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Occupational cohort study of asbestos-cement workers in a contaminated site in Sicily (Italy)

Studio di coorte occupazionale dei lavoratori di una fabbrica di produzione del cemento-amianto in un sito contaminato della Sicilia

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ABSTRACT

OBJECTIVES: to analyse the asbestos-related diseases risk among the former workers of Sacelit asbestos-cement plant, operating in San Filippo del Mela (Sicily: 1958- 1993).

DESIGN: cohort study.

SETTING AND PARTICIPANTS: 228 subjects were employed in Sacelit from 1958 to 1993. Due to the available observation periods, the analyses of the different outcomes were performed for the subjects alive at the beginning of the respective follow up periods: mortality (1986-2018) was analysed for 204 subjects (177 men, 27 women), hospitalization (2001-2016) for 164 workers (139 men, 25 women) and the incidence of mesothelioma (1998-2016) was estimated for 178 subjects (153 men, 25 women).

MAIN OUTCOMES MEASURES: mortality (Standardized Mortality Ratio: SMR) and hospitalization (Standardized Hospitalization Ratio: SHR) from specific diseases were analysed. Incidence (Standardized Incidence Ratio: SIR) of mesothelioma cases was detected, also. SMR (1986-2014), SHR (2001-2016) and SIR (1998-2016), with 95% Confidence Intervals, were computed with respect to the regional rates, with STATA11.

RESULTS: in the men cohort, mortality from lung (17 cases, SMR 2.83) and pleural cancers (5 cases, SMR 30) and from asbestosis (15 cases, SMR 1,930) was in excess. The risk of hospitalization was in excess, in both genders, from lung cancer (men: 6 cases, SHR 4.1; women: 2 cases, SHR 8.6) and asbestosis (men: 17 cases, SHR 1,304; women: 6 cases, SHR 2,455). The incidence of mesothelioma was in excess in men (5 cases, SIR 23.9); no female cases of mesothelioma were observed.

CONCLUSIONS: a high occurrence of asbestos-related diseases in the cohort, particularly among men, was observed. The excess of hospitalization from asbestosis and lung cancer was highlighted also in women. The prosecution of the on-going health surveillance plan is particularly appropriated.

Keywords: asbestos, occupational cohort, mesothelioma, asbestosis, asbestos-cement

WHAT IS ALREADY KNOWN

- Asbestos is an ascertained carcinogen and the health impact of occupational exposure to asbestos is well documented.
- In Sacelit asbestos-cement plant (1958-1993), San Filippo del Mela (Sicily), a widespread occurrence of asbestos fibres in workplace was documented by the Committee of former workers.
- A high incidence of asbestos related diseases was reported in population living in the area.

WHAT THIS PAPER ADDS

- Estimates of the risk of mortality and hospitalization from asbestos-related diseases and of the incidence of mesothelioma in the cohort of former workers of Sacelit plant (San Filippo del Mela).
- A high risk of asbestos-related diseases in the cohort, particularly among men, was observed; the risk of hospitalization from lung cancer and asbestosis was in excess in both genders.

RIASSUNTO

OBIETTIVI: analizzare il rischio di patologie correlate ad amianto tra gli ex-lavoratori della fabbrica di cemento-amianto Sacelit di San Filippo del Mela (Sicilia: 1958-1993).

DISEGNO: studio di coorte.

SETTING E PARTECIPANTI: in Sacelit sono state impiegate 228 persone. Data la disponibilità dei periodi di osservazione delle banche dati, le analisi dei diversi esiti sono state eseguite per i soggetti in vita all'inizio dei rispettivi periodi di follow up: la mortalità (1986-2018) è stata analizzata per 204 soggetti (177 uomini, 27 donne), l'ospedalizzazione (2001-2016) per 164 (139 uomini, 25 donne), l'incidenza di mesoteliomi (1998-2016) per 178 lavoratori (153 uomini, 25 donne).

PRINCIPALI MISURE DI OUTCOME: sono state analizzate la mortalità (rapporti standardizzati di mortalità, SMR) e l'ospedalizzazione (rapporti standardizzati di ospedalizzazione, SHR) per specifiche patologie. È stata indagata anche l'incidenza di mesotelioma (rapporti standardizzati di incidenza, SIR). Sono stati calcolati SMR, SHR e SIR, con i relativi Intervalli di Confidenza al 95%, rispetto ai tassi regionali, con STATA11.

RISULTATI: tra gli uomini della coorte è in eccesso la morta-

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lità per tumore polmonare (17 casi, SMR 2,83) e pleurico (5 casi, SMR 30) e per asbestosi (15 casi, SMR 1.930). Il rischio di ospedalizzazione è in eccesso in entrambi i generi per il tumore del polmone (uomini: 6 casi, SHR 4,1; donne: 2 casi, SHR 8,6) e per asbestosi (uomini: 17 casi, SHR 1.304; donne: 6 casi, SHR 2.455). L'incidenza del mesotelioma è in eccesso negli uomini (5 casi, SIR 23,9); non sono state osservate diagnosi di mesotelioma nelle donne.

