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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

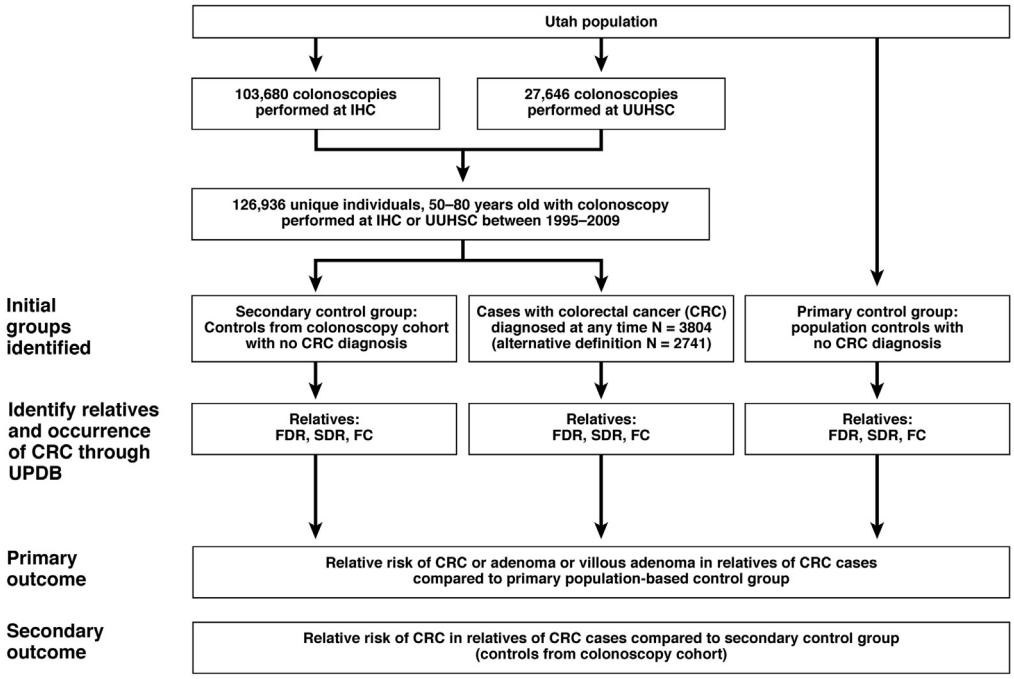
Colonoscopy data was extracted from the institutional records using Current Procedural Terminology codes 45378, 45379, 45380, 45383, 45384, and 45385. Index case subjects (probands) were defined as those who underwent colonoscopy and had a diagnosis of CRC (CRC diagnosis could have occurred before, coincident 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



Abbreviations: FDR (first-degree relative; parent, child, sibling), SDR (second-degree relative; aunt/uncle, niece/nephew, grandparent/grandchild), FC (first-cousin). UPDB - Utah Population DataBase.

Figure 1. Study flow diagram.

to 1 to index cases) were selected exclusively from the colonoscopy cohort of those without a diagnosis of adenomas or CRC. A subgroup analysis was performed using this restricted secondary control population.

Spousal Analysis

We limited spousal analysis to those index cases and controls who had children, no childless index cases or controls were included. Spouses were defined as the married or unmarried co-parent of the index cases or controls who had children determined from the UPDB records (71% and 68% of all index cases or controls, respectively). The relative risk of CRC diagnosed in spouses of index cases was determined by comparison of CRC occurrence in these relatives compared with spousal relatives of population controls.

Statistical Analysis

By using software developed specifically for the UPDB kinship analysis and in conjunction with the software package R (R version 3.0.2 for Linux OS, Vienna, Austria), the magnitude of familial risk was estimated by Cox regression to assess the relative risk of CRC and adenoma for FDRs, SDRs, FCs, and spouses of colonoscopy patients who were diagnosed with CRC themselves.[16] This is presented as a hazard rate ratio of recurrence (HRR). Those who died without a diagnosis or who were not diagnosed by 2012 were treated as right-censored. The HRR represents the ratio of the hazard rate for the occurrence of CRC and adenoma among relatives of the index cases with the comparable hazard rate among the relatives of the controls. Specific groups of relatives (FDRs, SDRs, FCs, and spouses) of index cases were compared with the comparable relatives of the matched controls. Analyses were performed separately for each relationship group (FDRs, SDRs, FCs, spouses). Covariates in the Cox regression models included sex and birth year, and left and right censoring was performed as described in the Supplementary Materials and Methods. Because observations within families are nonindependent, the Huber–White sandwich estimator of variance for clustered data was used because it accounts for departures from standard statistical assumptions.[16,17] This analysis corrects for any families that were analyzed multiple times because of multiple CRC cases within the family. To determine if the risk of CRC in relatives of index patients (probands) younger than 60 years old were statistically greater than those of index CRC patients older than the age of 60, a case–case analysis also was completed in which CRC occurrence in the first-degree relatives of CRC cases younger than age 60 years was compared with relatives of CRC cases older than age 60. Additional details are included in the Supplementary Materials and Methods.

