Health impact of the exposure to fibres with fluoro-edenitic composition on the residents in Biancavilla (Sicily, Italy): mortality and hospitalization from current data

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Abstract
Introduction. The objective of this chapter is to study the health impact of the exposure to fibres with fluoro-edenitic composition on the residents in Biancavilla (Sicily, Italy), in terms of mortality and hospitalization. The diseases which international scientific literature indicates as associated with asbestos exposure were taken into consideration: mesothelioma of pleura, peritoneum, pericardium and tunica vaginalis testis, malignant neoplasm of larynx, malignant neoplasm of trachea, bronchus and lung, malignant neoplasm of ovary, pneumoconiosis; moreover, in order to describe the health profile of the study population, large groups of diseases were taken into consideration.
Material and methods. Current data (available in the Data Bases of the Unit of Statistics of ISS) regarding mortality and hospitalization were analyzed. Standardized Mortality Ratios, Standardized Hospitalization Ratios and Age-standardized Death Rates were calculated. The demographic background of the population residing in Biancavilla was also outlined.
Conclusions. Our findings support the etiologic role of fibres with fluoro-edenitic composition in the occurrence of the above mentioned diseases, already observed in other studies.

Key words
• mortality
• hospitalization
• health profile
• asbestos
• fluoro-edenite

INTRODUCTION

The observation of an excess risk of pleural mesothelioma in the community of Biancavilla, subsequently attributed to the inhalation of fibres with fluoro-edenitic composition, as reported in this same issue by Bruno *et al.* and by Bruni *et al.*, was originally made in the frame of a national surveillance program of mortality from malignant pleural neoplasms in over 8000 Italian municipalities. The original observation concerned the time window 1988-1992 [1], and it was then confirmed by subsequent reports of the mesothelioma surveillance project, concerning, respectively, the years 1995-2002 [2] and 2003-2009 [3].

As extensively discussed by Bruno *et al.* in this same issue, incidence data concerning pleural mesothelioma have substantially confirmed the indications provided by mortality figures. Even if mortality is a proxy of

incidence, and can be affected by a higher degree of diagnostic misclassification, it has the advantage of being available for all Italian municipalities since 1980 (previously, mortality data could be investigated only at provincial level, that means a much lower specificity, since Italy has over 8000 municipalities versus 100 Provinces).

The objective of this paper is to study the health impact of the exposure to fibres with fluoro-edenitic composition on the residents in Biancavilla, in terms of mortality and hospitalization. The international scientific literature indicates some diseases as associated to asbestos exposure: among neoplastic diseases, mesothelioma of pleura, peritoneum, pericardium and tunica vaginalis testis, malignant neoplasm of larynx, malignant neoplasm of trachea, bronchus and lung, malignant neoplasm of ovary; among respiratory

diseases: pneumoconiosis (asbestosis) [4]. If the latter is not properly diagnosed, it is possible to detect excesses of chronic respiratory diseases and total respiratory disease among asbestos-exposed subjects.

Therefore, in this study, mortality and hospital discharge data due to the abovementioned diseases were analyzed. Moreover, in order to describe the health profile of the population at study, large groups of diseases were taken into consideration: infectious diseases, all neoplasms, diseases of the circulatory system, diseases of the digestive system and diseases of the genitourinary system.

The demographic background of the population residing in Biancavilla was also outlined.

MATERIAL AND METHODS
Demographic framework

Demographic data regarding the municipality of Biancavilla and Sicily Region were available from the Italian National Institute of Statistics (Istituto Nazionale di Statistica, ISTAT). The age and gender distribution of residents in Biancavilla was described showing the age-pyramid; in order to compare these distributions with the ones of the whole Sicilian population the Kolmogorov-Smirnoff test wad used.

Mortality

The data source was the Italian Mortality Data Base, run by the Office of Statistics of ISS, based on official mortality and demographic data, released from ISTAT.