CONCLUSIONI: nella coorte è stata evidenziata un'elevata occorrenza di patologie correlate ad amianto, in particolare tra gli uomini. L'eccesso di ricoveri per asbestosi e tumore polmonare è stato osservato anche tra le donne. Il prosieguo del piano di sorveglianza sanitaria in corso è particolarmente appropriato.

Parole chiave: amianto, coorte occupazionale, mesotelioma, asbestosi, cemento-amianto

INTRODUCTION

Asbestos is one of the most widespread occupational carcinogens: the World Health Organization (WHO) has estimated that around 125 million people worldwide are currently exposed to asbestos at workplace.¹ According to the International Agency of Research for Cancer (IARC), there is sufficient evidence that all asbestos fibres cause malignant mesothelioma, lung, larynx and ovary cancers. A limited evidence for pharyngeal, stomach and colorectal cancers has also been defined.² Others non-communicable diseases like pleural fibrosis (plaques and thickening) and asbestosis are caused by asbestos exposure in addition to the neoplastic diseases. The global burden of disease attributable to occupational exposure to asbestos was estimated at approximately 107,000 deaths in 2004, of which 59,000 were from mesothelioma.³ The improvement of early diagnosis and the establishment of registers of the people exposed to asbestos is among the public health actions recommended by the WHO.¹

Italy was one of the main countries that produced and imported raw asbestos until the ban in 1992 (Italian law n. 257, 27th March 1992). 1,340 deaths from mesothelioma per year were detected from 2003 to 2014 in Italy.⁴ The most recent report of the Italian Registry of Mesothelioma (ReNaM) has put in highlight 27,356 incident cases of mesothelioma during 1993-2015, equal to 1,189 per year. The most of these cases reported were due to exposure at workplace, yet also domestic and environmental exposures were highlighted.⁵

A recent analysis of the Italian pool of 43 asbestos exposed workers cohorts (42 occupational cohorts and one of workers wives) showed mortality excesses from asbestos-related diseases and their temporal trends by duration of exposure and time since first exposure (TSFE).⁶ In August 2019, a pooled analysis of Italian asbestos-cement plant cohorts was published, including 12,578 workers, 10,275 men and 2,303 women. An increase of mortality risk from asbestos-related diseases, namely asbestosis and malignant neoplasms (MN) of pleura, peritoneum, lung and ovary, was shown. After 40 years of TSFE pleural MN showed a plateau, while peritoneal MN showed a continuous increase and the trend of lung cancers showed a flattering.⁷

The aim of the present paper is to investigate the health status of the former workers in Sacelit asbestos-cement plant (San Filippo del Mela, Sicily) and to estimate the asbestos-related disease risks in the cohort. The estimates were performed also considering temporal factors, i.e. duration of job and time since the first exposure (TFSE). The results of the present investigation may contribute to estimate the health impact of asbestos cement production at global level and, particularly, after more than 25 years from the ban of asbestos in Italy.

The asbestos-cement plant (Sacelit Company) was active in San Filippo del Mela municipality (Sicily, Italy) from 1958 to 1993. The municipality is included in area defined by Sicilian Regional Government "area of high risk for environmental crisis". This municipality is also included as part of the National Priority Contaminated Site (NPCS) named Milazzo, where several industrial facilities are localized, such as power plant, refineries and steel plants.

An investigation on mesothelioma incidence in populations living in contaminated sites (SENTIERI Project) founded an excess of mesothelioma in male population living in Milazzo NPCS: seven of the 13 observed cases had an ascertained occupational exposure to asbestos fibres.⁸

A more recent report of ReNaM, on the occurrence of occupational diseases in the same Italian NPCSS, reported excesses of occupational asbestos-related diseases among the workers of both genders resident in Milazzo site. The asbestos-cement plant is mentioned as one of the involved occupational sectors.⁹

Data of environmental monitoring inside Sacelit factory were not available. The presence of high levels of asbestos fibres contamination in the workplace, particularly until mid-1970s, was reported by the former workers Committee. Chrysotile and crocidolite fibres, in total about 1,968 tons/year, were processed with cement material (15,600 tons/year), without any personal or environmental protection until the early Seventies. All mixture procedures were manual until the early Seventies. In 1984, local ventilation units were installed to aspirate the dust.¹⁰

A previous paper described the occurrence of high number of workers of the Sacelit affected by asbestos related diseases.¹¹

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METHODS**COHORT DESCRIPTION**

The cohort was established identifying workers from the list of the former workers Committee, using the Company files. The data were validated by official records of the Italian Workers Compensation Authority (Inail) database. No information on job title and tasks was available at the start of the present analysis. Personal data and occupational period, from hiring date to cessation data, of each worker were recorded.

