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Natural carcinogenic fiber and pleural plaques assessment in a general population: A cross-sectional study

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ABSTRACT

Natural carcinogenic fibers are asbestos and asbestiform fibers present as a natural component of soils or rocks. These fibers are released into the environment resulting in exposure of the general population. Environmental contamination by fibers are those cases occurred in: rural regions of Turkey, in Mediterranean countries and in other sites of the world, including northern Europe, USA and China.

Fluoro-edenite(FE) is a natural mineral species first isolated in Biancavilla, Sicily. The fibers are similar in size and morphology to some amphibolic asbestos fibers, whose inhalation can cause chronic inflammation and cancer.

The aim of the current study is to assess the presence and features of pleural plaques (PPs) in Biancavilla's general population exposed to FE through a retrospective cross-sectional study. All High-Resolution Computed Tomography (HRCT) chest scans carried out between June 2009 and June 2015 in Biancavilla municipality hospital site (exposed subjects) were reviewed. The exposed groups were 1:1 subjects, matched according to age and sex distributions, with unexposed subjects (n.1.240) randomly selected among HRCT chest scans carried out in a Hospital 30 km away from Biancavilla. Subjects from Biancavilla with PPs were significantly more numerous than the control group ones (218 *vs* 38). Average age of either group was >60 years; the age of exposed subjects was significantly ($p=0.0312$) lesser than the unexposed group. In exposed subjects, in most PPs thickness ranged between 2 and 4.9 cm(38%, $n=83$); while in unexposed ones PPs thickness was less than 2 cm (55%, $n=21$). As to the size of PPs in exposed subjects, in most cases it ranged between 1 cm and 24% of chest wall (53%, $n=116$); while in unexposed ones the size of PPs was lesser than 1 cm (23%, $n=58$). Among exposed subjects, 36 cases (17%) PPs were detected with calcification, whereas in unexposed ones only three (8%) presented calcification. 137 lung parenchymal abnormalities were observed in exposed group; whereas, 12 lung parenchymal involvement were registered in unexposed subjects. The RR for PPs is 6,74 CI 95% (4,47–9,58) $p<0{,}0001$ in the exposed population. These findings, suggested the urge to extend the screening on the possible involvement of the respiratory tract to all Biancavilla's population, particularly in those aged more than 30. Besides, it seems essential to start indoor monitoring Biancavilla's municipality.

1. Introduction

Occupational and/or environmental exposure to various types of asbestos fibers is associated with an increase in the incidence of both malignant and non-malignant respiratory diseases (Alberg and Samet, 2003; LaDou, 2004; Fujimoto et al., 2015). Lung cancer

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and malignant mesothelioma (MM) are the main malignant diseases (Prazakova et al., 2014). Non-malignant effects of exposure to asbestiform fibers include lung function impairment, pleural plaques (PPs), pleural effusions, diffuse pleural thickening and parenchymal fibrosis (Hillerdal, 1981; Guidotti et al., 2004; Cugell and Kamp 2004; Gevenois et al., 1998).

PPs can occur even after relatively low exposure to asbestiform fibers and are the most common among non-malignant effects (Clin et al., 2011; Laurent et al., 2014; Maxim et al., 2015; Kim et al., 2015).

Environmental exposure to asbestiform fibers has been described in several areas of the world, including Greece, Turkey, Cyprus, Corsica, New Caledonia, Afghanistan, Russia, Montana (USA) and Italy (Constantopoulos, 2008; Voisin et al., 1994; Schüz et al., 2013; Sullivan, 2007; Szychlinska et al., 2014; Paoletti et al., 2000).

