PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (http://bmjopen.bmj.com/site/about/resources/checklist.pdf) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers’ comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Clustering of malignant pleural mesothelioma in asbestos factories: a subgroup analysis in a 29-years follow-up study to identify high-risk industries in Taiwan</th>
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<tr>
<td>AUTHORS</td>
<td>Lee, Lukas Jyunh-Hsiarn; Lin, Cheng-Kuan; Pan, Chih-Hong; Cheng, Yawen; Chang, Yu-Yin; Liou, Saiou-Hsing; Wang, Jung-Der</td>
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VERSION 1 – REVIEW

<table>
<thead>
<tr>
<th>REVIEWER</th>
<th>Mikio Okazaki</th>
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<td>REVIEWER</td>
<td>Center of Chest Medicine and Surgery, Ehime University, Japan</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>09-Jan-2018</td>
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<tr>
<td>GENERAL COMMENTS</td>
<td>The authors demonstrated that workers in asbestos cement, thermal insulation petrochemical factories and shipyard were at significantly increased risk for MPM by a retrospective cohort of workers employed in asbestos industries. The authors recommend to establish a medical screening program in conclusion, but it has already been well known that asbestos exposed workers require the medical check programs. The authors should describe clearly what are the new findings. Furthermore, more MPM patients may be needed to elucidate the research question clearly, because there are only 18 MPM patients in the study.</td>
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<th>REVIEWER</th>
<th>Bushra Mina, MD</th>
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<tr>
<td>REVIEWER</td>
<td>Lenox Hill Hospital New York, USA</td>
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<tr>
<td>REVIEW RETURNED</td>
<td>17-Jan-2018</td>
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<tr>
<td>GENERAL COMMENTS</td>
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<td>REVIEWER</td>
<td>University of Sydney, Australia</td>
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<tr>
<td>REVIEW RETURNED</td>
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Taiwan. There is no doubt this is a major concern for exposed workers.

The manuscript is very well written, and the results clearly presented.
I have very little to add to improve this manuscript other then two main points:

1. The authors refer to the possibility of annual screening CT scans, citing work in lung cancer screening. There is little data to support annual screening of asbestos exposed individuals. In NSW, Australia, exposed workers have a one-off chest x-ray and are only assessed again if symptomatic. I wonder if the authors may consider the importance of screening for lung cancer itself, rather than MPM given the increased risk of this tumour in asbestos exposed people? Furthermore, any screening program should be set-up to evaluate the effectiveness of this at early detection and treatment.

2. In Australia, UK, etc, there is a recognised increased risk of MPM in the spouses (usually wives) of asbestos exposed workers who were exposed while washing clothing. Is this likely to be a problem in Taiwan? Also, family members of workers have been exposed by to it yourself repairs and building at home, when workers took asbestos containing materials home to use themselves. Is this likely to be a problem in Taiwan. Could you perhaps includes some suggestions as to how this could be addressed through education and screening of exposed workers.

Finally I noted some highlighting on Table 2, is this intended to be there?

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REVIEWER
Wei-Ting Hwang
University of Pennsylvania Perelman School of Medicine, USA

REVIEW RETURNED
06-Apr-2018

GENERAL COMMENTS
This manuscript reported analysis results of a retrospective cohort of workers with occupational exposure of asbestos during the period of 1950-1989 and compared the incidence of malignant pleural mesothelioma (MPM) with general Taiwanese population. Overall the manuscript has a straightforward objective and the methodologies used were in general appropriate for this objective. However, all sections of the manuscript can be further developed. Some areas for improvement are noted below.

1. Additional information should be provided in the Introduction section including the history of asbestos use (industry and non-industry) in Taiwan (e.g., when was the asbestos industry started and ended, when was it ban for its use and/or manufacturing, etc.) and general epidemiology of MPM in Taiwan (e.g., incidence/prevalence of MPM over the time, trends, general characteristics of those affected by MPM, etc)

2. More information on this retrospective cohort can be provided. Does it capture all the workers as it intends to capture? If not, what’s the participation rate? What were the recruitment methods to enroll the subjects into this cohort? Why the time period for this cohort is relevant here?