HEALTH OUTCOMES

Cause-specific of mortality and hospitalization, as well as mesothelioma incidence, were investigated.

MORTALITY ANALYSIS

Due to the availability of mortality data, the follow up period considered for mortality analysis was limited to January 1st 1986-December 31st 2018. Therefore, the analysis excluded deaths and person-years at risk before 1986. Information on vital status, or the cause of death, of each subject, during from 1986 to 2003 were acquired by the Local Health Authority. For the follow period 2004-2018, for which it existed the available of the data from the individual Regional Mortality Register, a record linkage with the cohort's subjects list was performed. Twenty out of the 228 workers employed at Sacelit deceased before 1986 (8.8%) and 4 subjects (1.7%) were lost at follow up because emigrated outside of the region. The mortality analysis was performed for 204 subjects, 177 men and 27 women, corresponding to 4,975 person-years at risk.

The *a priori* diseases of interest were identified. Moreover, the causes of death included in the recent Italian pooled analyses of asbestos exposed workers cohorts^{6,7} were considered for the analysis. Then the analysis included the main groups of causes of death, cancers associated with asbestos, following the IARC evaluation, and asbestosis. According to the classification system of death causes of the individual Regional Mortality Registry, the 9th revision of the International Classification of Diseases was used. The table S1 (see on-line supplementary material) reports the considered causes and the corresponding codes. For each deceased the main cause reported on the death certificate we considered.

HOSPITALIZATION ANALYSIS

In order to evaluate morbidity, a record linkage of personal data of cohort subjects with regional Hospital Discharge (HD) database was performed. Due to the availability of data, the follow up period in HD analysis included the years from 2001 to 2016. The analysis was performed on 164 subjects alive at 2001, 139 men and 25 women, corresponding to 1,527 person-years at risk.

The Sicilian Regional HD database detects the HDs of all residents in Sicily, including the hospitalizations of the Sicilian residents that occurred outside the Region.

The first diagnosis reported in HDs was considered. The repeated hospitalizations for the same cause of each subject were excluded. The analysis was performed for cancers related to asbestos exposure, following the IARC evaluation, asbestosis, circulatory and respiratory diseases. The latter group of causes were included to identify a possible effect of "healthy worker" and of smoking habits in the cohort.

INCIDENCE OF MESOTHELIOMA

The incident cases of mesothelioma were provided by the Sicilian Regional Operative Centre of the National Registry of Mesothelioma (COR Sicily). The COR Sicily was established in 1998 and the registration period of the mesothelioma included in this study started from 1998 until to 2017. The subjects of the cohort with a diagnosis of mesothelioma were detected by a manual record linkage between the list of the cohort's workers alive in 1998 (153 men and 25 women) and the COR Sicily database. All cases of mesothelioma regardless the level of diagnostic certainty used by the COR Sicily were included, then all the diagnosis of mesothelioma classified as ascertained, possible or probable, according to the national rules of the ReNaM^{5,12} were considered.

STATISTICAL ANALYSES

The Standardized Mortality (SMR), Hospitalization (SHR) and Incidence (SIR) Ratios, for each outcome, were computed with respect to the Regional figures. The Regional mortality rates on the basis of population and cause-specific mortality database of Italian National Institute of Statistics (Istat) were computed stratified by 5-year age groups, time-period and gender. The Regional hospitalization rates, stratified by gender, 5-year age groups and time-period, were computed on the basis of the cases reported in the Regional HD Register and Istat population database. The same method was used to compute the regional rates of mesothelioma incidence, on the basis of the cases drawn by COR Sicily and the Istat population records.

In each analysis, the subjects of the cohort contributed to the person-years at risk, from the start of observation period, or the hiring date (if it was subsequent to the start of follow up), to the end of the follow up, or to the date of the occurrence of the outcome (death, hospitalization, or mesothelioma diagnosis). For each analysis, the deaths and the person-years at risk before the beginning of observation period were excluded.

The mortality analyses from asbestos-related diseases were carried out by work duration, time since the first

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exposure (TSFE, latency) and age of hiring. The SMRs (1986-2018 period), SHRs (2001-2016 period) and SIRs (1998-2017 period), with the corresponding 95% Confidence Interval (95%CI), were computed under the hypothesis that the observations were distributed according a Poisson distribution and the risks were estimated respect to the regional figures.

The database was processed according to the European Union General Data Protection Regulation (<https://gdpr-info.eu/>) and the data analyses were performed using software STATA 11.

RESULTS

Two hundred and twenty-eight workers, 200 men and 28 women, were employed in Sacelit factory from 1958 to 1993. Due to the availability of outcomes data, the analyses were performed only for the subjects alive at the beginning of each follow up period, as described above.

