OR=2.10; 95% CI=1.10-4.10), especially in combination with the GSTM1 null genotype (OR=3.60; 95% CI=1.30-9.60). GSTT1 null and CYP1A1 Msp1 T6235C (T/C+C/C) genotype carriers exposed to arsenic, uranium, asbestos and other chemical agents have an increased risk of lung cancer respect to not exposed wild type genotypes (OR=1.33; 95% CI=0.67-2.64, OR=2.20; 95% CI=1.11-4.35, respectively).

Conclusions: Genetic polymorphisms might modulate individual susceptibility to lung cancer and pleural mesothelioma in occupationally exposed subjects.

Key words: lung cancer; pleural mesothelioma; occupational; gene; polymorphism

INTRODUCTION

Lung cancer is the most frequent neoplasm among men in most countries [1]. Together with pleural malignant mesothelioma, lung cancer affects lungs and chest with an estimated 1.6 million of new cases and 1.4 million deaths annually [2,3]. Regarding malignant mesothelioma, its incidence has increased significantly after the second half of the 20th century, with more than 90% of the cases attributed to pleural mesothelioma [4]. According to some
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METHODS

Literature search and eligibility criteria

Identification of the studies was carried out through a search of MEDLINE, ISI Web of science, and SCOPUS databases, up to September 30th, 2016, by two independent investigators (SM and JS). The search strategy was based on combinations of the following terms and their synonyms: [occupation* AND “genetic polymorphism*” AND cancer], with the restriction to English language.

Studies were considered eligible if they assessed the association between occupational exposures and lung cancer/mesothelioma risk in relation with genetic polymorphisms, and if they reported effect measures such as odds ratios (OR), relative risks (RR) and 95% confidence intervals (CI) or relevant information to calculate them. A manual search of reference lists from included studies was also used in order to identify additional studies.

Data extraction

From each study the following information were extracted: first author, publication year, study design, location of the study, number of cases/controls according to each genotype, carcinogenic agent, intensities of occupational exposures, genes, polymorphisms and genotypes, number of cases/controls for each genotype, effect measures with corresponding 95% CI. If available, information regarding smoking, alcohol consumption and dietary habits, which might have modified the effect of occupational agents on lung cancer and mesothelioma risk were also extracted.

The systematic review was undertaken according to the “Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA)” guidelines.

RESULTS

Out of 1451 potentially relevant records identified, 280 were assessed for eligibility. Sixteen studies [12, 15–29] were ultimately included in the systematic review (Fig.1).

The main characteristics of the included studies are reported in Tables 1a and 1b.

Ten studies were on lung cancer, five on pleural mesothelioma, and one reported both diseases. The most frequently investigated polymorphisms were GSTM1, GSTT1, NAT2 and CYP1A1 genes (Tables 2, 3, 4, and 5).

GSTM1 genotype

Seven studies reported the association between GSTM1 genotype and asbestos exposure on risk of lung cancer or pleural mesothelioma [12, 15–17, 25, 28, 29]. Two studies showed that GSTM1 null carriers are at increased risk of lung cancer or pleural mesothelioma. London et al 1995b reported an increased risk of lung cancer among subjects with GSTM1 null genotype possibly exposed to asbestos respect to GSTM1 present [OR=1.89; 95% CI=1.03-3.46] [28]. The authors associated possible exposure with the following working activities: floor installation, roofing, welding, smelting, foundry, engine repair, rubber work, building renovation, and truck driving.

authors, 250,000 new cases of malignant mesothelioma are expected over the next decades, presuming the peak in incidence to occur in the period of 2015-2020 [5].

Besides tobacco smoking, which is unequivocally the main cause of lung cancer, environmental and occupational risk factors are also playing a significant role [6]. The attributable fraction for lung cancer due to occupational exposures has been reported to be between 7-15% in men, and 2-9% in women, with estimated number of deaths 29300 and 3200, respectively [7]. The major contributors with sufficient evidence in humans are agents such as asbestos, diesel engine emissions and other mixtures of polycyclic aromatic hydrocarbons, crystalline silica, arsenic and some heavy metals, while acid mists and welding fumes are the agents with limited evidence [8, 9]. Even though the World Health Organization defines asbestos as “the most important occupational carcinogen causing about half of the deaths from occupational cancer”, it is still present in some industrialized countries [10]. Furthermore, asbestos fibers are thought to be responsible for more than 80% of pleural malignant mesothelioma cases worldwide, whose number increase everyday [11].