3. It is unclear why the study needs to exclude those subjects that works in the factories that did not have produced any MPM cases. At least the information on what types of factories and locations, sample sizes and cumulative person-year should also be provided.
4. It is also unclear why the analysis unit for computing RR would be the individual factories if it was to show geographic clustering. Using the data to inform clustering and then identify which types of exposures are possible (factory nearby) may be more relevant. Alternatively, one can consider combining and stratifying factories according to categories (E.g., shipbuilding).

5. The use of the relative risk (RR) is ok for the purpose of this study, but when comparing to a reference population, it is more commonly to use standardize incidence rate (SIR) instead. This statistics can also properly be adjusted for different age and sex distribution.

6. It is not clear why 20 years was selected to cut off those subjects without MPM while MPM cases with short follow-up were still included in the analysis. Sensitivity analysis using different years (E.g., 30, 40, 50) may be needed. Conceptually all workers should contribute to person-years at risk; exclusion for those MPM cases with short follow-up may be more relevant because the disease may be due to exposure outside/prior to contact the factory.

7. Authors noted that the rates done in this report was not age and sex adjusted. It is not clear why the authors did not do the adjustment. They should have the data to such adjustment.

8. Can also include discussion of the changing diagnosis criteria for MPM over time and its implications as MPM may be not diagnosed as mesothelioma in early days.

9. Also should include discussion on possible environmental or non-occupational exposure to asbestos to those MPM cases.

10. Table 1 and Table 2 contain similar/overlapping information and can be combined.

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1  
Reviewer Name: Mikio Okazaki  
Institution and Country: Center of Chest Medicine and Surgery, Ehime University, Japan

The authors demonstrated that workers in asbestos cement, thermal insulation petrochemical factories and shipyard were at significantly increased risk for MPM by a retrospective cohort of workers employed in asbestos industries. The authors recommend to establish a medical screening program in conclusion, but it has already been well known that asbestos exposed workers require the medical check programs. The authors should describe clearly what are the new findings. Furthermore, more MPM patients may be needed to elucidate the research question clearly, because there are only 18 MPM patients in the study.

Response: Thank you for the constructive comment. For the last 2 decades, asbestos company managers have raised questions all the time to scholars and governmental officials about whether there is increased cancer in all different kinds of asbestos manufacturing processes because of only fragmentary and sporadic reports. And their lobby to the Legislative Yuan (congress in Taiwan) have been very heavy to resist the total ban for asbestos. What's new in this study is that we are the first in Taiwan to provide evidence showing that there are significant increases of malignant pleural mesothelioma (MPM) comprehensively for different types of asbestos manufacturing processes, including asbestos cement, thermal insulation, and shipyard. Following your kind advice, we have described the important findings in Taiwan clearly in the revised manuscript as below:

Abstract Conclusion: “This nationwide study in Taiwan comprehensively show different asbestos manufacturing processes, including asbestos cement, thermal insulation, and shipbuilding industries, were at significantly increased risks for MPM.” (Page 2, lines 18-20)
Discussion, the 1st paragraph: To the best of our knowledge, this is the first retrospective cohort study of the nationwide asbestos related factories in Taiwan to identify the high-risk industries. It highlights that workers employed in asbestos cement, thermal insulation, shipbuilding industries were at significantly increased risks for MPM. (Page 9, lines 17-20)

Because of the relatively long latency period of MPM, we observed only 18 cases in this study through linkage with the national cancer registry from 1950 to 2009 using the cohort established by labour insurance records from 1980-1989. We will conduct a follow-up study to extend the follow-up period up to 2014 to include more incident cases of MPM in the near future.

Reviewer: 2
Reviewer Name: Bushra MIna, MD
Institution and Country: Lenox Hill Hospital, New York, USA

The articles address a concern regarding occupational hazard in Taiwan. The study mirror previous epidemiological publication addressing the same concern in different countries such as Italy and UK. It also highlights the need to have extend health surveillance for high risk factory workers.