Table 1 describes the studied cohort and the subjects considered in the different analyses.

MORTALITY (1986-2018). Mortality analysis included 204 subjects, corresponding to 4,810 person-years at risk, 4,063 for men and 747 for women. 92% of them were hired in Sacelit before the Seventies and the average duration of job was 18 years (data not shown).

One hundred and twenty five of 204 subjects deceased during the observation period, 117 men and 8 women.

The cause of death was not available for ten of the deceased subjects, then they were computed only in "all causes" mortality and they did not contribute to the specific-causes.

Table 2 shows the results of mortality analysis. The general mortality is in excess among men, while is lower than that expected from the regional figure among women. Excesses of mortality from all cancers were found among men, regarding in particular cancers of stomach, respiratory and lymphoematopoietic systems. No woman deceased from

	MALES			FEMALES			ALL		
	n.	%	PY*	n.	%	PY*	n.	%	PY*
MORTALITY (1986-2018)									
STATUS AT FOLLOW-UP									
Alive	59	33.3		19	70.4		79	38.7	
Deceased	118	66.7		8	29.7		125	61.3	
Lost to follow-up	4	2.3		0			4		
Total analysis	177		4,187.8	27		787.03	204		4,974.8
DURATION OF EMPLOYMENT (YEARS)									
<10	45	25.4	1,153.4	14	51.8	453	59	28.9	1,606.4
10-19	39	22.0	691.4	4	14.8	83	43	21.1	774.6
20-29	63	35.6	1,525.0	3	11.1	96	66	32.3	1,621.2
30+	30	16.9	817.9	6	22.2	154.7	36	17.6	972.6
LATENCY (YEARS)									
<20	2	1.1	7.7	0			2	0.99	7.7
20-29	13	7.3	127.8	1	3.7	0.2	14	6.90	127.9
30-39	36	20.3	560.7	2	7.4	21.1	38	18.6	581.8
40-49	53	29.9	1,166.2	1	3.7	18.6	54	26.5	1,184.8
50-59	62	35.0	1,962.5	18	66.7	582.2	80	39.2	2,544.7
60-69	11	6.2	362.8	5	18.5	165	16	7.8	527.8
HOSPITALIZATION (2001-2016)									
STATUS AT FOLLOW-UP									
No hospitalized	37	26.6		7	28.0		44	26.8	
Hospitalized	102	73.4		18	72.0		120	73.2	
Lost to follow-up	0			0			0		
Total analysis	139		1,306.3	25		221	164		1,527.3
INCIDENCE OF MESOTHELIOMA (1998-2017)									
STATUS AT FOLLOW-UP									
No mesothelioma	148	97.2		25	100.0		173	97.2	
Cases of Mesothelioma	5	2.8		0			5	2.8	
Lost to follow-up	0			0			0		
Total analysis	153		2,150.7	25		466.8	178		2,617.5

* person-years at risk, computed from the beginning of follow-up / *anni-persona a rischio, calcolati dall'inizio del follow-up*

Table 1. Description of cohort and subjects considered in the different outcomes analyses.

Tabella 1. Descrizione della coorte e soggetti considerati in ciascuna analisi.

