Appendectomy, Appendicitis, and Large Bowel Cancer

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ABSTRACT

A cohort of 167,561 persons who received multiphasic health checkups were followed up for cancer development. A history of appendectomy showed slightly negative nonsignificant associations with the development of cancer of the colon, rectum, and all sites combined. By inference, the relation of appendicitis with these cancers was also inverse. Upper 95% confidence limits were compatible only with small positive associations of appendectomy and appendicitis with these cancers. These data do not support the view that removing the appendix increases cancer risk by diminishing immunocompetency. A link between appendicitis and large bowel cancer has been noted in intersociety correlations and has been hypothesized to be due to prevention of both by a high-fiber diet. However, appendicitis does not appear to be a useful predictor of large bowel cancer within a developed society.

INTRODUCTION

In 1969, Burkitt (1) proposed that large bowel cancer is one of a group of diseases of the digestive system that shows large geographical variation in incidence because of differences in the consumption of dietary fiber. Epidemiological studies and clinical observations had indicated that appendicitis, cancer, polyps, and diverticular disease of the large bowel were common in the Western world and rare in rural Africa. Proposed biological mechanisms for fiber's preventive effect on colon cancer include reduction of exposure to carcinogens due to more rapid fecal transit, dilution of carcinogens, and other beneficial effects on bowel contents, particularly bile acids and fecal flora (2). Increased intraluminal pressures associated with a low-fiber diet have been suggested to foster the development of appendicitis by contributing to the blockage of the appendiceal lumen and interfering with circulation to the mucosa (3).

The strong correlation between appendicitis and large bowel cancer among societies (1) raises the question as to whether the occurrence of appendicitis is a useful predictor of this form of cancer in individuals within a society. Studies to date have looked at appendectomy rather than appendicitis per se as a possible risk indicator and have not provided a clear answer (4-8).

There is also a possible causal link between appendectomy and cancer. The appendix contains significant lymphoid tissue, and it has been suggested that, rather than being a useless vestigial organ, it may play some role in immunocompetency (6).

This study examined the relation of appendectomy and appendicitis to risk of subsequent cancer of the large bowel and cancer of all sites combined.

SUBJECTS AND METHODS

The subjects were subscribers of the Kaiser Permanente Medical Care Program and underwent a multiphasic health checkup (9) in its Oakland or San Francisco medical center between 1964 and 1972.

RESULTS

There was no evidence of an association between appendectomy and cancer of the colon, rectum, or all sites combined (Table 2). In fact, the incidence of these cancers was slightly higher in those without, than in those with, a history of appendectomy. The upper 95% confidence limits implied for men and women, respectively, possible excess risks no greater than 8% and 16% for colon cancer, 8% and 33% for rectal cancer, and 7% and 3% for all cancer.

DISCUSSION

A history of appendectomy was not a risk indicator for subsequent cancer of the colon, rectum, or all sites combined in this large cohort. The latency period studied ranged up to 16 yr after completion of the questionnaire, with a mean of 10 yr. Since the date of appendectomy was not recorded, only the minimum interval from appendectomy to cancer is known. Since the mean age at appendectomy in our program is 30.4 yr (1979 to 1987 data) and the mean age at entry of our study cohort was 40.2 yr, these data probably provide useful information covering at least a few decades of latency.

The question that ascertained a history of appendectomy

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referred to the period before 1 yr prior to the checkup. Some people classified as having no appendectomy might have had one during the prior year. There was another question that asked about "any operations . . . in the past year," but the specific operations were written on the form and not transferred to computer storage. Altogether, 5.6% of men and 6.7% of women of the study group indicated that they had had some operation in the past year. Since only a small fraction of these would have been appendectomies, the misclassification introduced by using only the "before one year ago" question was negligible. Although some errors and misclassification inevitably occur in questionnaire responses, it is likely that the vast majority of subjects knew whether they had an appendectomy and recorded the information accurately. The likely low rate of appendectomy during the previous year and the aging of the cohort away from the time of life when most appendectomies are done (70.5% below age 40, 1979 to 1987 Kaiser Permanente data) both suggest that few of the persons without appendectomy would have had this operation during follow-up, and that misclassification for this reason would have had little effect on our findings.