The risk for lung cancer and malignant pleural mesothelioma cannot be solely attributable to occupational agents [12]. Genes may modify the individual response in such a way that the host is more or less likely to develop a disease [13]. In the last decade many studies reported that polymorphism in genes involved in xenobiotic and oxidative metabolism (Phase I and Phase II enzymes) or in DNA repair processes may play an important role in the etiology and pathogenesis of these diseases [14–17]. Among them, glutathione S-transferase family genes represent a relevant candidate gene for lung cancer and pleural mesothelioma susceptibility because of its involvement in the metabolism of some carcinogens, occupational agents and environmental toxins.

This systematic review aims to summarize the current knowledge on the relationship between genetic polymorphisms, occupational exposures, lung cancer and mesothelioma.
In the study by Malats et al., an increased lung cancer risk was observed in group exposed to occupational agents for null genotype respect to present genotype, although not statistically significant (OR=10.70; 95% CI=0.40–260.00) [29]. Concerning pleural malignant mesothelioma, similar influence of GSTM1 null genotype among exposed subjects was reported after comparison with present genotype among not exposed subjects (OR=2.30; 95% CI=1.00–5.60) [16] (Table 2).

Individuals with combined GSTM1 null and NAT2 slow acetylator genotypes have 4-fold risk of developing pleural malignant mesothelioma compared to those with the GSTM1 present and NAT2 fast acetylator genotypes (OR=3.60; 95% CI=1.30–9.60) [15] (Table 2).

**GSTT1 genotype**

Five studies [12, 15, 17, 25, 29] reported on the association between GSTT1 genotype and asbestos exposure on risk of lung cancer or pleural mesothelioma. López-Cimia reported two borderline statistically significant results concerning lung cancer risk [25]. After comparison of GSTT1 present genotype subjects occupationally exposed to arsenic, uranium, asbestos and other chemical agents (Occupational list A which includes occupations known to be associated with lung cancer) with subjects with the same genotype not occupationally exposed, the reported unadjusted OR was of significance, but after adjusting for age, family history of any cancer, and pack-years, the significance faded. Similar results were obtained after comparison of GSTT1 null carriers exposed to various chemical agents (Occupational list A) with not occupationally exposed GSTT1 present genotype carriers: unadjusted OR was of a borderline statistical significance which after adjustment was 1.33; 95% CI=0.67–2.64, (Table 3).

Regarding pleural mesothelioma, different response to occupational asbestos exposure in two populations was reported for GSTT1 null genotype, although not statistically significant. It showed a protective effect in Italian population and an opposite result in Finnish population when GSTT1 null genotype carriers were compared with GSTT1 present genotype carriers (OR=0.80; 95% CI=0.40–1.80, OR=1.30; 95% CI=0.40–3.90, respectively) [17] (Table 3).
### TABLE 1A. Main characteristics of the included studies on lung cancer