Mortality data, at international level, are codified according to the International Classification of Disease (ICD); it has been revised approximately every 10 years; the purpose of the revision is to stay abreast of medical advances in terms of disease nomenclature and etiology. In Italy, deaths have been codified according to the Ninth Revision (ICD-9) until 2002 [5]; since 2003, the Tenth Revision (ICD-10) has been adopted [6]. ICD-10 differs from ICD-9 in several respects, first of all, ICD-10 is far more detailed than ICD-9, with about 12 000 categories compared with about 5000 categories [7, 8]. Moreover, whilst the classification of neoplastic disease in ICD-9 was only topographic, ICD-10 allows also morphological distinction; therefore it is possible, since 2003 data, to study deaths from pleural and peritoneal mesothelioma (ICD-10 codes: C45.0 and C45.1 respectively). Until 2003, deaths due to mesothelioma were codified by a unique and non specific ICD-9 code: 163 "malignant neoplasm of pleura"; the code for this disease in ICD-10 is C38.4.

The following analysis of mortality data were performed:

a) estimate of standardized mortality ratio (SMR): reference population, Sicilian Region, study period 2003-2010

SMR_i, referred to residents in a selected geographic area i, is defined as the ratio between the number of observed and expected deaths, $SMR_i = \dfrac{\sum_j e_{ji}}{\sum_j T_j n_{ji}} \times 100$

Where, for each age-group j: e_j are the observed events (deaths), n_j is the population and T_j is the

death rate of the reference population (regional population).

As well as the point estimation of SMR, also its confidence interval were calculated (CI 90%); if the observed deaths were less than 100, CI was estimated based on Poisson's distribution, otherwise, on the Byar method;

b) time trend 1980-2010 of age-standardized death rates (ASR) from malignant neoplasm of pleura: until 2002 it was codified by ICD-9 163, after 2002, two codes are to be taken into consideration: ICD-10 45.1 and ICD-10 38.4. The rates have been standardized using the direct method, having the 2001 Census population as reference population. The ASR were referred to 100 000 persons;

c) estimate of SMR from malignant neoplasms of pleura (MNP) in young adults (≤ 50 years) as a proxy for environmental exposure to fluoro-edenite fibres in childhood (reference population, Sicilian Region, study period 1980-2010: ICD-9, code 163 (1980-2002), and ICD-10, codes C45.0 and C38.4 (2003-2010).

In the abovementioned analyses, mortality data referred to the years 2004 and 2005 were not analyzed, given that they were not available from ISTAT.

Hospitalization

The source of data regarding hospitalizations in Italy is the Hospital Discharges Forms Data Base (HDF); in Italian, "schede di dimissione ospedaliera (SDO)". Information on hospitalizations contained in HDFs are collected by all Italian public and private hospitals and are then transmitted to the Ministry of Health. The data collected include information such as demographics (gender, date and place of birth, place of residence and so on), admission and discharge data, principal diagnosis and up to five secondary diagnoses. To code diagnoses, ICD 9-CM (International Classification of Diseases-Clinical Modification, Ninth Revision) is used [9].

In the HDF Data base that the Ministry of Health transmits to the Unit of Statistics of the Istituto Superiore di Sanità, each discharge form contains also an anonymous code, unique for each individual; therefore, it is possible to analyze the information regarding persons that are hospitalized, and not only the hospitalizations. Only the main diagnosis reported in the HDF was taken into consideration and if , during the study period, an individual had been hospitalized for the same diagnosis more than once, only the first hospitalization that occurred during the study period was considered [10, 11].

The following analysis was performed: estimate of standardized hospitalization ratio (SHR) reference population, Sicilian Region, study period 2005-2010; the diagnoses taken into consideration are the same analyzed for mortality study.

The definition of SHR is analogous to that of SMR; also for SHR CI 90% were calculated.

In geographical studies of environment and health, confounding from social and economic factors may occur. To control such confounding effect, standardization

Table 1
Number of observed deaths (Obs), standardized mortality ratio adjusted for deprivation (SMR DI), regional reference; 90% confidence interval (CI 90%); period: 2003-2010 (2004-2005 not available from ISTAT). Men and women

Causes of death	Men		Women	
	Obs	SMR DI (CI 90%)	Obs	SMR DI (CI 90%)
All causes (general mortality)	528	97 (90-104)	561	105 (98-113)
Infectious and parasitic diseases	4	59 (20-135)	4	66 (23-151)
All neoplasms	136	83 (72-96)	107	91 (77-107)
* Malignant neoplasm of larynx	< 3		< 3	
* Malignant neoplasm of trachea, bronchus and lung	35	86 (63-114)	11	128 (72-212)
* Pleural mesothelioma	5	379 (149-797)	6	1128 (491-2226)
* Peritoneal mesothelioma	< 3		< 3	
* Malignant neoplasm of ovary (F)			4	77 (26-177)
Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue	13	94 (56-150)	11	103 (58-171)
Diseases of circulatory system	251	123 (111-137)	297	121 (110-134)
Diseases of respiratory system	42	91 (69-118)	25	115 (80-161)
Acute respiratory diseases	< 3		< 3	
Chronic respiratory diseases	37	114 (85-150)	19	165 (108-242)
* Pneumoconiosis	< 3		< 3	
Diseases of digestive system	9	42 (22-73)	11	56 (32-93)
Diseases of genitourinary system	9	85 (44-148)	8	79 (39-143)

