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ENVIRONMENTAL AND OCCUPATIONAL RISK FACTORS AND PREDICTORS OF SURVIVAL AMONG MALIGNANT PLEURAL MESOTHELIOMA PATIENTS

By

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Abstract

Introduction: Malignant pleural mesothelioma (MPM) remains a serious health problem due to the poor outcome of different therapies. In Egypt, it is mainly attributed to an environmental origin with a high incidence in women and young adults. **Aim of work:** To identify risk factors of malignant pleural mesothelioma and to carry out survival analysis for malignant pleural mesothelioma patients attending outpatient clinic of Clinical Oncology department at Ain Shams University hospital. **Materials and methods:** Ninety cases with pathologically confirmed MPM attending the outpatient clinic of clinical oncology department at Ain Shams University hospital were interviewed. Patients in critical conditions who needed hospitalization or palliative treatment were excluded. Included patients were then followed up for two years starting from the date of diagnosis. **Results:** Logistic regression analysis revealed that living in industrial areas, household exposure to asbestos and history of smoking were significant risk factors of MPM. The mean survival duration of all cases was 24.49 months. Cox regression analysis revealed that factors predicting survival were age and gender. The difference in survival between patients treated with different treatment modalities was not statistically significant. **Conclusion:** Environmental and household exposure to asbestos as well as smoking play an important role in occurrence of MPM. Age and gender were significant predictors of survival of patients. Strict measures to reduce pollution and thus rates of MPM should be adopted in addition to community

awareness of the possible risk factors and preventive measures. Moreover, development of a national record system is required to determine the true size and scope of this environmental problem in Egypt.
Keywords: Malignant pleural mesothelioma; Risk factors; Environmental factors; Asbestos and Survival analysis.

Introduction

Malignant mesothelioma is a lethal tumor arising from the mesothelial lining of the pleura, less frequently, from the peritoneal and pericardial serous membranes, or from the tunica vaginalis of the testis (Robinson, 2012). The causal association with asbestos exposure has been demonstrated so far. The International Agency for Research on Cancer confirmed that all forms of asbestos are carcinogenic for humans. It has been intensively used in a number of industrial applications in almost all Western countries between the 1950s and the 1980s due to its high tensile strength , thermal and chemical resistance (Marinaccio et al., 2018). At present, its use is banned in many countries, but it is still used in many places worldwide particularly in developing countries (Kang et al., 2013).

Although mesothelioma is recognized as an occupational disease, living near an industrial or natural source of asbestos or living with a person occupationally exposed to asbestos have also been associated with it (Marinaccio et al., 2012). The long latency period between exposure to asbestos and the onset of mesothelioma, which can range from 15 to 60 years, means that mesothelioma cases will continue to be present (Moore et al., 2008).

The clinical course of mesothelioma is represented by steady deterioration to death over 1 to 2 years and the prospects for curative treatment are not good (Akl et al., 2010). Accordingly, it remains a serious health problem. In addition to the direct costs to the health care system, legal claims represent a significant economic burden (Balla et al., 2008).

The incidence rates are predicted to increase dramatically in developing countries due to poor regulation of asbestos use (Awad, 2011). In Egypt, malignant pleural mesothelioma (MPM) is mainly attributed to environmental exposure to asbestos (Ismail et al., 2006). There are 14 factories using

asbestos in Egypt (Akl et al., 2010). These factories contaminate an area of approximately 5–7 km in radius, which explains the high incidence of mesothelioma near industrial areas. Accordingly, the Ministerial Council decided to ban asbestos imports in 2004 (Anwar et al., 2014).

Epidemiological data on mesothelioma cases from the hospital-based cancer registry of the Clinical Oncology Department of Ain Shams University teaching hospital for the year 2013 revealed that 3.9% of all registered cancer cases at the department were MPM cases, about 60 years old, 65% of them were females and 35% were males (Furuya et al., 2014).

In most disease models, survival analyses are the gold standard for measuring the efficacy of medical interventions such as therapeutics or vaccines. In Egypt, the survival age varied between 6 to 15 months with median survival of approximately 1 year from diagnosis (Awad, 2011).