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Study design</th>
<th>Control source</th>
<th>Exposure classification</th>
<th>Occupational setting/Job tasks</th>
<th>Gene</th>
<th>Occupational agent</th>
<th>Significant outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caporaso et al., 1989</td>
<td>Case control</td>
<td>Hospital based</td>
<td>None Possible (Likely)</td>
<td>Pipe fitters, shipyard workers</td>
<td>Debrisoquin metabolic phenotype</td>
<td>Asbestos</td>
<td>RR adjusted: EM not E vs. PMe/WF not E EM possibly/likely E vs. PMe/WF not E EM not E vs. PMe/WF not E EM possibly/likely E vs. PMe/WF not E</td>
</tr>
<tr>
<td>London et al., 1992a</td>
<td>Case control</td>
<td>Population based</td>
<td>None Possible</td>
<td>Not specified</td>
<td>CYP1A1</td>
<td>Asbestos</td>
<td>OR adjusted: Null possible E vs. Present possible E</td>
</tr>
<tr>
<td>London et al., 1992b</td>
<td>Case control</td>
<td>Population based</td>
<td>None Possible</td>
<td>Heating/cooling systems, shipyard work, welding</td>
<td>GSTM1</td>
<td>Asbestos</td>
<td>OR adjusted: Mutant type, EM possible</td>
</tr>
<tr>
<td>Malats et al., 2000</td>
<td>Case control</td>
<td>Population and hospital based</td>
<td>Yes</td>
<td>Not reported</td>
<td>GSTM1</td>
<td>Not specified</td>
<td>–</td>
</tr>
<tr>
<td>Scheppele et al., 2002</td>
<td>Case control</td>
<td>Population based</td>
<td>Exposed Not Exposed</td>
<td>Processing machine trade occupations</td>
<td>MPO</td>
<td>Asbestos</td>
<td>Univariate and adjusted multivariate OR: mut met</td>
</tr>
<tr>
<td>Bukiñevicz et al., 2004</td>
<td>Case control</td>
<td>Hospital based</td>
<td>None Possible</td>
<td>Welders, drivers, mechanics, industry workers and painters</td>
<td>XPA</td>
<td>Agent not specified among asbestos, mineral fibers, metals, coal products</td>
<td>OR adjusted: Homozygous E vs. Heterozygous E possible</td>
</tr>
<tr>
<td>Wang et al., 2004</td>
<td>Case control</td>
<td>Population-based</td>
<td>Low High</td>
<td>Construction, boilermaking</td>
<td>MnSOD</td>
<td>Asbestos</td>
<td>OR adjusted:</td>
</tr>
<tr>
<td>Ewis et al., 2006</td>
<td>Case control</td>
<td>Not reported</td>
<td>Lung cancer all exposed</td>
<td>Stomach cancer exposed vs. non</td>
<td>Chromate industry workers</td>
<td>Surfactant Protein-B Gene</td>
<td>Chromate lung cancer cases vs. chromate control cases Chromate lung cancer SCC with variant gene Chromate chromate-related SCC wt</td>
</tr>
<tr>
<td>Schneider et al., 2009</td>
<td>Case control</td>
<td>Unexposed factory control group</td>
<td>Not reported</td>
<td>Occupationally derived lung cancer workers</td>
<td>CYP1A1</td>
<td>Asbestos, silica dust, ionizing radiation</td>
<td>–</td>
</tr>
<tr>
<td>Gua et al., 2010</td>
<td>Case control</td>
<td>Panel I/II community based</td>
<td>Cases-coal exposed Controls not exposed</td>
<td>Panel I/II</td>
<td>HSPB1</td>
<td>PAs</td>
<td>OR adjusted: Panel I T7/G7 &gt; C GC vs. GG GC&gt;CC vs. GG</td>
</tr>
<tr>
<td>López-Cima et al., 2012</td>
<td>Case control</td>
<td>Hospital based</td>
<td>Worker from list A occupation*: no/yes</td>
<td>Asbestos, uranium, asbestos and talc miners, Coke plant and gas production workers</td>
<td>CYP1A1 GSTM1 GSTT1</td>
<td>Agent not specified among arsenic, uranium, asbestos, iron</td>
<td>CYP1A1 OR adjusted: T/C+C/C-list A vs. T/T-no list A</td>
</tr>
</tbody>
</table>