In Italy, a 10-year study of mortality from MM (1988–1997) highlighted an unexpected cluster in Biancavilla, Sicily (Paoletti et al., 2000; Comba et al., 2003) that was confirmed by later studies (Bruno et al., 2014). The high mortality rate was attributed to exposure to a fibrous amphibole, identified as fluoro-edenite (FE) (Gianfagna and Oberti, 2001), which is chemically similar to tremolite, except that its OH groups are replaced by fluorine. FE fibers were found in inert materials, such as sand and rubble, extracted from a stone quarry in Mt. Calvario, on the outskirts of the town (South-East) and in sheep lymph nodes (Fazzo et al., 2014; Ledda et al., 2016; Rapisarda et al., 2005).

This material had been employed locally in construction work for about 50 years (Paoletti et al., 2000; Comba et al., (2003). The quarry was shut down in 1998 (Miozzi et al., 2016).

On the basis of *in vivo*, *in vitro* and epidemiological surveys (Ballan et al., 2014; DeNardo et al., 2004; Loreto et al., 2008; Martinez et al., 2006; Soffritti et al., 2004) the International Agency for Research on Cancer (IARC; Lyon, France) classified FE as carcinogenic to humans (Grosse et al., 2014).

A study conducted on Biancavilla's general population also showed a higher incidence of chronic obstructive lung disease (Biggeri et al., 2004).

Recently, an excess of non-malignant pleural lesions has been described by Rapisarda et al. (2015a, 2015b) in subjects occupationally exposed to FE.

The aim of the current study is to assess the presence and features of PPs in Biancavilla's general population exposed to FE through a cross-sectional study.

2. Methods

2.1. Study design

The study was performed in accordance with the Declaration of Helsinki of the World Medical Association with the approval of Institutional Ethics Committee of Hospital of the University of Catania (ref. no.: 768/2014). In this retrospective study we reviewed all High-Resolution Computed Tomography (HRCT) chest scans carried out between June 2009 and June 2015 in Biancavilla municipality hospital site (exposed subjects).

Data collection included also personal data (age, domicile, etc.) and was stratified by gender and age.

The exposed groups were 1:1 subjects, matched according to age and sex distributions, with unexposed subjects randomly selected among HRCT chest scans carried out in a Hospital 30 km away from Biancavilla.

Inclusion criteria for exposed population were to have been born and living in Biancavilla's municipality. Exclusion criteria were not to have been born and living in Biancavilla's municipality. For unexposed group the inclusion criteria were to have been born and living at least 30 km away from Biancavilla. Exclusion criteria were to have been born and living in Biancavilla's municipality.

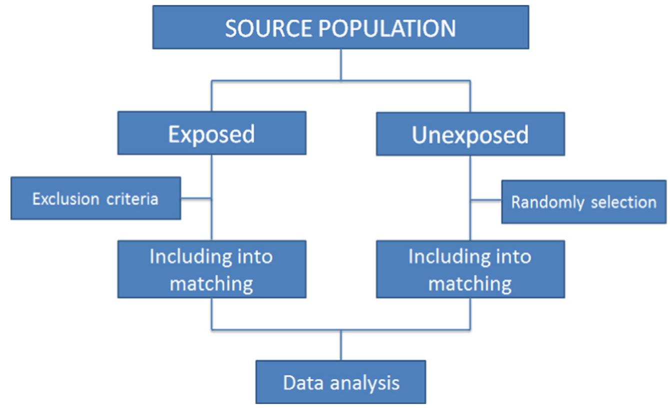

Fig. 1. Schematic flow diagram of enrollment and matching process.

In both groups, patients who had undergone more than one HRCT test were considered only once (the first scan). Fig. 1 schematizes the enrollment and matching process of source population.

HRCT scan tests that did not comply with the requirements stated by Clin et al. (2011) were rejected. Briefly, here follow the technical faults that classified the test as *"insufficient"*: inappropriate slice thickness preventing correct analysis of the parenchyma; failure to produce sections in the prone position in the case of suspected interstitial abnormalities observed in images in the decubitus position; prominent motion artifacts due to insufficient apnea.

2.2. Assessment of PPs

All available HRCT were submitted for randomized, independent, double reading (and triple reading in the case of disagreement) focused on benign asbestos-related abnormalities. Radiologists also received specific training in the interpretation of HRCT scans by experienced chest radiologists and occupational physicians.