The percentage of FDRs and SDRs diagnosed with CRC based on age groups also was computed.

Results

This report analyzed the relative risks (HRR) for colon and rectal cancer and adenomatous polyps from 27,646 colonoscopy patients at the UUHSC and 103,680 colonoscopy patients from IHC. When combined and accounting for patients who had procedures performed in both hospital systems there were 126,936 unique individuals who had undergone a colonoscopy. There were 3804 patients in this cohort who were diagnosed with CRC and they defined the index case (proband) population. Of these individuals, 2741 had a diagnosis of CRC coincident with or after their index or first colonoscopy and were included in the sensitivity analysis.

Table 1. Descriptive Characteristics of Colonoscopy Patients With Colorectal Cancer (Index Cases) and Matched Controls

	Index cases[a]	Population controls (5:1)[b]	Colonoscopy controls (5:1)[c]
N	3804	19,020	13,234
Men (%)	2034 (53.5)	10,170 (53.5)	6777 (51.2%)
Women (%)	1770 (46.5)	8850 (46.5)	6457 (48.8%)
Median age at diagnosis (cases) or age at last follow-up evaluation (controls), *y*	66	70	68
Known church affiliation[d]	1292 (34.0)	6369 (33.5)	4599 (34.8)
Mean FDRs per subject	4.5	4.4	4.6
Median (range) FDRs per subject	4 (1–25)	4 (1–23)	4 (1–22)
Mean SDRs per subject	8.6	7.2	9.6
Median (range) SDRs per subject	4 (0–87)	2 (0–67)	4 (0–81)
Mean FCs per subject	12.8	8.9	11.6
Median (range) FCs per subject	0 (0–96)	0 (0–89)	2 (1–114)

[a]Utah Cancer Registry data for CRC diagnoses from 1966 to 2009.
[b]Controls selected from Utah population without diagnosis of CRC ever. Matched 5:1 on sex and birth year and had follow-up evaluation at least as long as date of case diagnosis.
[c]Controls selected from colonoscopy cohort, without findings of adenomas or CRC. Matched 5:1 (to 2649 cases who had relatives in the colonoscopy cohort) on sex and birth year and had follow-up evaluation at least as long as date of case diagnosis.
[d]Affiliation with the Church of Jesus Christ of Latter-day Saints.

Table 1 shows the descriptive features of index cases (colonoscopy patients with a diagnosis of CRC) and index controls (the primary control group, which was population-based, and the secondary control group, which was from the colonoscopy cohort) in this study. The median age of the index cases was 66 years and the median age of the population controls was 70 years, and 68 years for colonoscopy controls. The median age of controls was slightly higher than that of cases at the time of their selection for analysis because controls (matched on birth year) had to have follow-up evaluation in the UPDB for at least as long as the respective index case based on age at diagnosis. Affiliation with the Church of Jesus Christ of Latter-day Saints (or Mormons) was similarly high for index cases and controls and was associated with proscriptions against alcohol consumption and cigarette smoking.[18] For index cases and population or colonoscopy controls, the mean number of FDRs, SDRs, and FCs with adequate follow-up evaluation in Utah was similar, reducing the likelihood of detection bias.

Table 2 shows the distribution of CRC among relatives of index cases and controls based on the degree of relationship. Controls for this analysis and those that followed were population-based controls unless otherwise stated. An increased risk of CRC was found in FDRs (HRR, 1.79; 95% CI, 1.59–2.03), SDRs (HRR, 1.32; 95% CI, 1.19–1.47), and FCs (HRR, 1.15; 95% CI, 1.07–1.25) of index cases compared with CRC occurrence in FDRs, SDRs, and FCs of population controls. The magnitude of risk associated with CRC in a relative was dependent on the degree of relationship. Importantly, we found no statistically significant increased risk of CRC in spouses of index cases compared with spouses of controls (HRR, 1.24; 95% CI, 0.92–1.66).