MORTALITY													
CAUSE OF DEATH	ICD-9 CODES	MALES				FEMALES				OVERALL			
		OBS	EXP	SMR	95%CI	OBS	EXP	SMR	95%CI	OBS	EXP	SMR	95%CI
All causes (complications of pregnancy, childbirth, and the puerperium excluded)	0001-6299, 6800-7999	117	87.75	1.33	(1.11-1.60)	8	10.36	0.77	(0.39-1.54)	125	98.11	1.27	(1.07-1.52)
Malignant neoplasms (MN)	1400-2089	43	25.27	1.70	(1.26-2.29)	0	3.76			43	29.04	1.48	(1.10-2.00)
MN of the lip, oral cavity, and pharynx	1400-1499	0	0.37			0	0.06			0	0.43		
MN digestive organs (peritoneum included)	1500-1599	6	8.66	0.69	(0.31-1.54)	0	1.26			6	9.92	0.60	(0.27-1.35)
MN of the stomach	1510-1519	2	1.46	1.37	(0.34-5.49)	0	0.20			2	1.65	1.21	(0.30-4.84)
MN of the small intestine	1520-1529	0	0.04			0	0.01			0	0.05		
MN of the colon-rectum	1530-1549	1	2.79	0.36	(0.05-2.55)	0	0.41			1	3.20	0.31	(0.04-2.22)
MN of the colon	1530-1539	1	2.12	0.47	(0.07-3.35)	0	0.32			1	2.44	0.41	(0.06-2.92)
MN of the rectum	1540-1549	0	0.67			0	0.10			0	0.77		
MN of the liver and intrahepatic bile ducts	1550-1552	1	1.91	0.52	(0.07-3.72)	0	0.27			1	2.18	0.46	(0.06-3.25)
MN of the peritoneum and retroperitoneum	1580-1589	1	0.11	8.86	(1.25-62.90)	0	0.02			1	0.13	7.69	(1.08-54.56)
MN of the peritoneum	1588-1589	1	0.07	13.6	(1.92-96.80)	0	0.01			1	0.09	11.7	(1.65-83.13)
MN of the respiratory organs	1600-1659	22	6.64	3.31	(2.18-5.03)	0	1.03			22	7.67	2.87	(1.89-4.36)
MN of the larynx	1610-1619	0	0.38			0	0.05			0	0.43		
MN of the lungs	1620-1629	17	6.01	2.83	(1.76-4.55)	0	0.94			17	6.95	2.45	(1.52-3.94)
MN of the pleura	1630-1639	5	0.17	29.90	(12.00-72.00)	0	0.03			5	0.20	25.4	(10.60-61.00)
MN of the uterus	1790-1809, 1820-1829					0	0.07						
MN of the ovaries	1830-1839					0	0.06						
MN of the prostate	1850-1859	2	1.54	1.30	(0.32-5.19)								
MN of the bladder	1880-1889	3	1.18	2.54	(0.82-7.88)	0	0.15			3	1.33	2.25	(0.73-6.98)
MN of unspecified site	1990-1999	1	0.85	1.17	(0.17-8.32)	0	0.13			1	0.98	1.02	(0.14-7.22)
Leukaemia and lymphoma	2000-2089	6	2.01	2.98	(1.34-6.63)	0	0.30			6	2.32	2.59	(1.16-5.77)
Psychiatric diseases	2900-3199	0	1.34			0	0.13			0	1.47		
Neurological diseases	3200-3599	6	2.42	2.48	(1.11-5.52)	0	0.33			6	2.75	2.18	(0.98-4.86)
Cardiovascular diseases	3900-4599	27	36.68	0.74	(0.50-1.07)	5	3.62	1.38	(0.58-3.32)	32	40.3	0.79	(0.56-1.12)
Respiratory diseases	4600-5199	21	6.17	3.40	(2.22-5.22)	1	0.62	1.60	(0.23-11.38)	22	6.79	3.24	(2.13-4.92)
Acute respiratory infections	4600-4669, 4800-4879	0	0.74			0	0.07			0	0.81		
Chronic-obstructive respiratory diseases	4900-4969	0	3.89			0	0.37			0	4.27		
Pneumoconiosis	5000-5059	17	0.10	164	(102-264)	1	0.01	101	(14.3-720)	18	0.11	158	(99.8-252)
Asbestosis	5010-5019	15	0.01	1,930	(1,164-3,202)	1	0.00	607	(85.5-4307)	16	0.01	1,699	(1,041-2,773)
Digestive diseases	5200-5799	4	4.11	0.97	(0.37-2.59)	0	0.53			4	4.64	0.86	(0.32-2.30)
Genitourinary diseases	5800-6299	2	1.78	1.12	(0.28-4.48)	0	0.19			2	1.98	1.01	(0.25-4.04)
Poorly specified causes	7800-7998	3	1.77	1.69	(0.55-5.25)	1	0.12	8.19	(1.15-58.1)	4	1.89	2.11	(0.79-5.63)
Accident and violence	8000-9999	1	2.89	0.35	(0.05-2.46)	0	0.37			1	3.26	0.31	(0.04-2.17)

OBS: observed cases / casi osservati; EXP: expected cases / casi attesi; SMR: standardized mortality ratio / rapporto standardizzato di mortalità; CI: confidence interval / intervallo di confidenza

Table 2. Mortality in the cohort study (1986-2018).

Tabella 2. Mortalità nella coorte in studio (1986-2018).

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	LUNG CANCER			NEOPLASMS OF PLEURA			ASBESTOSIS		
	OBS	EXP	SMR (95%CI)	OBS	EXP	SMR (95%CI)	OBS	EXP	SMR (95%CI)
LATENCY (years)									
<20	0	0	-	0	0		0	0	
20-29	3	0.07	43.50 (14-135)	0	0		0	0	
30-30	6	0.55	10.90 (4.89-24.2)	0	0.01		0	0	
40-49	6	1.72	3.50 (1.57-7.78)	4	0.05	84.60 (31.7-225)	6	0	3,878 (1,742-8,633)
50-59	2	3.78	0.53 (0.13-2.11)	1	0.11	9.17 (1.29-65.1)	9	0.01	1,437 (747-2,761)
60-69	0	0.83		0	0.03		1	0	714 (100-5,069)
DURATION OF WORK (years)									
<10	6	1.87	3.20 (1.44-7.12)	0	0.06		1	0	375 (52.9-2,665)
10-19	2	1.13	1.77 (0.44-7.09)	0	0.03		4	0	3,237 (1,214-8,624)
20-29	7	2.64	2.65 (1.26-5.56)	3	0.07	43.00 (13.8-133)	7	0	1,958 (934-4,109)
≥30	2	1.31	1.53 (0.38-6.11)	2	0.04	53.30 (13.3-213)	4	0	2,055 (771-5,475)

