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Increased Risk of Colorectal Neoplasia Among Family Members of Patients With Colorectal Cancer: A Population-Based Study in Utah

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This article has an accompanying continuing medical education activity on page e15. Learning Objective: Upon completion of this exam, successful learners will be able to: (1) discuss the increased risk of CRC among individuals with a family history of CRC in a first-degree relative; (2) discuss the increased risk of adenomas among individuals with a family history of CRC in a first degree relative; (3) discuss the hazard ratios for this increased risk among individuals with a first-degree relative or a second-degree relative with a history of CRC.

BACKGROUND & AIMS: Colorectal cancer (CRC) frequently develops in multiple members of the same families, but more data are needed to prepare effective screening guidelines. We quantified the risk of CRC and adenomas in first-degree relatives (FDRs) and second-degree relatives and first cousins of individuals with CRC, and stratified risk based on age at cancer diagnosis. **METHODS:** We performed a case-control study of Utah residents, 50–80 years old, who underwent colonoscopy from 1995 through 2009. Index cases (exposed to colonoscopy) were colonoscopy patients with a CRC diagnosis. Age- and sex-matched individuals, unexposed to colonoscopy (controls) were selected to form the comparison groups for determining risk in relatives. Colonoscopy results were linked to cancer and pedigree information from the Utah Population Database to investigate familial aggregation of colorectal neoplasia using Cox regression analysis. **RESULTS:** Of 126,936 patients who underwent a colonoscopy, 3804 were diagnosed with CRC and defined the index cases. FDRs had an increased risk of CRC (hazard rate ratio [HRR], 1.79; 95% confidence interval [CI],1.59–2.03), as did second-degree relatives (HRR, 1.32; 95% CI, 1.19–1.47) and first cousins (HRR, 1.15; 95% CI, 1.07–1.25), compared with relatives of controls. This risk was greater for FDRs when index patients developed CRC at younger than age 60 years (HRR, 2.11; 95% CI, 1.70–2.63), compared with older than age 60 years (HRR, 1.77; 95% CI, 1.58–1.99). The risk of adenomas (HRR, 1.82; 95% CI, 1.66–2.00) and adenomas with villous histology (HRR, 2.43; 95% CI, 1.96–3.01) also were increased in FDRs. Three percent of CRCs in FDRs would have been missed if the current guidelines, which stratify screening recommendations by the age of the proband, were strictly followed. **CONCLUSIONS:** FDRs, second-degree relatives, and first cousins of patients who undergo colonoscopy and are found to have CRC have a significant increase in the risk of colorectal neoplasia. These data should be considered when establishing CRC screening guidelines for individuals and families.

Keywords: Colon Cancer; Adenomatous Polyps; Recurrence Risk; Genetic.

Colorectal cancer (CRC) is the fourth most common cancer in the United States and is the second leading cause of cancer-related mortality.[1] Heritability is one of the strongest risk factors for CRC and familial clustering of CRC is common outside of a defined genetic syndrome (eg, familial adenomatous polyposis or Lynch syndrome.[2]

Screening interventions such as colonoscopy are offered earlier to individuals with a family history of CRC. Specifically, current multisociety guidelines recommend that patients with a first-degree relative (FDR) with CRC or an advanced adenoma before age 60 should undergo screening colonoscopy starting at age 40, or 10 years before the diagnosis age of the index patient, and repeat surveillance every 5 years.[3] These current recommendations are based primarily on a prospective study by Fuchs et al,[4] which found that FDRs of CRC patients had a risk of CRC at age 40 that was similar to the risk of CRC in average-risk patients at the age of 50 (relative risk [RR], 1.72; 95% confidence interval [CI], 1.34–2.19).

Because current guidelines advise earlier screening for those with a family history of CRC as described earlier, it is important to validate the increased risk of CRC and adenomatous polyps in relatives of patients with CRC in a population-based study, and to examine the risk in immediate and more distant relatives, as well as by age groups.

In this population-based, case-control study our primary objectives were to quantify the risk of CRC and adenomas in the relatives (FDRs, second-degree relatives [SDRs], first

Abbreviations used in this paper: **CI, confidence interval; CRC, colorectal cancer; FC, first cousin; FDR, first-degree relative; HRR, hazard rate ratio; IHC, Intermountain Healthcare; RR, relative risk; SDR, second-degree relative; UCR, Utah Cancer Registry; UPDB, Utah Population Database; UUHSC, University of Utah Health Sciences.**

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cousins [FCs], and spouses) of individuals with CRC, stratified by age of cancer diagnosis. In addition to first-degree relatives, our study was able to assess the risk of cancer or adenomatous polyps in distant relatives (SDRs or FCs) and spouses of individuals with CRC, and also examined this risk based on the age at CRC diagnosis. Comprehensive family history was available through extensive Utah genealogies linked to a statewide cancer registry and medical records that did not rely on self-report. Our study design was feasible because of these unique linked resources.