Advanced age, poor health condition, male sex, and sarcomatoid histological subtype are all poor prognostic factors. However, there is no consensus regarding treatment (Rascoe et al., 2012).

Attempts to establish national Cancer Registry Program of Egypt was initiated in 2008 in the Governorate of Aswan through hospital-based registries (Ibrahim et al., 2014). Due to the absence of a comprehensive national population-based cancer registry in Egypt, there is scant epidemiological data on MPM incidence (Adel et al., 2011).

Studying the epidemiology of MPM through hospital-based registries in Egypt is mandatory as well as the factors that affect the survival of patients.

Aim of work

To identify risk factors of malignant pleural mesothelioma and to carry out survival analysis for malignant pleural mesothelioma patients attending outpatient clinic of Clinical Oncology department at Ain Shams University hospital.

Materials and methods

- Study Design: The study was designed in two phases:

- Phase I: A case control study design was applied to identify the risk factors of malignant pleural mesothelioma.
- Phase II: A cohort study was used to carry out survival analysis

where cases who agreed to fill in the questionnaire were followed for two years starting from date of pathological confirmation of diagnosis.

- Place and duration of the study: Cases were selected from the Clinical Oncology outpatient clinic specialized in lung and genitourinary tumors at Ain Shams University hospital. The clinic was open 5 days per week where approximately 3 to 4 cases of MPM were seen every week.

Data collection started in April 2014 and continued till July 2015. Cases were collected retrospectively from medical records; the first case was diagnosed in the 30th of May 2012 and the last case included in the study was diagnosed in the 13th of July 2013.

- Study sample:

Most of the patients received chemotherapy in the form of cycles, sometimes patients received additional radiotherapy sessions, and decortication surgery was done for a few cases. Patients with pathologically confirmed malignant pleural mesothelioma were included in the first phase of the study and hospitalized patients who were in a critical condition were excluded. The control group was recruited from relatives of inpatients in Obstetrics and Gynecology hospital at Ain Shams University hospital.

A sample size of 90 cases of mesothelioma was used to carry out the survival analysis based on a Cox regression of the log hazard ratio on a covariate with a standard deviation of 2 achieves 80% power at a 0.05 significance level to detect a regression coefficient equal to 0.3. It was adjusted since a multiple regression of the variable of interest on the other covariates in the Cox regression was expected to have an R-Squared of 0.5. A similar number of controls, matched for age and gender, were included in the study. This sample size was suitable to test an Odds Ratio of at least 2 if the exposure in the control group ranges from 0.2 to 0.7 (Schoenfeld, 1983).

The clinic was visited three randomly selected days per week. All patients attending the clinic and fulfilling the criteria were enrolled in the study after agreeing to participate. The cases and controls were matched for age and gender.

- Study methods:

- An interview questionnaire was

developed by the researcher to study the epidemiology of malignant pleural mesothelioma. It included both open-ended and closed-ended questions about sociodemographic data including, gender and residence details to determine environmental exposure to asbestos (place, materials used in building, nearby factories), occupational history to determine occupational exposure to asbestos, history of living with someone who works in high risk occupation to determine domestic exposure to asbestos, and family history of the disease.

A pilot study was done to assess validity, acceptability and comprehension of the questionnaire and necessary requirements were done.

- Patients' medical records were used to extract other data regarding method of diagnosis and lines of treatment.

- A follow-up study was then performed to carry out survival analysis,. All participating patients in phase I (90) were included in the survival analysis. Survival was measured from the date of diagnosis. All the patients were followed up for a minimum period of 2 years or until death where follow-up was done during the patients' visits to the outpatient clinic and through mobile phone calls. The overall survival was defined as the interval between the date of diagnosis and death or date of last follow-up.

Consent

Informed consents were obtained from all participants and confidentiality of data was guaranteed.

Ethical approval

Research conduction approval was obtained from Ain-Shams University Ethical Committee. Administrative approval was also obtained.

