COLONIC ADENOMA RISK IN FAMILIAL COLORECTAL CANCER—A STUDY OF SIX EXTENDED KINDREDS

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OBJECTIVES: Most colorectal cancers (CRCs) arise from adenomatous polyps, but the effects of CRC family history on adenoma risk are not well known. This issue is clinically relevant since several medical societies currently recommend earlier and more rigorous colorectal screening for individuals with a strong family history of CRC.

METHODS: Colonoscopies were performed in 236 first-, second-, and third-degree relatives of 40 index CRC cases from six large kindreds selected from a large population database. The kindreds were selected for significantly greater risk of CRCs compared with the overall population. Known hereditary colon cancer syndromes were clinically and genetically excluded.

RESULTS: Thirty-seven percent of relatives were found to have adenomas on colonoscopy. The average age of diagnosis for colon cancer was 63 yr and advanced adenomas 56 yr. Independent predictors of adenomatous polyps in the relatives were advancing age (P < 0.0001), male gender (P < 0.001), and greater degree of relation to CRC cases (P < 0.01). There was no significant predilection of colorectal tumors for the right or left colon. A higher degree of relationship to CRC cases was a significant predictor of having simple and advanced adenomas, but not hyperplastic polyps after adjustment for age and gender.

CONCLUSIONS: These data support the current recommendations for colonoscopy starting before the age of 50 yr in individuals with a strong family history of CRC.

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family history of CRC undergo CRC screening, preferably with colonoscopy, and earlier than the recommended age of 50 yr for the general population.

Colonoscopy is very effective in decreasing the incidence of CRC by the removal of adenomatous colon polyps (10). However, the risk of adenomatous polyps in men or women of different ages with respect to family history of CRC cases is not well defined. In this study, we evaluated adenoma risk in very large extended families with a strong family history representing the familial high-risk CRC classification. Not all of the families fulfill Amsterdam criteria, but they demonstrate strong familial clustering and high-risk CRC features, which constitute a small but important fraction of common familial CRC cases. We evaluated adenoma risk based on the degree of relationship to CRC cases in the first-, second-, and third-degree relatives of CRC cases. We demonstrate that the degree of relationship is a predictor of developing adenomas.

METHODS

This study was approved by the Institutional Review Board of the University of Utah. Informed consent was obtained from all research participants.

Identification of Families With Familial Risk CRC

The Utah Population Database (UPDB) is a genealogic resource containing over 5 million individual records of people who had a significant life event (birth, death, childbirth) in Utah or who are ancestral to current members of the Utah population. Probabilistic record linking methods, which take into account common identifiers to link records from one source to another, have been used to link approximately 40% of Utah Cancer Registry records (1966–present) to individuals in UPDB (11). Families were identified from UPDB as having a statistical excess of CRC as compared to the database as a whole (11). Families for study were selected as having a \( P \) value for familial aggregation less than 0.05 and an increased Familial Standardized Incidence Ratio (FSIR) of CRC, FSIR is calculated as the ratio of observed to expected CRCs as previously described (12). \( P \) values for the families are calculated under the assumption of no familial aggregation of CRC based on Poisson probability of observed number of cases. Pedigrees were reviewed for all cancers, dominant inheritance patterns, and availability of age-appropriate participants. Families were not pursued if the pedigrees demonstrated obvious cancer patterns of known syndromes. For example, families with a young onset of first-degree relatives with CRC along with uterine cancer were not included as they most likely represented a hereditary nonpolyposis colorectal cancer (HNPCC) family.

CRC cases in the families were contacted by the Utah Cancer Registry through a letter asking them, or their next of kin, permission to be contacted by the study. The study then contacted interested individuals and expanded the kindred through family referral. In total, six large kindreds with multiple CRC cases are included in this study (Table 1). All six kindreds were of Caucasian descent. Cancer cases were only included if they were confirmed by the cancer registry, medical record, or reported with confidence by the affected individual or a first-degree relative (13). The degree of relationship between individuals is precisely known and the genome-wide genetic linkage analysis described below supports these relationships.