Sensitivity analysis using the subcohort of individuals diagnosed with CRC coincident with or after with their colonoscopy showed a similar increased risk of CRC in relatives that also was dependent on the degree of relationship and age of the case (Supplementary Tables 1, 2, and 3). Analysis using the secondary control population selected exclusively from the colonoscopy cohort without findings of colorectal adenomas or CRC also showed a similar increased risk of CRC in FDRs, SDRs, and FCs (Supplementary Table 4).

We also looked at the relative risk for adenoma and advanced villous adenoma polyps in the relatives of CRC index cases compared with relatives of population controls (Table 3 and Supplementary Table 5). The HRR of an

Table 2. Risk for CRC in Relatives of CRC Cases With Primary Control Group (Population-Based Controls)

	CRC index cases		Population-based controls				
Relationship	Affected	Unaffected	Affected	Unaffected	HRR	95% CI	*P*
FDR	396	16,761	1105	82,319	1.79	1.59–2.03	<.001
SDR	533	32,326	1652	134,405	1.32	1.19–1.47	<.001
FC	932	47,886	2869	166,543	1.15	1.07–1.25	<.001
Spouse	58	2650	223	12,760	1.24	0.92–1.66	.16

NOTE. Data show CRC in relatives of index cases diagnosed from 1966 to 2009 in the UCR.

Table 3. Risk for Any Adenomas in Relatives of CRC Cases

	CRC index cases		Population-based controls				
Relationship	Affected	Unaffected	Affected	Unaffected	HRR	95% CI	*P*
FDR	626	16,565	1700	81,881	1.82	1.66–2.00	<.001
SDR	540	32,344	1890	134,495	1.19	1.08–1.31	<.001
FC	1334	47,508	4165	165,472	1.10	1.04–1.17	.002

adenoma in an FDR was 1.82 (95% CI, 1.66–2.00), in an SDR was 1.19 (95% CI, 1.08–1.31), and in an FC was 1.10 (95% CI, 1.04–1.17) of CRC index cases compared with relatives of controls (Table 3). An increased risk for an advanced villous adenoma also was found in FDRs of cases with CRC compared with FDRs of controls (HRR, 2.43; 95% CI, 1.96–3.01) (Supplementary Table 5). Sensitivity analysis using the subcohort of individuals diagnosed with CRC coincident with or after their colonoscopy showed a similar increased risk of adenomas in relatives dependent on the degree of relationship and age of cases (Supplementary Tables 6 and 7). A similar increased risk was found when the secondary control group (from the colonoscopy cohort) was used (Supplementary Tables 8 and 9).

When stratified by age at CRC diagnosis in index cases, FDRs of those diagnosed with CRC at younger than age 60 years had a greater than 2-fold increased risk of CRC compared with relatives of controls (FDRs: HRR, 2.11; 95% CI, 1.70–2.63). However, even for index cases diagnosed with CRC at age 60 years and older, FDRs had an increased risk of CRC (HRR, 1.77; 95% CI, 1.58–1.99) (Table 4). A similar increased risk of adenomas was seen in the FDRs of index cases diagnosed with CRC at younger than age 60 years (HRR, 2.04; 95% CI, 1.74–2.39) or older than 60 years (HRR, 1.58; 95% CI, 1.37–1.83) (Table 5). A sensitivity analysis using the alternate definitions of CRC diagnosis in relation to colonoscopy (ie, conincident with or after colonoscopy) produced similar results when stratified by age of CRC diagnosis in the index case (Supplementary Tables 2 and 3).

First-degree relatives of CRC cases diagnosed at younger than age 60 years had a statistically greater risk of CRC than those of CRC cases diagnosed at age 60 years and older in a case–case analysis. The risk of CRC in FDRs of index CRC patients younger than age 60 years was increased 1.5-fold (HRR, 1.50; 95% CI, 1.19–1.89) compared with relatives of CRC patients older than age 60 years (Supplementary Table 10).

The breakdown by age group of first- and second-degree relatives of cases diagnosed with CRC stratified by age shows that 3% of CRCs would have been missed using present guidelines that do not advise screening at a younger age for FDRs of persons with CRC older than age 60 years (Table 6).