Methods

Design

This study was approved by the Institutional Review Boards of the University of Utah and Intermountain Healthcare (IHC) 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), the resource for the data used in this analysis.

We performed a population-based, case-control study of Utah residents, between 50 and 80 years of age, who underwent a colonoscopy between February 15, 1995, and January 31, 2009, at IHC and/or the University of Utah Health Sciences (UUHSC) clinical facilities. De-identified medical information on these patients was merged with family structure data in the UPDB genealogies, which also includes cancer histories from the Utah Cancer Registry (UCR), a Surveillance, Epidemiology, and End Results registry, to investigate the familial aggregation of colon adenomas and CRC.

Description of the Databases

This investigation took advantage of unique Utah databases. The study required patient-level data integration between IHC, the UUHSC, and the UPDB. The UPDB combines genealogies with data from statewide resources, including the UCR, statewide inpatient discharge and ambulatory surgery records, driver license data, as well as birth and death certificates. This resource also has been linked to the demographic records from the UUHSC[5] and IHC.[6] In combination, the UUHSC and IHC together provide cancer-related care to more than 85% of the contemporary Utah population. 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.[7] Of particular interest for this study was the inclusion of the UCR records as part of the UPDB. The UCR is a statewide cancer registry established in 1966, and since 1973 it has been part of the Surveillance, Epidemiology, and End Results network of the National Cancer Institute registries. Given an ongoing and accurate assessment of family history of cancer that does not depend on self-report, the UPDB provides a valuable resource for a thorough analysis of the familial nature of CRC.

Linkage of Electronic Medical Record Data to the UPDB

These linked resources have been used to assess colonoscopy screening rates in high-risk individuals[8] as well as recent studies on familial aggregation of adenomas,[9] missed-interval CRCs,[10] preeclampsia,[11] spontaneous preterm delivery,[12] cancer in twins,[13] heritability of inflammatory bowel disease,[14] and effects of family conditions on later-life mortality.[15]

Study Definition

Colonoscopy data was extracted from the institutional records using Current Procedural Terminology codes 45378, 45379, 45380, 45383, 45384, and 45385. Index case subjects (probands) were defined as those who underwent colonoscopy and had a diagnosis of CRC (CRC diagnosis could have occurred before, coincident with, or after colonoscopy). Sensitivity analyses were performed to determine whether results differed if the CRC diagnosis occurred coincident with colonoscopy or after colonoscopy. CRC and adenoma occurrence at colonoscopy was obtained from institutional records and CRC diagnosis before or after colonoscopy, and in relatives of index cases and controls were obtained from the UPDB (Figure 1). The relative risk of CRC diagnosed in FDRs, SDRs, and FCs of index cases was determined by comparison of CRC occurrence in these relatives compared with relatives of population controls. To evaluate the risk of adenomas in relatives of index cases, adenomas were identified through pathology reports. For this study, advanced polyps were defined as those that had any component of villous histology, also identified through pathology reports. The linked pathology database did not have information on polyp size or high-grade dysplasia, which are the other criteria associated with a definition of an advanced adenoma ($\geq$10 mm or high-grade dysplasia).

Primary Control Group Selection

Population controls were selected randomly from the UPDB and matched 5:1 to index cases by sex and birth year. The controls were selected without replacement (ie, controls were used only once). Once index controls were selected, their relatives were determined from the UPDB genealogies and any relatives within relationship categories (FDRs, SDRs, and FCs) with or without CRC or adenoma subsequently were identified to form the comparison group for determining risk in relatives of index cases. In addition to having genealogy information to determine family relationships in the UPDB, controls had to have the following: (1) medical follow-up evaluation at least as long as their respective matched index case (ie, follow-up evaluation was based on the most recent date an individual had an event recorded in Utah from vital records (deaths, births, adoptions, marriages, and divorces, Utah Driver's license registrations and renewals, voter registrations, and inpatient discharges and ambulatory surgery records); and (2) no history of CRC. Records are linked from these various sources at least annually to the UPDB. Because IHC and the UUHSC provide the majority of health services in Utah, study controls who received health-related services were highly likely to be seen within these 2 systems. Controls were selected as not having CRC so the occurrence of this malignancy in their FDRs, SDRs, and FCs could be compared with the relatives of index cases in whom CRC has occurred.

Secondary Control Group Selection

A second group of controls with family relationships in the UPDB (also matched by sex and birth year in a target ratio of 5