Response: Thank you very much for the positive comment.

Reviewer: 3
Reviewer Name: Haryana Dhillon
Institution and Country: University of Sydney, Australia

This manuscript provides a very clear, succinct and accessible report of the estimated risks of malignant pleural mesothelioma (MPM) in factory workers with possible exposure to asbestos in Taiwan. There is no doubt this is a major concern for exposed workers.

The manuscript is very well written, and the results clearly presented.

Response: Thank you very much for the positive comments.

I have very little to add to improve this manuscript other then two main points:

1. The authors refer to the possibility of annual screening CT scans, citing work in lung cancer screening. There is little data to support annual screening of asbestos exposed individuals. In NSW, Australia, exposed workers have a one-off chest x-ray and are only assessed again if symptomatic. I wonder if the authors may consider the importance of screening for lung cancer itself, rather than MPM given the increased risk of this tumour in asbestos exposed people? Furthermore, any screening program should be set-up to evaluate the effectiveness of this at early detection and treatment.

Response: Thank you for the constructive comment. We agree with you that there is little data to support annual screening of asbestos exposed individuals using chest X-ray, as the same opinion of the consensus report: Helsinki criteria 2014. Evidence has accumulated to support CT screening is effective in asbestos-exposed workers. A systematic review with meta-analysis published in 2014 concluded CT screening in asbestos-exposed workers as being effective in detecting asymptomatic lung cancer, with a prevalence of all lung cancers detected of 1.1%. A recent prospective study of 2,132 Japanese asbestos-exposed workers documented low dose CT identified 45 cases of lung cancer (2.3%) and 7 cases of MPM (0.3%).
Following your constructive advice, we have revised the manuscript as follows:

“we recommend setting up a national long-term surveillance system for the early detection of ARDs in Taiwan, which is in accordance with the policy recommendations of the 18th Collegium Ramazzini statement in 2016. Screening program with computed tomography (CT) may be a potential option for the asbestos-exposed workers with sufficiently high risk of lung cancer, as suggested by the 2014 Helsinki criteria. A systematic review with meta-analysis published in 2014 concluded CT screening in asbestos-exposed workers as being effective in detecting asymptomatic lung cancer, with a prevalence of 1.1%. A recent prospective study of 2,132 Japanese asbestos-exposed workers reported that low dose CT identified 45 cases of lung cancer (2.3%) and 7 cases of MPM (0.3%). However, further cost-effectiveness analysis on CT screening is needed for categorizing high-risk groups.” (Page 13, lines 14-24)

2. In Australia, UK, etc, there is a recognised increased risk of MPM in the spouses (usually wives) of asbestos exposed workers who were exposed while washing clothing. Is this likely to be a problem in Taiwan?

Also, family members of workers have been exposed by do-it-yourself repairs and building at home, when workers took asbestos containing materials home to use themselves. Is this likely to be a problem in Taiwan?

Could you perhaps includes some suggestions as to how this could be addressed through education and screening of exposed workers.

Finally I noted some highlighting on Table 2, is this intended to be there?

Response: Thank you for the comments. Yes, environmental and para-occupational exposure to asbestos is also a public health concern in Taiwan. Based on a case series of 93 MPM patients at the National Taiwan University Hospital, a medical center in northern Taiwan [Wu TH et al., 2018], the recorded occupational asbestos exposure is only 23%. There were several female cases without reported occupational exposure to asbestos in this case series. For example, one female patient of MPM’s husband was a worker at an automobile repair and was exposed to asbestos fibers from the task of replacing brake linings that contained asbestos. This female MPM patient was likely exposed to asbestos from washing her husband’s clothing.