Discussion

The risks for CRC in FDRs (ie, immediate relatives) of large-bowel cancer patients in the present study are similar to findings of studies from France,[19] Sweden,[20] and Australia.[21] In addition, systematic reviews and meta-analyses incorporating 47 CRC familial risk studies provide similar risks in FDRs, despite differences in study design and populations examined.[22–24] The present investigation adds considerable support to these investigations and expands their findings by examining familial risk in a population-based data set, by including both CRC and adenomatous polyps in the study and by assessing familial risk in both immediate and more distant relatives. The size, genealogic-based, and state-wide nature of the study circumvents ascertainment biases and recall biases that are inherent to many studies and allows precise risk determinations in more distant relatives by age group.

Complete cancer occurrence in subjects was determined by including CRC diagnosis before, coincident with or after colonoscopy, to establish our case groups; and similar colorectal neoplasia risks were determined in relatives in each of these 3 groups. The primary case definition was based on the ability to ascertain the most cases from the database and thereby allow maximum subgroup analysis.

Table 4. Risk for CRC in Relatives of CRC Cases, Stratified by Age of CRC Diagnosis

	CRC index cases <60 y			CRC index cases ≥60 y		
Relationship	HRR	95% CI	*P*	HRR	95% CI	*P*
FDR	2.11	1.70–2.63	<.001	1.77	1.58–1.99	<.001
SDR	1.41	1.19–1.66	<.001	1.17	1.02–1.34	.02
FC	1.10	0.91–1.33	.33	1.16	1.06–1.26	.001
Spouse	1.11	0.54–2.31	.77	0.93	0.63–1.36	.69

Table 5. Risk for Any Adenomas in Relatives of CRC Cases, Stratified by Age of CRC Diagnosis

	CRC index cases < 60 y			CRC index cases ≥ 60 y		
Relationship	HRR	95% CI	*P*	HRR	95% CI	*P*
FDR	2.04	1.74–2.39	<.001	1.58	1.37–1.83	<.001
SDR	1.69	1.42–2.02	<.001	1.15	0.99–1.34	.08
FC	1.03	0.92–1.15	.65	1.20	1.11–1.29	<.001

Table 6. Percentage of Relatives Diagnosed With CRC Based on Age, Stratified by Age of CRC Index Case

Relationship	Age groups	CRC cases, N (%)	CRC cases <60 y, N (%)	CRC cases ≥60 y, N (%)
FDR with CRC	30 to <40 y	2 (0.5)	2 (1.6)	0 (0.0)
	40 to <50 y	18 (4.5)	10 (7.9)	8 (3.0)
	50–89 y	376 (95.0)	114 (90.5)	262 (97.0)
SDR with CRC	30 to <40 y	6 (1.1)	4 (1.8)	2 (0.6)
	40 to <50 y	14 (2.6)	10 (4.5)	4 (1.3)
	50–89 y	513 (96.3)	206 (93.6)	307 (98.0)

Age stratification and alternate outcomes such as advanced villous adenoma occurrence in relatives were particularly important variables that would best be served by a large data set. Alternate case definitions then were chosen to verify the accuracy of the first definition findings and be certain an alternative selection schema did not affect results. We also were able to use alternate control groups (a primary control group selected from the entire Utah population or a secondary control group from those restricted to adenoma/CRC-free controls from the same colonoscopy cohort as cases) and found similar risks of CRC in relatives. These consistent findings that use alternate case definitions and control groups strongly indicate that our results are robust across samples and circumstances.

The study is applicable to typical clinical practice care settings because it includes both a large academic medical center and a large managed care organization that together provide care to approximately 85% of Utah's population. By nesting the study design within a large colonoscopy cohort, the investigation reflects the daily practice of gastroenterologists and the patients they meet in their endoscopy practices. The population of Utah is also representative of US/European white populations with a low level of inbreeding.[7] Hence, the results are applicable to similar populations in the United States.

The findings of increased neoplasia risk in more distant relatives compared with spouses favors an inherited component to explain the risk in families. A Swedish Family-Cancer data base study with spouse controls found similar results.[25] In the present study spouses showed a slight, but nonsignificant, increase in cancer risk but the analysis may have been underpowered to detect such a small difference (Table 2). The risk levels in more distant relatives and spouses alone were not sufficient to indicate more aggressive screening than the general population. Another caveat was that a modest proportion of index cases (15%) with an affected FDR also had an affected SDR or FC. It is possible that risk estimates may be inflated by such families because more than one proband of these families would have been analyzed for familiality. To address this issue we applied analytic techniques that corrected for the multiple analysis of large families (Supplementary Materials and Methods).

