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

Sonja Milovanovic[1], Jovana Stojanovic[1], Roberta Pastorino[1], Ivo Iavicoli[2], Stefania Boccia[3]*

(1) Institute of Public Health- Section of Hygiene, Università Cattolica del Sacro Cuore, Largo F. Vito 1, 00168, Rome, Italy
(2) Department of Public Health-Section of Occupational Medicine,Università degli Studi di Napoli Federico II, Naples, 80138, Italy
(3) Institute of Public Health- Section of Hygiene, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario "A. Gemelli", Largo F. Vito 1, 00168, Rome, Italy

CORRESPONDING AUTHOR: *Roberta Pastorino - Largo Francesco Vito 1, 00168, Rome, Italy, E-mail: roberta.pastorino@unicatt.it - Telephone number: 0039-06-35001527, Fax: 0039-06-35001522,*

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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

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.

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/pleural 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).

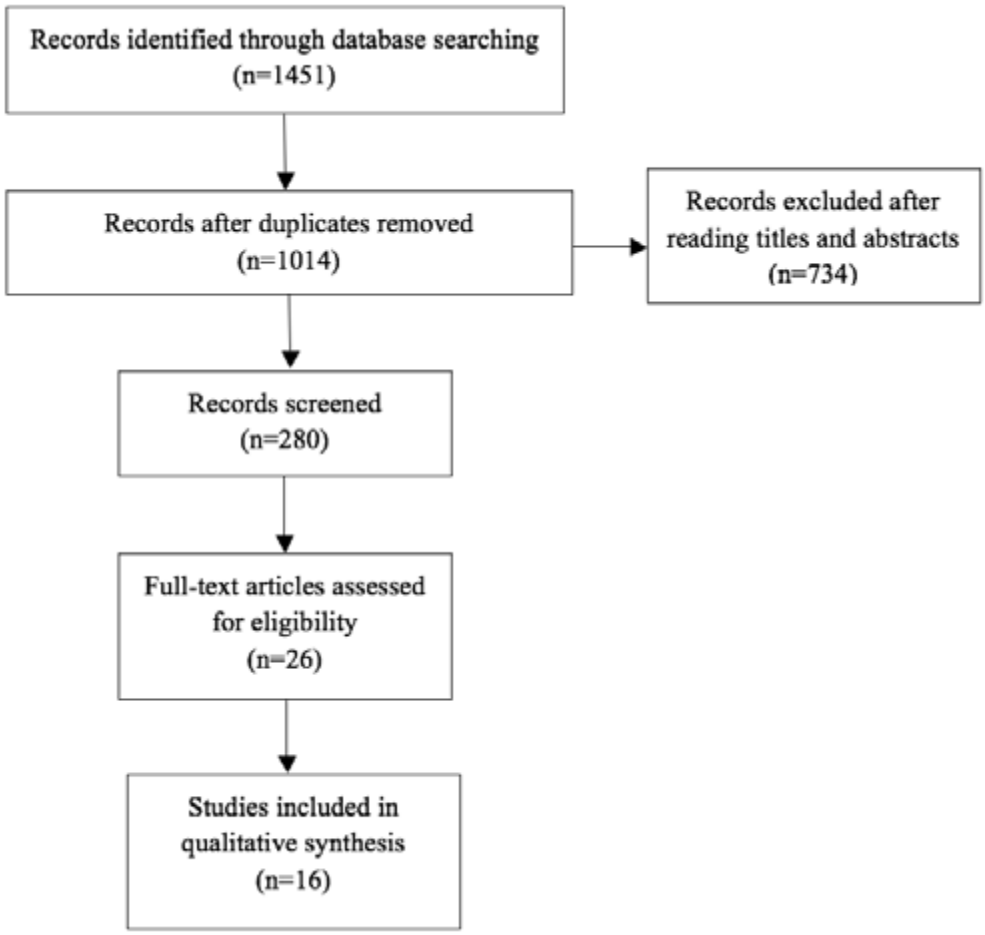
The main characteristics of the included studies are reported in Tables 1a and 1b.

