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Neugut et al. (1) identified the small proportion of patients who developed a second primary lung cancer after a first primary carcinoma associated with cigarette smoking (cancers of lung, breast, and head and neck) from National Cancer Institute records (2). Cases were excluded on a number of grounds to reduce the chance that the second neoplasm was simply a recurrence of the first. Their aim was to explore whether lung cancer occurring as a second primary neoplasm had the same histological distribution as lung cancer occurring as a first primary neoplasm. Comparisons in the paper are between the histological classifications of over 100,000 de novo lung cancer patients (who may or may not later develop a second cancer) with those of small groups of patients with second primary lung cancers, with a particular type or site of first tumor. While the comparisons they made are interesting, there are other pertinent analyses that they could have made.

It is possible that the histological distribution of first and second cancers will differ as a consequence of the high mortality of particular histological subtypes (e.g., small cell carcinoma) rather than of any propensity for subtypes to repeat if a second tumor occurs. The 111,616 patients with a first primary lung cancer are shown to divide into the 30.9% who have squamous cell carcinoma, 28.4% who have adenocarcinoma, and 40.7% who have small cell or other carcinomas, whereas the histological distribution of the first primary lung cancers, for the 405 patients who later develop a second lung cancer, can be shown to be 39.5% squamous cell, 40.2% adenocarcinomas, and 20.2% small cell and other carcinomas. If a χ² test were used to compare these distributions, a highly significant result would be obtained, but such results are unremarkable when one group size is over 100,000; confidence intervals would be more useful (3).

Only a small minority of cancer patients develop second tumors (less than 0.5% of patients with first lung cancers appear in the group with second lung cancers), and they may be a special group in themselves. It would be interesting to compare the paired information on histological classification for subgroups of patients who develop cancer twice. Any analysis of such data must take into account the paired nature of such data. If it is wished to compare the marginal probabilities of each histological type, the appropriate technique is Stuart’s test and its associated confidence intervals (4, 5). This is an extension of the familiar McNemar’s test for binary paired data.

As an example, take the subgroup of patients who develop primary lung cancer twice, with over a year between diagnoses. Results from the study by Neugut et al. (Ref. 1, Tables 3 and 4) can be reorganized as the first two columns in Table 1 below. The third column showing the histological type of the second lung cancer for those whose first lung cancer was a small cell carcinoma has been invented to show a possible layout. Comparison would then be between the 39.5% of first cancers and the 32.3% of second cancers classified as squamous cell carcinomas, a difference of 7.2%. This difference is in the same direction, but of lesser magnitude, than that found by the comparison of second lung cancers with all first lung cancers in (1). The figures in the third column of the table are not genuine, but the difference between the proportions of squamous cell carcinomas on first and second lung cancers is not very sensitive to the likely distribution of histological subtypes of small cell and other cancers. If a χ² test were used to compare these distributions, a highly significant result would be obtained, but such results are unremarkable when one group size is over 100,000; confidence intervals would be more useful (3).

### Table 1: Distribution of histological types of first and second lung cancers for 405 patients who developed lung cancer twice

<table>
<thead>
<tr>
<th>Second lung cancer</th>
<th>First lung cancer</th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Squamous cell</td>
<td>Adenocarcinoma</td>
<td>Small cell carcinoma + other</td>
<td></td>
</tr>
<tr>
<td>Squamous cell</td>
<td>80</td>
<td>31</td>
<td>20</td>
<td>131 (32.3%)*</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>24</td>
<td>85</td>
<td>20</td>
<td>129 (31.9%)</td>
</tr>
<tr>
<td>Small cell carcinoma + other</td>
<td>56</td>
<td>47</td>
<td>42</td>
<td>145 (35.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>160 (39.5%)</td>
<td>163 (40.2%)</td>
<td>82 (20.2%)</td>
<td>405 (100%)</td>
</tr>
</tbody>
</table>

* Figures in italics are invented.
other carcinomas. Corresponding comparisons could be made for adenocarcinomas and remaining carcinomas.

This approach could be extended to other groups of patients who develop cancer twice, not necessarily at the same site. By concentrating on the paired information from patients with two primary cancers, useful information can be obtained on the tendency for the histology of a second cancer to repeat that of the first, which is complementary to the analysis presented in the original paper.

References
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