Only a few studies have examined the risk of CRC in relatives stratified by the age of CRC in the index case. Pooled risk estimates from these studies showed that relatives of an affected proband younger than age 50 years (RR, 3.55; 95% CI, 1.84–6.83) were at a greater risk of developing CRC than relatives of a proband older than age 50 years (RR, 2.18; 95% CI, 1.56–3.04).[23] These findings were consistent with our results in which first-degree relatives had an increased risk of CRC overall, although the magnitude of the risk was higher for relatives of those diagnosed at an earlier age (<60 y) (Table 4). Our case–case analysis further supports this age differential finding in that relatives of patients diagnosed at younger than age 60 years are at a 50% greater risk of CRC compared with relatives of patients diagnosed at an older age. These findings support the current recommendations that advocate for earlier screening in FDRs of individuals diagnosed at younger than age 60. Application of current screening guidelines to our study set shows that only 2.5% (10 of 396) of FDRs developed CRC at younger than the presently recommended ages to start screening (based on familial risk). This small miss rate further supports the current recommendations because population-based screening with a miss rate of less than 3% likely is adequate. Substantial cost (and possibly harm) related to more aggressive interventions may accompany any adjustment to the present guidelines and would need to be studied carefully before instigation.

It also is important to note that our study also clearly showed an increased CRC risk in relatives for older-age probands, a finding that has not been appreciated often. However, the level of risk probably does not justify more aggressive screening than is now given for the general population. Nonetheless, increased awareness of this risk may well serve as an incentive to get screening at all, and may add to the risk conferred by environmental and other personal factors.[26]

The occurrence of adenomas in relatives of CRC cases has not been examined in most studies of familial CRC. A French case-control study, however, found the occurrence of adenomas ≥10 mm to be increased 2.5-fold in subjects with a family history of colorectal cancer.[27] The present study showed an increased risk of any adenomas in CRC relatives as well as an increased risk of adenomas with villous histology.

Certain limitations of the present study are noteworthy. Patients with known hereditary cancer syndromes, in particular familial adenomatous polyposis and Lynch

syndrome, could not specifically be excluded. Because both of these conditions are rare, however, and together account for less than approximately 3% of all colon cancers, they are unlikely to modify the statistical associations shown. Another issue is that extraction of data from electronic medical records has limitations in the information that can be gathered. We were able to determine villous histology, which is one component of the definition of advanced adenomas, but we were not able to identify those adenomas with large size (>1 cm) or with high-grade dysplasia. These shortcomings somewhat limit the interpretation of risk associated with advanced adenomas. Another caveat was that the indication for colonoscopy was not ascertained specifically and perhaps might introduce bias. Many screening procedures also are coded for a diagnosis found at colonoscopy or other unrelated symptoms and thus it would be nearly impossible to establish a study population of only screening colonoscopies. However, we were able to examine this issue by performing a sensitivity analysis by altering the CRC case definition in relation to timing of colonoscopy and found consistent results. In addition, because the study was nested within a large colonoscopy cohort, the findings may reflect gastroenterologists' usual clinical practice of colonoscopy, which includes patients referred for screening as well as other indications. We also did not have information on the documented completeness of the colonoscopic examination or quality of the bowel preparation, although these issues are likely to be reflected similarly in both sets of relatives across the case and control groups. Dietary factors, medication (nonsteroidal anti-inflammatory drug use), and body mass index were not available for inclusion in our analysis, specific information regarding race and ethnicity were not available either. A common issue in prior studies was that relatives of index cases may be more likely to undergo colonoscopy and have adenomas found than controls. Although this may have been present in our study regarding adenoma analysis, colorectal cancer diagnosis, which is derived from the statewide registry, would not be affected. Also, we were able to show that a similar number of relatives of index cases and controls were available for analysis, and this should allow an accurate comparison of the relative risk of adenomas between relatives of cases and controls. A stratified analysis to interpret the effect of the index patient's age on familial risk of CRC also was subject to the limitations of interpretation of subgroup analyses. The population of Utah is representative of US/European Caucasian populations and our results thus are applicable to similar populations in the Unite States. The high rate of affiliation with the Church of Jesus Christ of Latter-day Saints in Utah and associated low rates of smoking and alcohol use in this population could differ from other populations.