Data management

Following data collection, it was entered using portable SPSS version18 (Statistical Package for the Social Sciences; SPSS Inc., Chicago, IL, USA) and suitable statistical tests were applied. A p-value of 0.05 was chosen as a level of significance throughout the study.

Results

The study included 180 subjects divided into 2 groups; 90 cases from the Clinical Oncology outpatient clinic at Ain Shams University hospital, diagnosed as MPM on a pathological basis and 90 matched controls. The mean age of cases was 54.72 ±10.95 years ranging from 28 to 85 years. About 53.3% of them were males with a male to female ratio 1.4:1. Regarding the control group, their mean age was 52.04±11.93 with the same male to female ratio as cases. There was no statistically significant difference between cases and controls regarding their age and gender (p>0.05).

Forty-one cases (45.6%) lived in Shoubra El-Khaymah (Qalyubia), 6 cases (6.7%) lived in Helwan district which are considered major industrial areas, while 5 cases (5.6%) lived in Giza governorate and the remaining 38 cases (42.2%) lived in other governates. Fifteen cases (16.7%) worked in asbestos-related occupations (high risk occupations) as plumbers, construction workers, electricians and mechanics.

Regarding the control group, 65.6% of them lived in governorates away from well-known industrial areas. Only 10% of controls lived near industrial areas and 12% of them worked in asbestos-related occupations (high risk occupations).

Table 1: Logistic regression model for risk factors of malignant pleural mesothelioma.

	B	Sig.	Odds ratio	95% CI	
				Lower limit	Upper limit
Residence#		**0.001****			
Helwan	-0.332	0.550	0.718	0.241	2.134
Shoubra El-Khaymah	1.505	**<0.001****	4.504	2.055	9.875
Giza	0.983	0.185	2.672	0.624	11.432
History of smoking	1.241	**0.001****	3.460	1.658	7.219
Live with somebody working in high risk occupation	1.476	**0.004****	4.377	1.607	11.916

#: Reference group = other governorates

**: Highly statistically significant (p<0.01)

To identify risk factors of malignant pleural mesothelioma, univariate analysis (chi square test) was performed first to identify the associated factors, followed by logistic regression analysis including only statistically significant factors identified by univariate analysis. It revealed that risk factors of malignant pleural mesothelioma were living in an industrial area as Shoubra El-Khaymah in Qalyubia governorate (OR=4.50, CI=2.06-9.88), living with someone who works in a high-risk occupation as plumbers, construction workers, electricians and mechanics (OR=4.377, CI=1.61-11.92) and history of smoking (OR=3.46, CI=1.66-7.22) (Table 1).

There was no statistically significant difference between cases and controls regarding occupational exposure to asbestos (X^2 =0.969, p value>0.05). About 63.3% of cases were exposed to x-ray for diagnostic purposes, however, there was no statistically significant difference between cases and controls regarding exposure to radiation (X^2=0.024, p value>0.05). Moreover, long term exposure to radiotherapy was not reported by any of the cases. There was no statistically significant difference between cases and controls regarding family history of the disease (X^2=1.006, p value>0.05). Only one case reported family history of malignant pleural mesothelioma (Data are not t

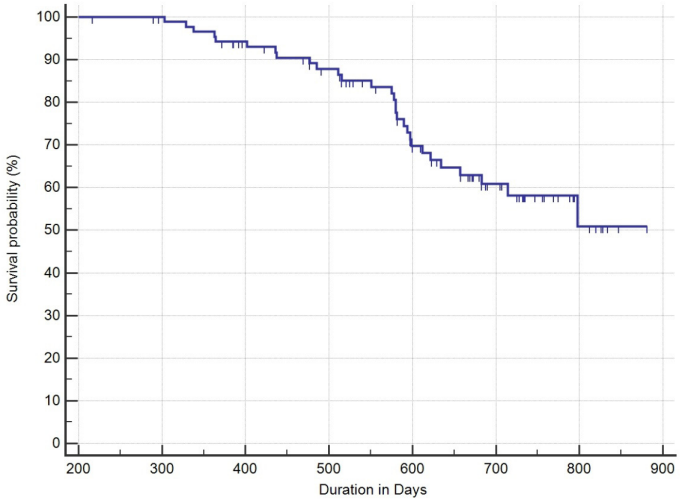

Figure 1: Kaplan Meyer survival analysis for all cases (Mean and median survival for all cases)

Survival curves were computed according to the method of Kaplan-Meier. Death was recorded in 29 patients in this study (11 males and 18 females). The mean survival duration of all cases (No=90) was 24.49 months (23.1-25.9 months) (Figure 1).

