Cumulative Incidence of Metachronous Colorectal Cancer

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The incidence of metachronous colorectal cancer has most often been reported as a crude rate: second cancers/index cancers. The reported incidence varies between 0.5 percent and 3.6 percent. However, these calculations do not take into account factors such as length of survival and length of follow-up. The cumulative incidence more accurately reflects the risk for developing a metachronous cancer and was determined in a retrospective analysis of 5,476 patients who were diagnosed with colon or rectal cancer between 1965 and 1985. The cumulative probability was calculated by determining the number of patients developing a metachronous colon cancer vs. the number remaining at risk at that point in time. The calculated annual incidence for metachronous tumors was 0.35 percent per year. The cumulative incidence at 18 years was 6.3 percent. Analysis also demonstrated that metachronous cancers were diagnosed at earlier stages than were index cancers (P = 0.04). Subgroup analysis was performed on patients diagnosed with metachronous cancer before and after 1980. There was a difference in the incidence of metachronous cancers between these two groups (P = 0.04). [Key words: Metachronous colorectal cancer; Second primary malignancy; Incidence; Cumulative incidence; Risk; Probability]

Patiens with a history of one colorectal cancer are at increased risk for developing additional, or metachronous, colorectal cancers. The extent of this risk has not been clearly defined. A review of the literature shows the reported incidence of metachronous colorectal cancer to be between 0.5 percent and 3.6 percent.1-12 These figures have been almost routinely reported as a crude rate, which is the number of patients developing disease (second cancers) divided by the total number of patients entered into the study (index cancers). This crude rate overlooks the fact that many patients die of their disease or of other causes before a second colorectal cancer may develop. It also does not take into account the length of follow-up. A more accurate assessment of the risk of metachronous cancer can be made using life-table methods to calculate the cumulative incidence. In this approach, adjustment is made for variable length of follow-up, and risk for a given period is estimated. This risk reflects the proportion of patients who would be expected to develop a second cancer if all were followed for the entire period.

PATIENTS AND METHODS

All tumor registries in Omaha and Lincoln, Nebraska, provided data for a retrospective review of 5,476 patients with an index colon or rectal cancer diagnosed during the 20-year period from 1965 to 1985. Follow-up was accomplished by local physicians and reported to the registries on a yearly basis until death or loss of follow-up. All additional malignant, but not benign, lesions were recorded by the registries. All patients identified with familial polyposis, ulcerative colitis, or carcinoma in situ were excluded. A metachronous tumor was defined as a second primary colorectal cancer occurring more than two years after the index cancer. Earlier lesions were defined as missed synchronous cancers. There were 68 metachronous lesions that were identified in 66 patients for a crude rate of 1.2 percent.

Statistical Analysis

The time from index diagnosis to metachronous cancer diagnosis was analyzed using product limit survival analysis (BMDP Statistical Software Inc., Los Angeles, CA). Comparison between initial cancers and metachronous cancers in terms of stage at diagnosis (classified as local, regional, or distant) was performed using the chi-squared test of association.

The number of colorectal cancers that would be
expected to occur after the index cancers in this cohort, based on cancer incidence in the general population, was calculated and compared with the actual number of metachronous cancers observed. Years at risk (from two years after the index cancer diagnosis to the end of follow-up) for each patient were divided into five-year age categories. Tables from the National Cancer Institute's "surveillance epidemiology and end results" program provided average annual incidence rates for cancer of the colon and rectum. The products of the rate in each age category and the number of person-years of risk in that age category were summed across age categories to provide the expected numbers of cancer diagnoses. The expected number was compared with the actual number using an accurate approximation of an exact Poisson test, attributed to Byar and described by Breslow and Day. Statistical significance was defined at \( P < 0.05 \).

**RESULTS**

Among the 66 patients who developed metachronous lesions, the age at diagnosis of the index cancer ranged from 34 to 88 years (mean, 67 years). The site distribution of the index cancers paralleled that of historic controls, with 62 percent of cancers being found on the left side, or distal to the splenic flexure. The greatest number of index lesions was found in the sigmoid colon (34 percent). Only 47 percent of metachronous lesions were left-sided, with 17 percent occurring in the sigmoid colon.

Figure 1 compares the number of patients who developed a second lesion with the total number of patients at risk at consecutive annual intervals from the index cancer. Although the number of patients with metachronous cancers appears to diminish with time, the proportion of metachronous lesions to total patients at risk appears to remain constant throughout the study period (Fig. 1). The average interval between index and metachronous lesions was seven years. The longest interval to a second cancer was 18 years during the 20-year follow-up period. A hazard plot (Fig. 2) further demonstrates that the ratio of metachronous to