In conclusion, we conducted a population-based, case-control study in Utah, showing that FDRs, SDRs, and FCs of colonoscopy patients with CRC are at increased risk of colorectal neoplasia (CRC, adenomas, and advanced adenomas). Increased risk was observed in all relatives regardless of age at the index patient's CRC diagnosis, although the risk was 50% greater for relatives of younger-age index cases. The study confirms and expands the evidence of common familial risk for CRC and should become part of the data considered when screening strategies are synthesized. Our data support the current screening guidelines for persons with a family history of CRC, primarily more aggressive screening for FDRs of persons with CRC at an age younger than 60 years. Risks for more distant relatives and for relatives of older index cases are not sufficient to advocate for increased screening, although this risk knowledge may be helpful in encouraging average-risk screening. Future studies to examine the risk of CRC in relatives of patients diagnosed with advanced adenomas are required to validate other components of the current CRC screening guidelines. Our study further supports an inherited component for common familial CRC because the increased risk was observed in both immediate and more distant relatives. Clinicians' awareness of the familial risks shown in this study will be of considerable assistance when working with individuals and families with CRC.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at http://dx.doi.org/10.1053/j.gastro.2014.07.006.

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Conflicts of interest
These authors disclose the following: Randall Burt is a consultant for Myriad Genetics and N. Jewel Samadder is a consultant for Cook Medical. The remaining authors disclose no conflicts.

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Supplementary Materials and Methods

Details of Statistical Methods and Analysis Software

Kinship analysis was conducted to address the familiality of colorectal cancer or adenoma in colonoscopy patients diagnosed with colorectal cancer. A specialized suite of software, Kinship Analysis Tools (http://www.huntsmancancer.org/research/shared-resources/utah-population-database/kinship-analysis-tools), is an integrated set of programs developed at the University of Utah Huntsman Cancer Institute specifically to take advantage of the particular resources of the UPDB, including genealogies and linked cancer records. The Kinclass module of Kinship Analysis Tools was used to count the number of affected (diagnosed with CRC or adenoma) and unaffected relatives of a specific kinship class. The software is run separately for each kinship class of the index cases and index controls. Relatives are counted as affected if they appear in the case file. Thus, sibling and parent/child relationships are counted reciprocally. This has been shown by Bai et al[1] to provide the least-biased results. Relatives are counted as unaffected if they do not appear in the case file and there is sufficient follow-up data to reasonably assume that if they were affected, they would have been detected. The follow-up criteria we used requires that the unaffected person had to be living in Utah after the start of the UCR and was seen as a patient by either IHC or the UUHSC health care systems. The output from the Kinclass program is a file with all the relatives of the specific kinship class together with their demographic information and diagnostic year, if applicable. The 2 files for each kinship class (1 for relatives of the cases and the other for relative of the controls) are concatenated, annotated appropriately, and then used by R for the statistical analysis. R was used to estimate the recurrence risk in relatives of the index cases, over the time period that statewide Utah Cancer Registry records were available with diagnoses from 1966 through 2009, using Cox proportional hazards regression models.[2] We independently verified the model estimation in R using SAS statistical analysis software (version 9.3, Cary, North Carolina). By using this software suite, we determined the risk of CRC to child and adult relatives of CRC index cases compared with population-based controls within these categories of relationships: FDRs, including parents, children, and siblings; SDRs, including grandparents/grandchildren, aunts/uncles, and nieces/nephews; and FCs.

Risk Estimation

Probands or index cases were colonoscopy patients between 50 and 80 years of age at the time of screening (colonoscopy between February 15, 1995, and January 31, 2009, based on Current Procedural Terminology codes 45378, 45379, 45380, 45383, 45384, and 45385) who also had colorectal cancer diagnosed between 1966 and 2009. Index cases were excluded from the population pool used for control selection. Random population controls with a follow-up year in Utah equal to or greater than the case year of diagnosis were selected from the UPDB and matched 5:1 to index cases on sex and year of birth (see the Materials and Methods section). Relatives of index cases and relatives of controls were determined from the UPDB genealogic records, and CRC or adenoma diagnoses in relatives were determined from the Utah Cancer Registry or medical records as described. The risk in relatives of probands compared with relatives of controls was determined for each category of relationship (FDRs, SDRs, and FCs) independently.