* Causes associated with exposure to asbestos.

Table 2
Number of observed cases (Obs), standardized hospitalization ratio adjusted for deprivation (SHR DI), regional reference; 90% confidence interval (CI 90%); period: 2005-2010. Men and women

Diagnosis on discharge	Men		Women	
	Obs	SHR DI (CI 90%)	Obs	SHR DI (CI 90%)
All causes (except complications of pregnancy, childbirth and puerperium)	5149	98 (96-100)	5521	98 (96-101)
Infectious and parasitic diseases	218	80 (71-89)	194	85 (75-95)
All neoplasms	384	89 (82-97)	347	97 (88-106)
* Malignant neoplasm of larynx	7	86 (40-162)	< 3	
* Malignant neoplasm of trachea, bronchus and lung	53	110 (87-139)	13	116 (68-184)
* Pleural mesothelioma	7	261 (122-489)	7	780 (366-1464)
* Malignant neoplasm of ovary (F)			11	80 (45-132)
Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue	37	86 (64-113)	27	75 (53-104)
Diseases of circulatory system	1136	98 (93-103)	971	96 (91-102)
Diseases of respiratory system	959	109 (103-115)	771	115 (109-122)
Acute respiratory diseases	281	80 (72-88)	274	96 (87-106)
Chronic respiratory diseases	196	145 (128-163)	187	242 (214-273)
Pneumoconiosis	7	396 (186-745)	5	1346 (530-2830)
* Diseases of digestive system	1010	89 (84-94)	862	85 (80-90)
Diseases of genitourinary system	298	79 (72-87)	284	89 (81-98)

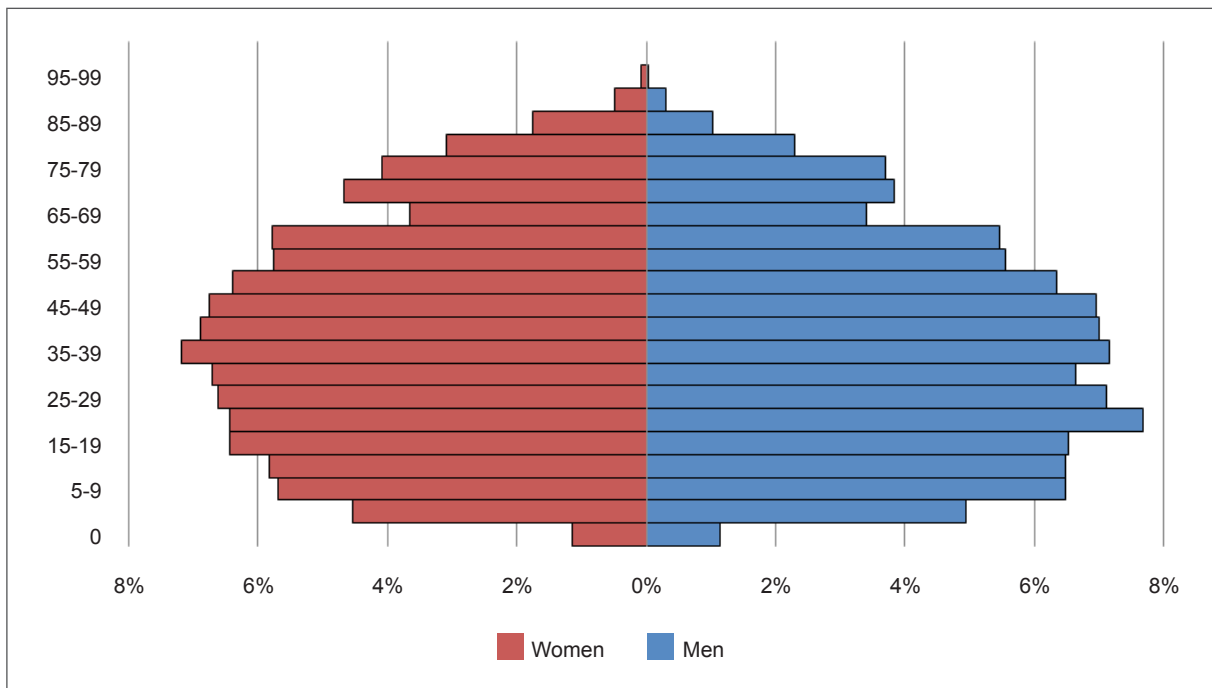* Causes associated with exposure to asbestos.