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.

FIGURE 1. Study selection flowchart



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. Lòpez-Cima 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 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

First author, year	Study design	Control source	Exposure classification	Occupational setting/ Job tasks	Gene	Occupational agent	Significant outcomes
Caporaso et al., 1989	Case control	Hospital based	None Possible Likely	Pipe fitters, shipyard workers	*Debrisoquine metabolic phenotype CYP2D6*	Asbestos PAHs[a]	RR adjusted[b]: EM[c] not E[d] vs. PMe/IM[f] not E EM possible[g]/likely[h] E vs. PM/IM not E EM not E vs. PM/IM not E EM possible/likely E vs. PM/IM not E
London et al., 1995a	Case control	-Population based -Medicare file	None Possible	Not specified	*CYP1A1*	Asbestos Motor vehicle exhaust	– –
London et al., 1995b	Case control	Population based	None Possible Probable	Heating./cooling systems, shipyard work, welding	*GSTM1*	Asbestos	OR adjusted[i]: Null possible[j] E vs. Present possible E
Malats et al, 2000	Case control	Population and hospital based	Yes No	Not reported	*GSTM1* *GSTT1*	Not specified	–
Schabath et al., 2002	Case control	Population based	Exposed Not Exposed	Processing, machine trade occupations	*MPO*	Asbestos	Univariate and adjusted multivariate OR[k]: wt[l] E vs. wt not E
Butkiewicz et al., 2004	Case control	Hospital based	None Possible	Welders, drivers, mechanics, industry workers and painters	*XPA*	Agent not specified among asbestos, mineral fibers, metals, coal products	OR adjusted[m]: Homozygous mt[n] E possible vs. Homozygous wt + heterozygous E possible
Wang et al, 2004	Case control	Population-based	No/low High	Construction, boilermaking	*MnSOD*	Asbestos	OR adjusted[o]: Homozygous mt not/low E vs. Homozygous wt not/low E
Ewis et al., 2006	Case control	Not reported	Lung cancer-all exposed SCC-exposed vs.never	Chromate industry workers	*Surfactant Protein-B Gene*	Hexavalent chromium	Chromate lung cancer cases vs. chromate control wt Chromate lung cancer SCC[p] with variant gene vs. Non chromate-related SCC wt
Schneider et al., 2009w	Case control	-Unexposed factory control group -Additional group: population based	Not reported	Occupationally derived lung cancer workers	*CYP1A1*	Asbestos, silica dust, ionizing radiation	–
Guo et al., 2010	Case control	Panel I-community based Panel II-hospital based	Cases-coal exposed Controls-not exposed	Panel I Wuhan Iron and Steel Group/ Corporation	*HSPB1*	PAHs	OR adjusted[q]: Panel I -1271 G> C GC vs.GG GC+CC vs. GG
							Panel I haplotype diplotype C-G-C vs. G-G-T GGT/CGC vs. GGT/GGT
López-Cima et al., 2012	Case control	Hospital based	Worker from list A occupation*: no/yes	Arsenic, uranium, asbestos and talc miners; Coke plant and gas production workers;	*CYP1A1* *GSTM1* *GSTT1* *GSTP1*	Agent not specified among arsenic, uranium, asbestos, iron	CYP1A1 OR[r] adjusted: T/C+C/C–list A[s] vs. T/T–no list A