The magnitude of familial risk was estimated from Cox regression models, adjusting for the number of biological relatives, their degree of relatedness, and their person-years at risk as described.[2] This is presented as an HRR of recurrence in a family member. The HRR based on a Cox regression model, an established method of duration analysis for prospective cohort studies,[3] often is used to estimate recurrence risk in families in retrospective cohort studies.[4–6] For the index cases and their matched controls, the matching design was accounted for in the analysis by controlling for sex and birth year as covariates in the model. Relatives were excluded from the analysis if they were older than age 105, died before the UCR started (1966), had a diagnosis of CRC from a death certificate or other record before 1966, were born after 1977, or the start year was greater than their age. Time was measured in years at risk. Left truncation for the years at risk was performed by adjusting the start year of the relative appropriately if they were born before the start of the UCR. The date of right-censoring for the relatives occurs at the years of their death or if they are currently alive or unaffected in 2012.

We also tested the proportional hazards assumption in our models over the very long analysis period beginning in 1966 and found no violation of the proportionality assumption.

Data Dependencies

Because controls were selected randomly and matched to an index case (proband) on birth year and sex, the Cox regression models controlled for sex and birth year. All relatives of index cases and matched controls with adequate follow-up information, who were linked to a UPDB pedigree comprising at least 2 generations, were included systematically in the calculations even if that relative had been counted previously. For example, in families that contained more than 1 sibling with colorectal cancer, each case was included as a separate index case and risk among all siblings of each case was calculated separately. This approach has been shown to lead to unbiased estimates of familial risk.[1,7] Because observations within families are nonindependent, a robust Huber–White sandwich estimator of variance for clustered data was incorporated,[7] in which family clustering was based on the index case's mother (or, in rare instances, the index case's father if data were not available for the mother) as shown in the Annotated Code.

Missing Data

As previously described, index cases (probands) were defined as those who underwent colonoscopy and had CRC before, at the time of, or after colonoscopy. All index cases had complete information for birth year, sex, date of colonoscopy, date of diagnosis of CRC, and family relationship information from genealogy records in the UPDB, which combines comprehensive statewide cancer and vital records with links to colonoscopy data and demographic records from the UUHSC and IHC enterprise data warehouses. The cohort from which population controls were selected randomly and matched 5:1 to index cases had complete information for birth year, sex, and had known follow-up dates in the UPDB from vital records, driver's license data, voter registrations, or other medical records, The pool of potential controls (3.4 million individuals, of whom ~900,000 were in the same range of birth years as index cases) had genealogy information in the UPDB and did not have a CRC diagnosis in statewide cancer records. Therefore, in the analysis, there were no missing data items and censoring was performed as described earlier.

Supplementary References

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Supplementary Table 1. Risk for CRC in Relatives of CRC Cases Diagnosed Coincident With or After Colonoscopy

	CRC index cases		Population-based controls				
Relationship	Affected	Unaffected	Affected	Unaffected	HRR	95% CI	*P*
FDR	130	9953	367	51,937	1.88	1.51–2.34	<.001
SDR	124	16,964	463	85,341	1.29	1.05–1.57	.01
FC	349	29,832	1554	141,825	1.10	0.98–1.25	.11
Spouse	27	1724	105	8804	1.35	0.87–2.09	.19

NOTE. Data for CRC in relatives of index cases diagnosed with CRC in the UCR, in the same year or after colonoscopy, are shown.

Supplementary Table 2. Risk for CRC in Relatives of CRC Cases, Diagnosed Coincident With or After Colonoscopy

	CRC index cases			CRC index cases <60 y			CRC index cases ≥60 y		
Relationship	HRR	95% CI	*P*	HRR	95% CI	*P*	HRR	95% CI	*P*
FDR	1.88	1.51–2.34	<.001	2.06	1.55–2.74	<.001	1.67	1.40–2.00	<.001
SDR	1.29	1.05–1.57	.01	1.48	1.21–1.82	<.001	1.22	1.05–1.42	.009
FC	1.10	0.98–1.25	.11	1.15	0.87–1.53	.44	1.15	1.04–1.27	.006

Supplementary Table 3. Risk for CRC in Relatives of CRC Cases, Diagnosed Coincident With Colonoscopy

