Colorectal Cancer Risk, Chronic Illnesses, Operations, and Medications: Case Control Results from the Melbourne Colorectal Cancer Study

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ABSTRACT

The associations between colorectal cancer risk and several chronic illnesses, operations, and various medications were examined in 715 colorectal cancer cases and 727 age/sex-matched controls in data derived from a large, comprehensive, population-based study of this cancer conducted in Melbourne, Australia. There was a statistically significant deficit among cases of hypertension, heart disease, stroke, chronic chest disease, and chronic arthritis and a statistically significant excess of "hemorrhoids" among cases, and all of these differences were consistent for both colon and rectal cancer and for both males and females. Although no statistically significant differences were found for other cancers, there were twice as many breast cancers among cases (16) than among controls (8) and also there were 9 uterine cancers among cases and only 2 among controls. There was a statistically significant deficit among cases in the use of aspirin-containing medication and vitamin supplements, and this was consistent for both colon and rectal cancer and for both males and females. There was a statistically significant excess of large bowel polypectomy among cases. The modeling of these significant associations simultaneously in a logistic regression equation indicated that hypertension, heart disease, chronic arthritis, and aspirin use were each independent effects and consistent for both colon and rectal cancer for both males and females and also that these effects were independent of dietary risk factors previously described in the Melbourne study. The possible relevance of these findings towards an understanding of colorectal cancer risk and etiology is discussed.

INTRODUCTION

This paper describes the associations found between colorectal cancer risk and several chronic illnesses, operations, and medications. The data are drawn from the case-control substudy arm of a large, comprehensive, population-based clinicopathological and epidemiological investigation of colorectal cancer, The Melbourne Colorectal Cancer Study (1). The objectives for obtaining these data on illnesses, operations, and medications were partly to examine some current hypotheses of colorectal cancer risk, partly to examine previously described associations between colorectal cancer and other cancers and partly as an exploratory step to stimulate the creation of new hypotheses of colorectal cancer etiology.

PATIENTS AND METHODS

Definition of Cases and Controls. All histologically confirmed new cases of colorectal adenocarcinoma diagnosed in the 12-month period April 1980 to April 1981 who were usual residents of Metropolitan Melbourne (population, 2.81 million) constituted the cases (1-3). Those with a past history of ulcerative colitis or familial polyposis coli (10 cases) were excluded. Community controls, who were age/sex frequency-matched with the cases, were randomly selected from the same geographic area from which the cases were chosen, according to a cluster-sampling plan devised by the Australian Bureau of Statistics (1, 2).

RESULTS

This analysis is of 715 cases (388 males and 327 females) and 727 controls (398 males and 329 females). There were 392 colon cancers and 323 rectal cancers among the cases. Cases and controls were group matched for age and sex, and the age and sex distribution of the cases and controls was therefore similar, with a mean age of 65 years (standard deviation of 10 for males and 12 for females).

Univariate Analyses of Associations

Illnesses. Table 1 summarizes the chronic illnesses findings. There was a statistically significant deficit among cases of hypertension, stroke, heart disease, chronic chest disease, and chronic arthritis, and these deficits were consistent in both colon and rectal cancer and in both males and females. Among cases, there was a statistically significant excess of "hemor-
rhoids” in both colon and rectal cancers. There was a statistically significant deficit of “indigestion or ulcer” reported by female cases, and this was similar for both colon and rectal cancer. No differences were found for asthma, diabetes, diverticular disease, “extreme nervousness and nervous breakdowns,” and allergies.

A past history of cancers other than colorectal cancer was seen in 85 cases and 75 controls, there being 92 instances in cases and 82 in controls (Table 2). Note that a past history of colorectal cancer was an exclusion for controls. For operations, all the “don’t know” responses were in relation to malignant or premalignant conditions and were distributed as follows: bowel polypectomy, 16 cases and no controls; gastric cancer surgery, 2 cases and no controls; prostatic cancer surgery, 27 cases and 3 controls; uterine cancer surgery, 17 cases and 8 controls; skin cancer surgery, 39 cases and 11 controls. Thus the 123 “don’t know” answers were distributed among cases in 101 instances and among controls in 22 instances. The distribution of cancer sites among cases and controls is described in Table 2, and in this table, for relative risk estimates, all “don’t know” responses were considered to be nonmalignant. There were no statistically significant differences either in the total number of other cancers, nor in any one site, and the rates were similar for colon and rectal cancer. It is noteworthy that there were twice as
many breast cancers among cases than among controls. The difference for uterine cancer was approaching statistical significance at the 5% level (P = 0.07; Table 2). Note that in the question on hysterectomy for uterine cancer, no distinction was made in the questionnaire between endometrial cancer and cervical cancer.

