Re: Extended Lung Cancer Incidence Follow-up in the Mayo Lung Project and Overdiagnosis

Marcus et al. (1) are to be commended for successfully carrying out the follow-up of the 1983 survivors of the Mayo Lung Project. We question, however, whether overdiagnosis of screening-detected lung cancer is a necessary or sufficient explanation of the observed results.

If we assume that successful randomization resulted in two study arms with a similar risk of lung cancer throughout follow-up, the existence of screening-related accelerated lung cancer diagnoses in the intervention group before 1983 should have led to a deficit of lung cancer incidence in the same arm after 1983. This redistribution is explained by the lead and length time advantages conferred by screening. However, not only was no lung cancer deficit observed in the screened group after 1983 but also there was an absolute excess of lung cancers in this screened group compared with the control arm. Thus, the true excess of lung cancers that was observed in the screened group after 1983 was larger than it appeared because it included both the lung cancer cases that erased the expected deficit and the observed cases in excess of the control arm. Marcus et al. note the latter component of the excess, but not the former, and describe this result as “perplexing.” When the true magnitude of this excess is considered, these results are more than just perplexing and require reconsideration of the overdiagnosis explanation.

We propose that oversurveillance of the intervention group provides a simpler explanation that reconciles all observations. The intervention group apparently had closer medical surveillance than the usual-care group, both before and after 1983. Evidence thereof can be found in Table 3 of Marcus et al. (1): more lung cancer cases were identified, 30 in the Mayo Clinic records and 18 in death certificates, for the intervention arm than for the usual-care arm. It is reasonable to assume that this medical oversurveillance already existed before 1983. Swensen et al. (2) have shown that lung cancer deaths may have been misattributed to other causes in the Mayo Lung Project. In the presence of oversurveillance, this misclassification is likely to have been higher in the usual-care than in the intervention group. Thus, oversurveillance from 1971 to 1996 could be responsible for a constant excess in lung cancers identified in the intervention group that would explain a fraction of the lung cancer case difference before 1983, do away with the deficit expected after 1983 attributed to lead and length time, and explain the observed excess in lung cancer cases in the intervention group after 1983.

Table 1 and Fig. 1 simulate a situation of oversurveillance. If we subtract 12.5% oversurveillance as indicated by Table 3 in Marcus et al. (48/379 = 0.127) for the 27 years of follow-up, we would expect an excess of 27 lung cancer cases in the intervention group before 1983.

<table>
<thead>
<tr>
<th>Follow-up time, y</th>
<th>Total [A]</th>
<th>Oversurveillance cases [B = A × 0.125]</th>
<th>Cases, accounting for oversurveillance [C = A − B]</th>
<th>Usual-care arm†, No. [D]</th>
<th>Difference, No. (95% CI) [C − D]</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–5</td>
<td>132</td>
<td>17</td>
<td>115</td>
<td>88</td>
<td>+27 (+20 to +35)</td>
</tr>
<tr>
<td>6–10</td>
<td>124</td>
<td>16</td>
<td>108</td>
<td>116</td>
<td>−8 (−15 to 0)</td>
</tr>
<tr>
<td>7–15</td>
<td>82</td>
<td>10</td>
<td>72</td>
<td>72</td>
<td>0 (−6 to +6)</td>
</tr>
<tr>
<td>16–20</td>
<td>87</td>
<td>11</td>
<td>76</td>
<td>84</td>
<td>−8 (−14 to −2)</td>
</tr>
<tr>
<td>21–25</td>
<td>61</td>
<td>8</td>
<td>53</td>
<td>58</td>
<td>−5 (−10 to 0)</td>
</tr>
<tr>
<td>26–27</td>
<td>5</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td>0 (−1 to +1)</td>
</tr>
</tbody>
</table>

* Adapted from Marcus et al. (1). CI = confidence interval.
† There were 491 subjects in the intervention arm and 422 in the usual-care arm.
Response

We thank Morabia and Markowitz for their comments concerning our extended lung cancer incidence follow-up of the Mayo Lung Project cohort. They posit that oversurveillance, rather than overdiagnosis, explains the excess of lung cancer cases diagnosed among intervention arm participants.

Because the correspondence does not explicitly define the term oversurveillance, we interpret it to mean that participants in the intervention arm received more medical attention than participants in the usual-care arm. The reasons for such visits are varied: evaluation or treatment of a chronic medical condition, or preventive visits, including annual physical and cancer screening exams. We mentioned in our article (1) that continuation of screening by intervention arm participants could produce an excess of cases because catch-up (i.e., after screening ends, the usual-care arm counterparts of the screen-detected cases in the intervention arm are diagnosed from symptomatic presentation) would not occur. Data in table 4 of our article, however, indicated otherwise. Patterns of imaging from 1999 through 2001 and frequency of imaging since 1983 were similar across arms. There was a suggestion, although not statistically significant, that persons in the usual-care arm actually were more likely to have frequent imaging.

We question whether the method of Morabia and Markowitz, which involved the source of lung cancer information, is more useful than reported imaging information in assessing oversurveillance. Furthermore, we are uncertain as to why their measure of oversurveillance was based solely on Mayo Clinic records and death certificates. Neither source provides direct evidence of oversurveillance. Mayo Clinic records may reflect choice of a major medical facility for treatment of cancer diagnosed elsewhere among persons familiar with that facility as a result of their trial experiences. Death certificates are not a reliable source for cancer diagnoses. We did not collect death certificates on either a complete or a random sample of participants but used death certificates in a final attempt to obtain evidence of a lung cancer diagnosis for participants known only to be dead. We disagree with the authors’ use of the statements from Swensen et al. (2) to support the use of death certificates as a measure of oversurveillance. Swensen et al. state that “some lung cancer deaths may have been misattributed to other causes” because of “temporal improvements in the detection and diagnosis of cancer.” Temporal improvements should affect the arms equally. Swensen et al. did not show misattribution; they merely hypothesized its existence for some lung cancers.

It would be naïve to believe that no oversurveillance, particularly in the form of screening, existed in this cohort after 1983 or that overdiagnosis did not exist before 1983. To fully discredit the existence of overdiagnosis, one would need to explain away 85, or 15%, of lung cancers diagnosed in the intervention arm. The estimate of 12.5% from Morabia and Markowitz, which was based on reports apparently supportive of their argument, does not suffice. An estimate that incorporates all sources (10.3%, 39 excess cases in the intervention arm of a total of 379 cases in the intervention arm), thus eliminating selectivity that could influence conclusions, further discounts the authors’ argument against overdiagnosis.

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KENNETH P. OFFORD

References


Notes

Editor’s note: Drs A. Morabia and S. Markowitz are expert witnesses for the plaintiff in a lawsuit (Caronia v. Philip Morris) that involves the use of helical computed tomography for lung cancer screening. Both declare that this correspondence was not supported or instigated by their involvement in this lawsuit.

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