*PAHs=Polycyclic aromatic hydrocarbons, RR adjusted= Relative risk adjusted for age and smoking (pack-years), EM=extensive metabolizers, E=exposed, PM=poor metabolizers, IM=intensive metabolizers, possible=individuals that fit neither of the categories (cat. 1: likely= exposure to asbestos in occupations such as pipe fitters, shipyard workers, boilermakers, or in the construction trades; or subjects who had stated exposure to asbestos, cat. 2: unlikely=subjects with no stated exposure who worked in settings considered unlikely to encounter occupational lung carcinogens, e.g., housewives, office workers), OR adjusted= adjusted for age, sex, race, and lifetime smoking history, possible=possible exposure included employment in floor installation, roofing, welding, smelting, foundry, engine repair, rubber work, building renovation, and truck driving, multivariate OR adjusted= by age, sex, smoking status, wt/wild type carriers, OR adjusted= for gender, age groups, and pack-year groups, mutant=mutant type, OR adjusted= adjusted for age, sex, ex smoker, current smoker, square root pack-years, years since quitting smoking, SCC=small cells cancer, OR adjusted= adjusted for age, sex, smoking status, pack-years, and family history of cancer, OR adjusted= Adjusted by age, family history of any cancer, and pack-years (non-smoker, <37PY, ≥37PY), list A= List A includes occupations known to be associated with lung cancer, slow genotype=NAT2 slow acetylators, fast genotype=NAT2 fast acetylators, OR adjusted= adjusted for age and sex, Schneider et al.=paper is overlapping for different diagnoses studied
### TABLE 1B. Main characteristics of the included studies on pleural mesothelioma

<table>
<thead>
<tr>
<th>First author, year</th>
<th>Study design</th>
<th>Control source</th>
<th>Exposure classification</th>
<th>Occupational setting/Job tasks</th>
<th>Gene</th>
<th>Occupational agent</th>
<th>Significant outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hirvonen et al., 1995</td>
<td>Case control</td>
<td>Blood donors</td>
<td>Moderate Low/ High</td>
<td>Employers in the manufacture of asbestos products</td>
<td>GSTM1</td>
<td>Asbestos</td>
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<td>NAT2</td>
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<td>Slow genotype cases vs. fast genotype cases</td>
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<td>Slow genotype high E cases vs. fast genotype high E cases</td>
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<td>Slow E cases vs. fast cases</td>
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<td></td>
<td></td>
<td>Combination of GSTM1 and NAT2: Null/Slow E vs. Present/Fast E</td>
</tr>
<tr>
<td>Neri et al., 2005</td>
<td>Case control</td>
<td>Population-based</td>
<td>Low, high</td>
<td>Shipyard workers</td>
<td>GSTM1</td>
<td>Asbestos</td>
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<td>GSTT1</td>
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<td>Low activity vs. high activity</td>
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<td>CYP1A1</td>
<td>mEH</td>
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<td></td>
<td>NAT2</td>
<td></td>
<td>Fast high E vs. slow high E</td>
</tr>
<tr>
<td>Dianzani et al., 2006</td>
<td>Case control</td>
<td>Population-based</td>
<td>Exposed vs. not exposed</td>
<td>Workers from asbestos cement factory in Casale</td>
<td>HRRCC1</td>
<td>Asbestos</td>
<td>OR adjusted: HRR vs. RR E</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>XRCC3</td>
<td>OGG1</td>
<td></td>
</tr>
<tr>
<td>Neri et al., 2006</td>
<td>Case control</td>
<td>Cohort of construction workers</td>
<td>Exposed cases and controls</td>
<td>Not specified</td>
<td>CYP1A1</td>
<td>Asbestos</td>
<td>–</td>
</tr>
<tr>
<td>Schneider et al., 2009</td>
<td>Case control</td>
<td>Cohort of construction workers</td>
<td>Exposed cases and controls</td>
<td>Not specified</td>
<td>GSTM1</td>
<td>Asbestos, silica dust, ionizing radiation</td>
<td>–</td>
</tr>
</tbody>
</table>