There is limited literature available to find the case of MPM whose exposure source related to do-it-yourself repairs and domestic exposure. However, based on the clinical experiences of recognizing occupational cancer of Dr. Lukas JH Lee, there were two cases of suspected asbestos-related lung cancer whose exposure scenario to asbestos dusts were quite similar. A 46-year-old man with stage VI lung adenocarcinoma, former smoker with 13.5 pack-years, had domestic exposure to asbestos dusts at age 15 from dry wall demolition during home re-modeling, and 6-month part-time job of cleaning and assisting in painting during home renovation when he was 30 year old. Another 49 year-old female patient with suspected asbestos-related lung cancer had domestic exposure to construction dusts from her home where her family has operated a building materials company, selling asbestos cement slate and tile.

Your advice is highly appreciated and we have added suggestions regarding education and screening of exposed workers as follows:

“In addition to occupational exposure, environmental and para-occupational exposure to asbestos is also a public health concern in Taiwan. We suggest that more resources should be invested in education of the general public and workers concerning the long-term health risks from asbestos exposure, and the existing asbestos in constructed buildings and environments should be labelled. Family members of asbestos workers could have para-occupational or domestic exposure, for example while washing contaminated clothing, and they must be educated to take precautionary procedures. Since environmental exposure to asbestos has induced the so-called third wave of
asbestos related diseases, the potential source of asbestos in place should be identified before
demolition and/or home renovation. Do-it-yourself asbestos removal is discouraged, and it is
recommended that licensed specialist firms are called in if any suspected asbestos-containing
material existed in the buildings. To increase public awareness of the risks of asbestos and to
promote prevention among the general public in Taiwan, there is “Asbestos Hazards Information
Section” webpage compiled by Taiwan EPA.” (Page 11, lines 8-20)

Finally, thanks for your careful reading. The highlighting in Table 2 has been deleted in the revised
manuscript.

10.1016/j.jfma.2018.04.001

Reviewer: 4
Reviewer Name: Wei-Ting Hwang
Institution and Country: University of Pennsylvania Perelmen School of Medicine, USA

This manuscript reported analysis results of a retrospective cohort of workers with
occupational exposure of asbestos during the period of 1950-1989 and compared the
incidence of malignant pleural mesothelioma (MPM) with general Taiwanese population.
Overall the manuscript has a straightforward objective and the methodologies used were in
general appropriate for this objective.

Response: Thank you for the positive comment.

However, all sections of the manuscript can be further developed. Some areas for
improvement are noted below.

1. Additional information should be provided in the Introduction section including the
history of asbestos use (industry and non-industry) in Taiwan (e.g., when was the
asbestos industry started and ended, when was it ban for its use and/or manufacturing,
etc.) and general epidemiology of MPM in Taiwan (e.g., incidence/prevalence of MPM
over the time, trends, general characteristics of those affected by MPM, etc)

Response: Thank you for the constructive comments. Following your kind advice, we have added the
following two paragraphs in the revised Introduction section.

(History of asbestos use in Taiwan)
“Taiwan used to be a country with asbestos mining and extensive import activities for manufacturing.
Wu HYJ et al. recently described the history of the asbestos use regulation process in Taiwan and the
associated factors leading to the total asbestos ban in 2018. The domestic asbestos mining industry
started from 1937 and ended its operation in 1985. Shipbreaking began in 1949, and it grew in the
1960s. During 1977-1988, Taiwan became the world's largest shipbreaking nation with approximately
65% of the obsolete ships in the world, which declined and ended operation in 1993. The majority of
asbestos used in Taiwan was imported, with the amount rising significantly in the mid-1970s and
peaking around 40,000 tons per year in the mid-1980s and then falling significantly in the early 1990s.
Most asbestos raw materials were consumed in industrial sectors: asbestos cement, abrasion
resistant products, insulation, textiles, and ships. A previous survey of occupational asbestos
exposure found many workplaces exceeding the permissible exposure level. The asbestos
manufacturing industries began to decrease from 1989 after enactment of Toxic Substances Control
Act by the Taiwan Environmental Protection Administration (EPA), which banned use of asbestos in
construction materials, including asbestos plate, pipe, and cement, and fiber cement boards (from
2008)15. Beginning in 2018, asbestos use is forbidden in all manufacturing in Taiwan. Taiwan is the
62nd country to implement a national policy on the total asbestos ban.” (Page 4, lines 17-25; page 5, lines 1-7)