Exclusion of Hereditary Polyposis and Lynch Syndrome

Due to the high penetrance of CRC in the kindreds, known hereditary CRC syndromes were excluded. Medical records and pathology reports for the index CRC cases were reviewed and none reported hamartomatous or adenomatous polyposis (defined as \( ≥10 \) polyps per colon). One individual in kindred 5234 had one 5 mm adenoma in his late 50’s and went on to have 14 cumulative adenomas over 18 yr, however no other individuals in the prospective colonoscopy study demonstrated polyposis. The two common mutations in the MUTYH gene leading to MYH-associated polyposis, Y165C and G382D, which constitute \( ∼85% \) of the mutations in the Caucasian population (14), were sequenced from blood-DNA in representative members with CRC or adenomatous polyps. No individuals tested, including the subject with 14 cumulative adenomas, carried either of the mutations as indicated on the pedigrees as MUTYH gene normal (MYH-N) (Supplementary Data).

Families with Lynch Syndrome have defects in the DNA mismatch repair genes which manifests as DNA microsatellite instability (MSI) in \( >90\% \) of colon cancers and \( ∼80\% \) of advanced adenomas (15, 16). MSI was evaluated in archived tumor blocks from one to two index CRC cases, or in the

### Table 1. Characteristics of Familial Colon Cancer Kindreds

<table>
<thead>
<tr>
<th>Kindred</th>
<th>( P ) Value</th>
<th>FSIR</th>
<th>Youngest CRC</th>
<th>Total CRC (Spouse)</th>
<th>AC</th>
<th>No. Examined by Colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>4562</td>
<td>0.001</td>
<td>4.6</td>
<td>45 yr</td>
<td>6 (1)</td>
<td>No</td>
<td>56</td>
</tr>
<tr>
<td>4586</td>
<td>0.035</td>
<td>4.2</td>
<td>45 yr</td>
<td>4 (1)</td>
<td>Yes</td>
<td>54</td>
</tr>
<tr>
<td>4853</td>
<td>0.028</td>
<td>7.8</td>
<td>65 yr</td>
<td>3 (1)</td>
<td>No</td>
<td>24</td>
</tr>
<tr>
<td>5234</td>
<td>0.005</td>
<td>2.3</td>
<td>53 yr</td>
<td>11 (1)</td>
<td>No</td>
<td>53</td>
</tr>
<tr>
<td>5275</td>
<td>0.002</td>
<td>12.4</td>
<td>35 yr</td>
<td>5</td>
<td>No</td>
<td>12</td>
</tr>
<tr>
<td>6694</td>
<td>0.0002</td>
<td>6.2</td>
<td>40 yr</td>
<td>7</td>
<td>Yes</td>
<td>37</td>
</tr>
</tbody>
</table>

\( P \) value is based on the null hypothesis that there is no familial aggregation of colorectal cancer. The Family Standardized Incidence Ratio (FSIR) is the ratio of colorectal cancers observed in the family from UPDB data divided by the number of cancers expected based on family structure and age. AC indicates if the family fulfills Amsterdam 1 or Amsterdam 2 criteria.
case where only one index colorectal case was available, a second case with a villous adenomatous colorectal polyp was used. Tumor and normal DNA were extracted as described previously (17) and analyzed using the “reference marker panel” (BAT25, BAT26, D2S123, D5S346, and D17S250) (18). None of the six kindreds demonstrated MSI (noted as microsatellite stable (MSS) on the pedigrees in Supplementary Data).

A genome-wide linkage scan was performed on all six kindreds to rule out linkage to known cancer susceptibility genes. A custom set of 325 short tandem repeat genetic markers with an average heterozygosity of 0.78 and an average spacing of 10.8 cM was used. CRC and adenomatous polyps were used as the phenotypic markers. Linkage analysis was carried out with the MLINK subroutine of the computer program FASTLINK (19, 20). An autosomal dominant model was assumed and the penetrance was set at 0.60 with an allele frequency of 0.001. No significant logarithm of the odds (LOD) scores (≥3.0, P = 0.0002) were identified in regions surrounding genes known to cause familial colon cancer (Supplementary Data, Table S1).

