The incidence of colorectal carcinoma was compared with the incidence of ABO and Lewis blood groups. The raw data showed the known overrepresentation of the Le(a-b-) phenotype, but also suggested an association of colorectal carcinoma with the Le(a-b+) phenotype in group O individuals. When the data were adjusted by taking into account the known loss of Lewis antigens by Lewis-positive patients, this association could be shown to be statistically significant. These results may indicate involvement of the secretory H antigen in colorectal carcinoma.

To determine whether there is an association between a disease and a given character, the frequency of the character in a sample of diseased persons is compared with its frequency in a healthy population of the same genetic stock. Cancers in general tend to show increased association with blood group A as compared with blood group O. The most significant association is a 20 percent higher incidence of stomach cancer with blood group A than with blood group O. Accumulated data from 11 multiracial studies have shown a slight association of colorectal carcinoma with group A; however, smaller individual studies show no statistical difference. There is no report of a significant association between secretors and nonsecretors of ABH-soluble blood group substances and the incidence of colorectal carcinoma.

The Lewis antigens are structurally related to the ABH blood group antigens and are formed by a complex process in which the Lewis and secretor fucosyl-transferases interact and compete with each other and other transferases to produce the known Lea and Leb antigens. In individuals with a Lewis gene, Le (about 94% of Caucasians), the Lewis antigens Lea and/or Leb are formed. If these Lewis-positive individuals also have a secretor gene, Se (about 80%), then the Leb antigen is formed; in individuals lacking Se, only Lea is made. The terms "secretor" and "nonsecretor" refer to the ability or inability to secrete large amounts of ABH substances in the saliva. As a result of these interactions, three red cell Lewis and related secretor phenotypes are found: Le(a-b-) secretors (8%), Le(a-b-) nonsecretors (2%), Le(a+b-) nonsecretors (20%), and Le(a-b+) secretors (70%).

In 1984 in Auckland, New Zealand, we tested 290 Caucasians being treated for colorectal carcinoma for ABO and Lewis red cell antigens. Observed ABO and Lewis frequencies were contrasted with expected New Zealand frequencies. Recently, it has been reported that the overrepresentation of the Le(a-b-) phenotype in colorectal carcinoma patients is due to a loss of expression of Lewis antigens on the red cells of Lewis-positive individuals. Although we had not determined the salivary Lewis status of our 290 patients, we reevaluated our data in light of these new findings.

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Materials and Methods

ABO and Lewis phenotypes were determined for 290 New Zealand Caucasians being treated for colorectal adenocarcinoma. Lewis phenotype frequencies were determined for 247 healthy Caucasian controls.

Anti-A and -B were locally prepared reagents (Biological Laboratories Ltd., Auckland, New Zealand). Anti-Lewis reagents of goat origin were supplied by Ortho Diagnostic Systems, Inc., Raritan, NJ. Testing was performed in test tubes according to manufacturers' instructions. After a 30-minute room temperature incubation of saline-suspended cells followed by centrifugation, agglutinations were read with a 10× magnification eyepiece.

Statistical analysis was performed using the Chi-square distribution and the t test. Expected frequencies for controls were calculated using control Lewis phenotype frequencies (as determined from 247 healthy Caucasian blood donors) and from published ABO frequencies. The data were also tested after being adjusted. This
theoretical adjustment was made because it is known that the Lewis phenotypes from colorectal carcinoma patients are skewed because of a loss of red cell antigens. This reassignment was done by calculating the excess of expected Le(a-b-) phenotypes and reassigning these data to the Lewis-positive phenotypes based on their respective frequencies. For example, in group O individuals, 19 Le(a-b-) phenotypes were observed, but only 7.8 were expected based on the control group's frequency. This excess of 11.2 was then reassigned to the Lewis-positive phenotypes, as +2.2 for the Le(a+b-) phenotype and +9.0 for the Le(a-b+) phenotype.

Results

No association between ABO groups and colorectal carcinoma was found (Table 1). Although there appears to be a slight association with group O, this was not statistically significant ($X^2 = 3.7$, 3 degrees of freedom, $0.3 > p > 0.2$).

Table 1. ABO blood group distribution in 290 colorectal carcinoma patients and the expected results as calculated from healthy controls

<table>
<thead>
<tr>
<th></th>
<th>O</th>
<th>A</th>
<th>B</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>150</td>
<td>108</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>No. of controls (expected)</td>
<td>137</td>
<td>117</td>
<td>27</td>
<td>9</td>
</tr>
</tbody>
</table>

When the distribution of the Lewis phenotypes in colorectal carcinoma patients and healthy controls were analyzed (Table 2), it was found that the patients' Lewis phenotypes did not conform with the expected distribution ($X^2 = 26.2$, 2 degrees of freedom, $p > 0.01$). The Le(a-b-) phenotype was found to be increased significantly in the patients, a finding that is in accord with two previous studies.

Table 2. Red cell Lewis phenotype distribution in 290 colorectal carcinoma patients and the expected results as calculated from healthy controls

<table>
<thead>
<tr>
<th></th>
<th>Le(a-b-)</th>
<th>Le(a+b-)</th>
<th>Le(a-b+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>37</td>
<td>64</td>
<td>189</td>
</tr>
<tr>
<td>No. of controls (expected)</td>
<td>17</td>
<td>61</td>
<td>212</td>
</tr>
</tbody>
</table>

The data were further analyzed for ABO/Lewis associations and compared with the expected distributions. It was found that ABO versus Lewis groupings did not conform with expected distributions ($X^2 = 39.7$, 11 degrees of freedom, $p > 0.01$). This non-conformity was due mainly to an excess of patients with the Le(a-b-) phenotype, but distribution of the Le(a-b+) phenotype also contributed.