OBS: observed cases / casi osservati; EXP: expected cases / casi attesi; SMR: standardized mortality ratio / rapporto standardizzato di mortalità; CI: confidence interval / intervallo di confidenza

Table 3. Mortality from ascertained asbestos-related diseases (with cases>0), by latency (years since the first exposure) and duration of work; men (1986-2018).

Tabella 3. Mortalità per malattie correlate ad amianto certe (con casi >0), per latenza (anni dalla prima esposizione) e durata lavorativa; uomini (1986-2018).

CAUSES	MEN			WOMEN			OVERALL		
	OBS	EXP	SHR (95%CI)	OBS	EXP	SHR (95%CI)	OBS	EXP	SHR (95%CI)
All causes	103	91.40	1.1 (0.93-1.3)	18	13.50	1.34 (0.84-2.1)	121	104.90	1.1 (0.97-1.4)
Malignant neoplasms (MN)	24	16.50	1.5 (0.98-2.1)	4	2.40	1.60 (0.61-4.4)	28	18.90	1.5 (1.0-2.1)
MN of peritoneum	1	0.04	23.6 (3.3-167.8)	0	0.01	0	1	0.05	20.6 (2.9-146)
MN of larynx	1	0.18	5.7 (0.8-40.5)	0	0.03	0	1	0.21	4.8 (0.68-34.1)
MN of lungs	6	1.40	4.1 (1.9-9.2)	2	0.23	8.60 (2.1-34.2)	8	1.70	4.7 (2.4-9.5)
MN of pleura	2	0.07	27.5 (6.9-109.9)	0	0.01	0	2	0.09	23.5 (5.9-93.9)
MN ovaries				1	0.38	2.70 (0.37-18.9)			
Cardiovascular diseases	44	38.40	1.1 (0.85-1.5)	2	5.20	0.39 (0.10-1.5)	46	43.60	1.06 (0.79-1.4)
Respiratory diseases	43	13.60	3.2 (2.3-4.3)	11	1.80	6.20 (3.4-11.2)	54	15.40	3.5 (2.7-4.6)
Acute respiratory infections	4	4.00	1.0 (0.38-2.7)	0	0.50		4	4.50	0.89 (0.34-2.38)
BPCO	11	5.00	2.2 (1.2-3.9)	3	0.65	4.60 (1.5-14.4)	14	5.70	2.5 (1.5-4.1)
Asbestosis	17	0.01	1,304 (811-2098)	6	0	2,455(1,103-5,464)	23	0.02	1,486 (988-2,237)

OBS: observed cases / casi osservati; EXP: expected cases / casi attesi; SHR: standardized hospitalization ratio / rapporto standardizzato di ospedalizzazione; CI: confidence interval / intervallo di confidenza

Table 4. Hospitalization from selected causes, by gender (2001-2016).

Tabella 4. Ospedalizzazione per specifiche patologie, per genere (2001-2016).

cancers or any asbestos-related disease, except one from asbestosis. Excesses of mortality from asbestos-related diseases were found among men. The excess of mortality from respiratory diseases (22 cases) is particularly due to deaths from asbestosis (15 cases). Mortality from cardiovascular diseases is similar to the predicted regional rate in both genders.

Table 3 shows the SMRs from asbestos-related diseases, stratified by TSFE and duration of job, among the males of the cohort. All deaths from lung cancer happened after more than 20 years from the hiring in Sacelit (TSFE). The two cases decedents from asbestosis and from pleural ma-

lignant neoplasms occurred after 40 years of TSFE, one of these worked in Sacelit for a period longer than 10 years and the other longer than 20 years, respectively.

HOSPITALIZATION (2001-2016). The analysis of the hospitalizations was performed on 164 subjects, 139 men and 25 women, still alive in 2001. Forty-three subjects were never hospitalized during the follow up period. Table 4 shows the SHRs by selected diseases. One case of malignant neoplasm (MN) of peritoneum and one of larynx were detected in HD in men and one case of ovary MN. Hospitalization from diseases other than asbestosis

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included in the pneumoconiosis code were not observed. The number of subjects hospitalized from lung cancer and from asbestosis were in excess with respect to the regional figures, among both genders.

The ages at the first hospitalization from asbestosis varied between 55 and 89 years in men and between 55 and 74 years in women. Two men of the cohort, one 65 and another 75, had an hospitalization from MN of pleura, with zero expected, both with a duration of work in Sacelit longer than 20 years.