Medications. With past medications (Table 3) there was a statistically significant deficit among cases consuming aspirin and aspirin-containing medications, vitamin C supplements, and these deficits were consistent for males and females. The statistically significant lower consumption of aspirin and aspirin-containing medications among cases remained after adjustment was made for those with arthritis, who may be supposed to be frequent users of aspirin-containing compounds (P < 0.001; RR = 0.63; 95% confidence interval, 0.50–0.78). The use of nonsteroidal antiinflammatory agents, steroids, oral contraceptives, sedatives, tranquillizers, and sleeping pills was similar for cases and controls and consistent for males and females, colon and rectal cancer combined (Table 3). When these groups of medications were analyzed by site (colon cancer and rectal cancer), the effects noted above were unaltered with the exception of nonsteroidal antiinflammatory agents, where a deficit was noted for colon cancer cases (RR = 0.66; 95% confidence interval, 0.47–0.92; P = 0.001) and this was consistent for both males and females.

Operations. A history of a previous bowel polypectomy showed a statistically significant excess in cases and there was also a statistically significant deficit of cases who had uterine curettage (Table 4). The rates of tonsillectomy, appendectomy, hemorrhoidectomy, cholecystectomy, hernia repair, hiatus hernia repair, peptic ulcer surgery, hysterectomy for nonmalignant lesions, breast lumpectomy, and prostatic surgery for nonmalignant lesions showed no statistically significant differences between cases and controls, colon and rectal cancer combined (Table 4).

When these operations were analyzed by site (colon cancer and rectal cancer) the effects seen above were unaltered, with the exception of breast lumpectomy, where the deficit was seen only in colon cancer cases (RR = 0.22; confidence interval, 0.06–0.78; P = 0.02). The numbers in this last subset were very small (3 cases and 14 controls).

**Multivariate Modeling of Significant Associations**

The illnesses and medications which were consistently statistically significantly associated with the risk of colorectal cancer in the univariate analysis were considered simultaneously in a logistic regression equation. The illnesses considered in this equation were hypertension, stroke, heart disease, chronic chest disease, and chronic arthritis and aspirin use. Although “hemorrhoids” were associated with the risk of colorectal cancer, this variable was not included because of the consideration that “hemorrhoid” symptomatology is likely to be confounded with that of colorectal cancer. Also vitamin supplements were not included in the modeling, because they form part of the dietary risk model, described below.

Chronic chest disease was removed from this equation because the P value associated with its inclusion was only 0.13. The resulting equation showed that both hypertension and stroke were only marginally significant (P = 0.07 and P = 0.06, respectively). The number reporting stroke was small (Table 1) and its effect compared with that of hypertension was considered to have less power; therefore stroke was excluded from the model at this stage. The model then included hypertension, heart disease, chronic arthritis, and aspirin use and was considered to be an adequate explanation of the associations found. These results were consistent across sex and site (colon and rectum) although less statistically powerful in the rectum (Table 5).

In the dietary part of the Melbourne study, a model of dietary risk factors was created. The dietary factors were highly statistically significantly associated with colorectal cancer risk (deviance change approximated by \( \chi^2 = 212 \), P < 0.001). These risk factors were: low intake of dietary fiber vegetables, nonsteroidal antiinflammatory agents, oral contraceptives, and sedatives. The dietary factors which were consistently statistically significantly associated with colorectal cancer risk (7) were: aspirin and aspirin-containing medications, and vitamin C supplements. The dietary factors which were inconsistently statistically significantly associated with colorectal cancer risk (7) were: vitamin A, vitamin E, cigarette smoking, alcohol intake, and coffee intake.

### Table 3 Distribution of medication use among cases and controls and relative risk estimates

<table>
<thead>
<tr>
<th>Medication</th>
<th>Males (cases, n = 388; controls, n = 398)</th>
<th>Females (cases, n = 325°; controls, n = 329)</th>
<th>Total (cases, n = 713; controls, n = 727)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Status</td>
<td>No. using</td>
<td>RR</td>
</tr>
<tr>
<td>Aspirin and aspirin containing</td>
<td>Case</td>
<td>41</td>
<td>0.58</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td>Nonsteroid antiinflammatories</td>
<td>Case</td>
<td>61</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>Case</td>
<td>21</td>
<td>1.69</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>Case</td>
<td>47</td>
<td>1.26</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>39</td>
<td></td>
</tr>
<tr>
<td>Tranquilizers and sedatives</td>
<td>Case</td>
<td>56</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Sleeping pills</td>
<td>Case</td>
<td>44</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Vitamin supplements Retinol</td>
<td>Case</td>
<td>8</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Case</td>
<td>20</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>46</td>
<td></td>
</tr>
</tbody>
</table>

* Two female cases with missing data excluded.