(General epidemiology of MPM in Taiwan)
“...The age-adjusted mortality rate of malignant mesothelioma (MM) in Taiwan was 1.14 cases per million per year with an increasing trend for both genders. The average annual incidence of MPM increased from 0.26 per million during 1980-1989 to 2.34 per million during 2005-2009. The trend is corroborated by 93 MPM cases diagnosed during 1977-2016 in a medical center in northern Taiwan. The health impacts from MPM were estimated to be on average 18.2 years of life lost compared with the general population, and reimbursement of lifetime healthcare expenditure by the National Health Insurance was $ USD 29,400with a 3% annual discount rate.” (Page 5, lines 8-14)

2. More information on this retrospective cohort can be provided. Does it capture all the workers as it intends to capture? If not, what’s the participation rate? What were the recruitment methods to enroll the subjects into this cohort? Why the time period for this cohort is relevant here?

Response: Thank you for the comment. The details of establishing this retrospective cohort were described in our previous work [Lin CK, et al. 2015], which mentioned “Asbestos-related factories were registered and categorized into seven groups by the Taiwan EPA to produce a roster profile of asbestos-related institutions. The roster profile includes the variables of value added tax (VAT) number, industrial classification, industrial code, industry name, industry address, contact phone number, main products, raw materials, industry registry, and corporation registry.” The recruitment was based on the records of labor insurance, and workers who once worked in the asbestos-related industries registered by Taiwan EPA were included as the occupational cohort. The labor insurance in Taiwan used to cover all the workers in the companies with more than five employees, and the database of labor insurance is comprehensive in recording the employment periods of each participant. Once a subject was included in the occupational cohort, the lifelong working history can be traced by the labor insurance if he or she is in insured status. Thus, the cohort captured all the workers insured by labor insurance and who had worked in relatively medium and large factories, but not included those uninsured, such as temporary labors, or those who have been employed in small-scale enterprises with less than five employees.

We have raised the issue in the discussion section: “Historically, many asbestos workers in Taiwan have been temporary labors, especially in the construction industry, or have been employed in small-scale enterprises, where occupational health is often loosely regulated and audited”. As we are focusing on the “MPM clustering” in Taiwan by epidemiological approach, those small-scale enterprises were beyond the scope of our current study.

We have briefly summarized the recruitment methods as follows: “The recruitment was based on the records of labor insurance, and workers who once worked in the asbestos-related industries registered by Taiwan EPA were included as the occupational cohort. The labor insurance in Taiwan used to cover all the workers in the companies with more than five employees, and the database of labor insurance is comprehensive in recording the employment periods of each participant. Thus, the cohort captured all the workers insured by labor insurance, but did not include those uninsured, such as temporary labors, or those who have been employed in small-scale enterprises with less than five employees.” (Page 6, lines 8-14)

(Why the time period for this cohort is relevant here?)
The time period of the cohort is relevant because by following from 1980 to 2009 through linkage with Taiwan Cancer Registry for the occupational cohort established from 1950, all subjects would have at least 20 years to maximal 60 years of follow-up to be identified as asbestos-related MPM given a long latency period.
3. **It is unclear why the study needs to exclude those subjects that works in the factories that did not have produced any MPM cases. At least the information on what types of factories and locations, sample sizes and cumulative person-year should also be provided.**

Response: Thank you for the comment. The data of types of asbestos factories, sample sizes and total (cumulative) person-years are presented in Table 1, and Supplementary Table 1 of the revised manuscript.