**Colonoscopic Evaluation**

Two hundred sixty-two relatives of CRC cases were invited to participate, and 236 of these (90%) underwent colonoscopy of which 185 were prospective and 51 retrospectively analyzed. Medical history and physical exam were completed for each patient. Colonoscopy with polypectomy was performed by participating endoscopists with standard preparation and monitoring. Each polyp was noted by location and size before being removed and sent for histopathological evaluation. Only the first-ever colonoscopy data were analyzed in this study to avoid including those who had previous polypectomies. Simple tubular adenomas were defined as epithelial polyps with low-grade dysplasia and lacking villous architecture. Advanced adenomatous polyps were defined as those having villous histology, high-grade dysplasia, and/or a diameter greater than 10 mm. Individuals with hyperplastic polyps are represented in the total number of patients who underwent prospective colonoscopy. The right colon was defined as proximal to the splenic flexure and the left colon as the splenic flexure through the rectum.

**Statistical Analysis**

CRC risk in male and female family members was calculated using survival analysis with Kaplan-Meier and proportional hazards methods (21). Analysis included UPDB data from all ascendants and UPDB recorded CRC cases of the six kindred founders.

Additional statistical analyses were performed using Statistica 6.0 (StatSoft Inc, Tulsa, OK). Univariate analysis of the relationship between total polyp count and age, gender, and nearest CRC relative was performed using Kruskal–Wallis analysis of variance. Logistic regression was used for multivariate models with binary response (presence of adenomas or advanced adenomas). Gender and trends for age and degree of relationship were included in the models. P values from likelihood ratio tests are reported. A Generalized Estimating Equation (GEE) model fit to the adenoma data for the combined cohort (22, 23). The GEE model allowed us to specify a correlation structure within each kindred. A logistic model for the binary response presence/absence of one or more adenomatous colon polyps, with age, sex, and a trend term for degree of relationship as predictors was used. An exchangeable correlation structure within each kindred was applied. Marginal effects are consistently estimated by GEE models even if the correlation structure is incorrectly specified (24). Robust Z scores were used to determine statistical significance of the GEE model terms.

The Wilcoxon matched pair test was used to compare the observed counts and adjusted counts of left- and right-sided adenomas. The adjusted counts were adjusted for age and gender using ANOVA.

**RESULTS**

**CRC Cases**

There were 36 colorectal adenocarcinomas in the six kindreds. Additionally, four spousal parents of study participants were diagnosed with CRC. An unusual coincidence whereby both parents have CRC was observed in two kindreds (K4853 and K5234). Thirty-eight cancers were confirmed by medical record or cancer registry data, one was a self-reported cancer pre-dating the cancer registry and one was reported by the child of a case diagnosed outside of Utah. The majority of the index CRC cases were diagnosed on the basis of symptoms or signs referable to their cancers, however two colon cancers were discovered during the prospective colonoscopy phase of this study.

The distribution by gender of the colorectal adenocarcinoma cases was relatively equal: 18 men and 18 women. Data from UPDB were used to calculate the cumulative risk of developing CRC in men versus women in all six families (Table 2). The four spouse CRC and one child-reported CRC were not included in the analysis. By age 90, men had a cumulative risk of 15% (95% CI 9–25) and women had a cumulative risk of 19% (95% CI 11–36), which is not statistically different. The mean age of adenocarcinoma diagnosis was 62.9 ± 13.8 yr (range 35–90) overall, and was not statistically different between men and women (P = 0.47 ANOVA, 64.0 ± 13.9 yr in men, 61.8 ± 14.1 yr in women). Location of the CRCs was defined in all but 3 of the 36 cases: 42% of the CRC were right-sided; 58% left-sided.