[a]PAHs=Polycyclic aromatic hydrocarbons, [b]RR adjusted= Relative risk adjusted for age and smoking (pack-years), [c]EM=extensive metabolizers, [d]E=exposed, [e]PM=poor metabolizers, [f]IM=intensive metabolizers, [g]possible=individuals that fit neither of the categories (cat. 1: [h]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), [i]OR adjusted= adjusted for age, sex, race, and lifetime smoking history, [j]possible=possible exposure included employment in floor installation, roofing, welding, smelting, foundry, engine repair, rubber work, building renovation, and truck driving, [k]multivariate OR adjusted= by age, sex, and smoking status,[l]wt=wild type carriers, [m]OR adjusted= for gender, age groups, and pack-year groups,nmt=mutant type, [o]OR adjusted= adjusted for age, sex, exsmoker, current smoker, square root pack-years, years since quitting smokingpSCC=small cells cancer, [q]OR adjusted= adjusted for age, sex, smoking status, pack-years, and family history of cancer. [r]OR adjusted = Adjusted by age, family history of any cancer, and pack-years (non-smoker, <37PY, ≥37PY). [s]List A= List A includes occupations known to be associated with lung cancer, [t]Slow genotype=NAT2 slow acetylators, [u]Fast genotype =NAT2 fast acetylators, [v]OR adjusted= adjusted for age and sex, [w]Schneider etm al.=paper is overlapping for different diagnoses studied

TABLE 1B. Main characteristics of the included studies on pleural mesothelioma

First author, year	Study design	Control source	Exposure classification	Occupational setting/ Job tasks	Gene	Occupational agent	Significant outcomes
Hirvonen et al., 1995	Case control	Blood donors	Moderate Low High	Employers in the manufacture of asbestos products	*GSTM1* *NAT2*	Asbestos	– Slow genotype[t] cases vs. fast genotype[u] cases Slow genotype high E cases vs fast genotype high E cases
Hirvonen et al., 1996	Case control	Population-based	Definite/probable Possible Unlikely/unknown	Construction workers	*GSTM1* *GSTT1* *NAT2*	Asbestos	– – Slow E cases vs. fast cases
							Combination of GSTM1 and NAT2: Null/slow E vs. Present/Fast E
Neri et al., 2005	Case control	Population-based	Low, high	Shipyard workers	*GSTM1* *GSTT1* *CYP1A1* *mEH* *NAT2*	Asbestos	– Low activity vs. high actitvity Fast vs. slow Fast high E vs. slow high E
Dianzani et al., 2006	Case control	Population-based	Exposed vs. not exposed	Workers from asbestos cement factory in Casale	*XRCC1* *XPD* *XRCC3* *OGG1*	Asbestos	OR adjusted[v]: RQ+QQ E vs. RR E – T/M E vs. M/M E, T/T+M/T vs. M/M –
Neri et al., 2006	Case control	Cohort of construction workers	Exposed cases and controls	Not specified	*CYP1A1* *GSTM1* *GSTT1* *EPHX1* *NAT2*	Asbestos	–
Schneider et al., 2009	Case control	-Unexposed factory control group -Additional group: population based	Not reported	Occupationally derived lung cancer workers	*CYP1B1*	Asbestos, silica dust, ionizing radiation	–

[a]PAHs=Polycyclic aromatic hydrocarbons, [b]RR adjusted= Relative risk adjusted for age and smoking (pack-years), [c]EM=extensive metabolizers, [d]E=exposed, [e]PM=poor metabolizers, [f]IM=intensive metabolizers, [g]possible=individuals that fit neither of the categories (cat. 1: [h]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), [i]OR adjusted= adjusted for age, sex, race, and lifetime smoking history, [j]possible=possible exposure included employment in floor installation, roofing, welding, smelting, foundry, engine repair, rubber work, building renovation, and truck driving, [k]multivariate OR adjusted= by age, sex, and smoking status,[l]wt=wild type carriers, [m]OR adjusted= for gender, age groups, and pack-year groups,nmt=mutant type, [o]OR adjusted= adjusted for age, sex, exsmoker, current smoker, square root pack-years, years since quitting smokingpSCC=small cells cancer, [q]OR adjusted= adjusted for age, sex, smoking status, pack-years, and family history of cancer. [r]OR adjusted = Adjusted by age, family history of any cancer, and pack-years (non-smoker, <37PY, ≥37PY). [s]List A= List A includes occupations known to be associated with lung cancer, [t]Slow genotype=NAT2 slow acetylators, [u]Fast genotype =NAT2 fast acetylators, [v]OR adjusted= adjusted for age and sex, [w]Schneider etm 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