Of more concern is the fact that not all appendectomies represent appendicitis, since some are performed incidentally during other abdominal operations. Additionally good surgical practice results in the removal of some normal appendices, in perhaps 20% to 25% of operations for suspected appendicitis (12), in order that no irreversibly inflamed ones be missed. What can be concluded about appendicitis, given our results for appendectomy? To estimate roughly the proportion of appendectomies that were incidental to other abdominal surgery, we noted how many patients with them also listed operations on the stomach, gallbladder, and colon, and in women also removal of the uterus. These additional operations were recorded by 8.2% of the men and 34.6% of the women with appendectomy. If we make the extreme assumption that the appendectomies in all of these persons were incidental and assume that appendicitis was not present in 25% of the remaining appendectomies, then 31% of the appendectomies in men and 51% of appendectomies in women did not represent appendicitis. If we assume further that appendectomy without appendicitis is not associated with risk, the dilution of true appendicitis by using appendectomy as its proxy implies that, for appendicitis, the negative associations observed should be more negative; that is, the relative risks should be 31%/1−(1−31%) or 45% farther from 1.0 in men (i.e., 0.71 for colon cancer, 0.45 for rectal cancer, and 0.96 for all cancer) and 51%/1−(1−51%) or 104% farther from 1.0 in women (i.e., 0.88 for colon cancer, 0.79 for rectal cancer, and 0.91 for all cancer). The upper 95% confidence limits of these relative risks, estimated by computer simulation, were similar to, or lower than, those for appendectomy. It would, of course, be preferable to draw conclusions about the risks associated with appendicitis by following a cohort with pathologically proven appendicitis. However, this study appears to rule out all but small increases in the risk of large bowel cancer associated with a history of appendicitis as well as with a history of appendectomy.

Does the absence of an association of appendectomy (or appendicitis) with large bowel cancer within our society cast doubt on the fiber hypothesis? Not necessarily. It may be that the vast majority of persons within our society consume much less fiber than rural Africans and that, at this low level, differences in characteristics other than fiber intake become more important in determining who will get appendicitis or large bowel cancer. Inter society variation is sometimes more revealing than interindividual variation (13).

Appendectomy itself has been suggested as a risk factor for cancer of several sites, quite independent of the postulated relation of appendicitis and colon cancer to a low fiber diet. In a literature review covering papers until 1982, Howson (6) observed that epidemiological data on this subject were inconclusive but noted that the appendix of humans and rabbits contains significant amounts of lymphoid tissue and reiterated the question of whether its removal could raise cancer risk by decreasing immunocompetency. More recent investigations continue to give conflicting results. Silingardi et al. (14) found that appendectomy did not increase the risk of subsequent malignant lymphoma. In a study with few appendectomized subjects, Vobecki et al. (5) found appendectomy associated with an elevated risk of colonic but not rectal cancer in men and with risk of neither in women. Fan and Zhang (7) found a history of appendectomy to be more common in hospitalized patients with cancers of the stomach, large bowel, and breast than among those with cerebral hemorrhage. It was not noted whether the patients with cerebral hemorrhage might have been less capable of giving such a history or, conversely, whether

<table>
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<th>Cancer site</th>
<th>Appendectomy</th>
<th>Cases</th>
<th>Age-adjusted rate/1000 person-years</th>
<th>Relative risk</th>
<th>Cases</th>
<th>Age-adjusted rate/1000 person-years</th>
<th>Relative risk</th>
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<td>Colon</td>
<td>Yes</td>
<td>48</td>
<td>0.41</td>
<td>0.80 (0.59-1.08)*</td>
<td>118</td>
<td>0.47</td>
<td>0.94 (0.76-1.16)</td>
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<td></td>
<td>No</td>
<td>317</td>
<td>0.51</td>
<td></td>
<td>318</td>
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<td></td>
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<tr>
<td>Rectum</td>
<td>Yes</td>
<td>14</td>
<td>0.12</td>
<td>0.62 (0.36-1.08)</td>
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<td>0.14</td>
<td>0.90 (0.61-1.33)</td>
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<td>0.19</td>
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<td>0.97 (0.89-1.07)</td>
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<td>4.62</td>
<td></td>
<td>3280</td>
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</table>

* Numbers in parentheses, 95% confidence interval.
greater efforts to elicit a history of past surgery would be made with patients about to undergo surgery for cancer. Linet and Cartwright (15) found a diminished risk of chronic lymphocytic leukemia in patients with appendectomy. Jarebinski et al. (8) found appendectomy to be associated with an elevated risk of rectal cancer when cases were compared to both hospital controls and neighborhood controls.

In conclusion, this study provides evidence against the hypotheses that a history of appendectomy or appendicitis indicates an increased risk of cancer of the colon, rectum, or all sites combined. These data provide no support to the view that a missing appendix lessens immunocompetency and thereby increases the likelihood of cancer. Our findings do not support the hypothesis that there is an appendicitis-colon cancer association due to low dietary fiber. However, an association between these two diseases may be easier to demonstrate in comparisons among, rather than within, societies.

ACKNOWLEDGMENTS

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REFERENCES

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