INCIDENCE OF MESOTHELIOMA (1998-2017). The analysis of the incidence of mesothelioma, using the COR Sicily database, included 178 subjects alive at 1998, 153 men and 25 women, corresponding to 2,618 person-years at risk (2,151 among men, 467 among women).

During the follow up period no women had had a diagnosis of mesothelioma.

Five men had been identified by the COR Sicily, 4 with a diagnosis of pleural mesothelioma (MPM) and one with peritoneal mesothelioma. The latter is the same subject hospitalized from MN of peritoneum (nosological code including peritoneal mesothelioma), considered in HD analysis. He was also included in mortality analysis among the subjects deceased from MN of pleura, according to the principal cause reported in death certificate. About the 4 subjects with MPM, two of them were hospitalized and deceased from MN of pleura, two were not included in HD analysis because died before 2001 (before the HD observation period), one from MN of pleura and another one from cardiovascular disease.

The SIRs exceeding 20 folds the regional figures were found for all mesothelioma (5 cases, SIR 23.9; 95%CI: 10-57.5) and MPM (4 cases, SIR 20.1; 95%CI: 7.55-53.6). The case of peritoneal mesothelioma was drawn with zero expected case.

The four subjects with pleural mesothelioma were 60-75 years old at time of the first diagnosis, that occurred after 30 years since the entry in Sacelit and with a period of work longer than 20 years.

The man with peritoneal mesothelioma was 65 years old and mesothelioma was diagnosed after 48 years from the beginning of work in Sacelit, where he worked for 31 years.

DISCUSSION

A high occurrence of asbestos-related diseases in the cohort was found in particular among males. The mortality analysis highlighted risks from MN of stomach, pleura, lungs and from asbestosis among males. The hospitalization analysis showed a high incidence of cases of MN of lungs and asbestosis, also among women of the cohort. The high incidence of mesothelioma among men was confirmed by COR Sicily database.

The high risk of mortality from asbestosis in men and the risk of hospitalization in both genders confirm the presence of high levels of asbestos fibres exposures,⁶ which has already been documented by the former workers Committee.

The lower risk of mortality from cardiovascular diseases, observed both in men and women cohort, with respect to the regional figures, suggests presence of a healthy worker effect and the lack of high differences in smoking habits between the cohort in study and the general population.⁶ In order to the high quality of mesothelioma case definition by COR-ReNaM,⁵ some considerations about the use of different health outcomes are still needed. In addition to mortality, the analysis of hospitalization data allowed the detection of both diseases with a high survival rate, such as asbestosis, and of subjects with lethal diseases, before the occurrence of the death. The latter issue could be particularly relevant for diseases with long periods of latency, such as cancer of lungs and mesothelioma. Moreover, the data drawn by COR Sicily provided a high quality in mesothelioma cases definition.

Mortality and hospitalization data are confirmed by COR. All subjects deceased from MN of pleura were identified by the COR database, having a diagnosis of mesothelioma, while the only one subject deceased from MN of peritoneum in 2018 was not detected by COR. The subjects that were identified by COR Sicily with a diagnosis of mesothelioma, had deceased during 1986 to 2018 from MN of pleura in agreement with COR, except for one of the workers who died from circulatory diseases. The two subjects hospitalized from MN of pleura and the other one from MN of peritoneum (nosological codes including mesothelioma) were also found in COR database.

The agreement between the different health information systems gives us confidence in the study findings, even if referred to different observation periods.

Due to the availability of periods that were limited the analyses were restricted to the subjects of the cohort alive at the beginning of each observation period, then the so called "immortal bias" could have been introduced.¹¹ Considering this bias, an under estimate of the observed risks cannot be excluded.

Moreover, the number of subjects constituting the cohort does not allow specific analyses of temporal trend risks by duration of work or TSFE, considered in recent papers.^{6,7,14}

The stratified analyses by different year-class periods, even if they were based on low number of expected cases, are compatible with the temporal trends found in the above mentioned pooled analyses of asbestos exposed cohorts.^{6,7} The Authors of the pooled analyses found increases of mortality from asbestosis and pleural cancers after 10-19 years of exposure duration, similarly in our cohort where who deceased from pleural malignant neoplasms

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had worked in Sacelit for more than 10 years (20-39 years) and who deceased from asbestosis for 10-39 years. About the TSFE, Ferrante and colleagues found excesses of lung cancer mortality after 19 years of TSFE, increasing up until 30-39 years of latency. Our results are similar, given that the decedents from this disease were observed in TSFE classes for 20 years or more.

