TRENDS OF PLEURAL CANCER MORTALITY IN A COHORT OF ASBESTOS WORKERS AFTER A LONG LATENCY: EVALUATION OF THE POSSIBLE ROLE OF ASBESTOS CLEARANCE.

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University of Eastern Piedmont, Italy
Piedmont Mesothelioma Register, Italy
Time since first exposure

Duration of exposure

Time since last exposure

Birth

Employment start

Employment cessation

End of Follow-up
Relation between incidence of mesothelioma and time since first exposure (I)

\[ I(T) = C(T - w)^K \]

Newhouse & Berry 1976

I: incidence rate

T: Time since first exposure

C: Cumulative exposure

w: Lag time

K: constant
Relation between incidence of mesothelioma and time since first exposure (II)

\[ I(T) = C(T - w)^K \exp(-\lambda T) \]  

Berri 1991

I: incidence rate

T: time since first exposure

C: Cumulative exposure

w: Lag time

K: constant

\( \lambda \): elimination rate of asbestos from the lung
Aim of the study

- Trend analysis of rates of pleural and peritoneal cancer according to time since first exposure to asbestos
- Comparison of the observed rates of pleural and peritoneal cancer with the rates expected by different models in order to evaluate if the Berry’s “elimination model” fits the data better than the Newhouse’s traditional model.
Cohort description

• **Subjects included in the study**: 3443 blue-collar workers active at the “Eternit” asbestos-cement plant of Casale Monferrato on 1st January 1950 or hired between 1950-1986.

• **Observation period**: 1950-2003

• **Person years of observation**: 116000
1. TSFE treated as a categorical variable
2. Linear spline models
3. Biologically-based models: comparison between the elimination model and the traditional model
Independent variables included in the Poisson regression models:

- Time since first exposure (categorical)
- Age (categorical)
- Calendar year (categorical)
- Sex (categorical)
Poisson regression. Rate Ratios by time since first exposure. Pleural cancer.

- 8 cases in < 20 years
- 24 cases in 20-29 years
- 48 cases in 30-39 years
- 40 cases in 40-49 years
- 19 cases in at least 50 years
Poisson regression. Rate Ratios by time since first exposure. Peritoneal cancer.
Statistical analysis II: Linear splines models

Variables included in the Poisson regression models:

- time since first exposure (linear splines)
- Age (categorical)
- Calendar year (categorical)
- Sex (categorical)
Poisson regression models using linear splines.
Poisson regression models using linear splines. Coefficients (Coeff.) and 95% confidence intervals (CI 95%)

<table>
<thead>
<tr>
<th>TSFE (years)</th>
<th>Pleural cancer</th>
<th>Peritoneal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>Coeff. 0.04</td>
<td>CI 95% (0.00 ; 0.08)</td>
</tr>
<tr>
<td>At least 40</td>
<td>-0.03</td>
<td>CI 95% (-0.07 ; 0.01)</td>
</tr>
</tbody>
</table>

Wald test for the equality of the two slopes

<table>
<thead>
<tr>
<th></th>
<th>Pleural cancer</th>
<th>Peritoneal cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>p = 0.02</td>
<td>p = 0.66</td>
</tr>
</tbody>
</table>
Statistical analysis III: Comparison between the elimination model and the traditional model

\[ I_T = C(T - w)^K \quad \text{Traditional model} \]

\[ \ln(I_T) = \ln(C) + K \ln(T-w) \]

\[ I_T = C(T - w)^K e^{-\lambda T} \quad \text{Elimination model} \]

\[ \ln(I_T) = \ln(C) + K \ln(T-w) - \lambda T \]
Statistical analysis III: Comparison between the elimination model and the traditional model

\[
\ln(I_T) = \ln(C) + K \ln(T-w)
\]

\[
\downarrow
\]

\[
\ln(M_T) = \ln(D) + K \ln(T-5)
\]

\[
\ln(I_T) = \ln(C) + K \ln(T-w) - \lambda T
\]

\[
\downarrow
\]

\[
\ln(M_T) = \ln(D) + K \ln(T-5) - \lambda T
\]
Comparison between the traditional model and the elimination model. Pleural cancer