HRCT scanning tests done in Biancavilla were performed using a General Electric Healthcare CT Scan (GE Healthcare, Fairfield, CT, USA).

HRCT scanning tests done in control hospital were performed using a Philips Healthcare Brilliance iCT (Koninklijke Philips Electronics N.V., The Netherlands, EU).

PPs were considered to be present on each hemithorax when either a single focal pleural abnormality with typical characteristics of a PP (circumscribed quadrangular pleural elevations with sharp borders and soft tissue density, possibly calcified, in typical postero-lateral and antero-lateral locations) or multiple bilateral less typical images with a typical location was detected. When associated with rounded atelectasis or parenchymal bands, pleural thickenings were considered to correspond with diffuse pleural thickening (fibrosis of visceral pleura) (Gevenois et al., 1998).

Thickness and extent of PPs were classified as proposed by Clin et al. (2011). The thickness was evaluated by classifying the most thickened plaque into four categories: <2/mm, 2–5/mm, 5–10/mm and >10/mm. The extent of PPs was assessed using a semi-quantitative method. The cumulative extent of PPs detected on each section was calculated and expressed as the percentage of the lateral chest contour as measured on a single axial section at the level of the carina.

This cumulative extent was graded according to four categories: less than 1 cm; between 1 cm and less than 25% of the chest contour; between 25% and less than 50% of the lateral chest contour; 50% or more of the lateral chest contour. It was also indicated the presence of calcifications.

Other abnormalities observed on the HRCT scan (rounded atelectasis; emphysema; thickness; bronchiectasis; fibrosis) were quantified.

2.3. Data analysis

Data analysis was performed using SPSS software version 20 (IBM, Milan, Italy). The main population characteristics and characteristics of the pleural plaques were expressed as the mean ± standard deviation (SD) or as the total number of participants with that characteristic and the percentage represented by that number.

Interobserver agreement among HRCT readers was also calculated as a series of Cohen kappa values: 0.01–0.20 = poor agreement; 0.21–0.40 = slight agreement; 0.41–0.60 = fair agreement; 0.61–0.80 = moderate agreement; 0.81–0.99 = substantial agreement (Landis and Koch, 1977).

A *t* test is used to compare the means of two groups. McNemar's test is performed to analyze this retrospective cross-sectional study and a p value ≤ 0.05 was considered significant.

3. Results

Over the six years analysed (2009–2015) 1365 (100%) subjects had been chest scanned at Biancavilla's Hospital Radiodiagnostics Operative Unit.

In relation to exclusion criteria, 63 (4%) subjects were excluded from the study as non resident in Biancavilla. 37 (3%) subjects repeated the HRCT more than once during our observation period and 25 (2%) were judged as *"insufficient"* due to technical defects. So 1240 HRCT scans of exposed population were stratified according to sex and age.

1240 unexposed subjects were enrolled randomly in a hospital 30 km far from Biancavilla and matched 1:1 by sex and age with exposed population. There is no statistical difference between years distributions (p = 0.0939). Table 1 reports the main characteristics of source population.

The overall level of agreement among radiologists was more acceptable as to observations; in detail, kappa values were: 0.76 for classification of thickness, 0.81 for cumulative extent and 0.92 for abnormalities observations.

The main features of study population according to the presence of PPs are shown in Table 2.

Table 1
Main characteristics of source population including matching stratified by sex and age.