In order to the mortality from pleural cancers, increasing SMRs until 30-39 years of TSFE were reported and we also found decedents in the 40-50 years TSFE class. Decedents from asbestosis in our cohort occurred after 40 years TSFE, and the pooled analysis observed the first cases after 10-19 years TSFE. The subjects with a diagnosis of mesothelioma occurred after 30-50 years of TSFE and had worked in Sacelit for a period longer than 20 years.

The inclusion of the present cohort in future meta-analyses of asbestos exposed cohorts could represent an opportunity to increase our knowledge about the temporal trends of these diseases.

Another limit of the present study is the lack of information about the job title of each worker, which made it impossible to estimate the individual asbestos exposure levels and to evaluate the presence of specific tasks at higher risk. However, considering the information of the former workers Committee about the workplace that reported the lack of well-separated areas for specific work activities, a rather homogeneous exposure level to asbestos fibres could be assumed.¹⁵

CONCLUSIONS

The present study shows a high occurrence of asbestos-related diseases in the cohort of Sacelit workers, in particular among men. The pursuance of the on-going health surveillance plan of workers by the Local Health Authority, included in the Extraordinary Plan of Intervention in the areas of high risk for environmental crisis in Sicily, is particularly appropriated.¹⁶

These results contribute to fill a gap in epidemiological surveillance of former workers in asbestos-cement plants in Italy, at local level, and to update the global estimates of the health impact of occupational asbestos exposure in the world.

The high health impact of asbestos-related diseases observed in the cohort of former workers exposed to asbestos in this setting, even after more than 25 years from the end of production, is consistent with that found in other national and international studies; these results can represent a strong indication for those Countries where asbestos plants are still operating.

Conflict of interest: none declared.

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REFERENCES

- World Health Organization (WHO). Informations about asbestos. Available from: https://www.who.int/ipcs/assessment/public_health/asbestos/en/
- International Agency for Research on Cancer (IARC). Asbestos. In: IARC Monographs on the Evaluation of Carcinogenic Risk to humans. Arsenic, metals, fibres, and dusts. Volume 100C. A review of human carcinogens. Lyon, 2012; pp. 219-309.
- Prüss-Ustün A, Vickers C, Haefliger P, et al. Knows and unknowns on burden of disease to chemicals: a systematic review. *Environ Health* 2011;10:9.
- Fazzo L, Minelli G, De Santis M, et al. Epidemiological surveillance of mesothelioma mortality in Italy. *Cancer Epidemiol* 2018;55:184-191.
- Marinaccio A, Binazzi A, Bonafede M, et al. National Register of Mesothelioma. VI Report. Milano: INAIL, 2018; pp. 1-278.
- Ferrante D, Chellini E, Merler E, et al. Italian pool of asbestos workers cohorts: mortality trends of asbestos-related neoplasms after long time since first exposure. *Occup Environ Med* 2017;74(12):887-98.
- Luberto F, Ferrante D, Silvestri S, et al. Cumulative asbestos exposure and mortality from asbestos related diseases in a pooled analysis of 21 asbestos cement cohorts in Italy. *Environ Health* 2019;18(1):71.
- Zona A, Fazzo L, Binazzi A, Bruno C, Corfiati M, Marinaccio A (eds). SENTIERI- Epidemiological study of residents in National Priority Contaminated Sites: Incidence of mesothelioma. *Epidemiol Prev* 2016;40(5) Suppl 1:1-106.
- Brusco A, Binazzi A, Altissimi A, et al. Occupational diseases in National Priority Contaminated Sites. Milano: Inail, 2019; pp. 1-315.
- Comitato permanente ex esposti amianto e ambiente. Amianto. Le fibre killer di asbesto sono ancora tra di noi. Available from: http://www.comitatoespostiamianto.it/upfiles/kfm/AMIANTO_KILLER_2.pdf
- Fazzo L, Nicita C, Cernigliaro A, et al. Mortality from asbestos-related causes and incidence of pleural mesothelioma among former asbestos cement workers in San Filippo del Mela (Sicily). *Epidemiol Prev* 2010;34(3):87-92.
- Marinaccio A, Binazzi A, Marzio DD, et al. Pleural malignant mesothelioma epidemic: incidence, modalities of asbestos exposure and occupation involved from the Italian National Register. *Int J Cancer* 2012;130:2146-54.
- Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ* 2010; 340:b5087.
- Oddone E, Ferrante D, Tunesi S, Magnani C. Mortality in asbestos cement workers in Pavia, Italy: a cohort study. *Am J Ind Med* 2017;60:852-66.
- Comitato permanente ex esposti amianto e ambiente. Available from: <http://www.comitatoespostiamianto.it/>
- Regione Sicilia. Delibera n. 131, 28 maggio 2015: Piano strutturale degli interventi sanitari nelle Aree a rischio ambientale della Sicilia. Available from: http://www.regione.sicilia.it/deliberegiunta/file/giunta/allegati/Delibera_131_15.pdf