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameter</th>
<th>Estimated value (CI 95%)</th>
<th>Likelihood Ratio Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination model</td>
<td>$K$</td>
<td>2.95 (1.23 to 4.67)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$\lambda$</td>
<td>0.06 (0.00 to 0.12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intercept</td>
<td>-16.9 (-20.7 to -13.1)</td>
<td>$p= 0.02$</td>
</tr>
<tr>
<td>Traditional model</td>
<td>$K$</td>
<td>1.27 (0.89 to 1.64)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intercept</td>
<td>-13.4 (-14.7 to 12.1)</td>
<td></td>
</tr>
</tbody>
</table>
Comparison between the traditional model and the elimination model. Peritoneal cancer

<table>
<thead>
<tr>
<th>Model</th>
<th>Parameter</th>
<th>Estimated value (CI 95%)</th>
<th>Likelihood Ratio Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elimination model</td>
<td>K</td>
<td>0.74 (-1.28 ; 2.76)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>( \lambda )</td>
<td>-0.05 (-0.11 ; 0.02)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intercept</td>
<td>-14.3 (-18.9 ; -9.73)</td>
<td>p = 0.22</td>
</tr>
<tr>
<td>Traditional model</td>
<td>K</td>
<td>2.12 (1.40 ; 2.83)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intercept</td>
<td>-17.3 (-19.9 ; -14.8)</td>
<td></td>
</tr>
</tbody>
</table>
Observed and fitted rates of pleural cancer by the traditional model up to 40 years of TSFE
Observed and fitted rates of pleural cancer by the traditional model up to 65 years of TSFE

Rates (per 1000) vs. Time since first exposure (years)

- Observed rates
- Rates expected by the traditional model
- Rates expected by the traditional model up to 40 years of TSFE
Observed and fitted rates of pleural cancer by the elimination model up to 65 years of TSFE
Observed rates of pleural cancer in different cohorts, against time since first exposure.

Modified from Selikoff 1991 and McDonald 2006
Observed rates of pleural cancer stratified by duration of the exposure and time since cessation of exposure.
Conclusions I: pleural cancer

- The rates of pleural cancer, rather than showing an indefinite increase, could reach a plateau when a sufficiently long time has elapsed since exposure.

- This is consistent with the suggestion that such a plateau could be related to the clearance of the asbestos from the lungs of the workers.

- Should this be the case, the number of pleural cancers caused by asbestos exposure predicted by currently used models could be overestimated.
Conclusions II: peritoneal cancer

- Peritoneal cancer showed a different trend, with a monotonic increase over time, suggesting no fiber clearance from peritoneum, at least not in the current observation period.

- Whatever the biological explanation, the different behaviour of pleural and peritoneal cancer mortality suggests that the time trends of these neoplasms should be analysed separately.
Thank you for your attention
Observed rates of peritoneal cancer in different cohorts, against time since first exposure.

Modified from Selikoff 1991 and McDonald 2006
Mesothelioma death rates among men by age and year of birth in UK

Hodgson et al 2005
Mortality rates of pleural cancer in men by age and calendar year in Piedmont (Italy).

Graphs by cal1

Modified from ISTAT
# Bio-persistence of crocidolite.

## Experimental studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of research</th>
<th>Estimated elimination rate $\lambda$</th>
<th>Half-life (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mussellman 1994</td>
<td>In vitro</td>
<td>0.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Eastes 1996</td>
<td>In vitro</td>
<td>0.1</td>
<td>7</td>
</tr>
<tr>
<td>Zoitos 1997</td>
<td>In vitro</td>
<td>0.1-0.4</td>
<td>2-7</td>
</tr>
<tr>
<td>Bellmann 1987</td>
<td>In vivo</td>
<td>0.1-0.5</td>
<td>1.5-7</td>
</tr>
<tr>
<td>Hesterberg 1996</td>
<td>In vivo</td>
<td>0.2</td>
<td>3.5</td>
</tr>
<tr>
<td>Bernstein 1996</td>
<td>In vivo</td>
<td>0.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>