**Colonoscopy Study**

Of the 236 members who underwent colonoscopy, only first-ever and complete colonoscopy data were included in the analyses to avoid confounding factors due to prior polypectomies or incomplete data. Medical records were abstracted for colonoscopies on 51 cases (22%) and the remainder underwent colonoscopy at the University of Utah Medical
The mean age at colonoscopy was 50.2 ± 11.5 yr (range 25–82 yr). Of these 236 individuals, 131 men underwent colonoscopy at a mean age of 50.0 ± 11.0 yr and 105 women underwent colonoscopy at a mean age of 50.5 ± 12.1 yr. One hundred forty-seven individuals had no adenomas (62%), 69 had one or more simple adenomas (29%), and 20 had advanced adenomas (8%). Among individuals with at least one colon adenoma, the mean number of adenomas (± standard deviation) per colon was 1.70 ± 1.20.

In order to study the effect of degree of relation on the incidence of colon neoplasms, the kindred members were separated into three groups. The first-degree relative group consists of individuals with at least one first-degree relative (parents, sibling, or child) diagnosed with CRC. The second-degree relative group is composed of individuals with no affected first-degree relative but at least one second-degree relative (aunts, uncles, grandparents, or grandchildren) diagnosed with CRC. The third-degree relative group is composed of individuals with no affected first- or second-degree relative but a third-degree relative affected with CRC. All 236 individuals studied fit into one of these three categories.

The relationship between formation of adenomatous polyps and age, gender, the degree of relation to a CRC case, and kindred was evaluated (Table 3). There was a significant trend to develop adenomas as subjects aged ($P = 0.0001$) and the degree of relationship to CRC cases ($P = 0.007$). Although men and women did not differ in their development of CRC, women did have significantly fewer adenomas ($P = 0.001$; Table 3 and Fig. 1). The mean number of adenomas within kindreds was not significantly different ($P = 0.54$) suggesting that belonging to a specific kindred was not a predictor. The effect of the within-kindred correlation was also evaluated using a GEE model, which allows for specification of a correlation structure within each kindred (22, 23). The estimated correlation between members of the same kindred, after adjusting for age, gender, and nearest CRC relative, was extremely small ($−0.0074$). After adjusting the data for the within-kindred correlation, age, gender, and nearest CRC relative remain statistically significant predictors of adenomatous polyp formation.

Advanced adenomatous polyps were found in 20 individuals (Table 4). Thirty percent had both villous histology and were $>10$ mm in size; 10% had villous histology...
alone; 60% were >10 mm alone; and none had high-grade dysplasia. The degree of relationship to CRC cases was a significant predictor of developing simple adenomas ($P = 0.046$) and advanced adenomas when adjusted for age and gender ($P = 0.029$), but not hyperplastic polyps ($0.65$). Gender and age, however, were not significant predictors of advanced adenomas ($P = 0.175$ and $P = 0.079$, respectively; Table 5), although this may be related to the limited size of the data set.

Others have reported an increased association of rightsided colonic adenomatous polyps in first-degree relatives of CRC cases (25). The sites of adenomas were compared between the first-, second-, and third-degree relatives and no statistical differences ($P = 0.69$) in the mean number of left- or right-sided adenomas were observed.

DISCUSSION

Six large kindreds were selected from the Utah Population Database for this study based on having a statistical excess of CRC as compared to the database as a whole. These families represent the more extreme subset of the CRC population with both high-risk CRC and familial clustering. Importantly, rigorous exclusion of the known hereditary CRC syndromes was performed. The use of a large population database with ascertainment of family history and cancers was a key advantage of this study since inaccuracy of family history data obtained from extended family members is well known (13). The large Utah Population Database families made statistical evaluation of excess cancers relative to the general Utah population possible. This study purposely evaluated large families with high-risk CRCs. This enabled not only analysis of adenoma risk in first-degree relatives of the CRCs, but also permitted the comparison to second and third degrees of relationship. The resulting analysis represents a well-characterized population with increased genetic homogeneity, rather than many small nuclear families with one or more CRC cases.

The colonoscopies revealed important risk factors for adenomatous polyps in relatives of CRC cases. As expected, there was a significant effect of age on the incidence of colonic adenomas. However, even after correction for the age of the relatives, male gender and closer degree of relation to a CRC case were independently and significantly associated with a greater incidence of simple and advanced adenomatous polyps. However, no such associations were observed for hyperplastic polyps throughout the colon.