**Note:** PAHs=Polycyclic aromatic hydrocarbons, RR=relative risk, RR adjusted= Relative risk adjusted for age and smoking (pack-years), EM=extensive metabolizers, E=exposed, PM=poor metabolizers, IM=intensive metabolizers, possible=individuals that fit neither of the categories (cat. 1: likely=exposure to asbestos in occupations such as pipe fitters, shipyard workers, boilermen, or in the construction trades; or subjects who had stated exposure to asbestos, cat. 2: unlikely=subjects with no stated exposure who worked in settings considered unlikely to encounter occupational lung carcinogens, e.g., housewives, office workers), OR=adjusted= adjusted for age, sex, race, and lifetime smoking history, possible=possible exposure included employment in floor installation, roofing, welding, smelting, foundry, engine repair, rubber work, building renovation, and truck driving, multivariate OR adjusted= by age, sex, and smoking status, wt= wild type carriers, OR adjusted= for gender, age groups, and pack-year groups, nmt=mutant type, OR adjusted= adjusted for age, sex, exsmoker, current smoker, square root pack-years, years since quitting smoking, SCC=small cells cancer, OR adjusted= adjusted for age, sex, smoking status, pack-years, and family history of cancer. OR adjusted= Adjusted by age, family history of any cancer, and pack-years (non-smoker, <3PY, ≥3PY). List A includes occupations known to be associated with lung cancer, Slow genotype=NAT2 slow acetylators, Fast genotype=NAT2 fast acetylators, OR adjusted= adjusted for age and sex, Schneider et al.=paper is overlapping for different diagnoses studied

### NAT2 genotype

When NAT2 genotype is concerned, four studies [12, 15–17] reported on the association between this genotype and asbestos exposure on risk of pleural mesothelioma. Neri et al. 2005. reported the association of NAT2 fast acetylator genotype with increased pleural mesothelioma risk, respect to NAT2 slow acetylator genotype of 1.74 [95% CI=1.02–2.96] [12]. After stratifying for degree of asbestos exposure the association was confined to the highly exposed cases (OR=2.14; 95% CI=1.15–3.98). Oppositely, the study by Hirvonen et al. reported an increased risk of pleural malignant mesothelioma among asbestos exposed NAT2 slow acetylators respect to fast
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A borderline significant positive association was observed between pleural mesothelioma and NAT2 slow acetylators with respect to slow acetylators in asbestos exposed Italian population (OR=1.90; 95% CI=1.00–3.40), while fast acetylator was protective in asbestos exposed Finnish population, although not statistically significant (OR=0.60; 95% CI=0.30–1.20) [17] (Table 4).

**CYP1A1 genotype**

Five studies [12, 17, 19, 25, 27] reported on the association between CYP1A1 genotype and asbestos exposure on lung cancer and pleural mesothelioma risk. Study conducted by Schneider et al. reported lower risk in terms of CYP1A1 T6235C genotypes among asbestos-exposed lung cancer cases, and on the other hand an increased risk among mesothelioma cases (OR=0.70; 95% CI=0.27–1.81, OR=1.12; 95% CI=0.30–4.14, respectively) [27]. A possible interaction between CYP1A1 sp1 T6235C genotype, occupational exposure and lung cancer risk was reported after comparison of subjects exposed to arsenic, uranium, asbestos and other chemical agents carrying combined genotype (T/C+G/C) with not occupationally exposed homozygotes (T/T) yielding a statistically significant result (OR=2.20; 95% CI=1.11–4.35) [25] (Table 5).
DISCUSSION

This systematic review has attempted to summarize studies on lung cancer and pleural mesothelioma due to the most frequent gene polymorphisms in association with occupational exposure. Papers included in the present study were mainly focused on the following genes: GSTM1, GSTT1, NAT2 and CYP1A1, with majority of the subjects occupationally exposed to asbestos.

Differences in individual susceptibility to occupationally induced carcinomas can be in part ascribed to polymorphic nature and diversities in activity of genes involved in metabolism of occupational carcinogens.

Considering the fact that GSTs are taking part in detoxification of many potentially carcinogenic compounds, their polymorphisms are considered important modifiers of individual risk to occupationally induced cancers [30, 31]. Thus, the observed association between the influence of GSTM1 null genotype and occupationally related lung cancer and pleural mesothelioma was not surprising [15, 28]. Concerning GSTT1 present genotype, it seemed that exposure to chemical compounds played a great role in examining the association with the risk of developing the disease. The same study reported that occupationally exposed individuals with GSTT1 null genotype might be at increased lung cancer risk when compared to GSTT1 present genotype carriers not occupationally exposed [25].