4. **It is also unclear why the analysis unit for computing RR would be the individual factories if it was to show geographic clustering. Using the data to inform clustering and then identify which types of exposures are possible (factory nearby) may be more relevant. Alternatively, one can consider combining and stratifying factories according to categories (E.g., shipbuilding).**

Response: Thank you for the comment. For this study, we aim to identify high-risk asbestos factories and industries first so that we shall be able to answer the managers of asbestos companies who have kept on raising questions of evidence of asbestos-related diseases for different manufacturing processes. The possible geographic clustering of MPM near the factories would be one of our future studies. Nonetheless, we have taken your suggestion to combine shipbuilding, and asbestos cement industries and presented the results in Tables 1-2, and Supplementary Table 1 of the revised manuscript.

5. **The use of the relative risk (RR) is ok for the purpose of this study, but when comparing to a reference population, it is more commonly to use standardize incidence rate (SIR) instead. This statistics can also properly be adjusted for different age and sex distribution.**

Response: Thank you for the comments. We agree with the Reviewer to use standardize incidence rate (SIR) to assess the cancer risk of the subjects working in the asbestos-related factories, as SIR for various cancer sites was already performed in our previous study [Lin CK et al., 2015]. This study aims to estimate different risks for different manufacturing processes.


6. **It is not clear why 20 years was selected to cut off those subjects without MPM while MPM cases with short follow-up were still included in the analysis. Sensitivity analysis using different years (E.g., 30, 40, 50) may be needed. Conceptually all workers should contribute to person-years at risk; exclusion for those MPM cases with short follow-up may be more relevant because the disease may be due to exposure outside/prior to contact the factory.**

Response: Thank you for the comments. Based on our previous study, male MPM cases had a median larceny period of 33.2 (range 22.7–56.4) years. It would be a reasonable assumption of with a minimum latency period of 20 years. Your suggestions are fully considered and we have applied sensitivity analyses using latency period of more than 30, 40, or 50 years and presented these results in the revised Table 2. The details of person-years and incidence rates of individual factories are presented in the Supplementary Tables 2-4.
<table>
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<td>(5.9-257.9)</td>
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<td>(0-141.3)</td>
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</table>

**Note:** Number in **bold** means significantly elevated eRR with 95% confidence interval beyond 1.

We have also modified the text to explain the latency period of 20 years, as follows:

“All male MPM cases had a median latency period of 33.2 (range 22.7–56.4) years, which could be a basis for minimum latency period of 20 years.” (Page 5, lines 21-22)

7. **Authors noted that the rates done in this report was not age and sex adjusted. It is not clear why the authors did not do the adjustment. They should have the data to such adjustment.**

Response: Thank you for the comments. We take your advice to present results in gender combined and gender-specific, as shown in Table 1 and Supplementary Table 1.

We tried to estimated the age-adjusted incidence rate (AAIR) as follows:
The observed number of MPM as the numerator and the total person-years of follow-up during 1980-2009 as the denominator were stratified by age groups, <40, 40-59, 60-79 and >=80 years, and then the incidence rates were adjusted by the direct age-adjusted method, with reference to the world standardized population in the year 2000.

We observed that incidence rates adjusted by the direct age-adjusted method would fluctuate largely, which was related to relatively small number of MPM in individual factories. For example, one male case of MPM diagnosed below age of 40 in the shipbuilding industry (no.1) would increase the AAIR, resulting an extremely high age-adjusted eRR of 1004.5. Therefore we decided not to do age-adjustment for eRR.

However, we have modified the text as follows: “Second, the eRR, as an indicator to capture the relative risk of specific factories, which can reveal for gender combined and also stratified by gender. However, age-adjustment was not practical because incidence rates adjusted by the direct age-adjusted method with reference to the world standardized population in the year 2000 would fluctuate largely, which was related to relatively small number of MPM in individual factories.” (Page 11, line 25; page 12, lines 1-5)

8. **Can also include discussion of the changing diagnosis criteria for MPM over time and its implications as MPM may be not diagnosed as mesothelioma in early days.**
Response: Thank you for the constructive suggestion. We have added the following sentences to describe the change of diagnostic criteria of MPM over time in Taiwan and its implications to underestimate the relative risk of MPM, as follows:

“During the 1970s, the pathological diagnosis of MPM was based on histology (hematoxylin-eosin stained sections), and musin histochemistry. At that time, the incidence of MPM was under-reported because many pathologists did not recognize the diagnosis. During the 1980s-1990s, Armed Force Institute of Pathology (AFIP) Altas of Tumor Pathology became the major reference for pathologists in Taiwan to diagnose MPM based on morphological characteristics. In the 1990s, there is a rapid growth in the application of immunohistochemistry. Immunohistochemical markers for diagnosing MPM have becomes widely applied since 2000 in Taiwan. The WHO classification of tumors of the pleura published in 2004 provides an international standard for pathologists, including in Taiwan. Such changing diagnostic criteria over time could probably underestimate the incidence of MPM, especially in early period of our study followed from 1980 to 2009. Since all cases were defined on histologically verified MPM based on ICD-O-3, it would be likely that the incidence rate ratio we estimated in this study underestimated the true relative risk.” (Page 12, lines 12-24)

9. **Also should include discussion on possible environmental or non-occupational exposure to asbestos to those MPM cases.**

Response: Thank you for the constructive suggestion. We summarised the exposure scenario of the 18 cases of MPM in asbestos factories as follows:

“For the 18 cases of MPM, the mean age (±SD) of first employment in the asbestos factories was 28.1 (±11.3) years (range 15-48), and mean work duration was 7.7 (±10.5) years (range 0.1-30.0); all of them started to enter the asbestos factories before 1982, when regulations of occupational exposure to asbestos was less restrictive, with an occupational permissible exposure limit of airborne asbestos set at 5 fiber/mL. All MPM cases had a latency period of more than 20 years.” (Page 9, line 4-9)

Following your suggestion, we added the following paragraph in the Discussion section:

“According to the guideline of Labor Insurance in Taiwan, MPM can be recognized as occupational cancer if they fulfill the criteria of (1) the diagnosis of MPM is histopathologically confirmed; (2) positive occupational history, working in the asbestos industry, (2) latency period more than 10 years. Therefore, all 18 MPM cases can be undoubtedly recognized as occupational cancer. Possibly a few cases might have concomitant exposure from environment or domestic exposure, such as living near the asbestos factory, or the other family member working in asbestos industries, but we have no information regarding any environmental or non-occupational exposure. ” (Page 11, lines 1-7)

10. **Table 1 and Table 2 contain similar/overlapping information and can be combined.**

Response: Thank you for the comment. We combined these two Tables of the previous version into Table 1 in the revised manuscript.

**Additional changes:**

Based on the suggestions from distinguished reviewers, we presented number of workers, total person-years of follow-up, estimated incidence rates, and eRR, for gender combined (Table 1) and by gender (Supplementary Table 1), and sensitivity analyses for latency period (Table 2) with the details (Supplementary Tables 2-4). The whole manuscript has been revised accordingly. In addition to a clean word file requested by the editor, we also upload a word file to show the changes with underline texts, and the other modified texts shown by the tracking function of the Microsoft Word.
REVIEWER
Mikio Okazaki
Department of Thoracic Surgery, Okayama University Hospital, Japan.

REVIEW RETURNED
22-Jun-2018

GENERAL COMMENTS
The manuscript was revised and improved much better. The revised manuscript show clearly different asbestos manufacturing processes, including asbestos cement, thermal insulation, and shipbuilding industries, were at significantly increased risks for MPM.

REVIEWER
Haryana Dhillon
University of Sydney, Australia

REVIEW RETURNED
19-Jun-2018

GENERAL COMMENTS
The authors have provided a detailed and thoughtful response to the four reviews submitted. I believe they have addressed the criticisms and comments raised.

I did note a typographical error:
Page 9 line 3 error ‘summplementay’ should be ‘supplementary’
Otherwise it is ready for publication.

REVIEWER
Wei-Ting Hwang
University of Pennsylvania, USA

REVIEW RETURNED
30-Jun-2018

GENERAL COMMENTS
This is a revised submission. The revised manuscript had addressed many of the concerns raised by the previous review and have significantly expanded several sections. A few remaining issues are noted below.

