Epidemiology and Familial Risk of Synchronous and Metachronous Colorectal Cancer: A Population-Based Study in Utah

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BACKGROUND & AIMS: **Patients diagnosed with colorectal cancer (CRC) are at risk for synchronous and metachronous lesions at the time of diagnosis or during follow-up evaluation. We performed a population-based study to evaluate the rate, predictors, and familial risk for synchronous and metachronous CRC in Utah.** Q17

METHODS: **All newly diagnosed cases of CRC between 1980 and 2010 were obtained from the Utah Cancer Registry and linked to pedigrees from the Utah Population Database.**

RESULTS: **Of the 18,782 patients diagnosed with CRC, 134 were diagnosed with synchronous CRC (0.71%) and 300 were diagnosed with metachronous CRC (1.60%). The risk for synchronous CRC was significantly higher in men (odds ratio [OR], 1.45; 95% confidence interval [CI], 1.02–2.06) and in patients age 65 years or older (OR, 1.50; 95% CI, 1.02–2.21). Synchronous CRCs were located more often in the proximal colon (OR, 1.70; 95% CI, 1.20–2.41). First-degree relatives of cases with synchronous (OR, 1.86; 95% CI, 1.37–2.53), metachronous (OR, 2.34; 95% CI, 1.62–3.36), or solitary CRC (OR, 1.75; 95% CI, 1.63–1.88) were at increased risk for developing CRC, compared with relatives of CRC-free individuals. Four percent of first-degree relatives of patients with synchronous or metachronous cancer developed CRC at younger ages than the age recommended for initiating colorectal cancer screening (based on familial risk), and therefore would not have been screened.**

CONCLUSIONS: **Of patients diagnosed with CRC, 2.3% are found to have synchronous lesions or develop metachronous CRC during follow-up evaluation. Relatives of these patients have a greater risk of CRC than those without a family history of CRC. These results highlight the importance of obtaining a thorough family history and adhering strictly to surveillance guidelines during management of high-risk patients.**

Keywords: Colon Cancer; Tumor; Heritable; Prevention.

Q18Q19 Colorectal cancer (CRC) is the third most common cancer in the United States and the second leading cause of cancer-related mortality in men and women.[1] Patients diagnosed with sporadic CRC are at risk of a synchronous CRC at the time of diagnosis as well as metachronous CRC during follow-up evaluation. Appropriate identification of patients at risk for metachronous CRC has important clinical implications for tailored surveillance programs and reduction of morbidity. Current treatment and surveillance guidelines do not account for synchronous–metachronous CRC as a category requiring modified management.[2] Heritability is one of the strongest risk factors for CRC and familial clustering of CRC is common outside of a defined genetic syndrome. Current screening guidelines account for family history of CRC as a risk factor for cancer and recommend earlier and more frequent surveillance.[3]

The aim of this study was to assess the incidence of synchronous and metachronous CRC in a large population-based cohort of patients with CRC and to Q20 identify patient- and tumor-related characteristics associated with its presence. Our study quantifies the risk of Q21

Abbreviations used in this paper: **CI, confidence interval; CRC, colorectal cancer; FAP, familial adenomatous polyposis; FC, first cousin; FDR, first-degree relative; OR, odds ratio; SDR, second-degree relative; UCR, Utah Cancer Registry; UPDB, Utah Population Database.**

1542-3565/$36.00
http://dx.doi.org/10.1016/j.cgh.2014.04.017

CRC in relatives (first-, second-, and third-degree) of individuals with synchronous and metachronous CRC compared with solitary CRC or no CRC. Our study design is feasible because of the unique linkage between the statewide cancer registry and comprehensive family pedigrees through Utah genealogy records.

Methods

Design

This study was approved by the Institutional Review Boards of the University of Utah and Intermountain Healthcare and by the Resource for Genetic and Epidemiologic Research (http://www.research.utah.edu/rge/), an administrative oversight board charged in 1982 by Executive Order of the Governor of Utah to govern access to the Utah Population Database (UPDB).