	Source population			
	Exposed		Unexposed	
N.	1240 (100%)		1240 (100%)	
Age in years, mean ± SD	55 ± 15.3[a]		56 ± 14.4[a]	
Male	687 (55%)		687 (55%)	
	Male	**Female**	**Male**	**Female**
Age ≤ 20 years	19 (3%)	12 (2%)	19 (3%)	12 (2%)
Age 21–30 years	53 (8%)	27 (5%)	53 (8%)	27 (5%)
Age 31–40 years	67 (10%)	49 (9%)	67 (10%)	49 (9%)
Age 41–50 years	124 (18%)	95 (17%)	124 (18%)	95 (17%)
Age 51–60 years	137 (20%)	115 (21%)	137 (20%)	115 (21%)
Age 61–70 years	149 (21%)	124 (22%)	149 (21%)	124 (22%)
Age ≥ 71 years	138 (20%)	131 (24%)	138 (20%)	131 (24%)

[a] no statistical difference between years distributions (p = 0.0939).

Table 2
Main characteristics of subjects with PPs.

	Exposed		Unexposed	
N.	218 (100%)		38 (100%)	
Age in years, mean ± SD	68 ± 13.8		73 ± 8.1	
Male	139 (64%)		36 (95%)	
	Male	**Female**	**Male**	**Female**
Age ≤ 20 years	0	0	0	0
Age 21–30 years	0	0	0	0
Age 31–40 years	0	0	0	0
Age 41–50 years	8 (6%)	2 (3%)	0	0
Age 51–60 years	33 (24%)	9 (11%)	0	0
Age 61–70 years	41 (29%)	25 (32%)	5 (14%)	0
Age ≥ 71 years	57 (41%)	43 (54%)	31 (86%)	2 (100%)

Subjects from Biancavilla with PPs were significantly more numerous than the control group ones (218 *vs* 38).

For the PP subjects belonging to the unexposed group we were able to track their previous occupational data. 28 (73%) subjects had been construction workers with exposure to asbestos; 4 (11%) had been harbour operators; 3 (8%) cleaners in industrial plants; 2 (5%) maintenance workers and 1 (3%) a car mechanic.

Average age of either group was > 60 years; the age of exposed subjects was significantly (p = 0.0312) lesser than the unexposed group.

Besides, the presence of women was higher in FE exposed subjects compared to the control group (n = 79 (36%) *vs* n = 2 (5%)).

Table 3 reports the main characteristics of PPs detected by HRCT in the 256 subjects.

In exposed subjects, in most PPs thickness ranged between 2 and 4.9 cm(38%, n = 83); while in unexposed ones PPs thickness was less than 2 cm (55%, n = 21). Among exposed, 27% (n = 58) presented thickness ranging between 5 and 9.9 cm and 4% (n = 9) ≥ 10 mm.

Only 2 of unexposed subjects (5%) presented PPs with thickness ranging between 5 and 9.9 cm, none with PPs ≥ 10 mm.

As to the size of PPs in exposed subjects, in most cases it ranged between 1 cm and 24% of chest wall (53%, n = 116); while in unexposed ones the size of PPs was lesser than 1 cm (23%, n = 58). Furthermore, 19% (n = 41) of exposed subjects revealed a PP size between 24% and 49% of the lateral chest wall and 6% (n = 12) of cases presented a PP size ≥ 50% of the lateral chest wall. Whereas, none of unexposed subjects revealed a PP size > 24% of the lateral chest wall.

Among exposed subjects, 36 cases (17%) PPs were detected with calcification, whereas in unexposed ones only three (8%) presented calcification.

137 lung parenchymal abnormalities were observed in exposed group; whereas, 12 lung parenchymal involvement were registered in unexposed subjects (see Table 4).

In particular, 93 (43%) subjects of the exposed group presented lung parenchymal fibrosis, while only 5 cases of unexposed group did.

McNemar's test has revealed that the RR for PPs is 6,74 CI 95% (4,47–9,58) p < 0,0001 in the exposed population.

4. Discussion

FE is a new mineral species recognised in 2001 (Gianfagna and Oberti, 2001). The exposure of Biancavilla's population is similar to the exposure of the general population to "naturally occurring asbestos" (NOA) (Bayram et al., 2013; Kanarek, 2011; Hansen et al., 1993).

Table 3
Characteristics of the PPs detected by HRCT in the 256 subjects.