TABLE 2. Studies reporting on *GSTM1* and occupational exposure to asbestos on development of pleural mesothelioma or lung cancer

First author, year	Number of subjects (cases/controls)	Mean age	Disease	Measure of association (OR, CI 95%, RR)
Hirvonen et al., 1995	44/270	56.6	Pleural mesothelioma	Null[a] E[b] cases vs. null not E cases 1.80 (1.00-3.50) Null high E vs. present[c] not E 2.30 (1.00-5.60)
Hirvonen et al., 1996	76/69	55.7	Pleural mesothelioma	Null E cases vs. present E in reference group 2.30 (0.80-7.10) GSTM1 and NAT2: null/slow[d] E vs. present/fast[e] E 3.60 (1.30-9.60)
Neri et al., 2005	80/255	Not reported	Pleural mesothelioma	Null high E vs. present high E 1.27 (0.68–2.38)
Neri et al., 2006	105/376	Not reported	Pleural mesothelioma	Null high E vs. present high E: Italians 1.20 (0.70–2.20) Finns 1.60 (0.80–3.30)
London et al., 1995b	356/731	Cases-64 Controls-63	Lung cancer	Null not E vs. present not E 1.03(0.68-1.55) Null possible[f] E vs. present possible E 1.89 (1.03-3.46) Null probable[g] E vs. present probable E 1.51 (0.55-4.15)
Malats et al, 2000	122/121	Cases-64 Controls-59	Lung cancer	Null not E vs. present not E 1.50 (0.80–2.7) Null E vs. present E 10.70 (0.4–260.00)
López-Cima et al., 2012	789 /789	Cases: 67 (33–84) Controls: 66 (30–87)	Lung cancer	≥1 null allele–No list A[h] vs. present/present–No list A 0.97 (0.75-1.24) present/present–List A vs. present/present–No list A 1.38 (0.86-2.22) ≥1 null allele–List A vs. present/present–No list A 1.18 (0.78-1.79)

[a]null=gene absent, [b]E=exposed, [c]present=gene present, [d]Slow genotype=NAT2 slow acetylators, [e]Fast genotype =NAT2 fast acetylators fpossible=possible exposure included employment in floor installation, roofing, welding, smelting, foundry, engine repair, rubber work, building renovation, and truck driving, [g]probable=probable exposure category included employment in insulation work or repair of heating/cooling systems, shipyard work, construction work prior to 1975, boilermaking, and coke-oven work. [h]list A=List A includes occupations known to be associated with lung cancer

acetylators (OR=2.10; 95% CI=1.10-4.10) [16]. A borderline significant positive association was observed between pleural mesothelioma and *NAT2* fast acetylators 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+C/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).

TABLE 3. Studies reporting on *GSTT1* and occupational exposure to asbestos on development of pleural mesothelioma or lung cancer

First author, year	Number of subjects (cases/controls)	Mean age	Disease	Measure of association (OR, CI 95%)
Hirvonen et al., 1996	*76/69*	*55.7*	Pleural mesothelioma	Null[a] E[b] patients vs. null in reference group 0.80 (0.10-4.70)
Neri et al., 2005	80/255	Not reported	Pleural mesothelioma	Null high E vs. present[c] high E 1.00 (0.45–2.24)
Neri et al., 2006	105/376	Not reported	Pleural mesothelioma	Null high E vs. present high E: Italians 0.80 (0.40–1.80) Finns 1.30 (0.40–3.90)
Malats et al., 2000	122/121	Cases-64 Controls-59	Lung cancer	Null not E vs. present not E 0.70 (0.40–1.30)
López-Cima et al. 2012	789 /789	Cases: 67 (33–84) Controls: 66 (30–87)	Lung cancer	≥1 null allele–No list A[d] vs. present/present–No list A 0.81 (0.60-1.09) present/present–list A vs. present/present–No list A 1.21 (0.86-1.70) ≥1 null allele–list A vs. present/present–No list A 1.33 (0.67-2.64)

