Epidemiology

Gallstones and the risk of cancer

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SUMMARY For both males and females the age-standardised prevalence of asymptomatic gallstones found at necropsy in 15 countries correlated strongly with age-standardised mortality from cancers of the uterus, large bowel, and stomach. When deaths from cholecystitis were used as another measure of the frequency of gallstones similar positive correlations were observed across 28 countries. The results suggest that cholelithiasis and several common cancers share similar epidemiological and perhaps metabolic factors.

In addition to the well-known association between cholelithiasis and biliary tract malignancy it has been suggested that gallstones may be linked through diet with colorectal cancer. However, efforts to correlate these two diseases in individual population groups have yielded conflicting results, perhaps because of methodological problems in choosing appropriate controls.

As gallstones are largely made up of cholesterol, any link between gallstones and bowel cancer might lend additional support to the cholesterol/bile acid hypothesis for the aetiology of bowel cancer. Furthermore, it seems reasonable that the presence or absence of gallstones might prove to be a more reliable indication of cholesterol 'burden' than blood cholesterol, which is difficult to associate with diet and which has not been positively correlated with colon cancer.

To clarify the problem of gallstones and cancer, the prevalence of gallstones in various countries has been estimated and correlated with available data on cancer mortality.

Methods

The prevalence of gallstones in healthy, asymptomatic individuals has been determined in only a few countries and therefore the reported frequency of asymptomatic gallstones discovered at necropsy was used as a substitute. From a review of available published studies since 1950, 15 countries were selected where there were sufficient age-specific data to calculate age-standardised rates for males and females above the age of 20 years. Prevalence rates were age-standardised by decade to a world population.

In addition, as death from biliary tract disease is nearly always related to gallstones, it seemed reasonable to use available mortality data for cholecystitis as another measure of the frequency of gallstones in different countries. Age-specific cholecystitis mortality rates by decade for 1978 and 1979 were collected from World Health Organization reports and used to calculate age-standardised rates for 28 countries where there were 100 or more deaths from cholecystitis. Age-standardised deaths from cholecystitis were related to the age-adjusted prevalence of gallstones at necropsy for both males ($r=0.76; P<0.01$) and females ($r=0.82; P<0.01$).

Table 1 Age-adjusted prevalence of asymptomatic gallstones at necropsy in 15 countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Gallstone prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
</tr>
<tr>
<td>Chile1</td>
<td>42.0</td>
</tr>
<tr>
<td>Czechoslovakia4</td>
<td>23.3</td>
</tr>
<tr>
<td>Sweden3</td>
<td>22.4</td>
</tr>
<tr>
<td>Scotland18</td>
<td>21.7</td>
</tr>
<tr>
<td>England11</td>
<td>20.5</td>
</tr>
<tr>
<td>West Germany15</td>
<td>20.0</td>
</tr>
<tr>
<td>New Zealand13</td>
<td>14.2</td>
</tr>
<tr>
<td>United States14</td>
<td>14.1</td>
</tr>
<tr>
<td>Australia15</td>
<td>13.9</td>
</tr>
<tr>
<td>Japan4</td>
<td>13.0</td>
</tr>
<tr>
<td>Ireland17</td>
<td>12.4</td>
</tr>
<tr>
<td>Norway14</td>
<td>10.4</td>
</tr>
<tr>
<td>Greece15</td>
<td>6.8</td>
</tr>
<tr>
<td>Singapore38</td>
<td>6.6</td>
</tr>
<tr>
<td>Thailand26</td>
<td>4.2</td>
</tr>
</tbody>
</table>

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Table 2  *Age-adjusted gallstone prevalence at necropsy, 1952-79, and age-adjusted mortality from cancer, 1974-75, in 15 countries*  

<table>
<thead>
<tr>
<th>Tumour location</th>
<th>Simple correlation coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Females</td>
</tr>
<tr>
<td>Uterus</td>
<td>0.93†</td>
</tr>
<tr>
<td>Colorectal</td>
<td>0.73‡</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.51</td>
</tr>
<tr>
<td>Stomach (excluding Japan)</td>
<td>0.75†</td>
</tr>
<tr>
<td>All sites</td>
<td>0.60§</td>
</tr>
<tr>
<td>Lung</td>
<td>0.02</td>
</tr>
<tr>
<td>Prostate</td>
<td>—</td>
</tr>
<tr>
<td>Breast</td>
<td>0.23</td>
</tr>
<tr>
<td>Skin</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Same countries as shown in table 1.
†P = <0.001; ‡P = <0.01; §P = <0.02; **P = <0.05.

Both of these measures of the frequency of gallstones in various countries were then correlated with age-standardised mortality rates for common human cancers and simple correlation coefficients (r) were calculated. Singapore was excluded from the analysis of uterine cancer because the total number of deaths for that site was less than 100.

**Results**

The age-standardised prevalence of asymptomatic gallstones discovered at necropsy (Table 1) varied markedly from country to country and, as expected, gallstones were approximately twice as common in females as in males. Significant positive correlations were found between the necropsy prevalence of gallstones and colorectal cancers, as well as all cancers in both males and females (Table 2). The correlation between gastric cancer and the necropsy prevalence of gallstones, which was nearly significant in the 15 countries studied, became significant in the remaining 14 countries (females: r = 0.75, P = <0.01; males: r = 0.71, P = <0.01) when Japan, the obvious outlier was removed. In females, the strongest correlation (r = 0.93; P = <0.001) was discovered between uterine cancer and gallstones (Figure). A strong correlation persisted (r = 0.82; P = <0.001) even after exclusion of Chile, a country with excessive rates for cholecystitis and uterine cancer.

Similar positive correlations were observed between age-standardised mortality from cholecystitis and age-standardised cancer mortality in the 28 countries studied (Table 3).

**Discussion**

The ideal method of measuring gallstone frequency would be to use radiographic surveys in asympto-

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**Figure**  Scattergram showing relationship between age-adjusted gallstone frequency at necropsy and age-adjusted frequency of asymptomatic gallstones in females at necropsy in 14 countries.
motic individuals. Such information is not available and therefore the two methods used represent a compromise. Clearly the prevalence of gallstones in a necropsy population may differ from the population at large, and deaths from cholecystitis, although usually caused by cholelithiasis, may be influenced by confounding variables such as the availability of medical care. Nevertheless, despite these drawbacks, there were similar correlations between both methods used to estimate gallstone frequency and cancer mortality data.

The correlation between cholelithiasis and uterine cancer was exceptionally strong and is consistent with a previous report of an increased frequency of gallstones in women with endometrial cancer.24

The association between gallstones and colorectal cancer was also strong. As increased cholesterol excretion may be implicated as a causative factor in cholelithiasis26 and as cholesterol is the major source for bile acids, this study strengthens the cholesterol/bile acid hypothesis for the aetiology of colorectal cancer.

There is no ready explanation for the unexpected correlation between gallstones and gastric cancer. It is of interest that this finding is consistent with the observation that Pima Indians of the Southwest United States, who are known to have a great excess of gallstones, also have a higher than expected incidence of gastric cancer.28

The findings reported here, although not implying a causal relationship, are consistent with the hypothesis that gallstones and several common human cancers share common risk factors. Additional studies of the incidence of cancer in carefully selected patients with and without gallstones are planned.

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References

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