	Exposed			**Unexposed**		
Plaque features	Unilateral plaques, n. 84 (39%)	Bilateral plaques n.134 (61%)	Total (%)[a] 218 (18%)	Unilateral plaques, n. 25 (69%)	Bilateral plaques n. 11 (31%)	Total (%)[a] 38 (3%)
Thickness, mm						
< 2	39 (46%)	29 (21%)	68 (21%)	16 (64%)	5(39%)	21(55%)
2–4.9	31 (37%)	52 (39%)	83 (38%)	9 (36%)	6(46%)	15(40%)
5–9.9	14 (17%)	44 (33%)	58 (27%)	0 (0%)	4(15%)	2(5%)
≥ 10	0 (0%)	9 (7%)	9 (4%)	0 (0%)	0 (0%)	0 (0%)
Size						
< 1 cm	36 (43%)	13 (10%)	49 (22%)	15 (60%)	7 (54%)	23 (58%)
1 cm–24% of lateral chest wall	45 (53%)	71 (53%)	116 (53%)	10 (40%)	6 (46%)	15 (42%)
24%–49% of lateral chest wall	3 (4%)	38 (28%)	41 (19%)	0 (0%)	0 (0%)	0 (0%)
≥ 50% of lateral chest wall	0 (0%)	12 (9%)	12 (6%)	0 (0%)	0 (0%)	0 (0%)
Calcification						
Yes			36 (17%)			3 (8%)

[a] This percentage refers to the population under study.

Table 4
Other abnormalities observed through the HRCT scan.

	Exposed n (%)[a]		**Unexposed** n (%)[a]	
	Unilateral abnormalities	**Bilateral abnormalities**	**Unilateral abnormalities**	**Bilateral abnormalities**
Rounded atelectasis	1 (0%)	1 (0%)	0 (0%)	1 (3%)
Emphysema	0 (0%)	6 (3%)	0 (0%)	2 (5%)
Thickness	0 (0%)	30 (14%)	0 (0%)	2 (5%)
Bronchiectasis	0 (0%)	2 (1%)	0 (0%)	1 (3%)
Fibrosis	4 (2%)	93 (43%)	1 (3%)	5 (13%)

[a] This percentage refers to the population under study with PPs.

As occurred in Biancavilla, NOA refers to the mineral as a natural component of soils or rocks. The release of NOA fibers into the air from rocks or soils by routine human activities or natural weathering processes represents a risk for human exposure (Bayram et al., 2013).

Several studies reported a high incidence of MM due to NOA in: rural regions of Turkey (Metintas et al., 2005; Senyigit et al., 2004; Dumortier et al., 1998; Yazicioglu et al., 1980; Döngel et al., 2013), Central Anatolia, caused by exposure to erionite fibers; in Mediterranean countries, including Corsica (Rey et al., 1993), Cyprus (McConnochie et al., 1987) and Greece (Constantopoulos, 2008), Finland (Koskinen et al., 1996) and in other sites of the world, including California (Pan et al., 2005); China (Luo et al., 2003) and New Caledonia (Baumann et al., 2011).

Also in our study, as in all previous NOA exposure ones (Bayram et al., 2013; Metintas et al., 2005; Yazicioglu et al., 1980; Rey et al., 1993; Koskinen et al., 1996; Luo et al., 2003; Baris et al., 1988), we have observed the presence of PPs in exposed population. In this survey, PPs were found in 16% (n=218/1240) of the screened population and more than 60% of patients affected with plaques were males.

Metintas et al. (2005) found that risk of PPs due to environmental asbestos exposure was associated with male gender. The great gender difference might be explained with the mobility of male subjects, as males are exposed to both indoor and outdoor asbestos sources. Besides, in addition to such use of plaster, fiber exposure may occur during farming on contaminated land and as a result of the continuous resuspension of fibers with the wind or traffic on unpaved roads (Döngel et al., 2013).