Table 2: Cox survival models of multivariable analysis.

Variables	Reference group	Wald	df	Sig.	Hazard ratio	95% CI for Hazard ratio	
						Lower	Upper
Gender	Male	5.157	1	**0.023***	2.469	1.132	5.385
Age	≤50	14.418	1	**<0.001****	1.079	1.037	1.122
Treatment #	Chemotherapy	0.000	1	0.989	1.009	0.282	3.607
	Radiotherapy	0.822	1	0.365	1.473	0.638	3.405

#: Reference group = the group receiving both chemotherapy and radiotherapy (combined)
*: Statistically significant (p<0.05)
**: Highly statistically significant (p<0.01)

Multivariate analysis of prognostic factors affecting survival of patients showed that younger age (p<0.001, Hazard ratio=1.08, 95% CI=1.04-1.12) and female gender (p=0.02, Hazard ratio=2.47, 95% CI=1.13-5.39) are significantly associated with longer survival of patients, while therapeutic plan was not. Means of survival duration were 24.01, 24.21, 21.83 months for patients treated with chemotherapy, radiotherapy and combined radiotherapy and chemotherapy respectively (Table 2).

Discussion

The mean age of cases in the current study was 54.72 ±10.95 years with nearly same proportion of both genders which is not far from those reported by Adel et al. (2011) where the mean age of their patients was 52.1 years and a male to female ratio of 1:1 was reported. Successful matching was indicated by the non-significant difference between cases and controls regarding their age and gender.

Residential exposure plays an important role in the current study where living in a major industrial area as Shoubra El-Khaymah in Qalyubia governorate was considered a risk factor of MPM (Table 1). This finding

agrees with the results of another Egyptian study done by Gaafar (2007), who found that 64.7% of cases (35.6% in Shoubra El-khaymah, 23.6% in El-Maasara and surrounding area, 5.2% in El Zytoon, and 0.5% in other areas) came from industrial areas.

Living with someone who works in a high-risk occupation was another risk factor which agreed with Marinaccio et al. (2012) who reported that living near an industrial source of asbestos or living with a person occupationally exposed to asbestos are associated with MPM.

The finding detected in our study that smoking was considered as a risk factor for MPM (Table1) contradicts with Cvitanović et al. (2003), in a study done in Croatia, who couldn't find any association between malignant pleural mesothelioma and smoking habit (p=0.617). In general, the role of cigarette smoking in the development of malignant mesothelioma has not been clearly established.

Contrary to Aguilar-Madrid et al. (2009), who found that occupational exposure to asbestos played an important role in developing MPM, representing 80.6% among cases and 31.5% among controls and the difference was statistically significant, the current study results could not find any statistically significant association between occupational exposure to asbestos and the development of MPM. Moreover, in a model performed by Hernández-Solís et al. (2013) that included family history of cancer, smoking, exposure to wood smoke and asbestos, of which, asbestos exposure was statistically significant with an odds ratio of 3.083.

In the current study, environmental non-occupational asbestos exposure was a main feature in Egyptian victims after the national legislation of banning the use of asbestos in industry which makes direct occupational exposure to asbestos rare nowadays. However, some small factories illegally continued to use asbestos fibers in their industry. Non-occupational cases of MPM living in areas contaminated by asbestos fibers has been well documented in several epidemiological studies including cases series, case-control studies, and a cohort study (Proietti, et al., 2006). Robinson (2012) in his study concluded that an increasing proportion of MPM is contributed to non-occupational asbestos exposure. In Germany, Karabin-kehl et al. (2013) stated that, although it has been almost 20 years

after the ban of asbestos in his country, yet incident cases were still occurring. This may be due to the long duration between exposure and appearance of the tumor which may extend to more than 40 years (Robinson, 2012) or old asbestos products which decayed by time leading to environmental pollution. In addition, improper disposal of asbestos wastes may lead to dispersion of asbestos fibers which has been confirmed by Eldin et al. (2005) who investigated asbestos fiber count in an area 0.5-7 km surrounding Sigwart El-Maasara company, asbestos fibers were found in the range of 0.002-3.02 f/cc with the highest count (3.02 f/cc) at Autostrade road.