* CI, 95% confidence interval.
curettage
Hysterectomy
surgery
Bowel repair
Peptic
lumpectomy
Prostatic

only, high intake of beef. These factors were fitted as possible meats" (as defined in the study), vitamin supplements, low or found for hypertension, heart disease, chronic arthritis, and of hypertension, stroke, chronic chest disease, chronic arthritis, cruciferous vegetables, dietary vitamin C, pork, fish, “other

aspirin use. Similar effects were found when the data were analyzed by colon cancer and rectal cancer (Table 5).


discussion
In the univariate analysis the statistically significant deficit of hypertension, stroke, chronic chest disease, chronic arthritis,
and aspirin use noted for cases is an interesting finding which challenges the cancer epidemiologist to generate new hypotheses of colorectal cancer etiology and risk. When all these factors were examined together in a logistic regression equation, the effects of stroke and chronic chest disease were very much reduced and so were removed from the consequent etiological model. The authors had no a priori hypotheses regarding colorectal cancer and these factors. Subsequent to these findings, diet was postulated to be the factor explaining the case-control differences found with hypertension, heart disease, chronic arthritis, and aspirin use. This was tested by fitting into a logistic regression model, simultaneously, the dietary risk factors (found in the Melbourne study (7) and described earlier under "Results") and the above illnesses and aspirin use. It was seen that the estimation of all these effects were unchanged, and then it was concluded that the diet risk factors were independent of the above illnesses and aspirin use.

The highly statistically significant deficit of chronic arthritis among cases applied to both males and females separately and was not explained by dietary differences. It may be that the control group was more active throughout their life and have developed degenerative arthritis related to sport or physical activity more often than the colorectal cancer cases. It has been found that physical activity, as seen both in occupational physical activity (8) and in avocational physical activity (9), is protective for colorectal cancer. It may be that with the greater physical activity, the controls are more prone to degenerative arthritis. A previous history of “hemorrhoids” was statistically significantly more common in the cases than in controls and this applied to both males and females. The interpretation of these findings is problematic, partly because the presence or absence of hemorrhoids was not verified in any other way apart from its being reported at the interview and partly because the word “hemorrhoids” is very loosely used for a variety of anorectal conditions other than internal hemorrhoids among lay people. Although for the cases, the illnesses were recorded prior to the onset of the symptoms of colorectal cancer, it is possible that for some of the cases, what was taken by them to be a symptom of “hemorrhoids” was in fact part of the symptomatology of their colorectal cancer. In spite of these serious problems of interpretation this difference is interesting and is consistent with Burkitt’s suggestion that there is an overlapping etiology between those who have colorectal cancer and hemorrhoids, inasmuch as both groups have a low intake of dietary fiber (10). Against this finding on hemorrhoids is that there were no differences in other illnesses postulated by Burkitt to have overlapping etiologies, namely appendicitis and diverticulitis (10).

An examination of the distribution of cancers other than colorectal cancer among cases and controls showed no statistically significant differences (Table 2). Based partly on interpopulation comparisons, it has been suggested that breast cancer and cancer of the endometrium is more frequent in colorectal cancer cases than others (11), and the Melbourne data are consistent with this view (Table 2). Of interest was the observation that in questions which relate to previous surgery which may have been done for a cancer, most of the “don’t know” answers were distributed among the cases (Table 2), perhaps indicating differences in recall, or possibly differences in the personalities of the two groups. If the hypothesis is accepted that those who develop cancer are often personalities who are passive, who internalize and repress their emotions, and who lack self-expression (12, 13), then the very high number of “don’t know” answers among the cases may be interpreted as “don’t want to know.”

There was a statistically significant deficit of the use of aspirin and aspirin-containing compounds among cases and these differences remained statistically significant after adjustment for hypertension, heart disease, chronic arthritis, and diet in both males and females (Table 5). This finding, whatever the mechanism may be, has potential significance in colorectal cancer chemoprevention and merits early confirmation. Aspirin is now widely used in the chemoprophylaxis of cardiovascular disease and may also be useful in a similar way in the prevention of colorectal cancer and perhaps also of other cancers. There was no statistically significant difference between cases and controls in the previous use of oral contraceptives and this was also the finding in two other case control studies (14, 15) and one cohort study (9), although in one of these there was a trend for protection against colon cancer (14) and in another a trend for risk of rectal cancer (15) with oral contraceptive use. The use of tranquilizers, sedatives, and sleeping pills was equally distributed among cases and controls and this was also found in another study on breast cancer and controls (12). This is in keeping with the finding that extreme nervousness or having had a nervous breakdown is similar among cases and controls (Table 1) and indicates that in the development of colorectal cancer, nervous tension and anxiety are not risk or etiological factors (12).

With the exception of uterine curettage and bowel polypectomy, the distribution of all other operations was similar between cases and controls (Table 4). There was a statistically significant deficit among cases of uterine curettage. The authors have no hypotheses about this finding. The finding of a 6-fold risk for colorectal cancer in those with a history of previous colorectal polypectomy is consistent with the view that those with adenomatous colorectal polyps require regular surveillance of their large bowel as a screening measure for colorectal cancer (16). There was no statistically significant association between previous cholecystectomy and colorectal cancer risk in this study (Table 4). While there was some evidence from earlier studies of an association between previous cholecystectomy and right colon cancer in females, this association has probably resulted from a bias due to confounding symptomatology, and on current evidence, it seems most unlikely that previous cholecystectomy is a risk for colorectal cancer (17, 18).

REFERENCES


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