In our study we also found a higher presence of women with PPs than in the unexposed group (79 *vs* 2). This, as reported in previous studies, is probably due to the fact that women were exposed to a higher degree of dusts (eg, by spending more time indoors with walls covered with fiber contaminated plaster) and for a longer time (Bayram et al., 2013).

Indoor and outdoor air sampling might help explain the great difference of PP rates between male and female subjects (Döngel et al., 2013).

Since 2000, various environmental surveys were carried out with the aim to determine the concentrations of the amphiboles in the area of Biancavilla, and, over the years, to prove the effectiveness of the reclamations. A consistent decrease in the environmental levels of the amphibole was registered over time in the outdoor areas of the town, although the real level of indoor exposure to FE has yet to be determined (Bruno et al., 2014).

The rate (16%) we reported of subjects with PPs is similar to that reported by Luo et al. (2003), who observed that Chinese villagers aged > 40 years had a PPs frequency of 20%. Metintas et al. (2005) in Eskisehir (Turkey), found PPs in 14,4% of subjects exposed. Çöplü et al. (1996) found PPs in 18% of 124 individuals older than 20 years from an Anatolian village. Instead, the PPs frequency we reported is higher than 9.5%, as reported by Döngel et al. (2013), who include in this percentage both MM and PP cases (3/2970 and 289/2970, respectively); and it is also greater than the 6.5% observed by Bayram et al. (2013). In another study, carried out in north eastern Corsica, in residents aged > 50 years, a 41% of PP frequency was observed (Rey et al., 1993).

Thus, the PPs prevalence varies highly in different cohorts. The radiological method (chest roentgenogram or thoracic CT), criteria used and experience of the reader, all play a role in the above mentioned variations. A limit of some studies is the low sensitivity of chest X-rays, which can lead to underestimate small PPs. Apart from this, factors such as age, sex, types of fiber, dose level and length of exposure, affect the risk of PPs (Metintas et al., 2005; Döngel et al., 2013; Hillerdal, Asbestos, 1997).

Besides, several studies have reported the association between the prevalence of PPs in asbestos exposed workers and time since first exposure (TSFE) and with age at first exposure (Metintas et al., 2005; Jarvholm, 1992; Paris et al., 2009).

Paris et al. (2009, 2008) using HRCT demonstrated strong relationships between asbestos exposure and PPs. Exposure determinants associated with the presence of PPs were TSFE and cumulative exposure. However, no relationship was observed between duration of exposure and PPs.

In a previous study on Biancavilla's construction workers we pointed out the correspondence between PPs and cumulative exposure, and all PP subjects had been born in Biancavilla (Rapisaret al., 2015a).

The American Thoracic Society (2004) underlined that TSFE was the parameter most frequently correlated with PPs. Koskinen et al. (1996), in a large survey of Finnish construction, shipyard and asbestos industry workers, reported a stronger relationship between PPs and TSFE than with duration of exposure. Ehrlich et al. (1992) also found that TSFE was the best predictor of the prevalence of PPs in 386 workers exposed to amosite. Algranti et al. (2001) found a relationship between TSFE and PPs in 828 former asbestos cement workers.

As to Biancavilla's case, TSFE corresponds to 1950 or the following years, since that is when the Mt. Calvario quarry started to work. Therefore for Biancavilla's inhabitants the TSFE coincides with birth for those born from 1950 on wards.

The presence of PPs in NOA subjects seems well related to lifetime exposure and in particular to birthplaces (Bayram et al., 2013).

In our study we considered birthplaces and data about residence. This data may represent a real lifetime exposure as Biancavilla residents were normally born there and spent their whole life in this municipality anyway. Biancavilla's inhabitants rarely come from other municipalities, since this little town is a rural place that, as often happens in the Sicilian hinterland, bases its economy on agriculture and cattle breeding, and then it does not offer many other work possibilities to people coming from other municipalities or living far from the town (30 km from Catania) (Gianfagna and Oberti, 2001; Musumeci et al., 2015; Ledda et al., 2013).