In general, MPM has a poor prognosis. The mean survival duration of MPM in the current study was 24.49 months (Figure 1). Some studies reported similar survival duration as an Italian study by Rea et al. (2007), where the median survival was 25.5 months. Others reported less survival duration as Bagheri et al. (2011) who found a mean survival of 10.5 months and more recently, Kucukoner et al. (2014), detected an average survival of 14.8 months. In addition, Marshall et al. (2015), in their study, concluded that survival of MPM patients is still poor and typically around 1 year. The relatively longer survival in the current study may be explained by the difference in selection criteria where patients in critical condition who need hospitalization or palliative treatment were excluded.

Age and gender were nominated as the prognostic factors affecting the survival of MPM cases (Table 2). This finding confirms the results of a recent study to identify factors associated with survival of patients in New South Wales. It included age and gender among the independent prognostic factors of MPM, where longer overall survival was associated with age <70 years old (13.5 versus 8.5 months; P<0.001) and female gender (12.0 versus 9.9 months; P<0.001) (Linton et al., 2014). Similarly, Taioli et al. (2015) investigated 14,228 pathologically diagnosed MPM patients and found that female gender and young age are two important predictors of survival in those patients, in addition to early stage of the disease, and treatment with surgery. Similarly, Sugarbaker et al. (2011), in their study of the clinical and pathological features of three-year survivors of MPM, found that female gender and younger

age were two independent predictors of longer survival. Furthermore, in a large population-based study in Italy by Montanaro et al. (2009), multivariate analysis showed that younger age at diagnosis and epithelioid histopathological type were associated with significantly reduced hazard ratios, however, predictive effect of female gender was of border-line statistical significance. The same study stated that treatment was not associated with a statistically significant improvement in survival.

In the current study, different therapeutic plans didn't significantly affect survival duration (Table 2). This finding agreed with the results of a Japanese retrospective study which compared different treatment modalities and found that there is no statistically significant difference in survival between patients receiving pemetrexed and those receiving other chemotherapy agents (Higashiguchi et al., 2012).

Moreover, Bagheri et al. (2011) reported that while there was a significant relationship between survival and age, there was no significant relationship between survival and therapeutic plan. On the contrary, Akl et al. (2010) reported statistically significant differences in survival time between patients subjected to different surgery, supportive treatment, chemotherapy and combined (chemotherapy and surgery). This controversy can be explained by the possible influence of selection bias where patients who undergo surgery, radiotherapy, chemotherapy or a combination, are fit to do so, and thus have better prognosis than those who do not, regardless of the anti-tumor effect of the therapy (Richards, 2017). However, randomized controlled clinical trials can clearly demonstrate the survival benefit for any mode of therapy or for combination therapy better than observational studies.

Conclusion

In conclusion, MPM is a growing health problem that needs more attention, despite banning the use of asbestos, still there are many cases of MPM were diagnosed at Oncology centers. This may be due to the long duration between exposure and appearance of the tumor or the presence of asbestos products which decayed by time and lead to environmental pollution. In Egypt, environmental and household exposure to asbestos plays an important role in the occurrence of malignant pleural mesothelioma which

is mainly concentrated in areas of high environmental pollution with asbestos.

Recommendations

Strict measures to reduce pollution and thus rates of MPM should be adopted in addition to community awareness of the possible risk factors and preventive measures. It is also recommended to encourage smoking quitting programs and to increase the community awareness of the long-term dangers of smoking. Moreover, development of a national record system is required to determine the true size and scope of this environmental problem in Egypt.

Conflict of interest

No conflict of interest has been declared.

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