Figure 1
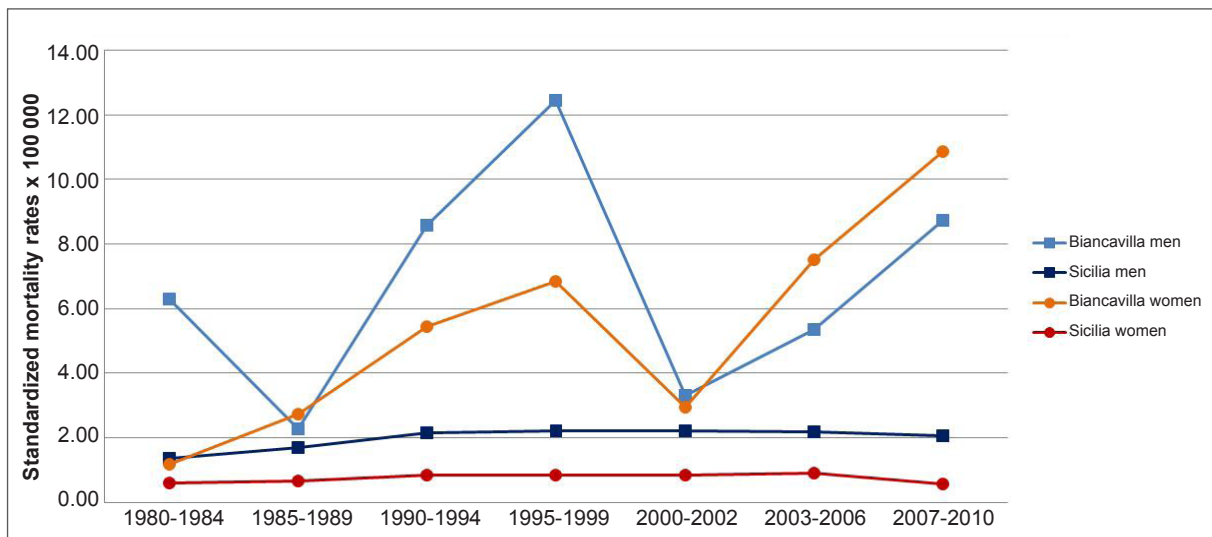Age pyramid of the population of the municipality of Biancavilla (population at 2011 Census).

Figure 2
Trend of age-standardized mortality rates from malignant pleural cancer; period: 1980-2010 (2004-2005 not available from ISTAT). Biancavilla and Sicily, by gender.

techniques have been extensively used since the mid-1990s, taking into consideration the "deprivation"; deprivation can be defined as "a state of observable and demonstrable disadvantage relative to the local community or the wider society or nation to which an individual, family, or groups belong" [12]. Deprivation indices are area-based measures of material and social disadvantageous circumstances, that is, indicators of relative deprivation at population level. To account for possible confounding from socioeconomic factors in SENTIERI Project, an *ad hoc* deprivation index (DI) was built using the 2001 National Census variables representing the following socioeconomic domains: education, unemployment,

dwelling ownership, and overcrowding [13, 14]. The SENTIERI DI was used to adjust all the ratios (SMR and SHR) calculated in this paper.

RESULTS

Biancavilla has 23703 inhabitants at the National Census of 2011; the age structure of the population is shown in *Figure 1* (age pyramid); the population of Biancavilla is older than the Sicilian Reference Population (p < 0.05).

The number of observed cases, SMRs, SHRs and their confidence interval, for mortality and hospitalization, gender and specific causes are reported in *Tables 1 and 2*.