Analysis of the ABO group distribution within each Lewis phenotype for the colorectal carcinoma patients revealed that the Lewis groupings conformed with that expected for the Le(a-b-) and Le(a+b-) phenotypes ($p > 0.9$) (data not shown). However, although the Le(a-b+) phenotype conformed ($X^2 = 6.6$, 3 degrees of freedom, $0.1 > p > 0.05$), the result suggested an association with group O overrepresented and group A underrepresented (Table 4).

Table 3. Lewis phenotype distribution within each ABO group in 290 colorectal carcinoma patients and expected results as calculated from healthy controls (results in brackets)

<table>
<thead>
<tr>
<th></th>
<th>Le(a-b-)</th>
<th>Le(a+b-)</th>
<th>Le(a-b+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>19 (7.8)</td>
<td>27 (28.9)</td>
<td>104 (100.3)</td>
</tr>
<tr>
<td>A</td>
<td>13 (6.7)</td>
<td>29 (24.7)</td>
<td>66 (85.6)</td>
</tr>
<tr>
<td>B</td>
<td>4 (1.5)</td>
<td>6 (5.7)</td>
<td>17 (19.8)</td>
</tr>
<tr>
<td>AB</td>
<td>1 (0.5)</td>
<td>2 (1.9)</td>
<td>2 (6.6)</td>
</tr>
</tbody>
</table>

Table 4. ABO blood group distribution within the 189 Le(a-b+) colorectal carcinoma patients and expected results as calculated from healthy controls (results in brackets)

<table>
<thead>
<tr>
<th></th>
<th>O</th>
<th>A</th>
<th>B</th>
<th>AB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le(a-b+)</td>
<td>104</td>
<td>66</td>
<td>17</td>
<td>2</td>
</tr>
</tbody>
</table>

Because it had previously been reported that many colorectal carcinoma patients with the Le(a-b-) phenotype were not true Lewis negatives, we reexamined our data after adjusting it. This was done by proportionally reassigning the excess of expected Le(a-b-) data to the Lewis-positive data. A significant difference was found in the distribution of the Le(a-b+) phenotype between group O and non-group O individuals. When just the Le(a-b+) phenotype data were examined (Table 5), the non-conformity was due to overrepresentation of the Le(a-b+) phenotype in group O individuals and underrepresentation in non-group O individuals ($t$ test, $t_0 = 2.2$, 0.05 $> p > 0.02$). The possibility that the excess of Le(a-b-) phenotypes came only or predominantly from the Le(a-b+) phenotype was also examined. This reassignment gave the same final probability as the more conservative proportional reassignment.

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(results not shown). Alternatively, the excess of Le(a–b–) phenotypes could have come predominantly from the Le(a+b–) phenotype, but the results of other workers do not support this.\(^5\)

**Table 5.** Blood group O distribution within the Le(a–b+) colorectal carcinoma patients and expected results for healthy controls (results in brackets)\(^6\)

<table>
<thead>
<tr>
<th>Group O Le(a–b+)</th>
<th>112 (96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-group O Le(a–b+)</td>
<td>92 (108)</td>
</tr>
</tbody>
</table>

\(^*\)Data have been adjusted by reassigning the excess of Le(a–b–) phenotypes to the Lewis-positive phenotypes (see text).

**Discussion**

In Lewis-positive secretors (Le[a–b+]), type-1 ABH antigens, Le\(^b\), and, to a lesser extent, some type 2 ABH antigens are expressed in the proximal half of the colon, and blood group substances A and Le\(^b\) may occasionally be present to a limited extent in distal colonic mucosa.\(^8\)-\(^10\) Le\(^a\) is expressed throughout the colon of Lewis-positive individuals, irrespective of the ABH secretor status. In the fetal colon and rectum, ABH-related carbohydrate antigens carried by type-1 chain core structures, as well as those carried by type 2 chain core structures, are expressed. However, after birth, these antigens gradually disappear or are reduced appreciably in the distal colon, with the exception of Le\(^a\), which remains expressed.\(^8\),\(^11\) Le\(^b\) expression in the fetal colon is directly related to the secretor status of the individual.\(^11\)

In colonic carcinoma, reexpression of ABH and Le\(^b\) antigens in distal colon carcinomas is the most frequent alteration to occur. The mechanism responsible is the derepression of oncofetal H gene function, resulting in, for example, the formation of blood group ABH, Le\(^b\), Le\(^x\), Le\(^y\), and T antigens. These antigens, expressed by fetal colonocytes, disappear from normal adult colonocytes and reappear (derepression) in colon cancer cells.\(^8\),\(^9\) This reappearance of some antigens appears to be regulated partly by reexpression of the \(a\)-2-fucosyltransferases.\(^12\)

The results presented here suggest that group O secretors are at a higher risk for colonic carcinoma than are non–group O secretors. The ABO association found in secretors suggests a possible relationship between expression of the secretory H antigen (H type-1) and colonic carcinoma. There seems to be no such association for nonsecretors. It appears that when the H type-1 antigen is not present (as in Le[a+b–] individuals) or is masked by addition of A or B immunodominant sugars, the incidence of colorectal carcinoma is either the same or less than expected, respectively.

It is important to note that the colon does not normally express the secretory antigens (Le\(^b\) or H type-1), although the fetal colon and cancerous colonic tissue do express these antigens. It is postulated that individuals with the ability to reexpress the oncofetal H type-1 antigen unmodified in the colon are at greater risk of developing colorectal carcinoma.

This preliminary study suggests that group O secretors are at a higher risk for colonic carcinoma than are non–group O secretors. It should be emphasized that although the raw data did suggest an association, the conclusions of this article are based on adjusted data. Further studies of an association between the ABO/Lewis/secretor systems and colorectal carcinoma are indicated. These studies should include salivary and family analyses.

**Acknowledgments**

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