A DIDACTIC DEVICE FOR TEACHING EPIDEMIOLOGY STUDENTS HOW TO ANTICIPATE THE EFFECT OF A THIRD FACTOR ON AN EXPOSURE-OUTCOME RELATION

Visualizing a three-dimensional relation among an exposure, an outcome, and a third factor is complicated, particularly when students are first being introduced to epidemiologic methods. The heuristic device described below can be used by teachers of epidemiology to help introductory students understand how a third factor will affect the association between an exposure and an outcome. The device is demonstrated using examples which assess the effects of potential confounding factors. However, it can be more generally applied to anticipate the effects of differential attrition, misclassification, and selection.

The heuristic device

Step 1. The first step is to consider the association between the potential confounding factor (PCF) and both exposure and outcome. If the PCF is related to both, it will have the unwanted effect of exaggerating or diminishing the true association of interest.

Step 2. The second step is to construct a conventional 2x2 table with exposure status depicted in the vertical dimension and outcome status depicted in the horizontal dimension.

Step 3. Next, knowledge of the association between the PCF and exposure and outcome (step 1) is applied to the 2x2 table (step 2) to anticipate the direction of the effect of a PCF on the primary exposure-outcome relation. This application can be most clearly demonstrated by example.

Example 1

Social class has been found to be negatively associated with both mental illness in childhood (exposure) and homelessness in adulthood (outcome). We can apply this knowledge to a 2x2 table constructed to reflect the hypothetical exposure-outcome relation between mental illness and homelessness. We begin with the "exposure" dimension of the table. Since low social class is associated with having a mental illness, we anticipate an overrepresentation of persons of low social class in the "exposed" ("a" and "b") cells. Moving to the "outcome" dimension, since low social class is associated with homelessness, we anticipate an overrepresentation of persons of low social class in the "outcome present" ("a" and "c") cells. With an overrepresentation of a factor related to outcome in the "a" and "b" cells and an overrepresentation of a factor related to exposure in the "a" and "c" cells, the size of the "a" cell will be exaggerated (figure 1). In general, exaggeration of the "a" cell and/or the "b" cell leads to a biased strengthening of the primary exposure-outcome relation.

Example 2

Univariate analyses have shown educational status to have a positive association with oral contraceptive use (exposure) and a negative association with cervical cancer (outcome). Therefore, in studying the relation between oral contraceptive use and cervical cancer, we anticipate an overrepresentation of persons with high educational attainment in the "exposed" ("a" and "b") cells, as well as in the "outcome absent" ("b" and "d") cells, resulting in an exaggeration in the size of the "b" cell (figure 1). Exaggeration of the "b" cell and/or the "c" cell leads to a spurious diminishing of the exposure-outcome relation.

Using this heuristic device, the epidemiology student can apply knowledge about the relation between a third factor and an exposure and outcome to the 2x2 table to anticipate the third factor’s effect on the association between exposure and outcome. The "trick" is to assess the effect of the PCF on the exposure and outcome dimensions of the table independently, note the overlapping cell in which the effect is compounded, and thereby ascertain the direction of the effect on the association of interest.

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We read with interest the paper of Benichou et al. (1), who reported the population attributable risk (PAR) of renal cell cancer for several risk factors in Minnesota. Since they stated that their study constitutes a first attempt to provide a comprehensive estimate of PAR for renal cell cancer (1), and given the widespread interest in PAR (2, 3), we think it is useful to summarize here the estimates obtained from a case-control study of kidney cancer conducted in northern Italy between 1985 and 1989 (4).

The study included 133 histologically confirmed cases of incident kidney cancer (87 men and 46 women) and 392 controls (293 men and 99 women) who had been admitted to hospital for a wide range of acute nonneoplastic diseases. On the basis of multivariate odds ratios (5, 6), ever smoking tobacco accounted for 26 percent of cases, low \( \beta \)-carotene intake (as a general indicator of fruit and vegetable intake) accounted for 18 percent, history of cystitis for 7 percent, and family history of kidney cancer in first-degree relatives for 3 percent (table 1). Ever smoking and low \( \beta \)-carotene intake together explained 38 percent of renal cell cancer cases, and the combination of these two factors plus history of cystitis and family history of kidney cancer explained over 45 percent of the cases. Body mass index was not associated with renal cell cancer risk in the study, and no information on hypertension was available.

Previous studies had shown consistent PAR estimates for tobacco smoking (7). A population-based case-control study based on 495 cases of renal cell cancer, conducted in the seven-county Minneapolis-St. Paul (Minnesota) metropolitan area between 1974 and 1979, estimated a PAR of 30 percent for men and 24 percent for women in relation to ever smoking (8). An international, multicenter population-based case-control study, conducted in Australia, Denmark, Germany, Sweden, and the United States between 1989 and 1991 and including a total of 1,732 renal cell cancer cases, reported an overall PAR for ever smoking of 18 percent (24 percent in men and 9 percent in women) (9). Thus, the PAR for smoking estimated in northern Italy (26 percent) was comparable to the PARs of most previous studies (7).

Although the two studies considered different risk factors for renal cell cancer, the study by Benichou et al. (1) and the Italian study (4) suggest that approximately half of renal cell cancer cases can be attributed to known risk factors for the disease. Given the prevalence of smoking in Italy, it appears that a considerable proportion of kidney cancers, corresponding to approximately 1,500 kidney cancer deaths per year (10), could be avoided by eliminating smoking and increasing the consumption of fruits and vegetables.

**REFERENCES**


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**Editor’s note:** In accordance with Journal policy, Benichou and colleagues were asked if they wished to respond to this letter, but they chose not to do so.

**TABLE 1.** Percentage population attributable risks of renal cell cancer according to selected variables, Milan, Italy, 1985–1989

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Population attributable risk (%)</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>25.8</td>
<td>5.9, 45.7</td>
</tr>
<tr>
<td>Low ( \beta )-carotene intake</td>
<td>17.5</td>
<td>–7.9, 42.8</td>
</tr>
<tr>
<td>History of cystitis</td>
<td>6.5</td>
<td>–1.7, 14.7</td>
</tr>
<tr>
<td>Family history of kidney cancer</td>
<td>2.7</td>
<td>–0.2, 5.7</td>
</tr>
<tr>
<td>Smoking + low ( \beta )-carotene</td>
<td>38.0</td>
<td>4.8, 71.2</td>
</tr>
<tr>
<td>Smoking + history of cystitis</td>
<td>34.1</td>
<td>13.0, 55.3</td>
</tr>
<tr>
<td>Smoking + family history of kidney cancer</td>
<td>28.5</td>
<td></td>
</tr>
<tr>
<td>Smoking + family history of kidney cancer + history of cystitis</td>
<td>33.7</td>
<td></td>
</tr>
<tr>
<td>All of the above</td>
<td>45.4</td>
<td></td>
</tr>
</tbody>
</table>