[a]null=gene absent, [b]E=exposed, [c]present=gene present, [d]list A=List A includes occupations known to be associated with lung cancer

TABLE 4. Studies reporting on genotype NAT2 and occupational exposure to asbestos on development of pleural mesothelioma

First author, year	Number of subjects (cases/controls)	Mean age	Disease	Measure of association (OR, CI 95%)
Hirvonen et al., 1995	44/270	cases-56.6 controls-41.1	Pleural mesothelioma	Slow genotype[a] cases vs. fast genotype[b] cases 2.10 (1.10-4.10) Slow genotype high E[c] cases vs fast genotype high E cases 3.70 (1.30-10.20)
Hirvonen et al., 1996	*76/69*	*55.7*	Pleural mesothelioma	Slow E cases vs. fast cases 3.80 (1.20-14.30)
Neri et al., 2005	80/255	Not reported	Pleural mesothelioma	Fast vs. slow 1.74 (1.02–2.96) Fast high E vs. slow high E 2.14 (1.15–3.98)
Neri et al., 2006	105/376	Not reported	Pleural mesothelioma	Fast high E vs. slow high E: Italians 1.90 (1.00–3.40) Finns 0.60 (0.30–1.20)

[a]slow=slow acetylator, [b]E=exposed, [c]fast=fast acetylator

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,

TABLE 5. Studies reporting on CYP1A1 and occupational exposure to asbestos on development of lung cancer or pleural mesothelioma

First author, year	Number of subjects (cases/controls)	Mean age	Disease	Measure of association (OR, CI 95%)
London et al., 1995a	144/230	63	Lung cancer	*Msp1 RFLP* Present[a] possible[b] E[c] vs. homod wt[e] possible E 2.20 (0.80-6.10)
López-Cima et al. 2012	789 /789	Cases: 67 (33–84) Controls: 66 (30–87)	Lung cancer	*Msp1 T6235C* T/C+C/C–No list A[f] vs.T/T–No list A 1.04 (0.77-1.39) T/T T/T–list A vs. T/T–No list A 1.15 (0.82-1.62) T/C+C/C–list A vs. T/T–No list A 2.20 (1.11-4.35)
Neri et al., 2005	80/255	Not reported	Pleural mesothelioma	*Msp1 RFLP* Hetero[g] + homo high E vs. Homo wt high E 0.77 (0.35–1.69)
Neri et al., 2006	105/376	Not reported	Pleural mesothelioma	*Msp1 RFLP* Hetero + homo high E vs. homo wt high E: Italians 0.90 (0.40–1.90) Finns 1.70 (0.60–4.90)
Schneider et al., 2009	490(105)/184	asbestos-related lung cancers 63.1 asbestos induced mesotheliomas 64.4 lung cancer patients 65.9 healthy unexposed control group 58.4 additional healthy control group 53.8	Pleural mesothelioma, lung cancer	*Msp1 T6253C* wt/mt[h] or mt/mt E vs. wt/wt not E (lung cancer) 0.70 (0.27-1.81) wt/mt or mt/mt E vs. wt/wt not E (mesothelioma) 1.12 (0.30-4.14)
				Ile462Val wt/mt or mt/mt E vs. wt/wt not E (lung cancer) 0.51 (0.14-1.83) wt/mt or mt/mt E vs. wt/wt not E (mesothelioma) 0.39 (0.10-1.54)

[a]=variant allele present, [b]=possible exposure, [c]=exposed, [d]=homozygous, [e]=wild type genotype (variant allele absent), [f]=List A includes occupations known to be associated with lung cancer (Arsenic, uranium, iron-ore, asbestos and talc miners; Ceramic and pottery workers; Iron and steel founding (casters, moulders and core makers); Copper, zinc, cadmium, aluminum, nickel chromates, beryllium blue collar workers; Platters; Shipyard/dockyard, railroad manufacture workers; Coke plant and gas production workers; Insulators, roofers and asphalt workers; and painters, [g]=heterozygous, [h]=mutant type (mutant genotype)

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 (*Msp1 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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