	CRC index cases			CRC index cases <60 y			CRC index cases ≥60 y		
Relationship	HRR	95% CI	*P*	HRR	95% CI	*P*	HRR	95% CI	*P*
FDR	1.77	1.53–2.05	<.001	2.16	1.61–2.89	<.001	1.62	1.35–1.94	<.001
SDR	1.39	1.24–1.56	<.001	1.63	1.33–2.01	.002	1.22	1.04–1.42	.01
FC	1.11	1.02–1.22	.02	1.08	0.82–1.43	.59	1.09	0.98–1.20	.10

Supplementary Table 4. Risk for CRC in Relatives of CRC Cases With Secondary Control Group (Selected Only From Colonoscopy Cohort)

	CRC index cases		Controls (from colonoscopy cohort)				
Relationship	Affected	Unaffected	Affected	Unaffected	HRR	95% CI	*P*
FDR	257	11,152	905	58,662	1.54	1.33–1.77	<.001
SDR	393	20,255	1474	106,554	1.42	1.26–1.60	<.001
FC	491	31,221	2201	150,457	1.20	1.01–1.14	.02

NOTE. Data are for CRC in relatives of index cases diagnosed with CRC in the UCR.

Supplementary Table 5. Risk for Advanced Adenomas in Relatives of CRC Cases

	CRC index cases		Population-based controls				
Relationship	Affected	Unaffected	Affected	Unaffected	HRR	95% CI	*P*
FDR	124	17,033	255	83,169	2.43	1.96–3.01	<.001
SDR	78	32,727	309	135,783	1.06	0.83–1.36	.63
FC	227	48,591	715	168,743	1.09	0.94–1.28	.25

NOTE. Data for adenomas with a villous component are shown.

Supplementary Table 6. Risk for Adenomas in Relatives of CRC Cases, Diagnosed Coincident With or After Colonoscopy

	CRC index cases			CRC index cases <60 y			CRC index cases ≥60 y		
Relationship	HRR	95% CI	*P*	HRR	95% CI	*P*	HRR	95% CI	*P*
FDR	1.76	1.57–1.97	<.001	2.07	1.69–2.55	<.001	1.51	1.26–1.80	<.001
SDR	1.22	1.08–1.38	.001	1.46	1.14–1.86	.002	1.13	0.92–1.38	.24
FC	1.12	1.04–1.21	.002	1.12	0.97–1.30	.11	1.17	1.07–1.29	<.001

Supplementary Table 7. Risk for Adenomas in Relatives of CRC Cases, Diagnosed Coincident With Colonoscopy

	CRC index cases			CRC index cases <60 y			CRC index cases ≥60 y		
Relationship	HRR	95% CI	*P*	HRR	95% CI	*P*	HRR	95% CI	*P*
FDR	1.91	1.69–2.15	<.001	2.18	1.77–2.68	<.001	1.58	1.31–1.90	<.001
SDR	1.27	1.12–1.44	<.001	1.53	1.19–1.96	<.001	1.15	0.94–1.41	.23
FC	1.13	1.05–1.22	.001	1.19	1.03–1.38	.02	1.23	1.12–1.35	<.001

Supplementary Table 8. Risk for Any Adenomas in Relatives of CRC Cases With Controls Selected Only From Colonoscopy Cohort

	CRC index cases		Controls (from colonoscopy cohort)				
Relationship	Affected	Unaffected	Affected	Unaffected	HRR	95% CI	*P*
FDR	425	10,984	1333	58,234	1.74	1.55–1.95	<.001
SDR	318	20,330	1303	106.725	1.28	1.12–1.46	<.001
FC	917	30,795	4590	161,894	1.07	0.99–1.16	.08

Supplementary Table 9. Risk for Advanced Adenomas in Relatives of CRC Cases With Controls Selected Only From Colonoscopy Cohort

	CRC index cases		Controls (from colonoscopy cohort)				
Relationship	Affected	Unaffected	Affected	Unaffected	HRR	95% CI	*P*
FDR	87	11,322	219	59,348	2.15	1.68–2.74	<.001
SDR	47	20,601	219	107,809	1.12	0.81–1.55	.49
FC	167	31,545	771	165,713	1.16	0.97–1.39	.09

NOTE. Data for adenomas with villous component are shown.

Supplementary Table 10. Risk for CRC in FDRs of CRC Cases Younger Than Age 60 Years Versus CRC Cases Older Than Age 60 Years: Case–Case Analysis

Relationship	HRR	95% CI	*P*
FDR	1.50	1.19–1.89	<.001