This study also shows that the median age of the exposed cases is lesser than the unexposed once. Indeed, stratifying by age, it is observed that 24% ($n=52$) of subjects from Biancavilla are ≤ 60 years old, compared to the unexposed, where no PP subjects are present in the same age ranges.

Similar results were reported by Metintas et al. (2005) who observed a PP frequency of 5.9% in the group aged 30–39 years and 20.4% in those aged 60–69 years.

In the literature, it is generally accepted that plaques are more related to time after first exposure than to the dose. PPs have a long latency time and are not found <10 years, and seldom <20 years, after the first exposure to asbestos, with most appearing only after 30 years (Hillerdal and Henderson, 1997; Nishimura and Broaddus, 1998). Consequently, the frequency of PPs increases with increasing age. For environmental exposure, where the population is exposed from birth, the first pleural changes will appear after 30 years of age and the prevalence of plaques increases with increasing age (Metintas et al., 2005).

Advanced age is associated with an increased risk of PPs, reflecting longer duration of exposure (Döngel et al., 2013).

From data confrontation with a previous study on Biancavilla's construction workers, it was observed that PP subjects were averagely younger than the population surveyed (49,3 *vs* 68,1). Besides, the lung parenchymal involvement of the workers amounted to 22% *vs* 73% of the present study (parenchymal interstice fibrotic involvement in 12% *vs* 44%) (Rapisarda et al., 2015a).

The occurrence of PPs in Biancavilla's masons at a younger age than the subjects of this study enables to assume that occupational exposure to FE fibers began early in their youth, as can be observed through the long working career of each patient. Whereas, the higher extension of PPs and the presence of several cases of pulmonary parenchymal fibrosis in the present population compared to the masons, also seems to depend on the longer times of exposure (Rapisarda et al., 2015a).

As in our study, also Conti et al. (2014), through hospital discharge control, have observed a lung parenchymal fiber involvement in Biancavilla's overall population.

Even a low level of exposure to asbestos and intermittent exposures can cause PP (Hillerdal and Henderson, 1997; Becklake and Case, 1994). The dose–response relationship for PPs is much weaker than that for parenchymal fibrosis, even if longer and heavier exposure will lead to more extensive plaques (Kishimoto et al., 1989; Bégin and Christman, 2001; Karjalainen et al., 1994).

The documented latency for the development of PPs and lung parenchymal fibrosis, is generally long between 20 and 30 years, MM may have an even longer latency period of 40 years or more (Cugell and Kamp, 2004).

It has been postulated that PPs develop due to intermittent asbestos exposure which allows time for the pleura to get rid of fibers. In contrast to this, lung parenchymal fibrosis is believed to occur due to heavy and more continuous exposure which overwhelms the fiber clearance mechanisms (Nishimura and Broaddus, 1998).

The mechanism through which FE generates PPs is still unknown. It is believed that it is similar to the one that asbestos fibers generate (Szychlinska et al., 2014; Miozzi et al., 2016).

Asbestos fibers that are inhaled and pass through the conducting airways are deposited on the Type 1 alveolar epithelial cells that cover the walls of the bronchiolar-alveolar duct bifurcations (Hillerdal, 1981). These phagocytic cells cause migration or “translocation” of fibers into the interstitium, where the larger fibers like amphiboles are retained (Rom et al., 1991, 1987). This may in some patients induce a macrophage-induced alveolitis (Rom et al., 1991). Alveolar epithelial cell injury damages the fibroblasts and myofibroblasts, causing them to produce increased extracellular matrix. This can result in fibrosis (asbestosis). The ability of the lung to clear the fibers becomes overwhelmed. The shorter asbestos fibers are then transported to the pleural surfaces by macrophages through the lymphatics, where they induce acute pleuritis, pleural effusion and fibrosis (Nishimura and Broaddus, 1998). Asbestos fibers travel *via* retrograde lymphatic drainage from the mediastinal lymph nodes to the retrosternal and intercostal lymphatics and thence to the pleural space (Huggins and Sahn, 2004).