Findings from several papers demonstrated inconsistency in behavior of some gene polymorphisms. One of the most obvious examples was NAT2 gene, involved in the activation and inactivation reactions of numerous xenobiotics. Two studies [15, 16] reported that NAT2 slow acetylators exposed to high levels of asbestos were at risk of developing pleural malignant mesothelioma.
while the other study [12] did not confirm this finding. In one previous pooled analysis, Betti et al. suggested that reason for obtaining different results may derive from a rather low number of cases and controls or differences in exposure levels across studies [32].

Neri et al. reported that NAT2 fast acetylator genotype seems to be associated with increased pleural mesothelioma risk in Italian population [17], whereas it has been previously demonstrated that it protects Finnish population exposed to asbestos from this malignancy [15, 16]. Different risk patterns of NAT2 genotypes in two populations might suggest that diverse metabolic pathways and intermediates are involved in the disease etiology arising from exposure to asbestos fibers. This would be consistent with the idea that oxidative pathways may differ according to mineral type and fiber length [17].

The CYP isoenzymes are well-known phase I catalyzing enzymes responsible for oxidation of various xenobiotics [31]. The association between CYP1A1 genotypes [Wsp1 T6235C and Ile462Val] and occupationally related lung cancer and pleural mesothelioma was not proven [27]. However, an increased lung cancer risk was reported for CYP1A1 Msp1 T6235C genotype among occupationally exposed subjects carrying combined genotype (T/C+C/C) [25].

To the best of our knowledge, this study represents the first effort to explore the modification effect of different gene polymorphisms on lung cancer and mesothelioma risk due to exposure to occupational agents.

In the review process there were some difficulties in obtaining a unique result and making a final conclusion because of the numerous gaps identified in the included studies. The most important was the lack of data regarding measures of exposure, such as biological monitoring measurements, duration of the employment and duration of the exposure to the occupational agents, which together may play a crucial role in determining their association with the disease risk. Majority of the studies did not provide details on occupational settings or precise definition of the job tasks of the participants. The information on residence
type (urban or rural living areas) of study participants was provided only in one study.

Therefore, in the interpretation of findings from this study some limitations should be considered. Generalizability of the results could be an issue, considering the fact that included studies did not focus on the same work settings and occupational exposure level assessment was not uniquely reported across the studies. Furthermore, some studies had difficulties to control for confounding for variables like smoking and ethnicity. Thus, interpretation of this kind of results should always be done with special attention because of the residual confounding.

Measurements of the concentration of xenobiotics or their metabolites in biological matrices can provide useful information in assessing the individual human exposure, effects and susceptibility to occupational risk factor. Bearing in mind that together with environmental exposure measurements they provide greater precision in risk estimates, they should be preferred in epidemiological studies.

Besides already mentioned genetic factors, the past decade has seen a great rise in understanding of mesothelioma’s immunobiology, and in the optimization of treatments for patients affected by this disease. Several novel and highly important therapeutic strategies were identified, but it seems that only the combination of bevacizumab with pemetrexed and cisplatin has improved survival in patients with advanced disease, as reported in one clinical trial. This therapy is currently unlicensed [33].

From a genomic point of view, this disease is characterized by a preponderance of tumour suppressor alterations, and therefore some additional therapeutic strategies are currently in process of development. Some promising results are obtained for currently tested agents such as inhibitors against angiogenesis, mesothelin and immune checkpoints inhibitors, as well as for their combinations [33].

This study contributes further evidence to the hypothesis that the onset of lung cancer and pleural mesothelioma is attributable to the potential interaction between the individual genetic profiles and exposure to occupational agents. Even though some results appeared to be divergent, some certain findings were observed in GST isoenzymes. Subjects carrying GSTM1 null genotype were at greater risk both to lung cancer and mesothelioma. Furthermore, pleural mesothelioma risk was altered among individuals lacking GSTM1 gene and being NAT2 slow acetylators.

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