The analysis of mortality and hospitalization from all cancers does not show excesses; considering specific neoplastic diseases, only mortality and hospitalization from pleural mesothelioma show excesses (mortality: men SMR 379, women SMR 1128; hospital discharges: men SHR 261, women SHR 780). The analysis for respiratory diseases presents excesses of mortality and hospital discharges for chronic respiratory diseases (women: SMR 165, SHR 115) and only for hospital discharges from all respiratory diseases (men SHR 109, women SHR 115) and in particular pneumoconiosis (men: SHR 396, women: SHR 1346). When considering other large groups of diseases, used to describe the health profile of the population of Biancavilla (infectious and parasitic diseases, diseases of circulatory system diseases of digestive system, of genitourinary system), only diseases of the circulatory system show excess ratio of mortality among both genders (men: SMR 123, women: SMR:121).

In *Figure 2* time trends of the age-standardized death rates (ASR) from malignant neoplasm of pleura in Biancavilla and in Sicily, by gender, are presented.

The fluctuating trend of ASRs among men and women in Biancavilla is depending on the low number of observed deaths occurred during the whole period (18 men and 16 women data not shown) but it is noteworthy that these values are, along the whole period, always higher than those observed in the Sicily Region.

As to mortality from malignant neoplasms of pleura (MNP) in young adults (≤ 50 years), in the period 1980-2010, 6 deaths *versus* 0.6 expected were observed (SMR = 1003, CI 90% 437-1980). Extending the analysis to municipalities located within a radius of 10 km from Biancavilla, the number of MNP deaths rose to 11 (SMR = 367, CI 90% 206-608).

DISCUSSION AND CONCLUSIONS

This study was conducted adopting the approach developed in the SENTIERI study [13]. The distinguishing feature of SENTIERI Project is the "*a priori* evaluation" of the epidemiological evidence of the causal association for each combination environmental exposure/cause of death selected for the analysis. This approach is interesting, since when performing epidemiologic studies, there is a risk for researchers to become data-driven. This can be the case when commenting results for causes showing an increase, possibly on the basis of statistical significance. In our study the pathologies taken into consideration were those indicated by the literature as associated with asbestos exposure.

When calculating standardized mortality/hospitalization rates, for the reference population the same data of the area units under study are needed: cases and populations stratified by gender and age categories. The reference population should be selected considering two different needs: a) it should be comparable to the studied populations for factors that can affect the health profile with the exception of the contamination at study; the differences in the

health profile between the compared populations should be ideally due only to the differences in environmental exposures, namely, to the contamination; b) it should be sufficiently numerous to obtain stable reference rates also for rare diseases. These two needs have opposite requirements, as the first one is usually negatively correlated with the dimension of the population, while the second one is positively correlated with the dimension of the population. The reference populations should be selected balancing these two needs. Usually one or two populations among the following are selected as reference population: national, and regional, local (*i.e.*, a population composed of populations residing in the neighborhood of the contaminated area). In the SENTIERI approach, and therefore in the present study, the regional population was used as reference.

The present study, as all epidemiological studies based on aggregate data, has limitations, but when considering diseases that according to few studies are considered as associated with the exposure to asbestos, it is noteworthy that both men and women residing in Biancavilla present excess mortality and hospitalization ratios from pleural mesothelioma; regarding the other diseases, excess in mortality from chronic respiratory diseases among women and hospitalization from diseases of the respiratory system, in particular chronic respiratory diseases. Our findings support the etiologic role of fibres with fluoro-edenitic composition in the occurrence of the above mentioned diseases, already observed in other studies [15-17]. Specifically, this report confirms the excess of hospitalization for pneumoconiosis firstly reported by Cernigliano *et al.* [16], that suggests the occurrence of environmental lung fibrosis. Furthermore, both mortality and hospitalizations from pleural mesothelioma present SMR and SHR higher among women than among men; this may reflect a higher level of fiber exposure for women, who are often engaged in activities such as sweeping of floors, balconies and sidewalks located in front of the houses [17].

Finally, the elevated excess mortality from malignant neoplasms of pleura among people aged 50 years or less, both in Biancavilla and among the municipalities surrounding Biancavilla, contributes to corroborate the hypothesis of the health impact of environmental exposure to fluoro-edenite fibres during childhood [18].

To conclude, the overall results of our study are supporting the association of exposure to fibres with fluoro-edenitic composition with mortality and morbidity from asbestos-related diseases.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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