Injury caused by asbestos fibers induces subpleural fibroblasts and mesothelial cells to produce scar tissue and collagen deposition, resulting in subpleural thickening (Cugell and Kamp, 2004; Mutsaers et al., 2004).

The response of the mesothelial cell to injury and the basement membrane to maintain their integrity is pivotal as to whether or not fibrosis occurs, and cytokines, growth factors and reactive oxygen species (ROS) are likely to play a role (Mutsaers et al., 2004). Studies of the causes of pleural fibrosis suggests that upregulation of genes for pro-fibrotic mediators such as transforming growth factor beta (TGF-β) and tumour necrosis factor alpha (TNF-α) are important in asbestos-induced fibrogenesis (Huggins andSahn, 2004).

In vivo and *in vitro* analyses of the biological reactivity of FE fibers has also demonstrated that they are able to cause the production of ROS, stimulation of the intrinsic and extrinsic apoptosis pathways, and induction of inflammatory processes through the activation of specific cytokines (Szychlinska et al., 2014; Loreto et al., 2008; Martinez et al., 2006; Grosse et al., 2014).

Calcification of PPs may occur in mature lesions (usually >30 years old) (Miles et al., 2008). In our study, calcifications were spotted in 17% (n=36) of subjects compared to unexposed (8%). Besides, a high number of calcifications can also be observed by comparing the mason patients (58%, n=25) (Rapisarda et al., 2015a).

The presence of PPs is associated with a higher risk of MM and lung cancer compared with workers with a similar exposure history but no plaques (Hillerdal and Henderson, 1997), but there is no evidence to suggest that they are in themselves pre-malignant (Miles et al., 2008). Maxim et al. (2015) in a recent review summarized the literature on the relation between the development of PPs and non-malignant and malignant diseases in cohorts exposed to asbestos and other fibers. They concluded that for certain types of asbestos, the development of PPs is correlated with malignant disease, but the evidence was consistent with the hypothesis that PP without other pleural diseases were a marker of exposure, rather than an independent risk factor.

Several studies, through the assessment of fibers deposition in lung and respiratory lymphnodes in sheep, enabled researchers to imagine a fiber contamination even outside Biancavilla urban area as well as outside it, including rural areas (Ledda et al., 2016; Rapisarda et al., 2005; DeNardo et al., 2004).

A recent study (Groppelli and Norini, 2011) carried out on geological evolution of the lower SW sector of Mt Etna has allowed to identified eruptive fissures of the same ageas Mt. Calvario, with similar volcanological and geochemical characteristics (Burragato et al., 2005). Authors reported that the locations of these volcanic products are potential sites where hydrothermal alteration may have occurred, with the formation of FE(Groppelli and Norini, 2011).

This study presents a number of limitations. First, the study population was selected from the database of Biancavilla's only hospital. The other radiodiagnostic private labs were not taken into account.

Secondly, a possibly more important weakness is the absence of data related to smoking habits (Maxim et al., 2015).

Thirdly, we were not able to take occupational exposures into account because the available records were unsatisfactory in this respect. Substantial exposure to commercial asbestos is highly unlikely in this population because there are no mines or asbestos-handling industries (such as shipyards or asbestos-cement factories) in Biancavilla (Paoletti et al., 2000).

5. Conclusion

In conclusion, in Biancavilla's residents there is a significantly higher RR of PP occurrence compared to unexposed ones.

Furthermore, as a matter of fact, PPs do not often present symptoms, then subjects who are diagnosed for this pathology are few, unless there is a parenchymal involvement or other pathologies. Therefore, the extension of this study to all Biancavilla's population, as hypothesized in similar studies, might bring to discover many more PP cases.

These findings, suggested the urge to extend the screening on the possible involvement of the respiratory tract to all Biancavilla's population, particularly in those aged more than 30. Besides, it seems essential to start indoor monitoring Biancavilla's municipality.

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