We performed a population-based cohort study of synchronous and metachronous CRC diagnosed in the state of Utah between 1980 and 2010 and recorded in the Utah Cancer Registry (UCR). This time period was selected because colonoscopy was widely available in the state and would best reflect present-day practice and minimize misclassification bias of synchronous CRC. De-identified medical information on these patients was merged with family structure in the UPDB genealogies to investigate the incidence, predictors, survival, and familial aggregation.

Description of Databases

This investigation takes advantage of unique Utah databases. The UPDB combines genealogies from the family history library maintained by the Church of Jesus Christ of Latter-Day Saints, dating back to the early 1800s, linked to data from statewide resources, including the UCR, driver license data, as well as birth and death certificates. There are currently more than 7.2 million unique individuals in the database and the Utah family histories represent pedigrees that may span as many as 12 generations. Previous demographic and genetic analyses have shown that the population recorded in the UPDB is genetically representative of US white and northern European populations with a low level of inbreeding.[4] The UCR is a statewide cancer registry established in 1966 and since 1973 it has been part of the SEER network of the National Cancer Institute registries. By state law, all incident cancer diagnoses must be reported to the UCR.

Study Population

Electronic records for patients with CRC were derived from the Utah Cancer Registry. The study cohort comprised 18,782 patients, diagnosed with colorectal cancer (adenocarcinoma) in the period from 1980 to 2010. Patients with an unknown site of diagnosis or nonadenocarcinoma were excluded.

Study Definitions

Synchronous CRC was defined according to the criteria previously defined by Warren and Gates[5] as follows: (1) pathologically proven adenocarcinoma; (2) diagnosed at the same time or within 6 months (≤180 d) of the initial diagnosis. Metachronous CRC was defined according to the criteria defined by Moertel et al[6] as follows: (1) pathologically proven adenocarcinoma; and (2) diagnosed more than 6 months (>180 d) after the initial carcinoma. Patients with more than 2 separate CRCs were defined as synchronous or metachronous based on the time between the first 2 cancer diagnoses. For synchronous cancers, stage and site were based on the most advanced tumor. For metachronous cancers, stage and site were based on the initial/first tumor. Patients diagnosed with one CRC were classified as having solitary CRC.

The localization of the tumors, originally specified according to the International Classification of Disease for Oncology, was regrouped into the proximal colon (cecum, ascending, colon, hepatic flexure, transverse colon) and the distal colon (splenic flexure, descending colon, sigmoid colon, rectosigmoid junction, and rectum).

Patients who had a molecular diagnosis of familial adenomatous polyposis (FAP with a confirmed APC mutation) were determined by a linkage to our institutions hereditary gastrointestinal cancer registry, which cares for the vast majority of FAP families in the state (>620 FAP patients). A sensitivity analysis was conducted by restricting the analysis to those with and without a diagnosis of FAP.

Study Analysis

The primary objectives of this study were as follows: (1) to compare patient and tumor characteristics between patients diagnosed with synchronous and solitary CRC, and (2) to compare patient and tumor characteristics between patients diagnosed with metachronous and solitary CRC, using separate models. We began with assessing bivariate associations using chi-square tests or analysis of variance, and then we assessed multivariable relationships using logistic regression. Age and sex were included in all models. No adjustments were made for multiple comparisons with the same reference population. The concordance between locations of multiple cancers (for patients with synchronous or metachronous CRC) was analyzed using the κ statistic, which is a measure of agreement between multiple ordered events. Agreement was moderate when the κ value was 0.41 or greater, and substantial when the κ value was greater than 0.61.[7,8] SAS (version 9.1; SAS Institute, Cary, NC) was used for data management and analysis.

Familial Risk Analysis

Relative risk of CRC in first-degree relatives (FDRs), second-degree relatives (SDRs), and first cousins (FCs) of patients with solitary, synchronous, and metachronous