1. Page 7. It is unclear that Line 5 noted that “The total person-years of follow-up were accumulated for each factory” while Lines 10-12 stated as “We defined total person-years at risk as the sums of the products of the number of workers who worked for more than 20 years times the mean follow-up years of the corresponding factory”. If the follow-up duration for the individual workers were known, why not just add up the durations directly?

2. It remains uncertain to me what should be the appropriate analysis unit to use for the RR estimation here, specifically individual factories versus types of factories/industries (e.g., combine all asbestos cement factories together). Although I can see the merit of using the individual factories as the analysis unit but it may be relevant to focus on identifying high risks industry.

3. More descriptions on those factories without MPMs may be needed. Are any of them belongs to asbestos-related industries? If so, how they are different from those factories of the same type that had associated MPM cases.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Mikio Okazaki
Institution and Country: Center of Chest Medicine and Surgery, Ehime University, Japan
The manuscript was revised and improved much better. The revised manuscript show clearly different asbestos manufacturing processes, including asbestos cement, thermal insulation, and shipbuilding industries, were at significantly increased risks for MPM.

Response: Thank you very much for your kind comment.

Reviewer: 3
Reviewer Name: Haryana Dhillon
Institution and Country: University of Sydney, Australia

The authors have provided a detailed and thoughtful response to the four reviews submitted. I believe they have addressed the criticisms and comments raised.

I did note a typographical error: Page 9 line 3 error ‘summplementay’ should be ‘supplementary’

Otherwise it is ready for publication.

Response: Thank you very much for the positive comments. The typographical error was corrected.

Reviewer: 4
Reviewer Name: Wei-Ting Hwang
Institution and Country: University of Pennsylvania Perelmen School of Medicine, USA

This is a revised submission. The revised manuscript had addressed many of the concerns raised by the previous review and have significantly expanded several sections. A few remaining issues are noted below.

1. Page 7. It is unclear that Line 5 noted that “The total person-years of follow-up were accumulated for each factory” while Lines 10-12 stated as “We defined total person-years at risk as the sums of the products of the number of workers who worked for more than 20 years times the mean follow-up years of the corresponding factory”. If the follow-up duration for the individual workers were known, why not just add up the durations directly?

Response: Thank you for the comment. To prevent confusion, we revised the sentence as “We defined the person-year-at-risk as the sum of the follow-up duration of workers who worked for more than 20 years in the corresponding factory.” (Page 7, lines 9-11)

2. It remains uncertain to me what should be the appropriate analysis unit to use for the RR estimation here, specifically individual factories versus types of factories/industries (e.g., combine all asbestos cement factories together). Although I can see the merit of using the individual factories as the analysis unit but it may be relevant to focus on identifying high risks industry.

Response: Thank you for the comment. For this study, we aim to identify high-risk asbestos factories and industries first so that we shall be able to answer the managers of asbestos companies who have kept on raising questions of evidence of asbestos-related diseases for different manufacturing processes. Both analysis units using individual factories and types of factories/industries are relevant to identify potentially high-risk industry, and we presented the results in both ways, as shown in Tables 1-2, and supplementary Tables 1-4.
3. More descriptions on those factories without MPMs may be needed. Are any of them belongs to asbestos-related industries? If so, how they are different from those factories of the same type that had associated MPM cases.

Response: Thank you for the comment. A total of 389 asbestos-related factories registered by Taiwan EPA were included in this study. We presented some comparison between the two groups in the results section: “The 8 factories with occurrence of MPM cases were factories with previous heavy asbestos exposure, while the other 381 factories constituted those with mild exposure. The average age to begin working at the factories was 22.5 years for workers with heavy exposure and 24.5 years for those with light exposure. The mean durations of employment for the former and the latter were 6.7 and 4.5 years, respectively.” (Page 8, lines 4-8)

VERSION 3 – REVIEW

<table>
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<tr>
<th>REVIEWER</th>
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<td>University of Pennsylvania, USA</td>
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<td>24-Sep-2018</td>
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