Previous studies have shown that the relative risk of CRCs is significantly related to the number and age of first-degree relatives of CRC cases (26). However, accurate assessment of the effects of degree of relation to CRC cases on the risk for simple and advanced adenomatous polyps has been lacking. Our finding that the degree of relation to CRC cases is significantly associated with the risk for simple and advanced colorectal adenomas brings justification to the more rigorous colon cancer screening recommendations for those with a strong family history of CRC. The similar incidence of adenomas in the right or left colon in first-degree relatives of CRC cases supports whole colon screening in those with a stronger family history as well.

The large difference between the occurrence of adenomas in men and women was striking. The women in the study had

**Table 4.** Degree of Relationship to Colorectal Cancer Case as a Predictor of Polyps

<table>
<thead>
<tr>
<th>Nearest CRC Relative</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Degree</th>
<th>2&lt;sup&gt;nd&lt;/sup&gt; Degree</th>
<th>3&lt;sup&gt;rd&lt;/sup&gt; Degree</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number subjects</td>
<td>102</td>
<td>104</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Zero simple adenoma (%)</td>
<td>59 (58)</td>
<td>73 (70)</td>
<td>26 (87)</td>
<td>0.046</td>
</tr>
<tr>
<td>1+ simple adenoma (%)</td>
<td>43 (42)</td>
<td>31 (30)</td>
<td>4 (13)</td>
<td></td>
</tr>
<tr>
<td>Zero advanced adenoma (%)</td>
<td>88 (86)</td>
<td>98 (94)</td>
<td>30 (100)</td>
<td>0.029</td>
</tr>
<tr>
<td>1+ advanced adenoma (%)</td>
<td>14 (14)</td>
<td>6 (6)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Zero hyperplastic polyp (%)</td>
<td>71 (70)</td>
<td>76 (73)</td>
<td>22 (73)</td>
<td>0.65</td>
</tr>
<tr>
<td>1+ hyperplastic polyp (%)</td>
<td>31 (30)</td>
<td>28 (27)</td>
<td>8 (27)</td>
<td></td>
</tr>
</tbody>
</table>

The $P$ value is from the likelihood ratio test from a logistic regression model with age, gender, and nearest CRC relatives as predictors and binary response presence/absence of one or more simple adenomas, or a reference logistic regression model of the presence/absence of advanced adenomas with age and gender only, or as predictors and binary response presence/absence of one or more hyperplastic polyps.
Our results showed a significance compared with sex- and age-matched controls (31). For net adenoma growth but not baseline adenoma occurrence compared with sex- and age-matched controls (31). Our results showed a significant relationship between the degree of relation to CRC cases and the incidence of simple adenomas. Furthermore, the incidence of advanced adenomas was significantly associated with degree of relation to CRC cases in our study as well. These results suggest that both initiation of adenomas and progression to advanced adenomas are influenced by the degree of relation to CRC cases.

The current recommendation to initiate earlier CRC screening in individuals with a strong family history of CRC arose largely from the observation that the average age of onset of CRC is significantly earlier in the hereditary CRC syndromes than for sporadic cases. The assumption was that a hereditary predisposition to CRC would shorten the length of time to develop colorectal neoplasms. In our study, the average age of diagnosis of CRC was 63 yr (vs 70 yr for the general population) and the average age of advanced adenomas was 56 yr, justifying earlier initiation of screening in high-risk individuals.

Since up to one-third of one’s risk for CRC can be attributed to heredity (25), it is important to seek out a family history of CRC. Although most regions in our country do not have the large families represented here, it is still imperative that a careful family history of CRC be obtained for first- and second-degree relatives in order to risk stratify individuals for screening. It is also important that close relatives of patients affected with CRC receive counseling for CRC screening.

In conclusion, the significant association between simple and advanced adenomatous polyps and the degree of relation to CRC cases provides important support of the current recommendations for earlier and more rigorous CRC screening for those with a strong family history of CRC. The lack of differences in the distribution of colonic adenomatous polyps between the right and left colon in first-degree relatives of CRC cases supports the current recommendations for using colonoscopy to screen those with a strong family history of CRC. The average age of detection of advanced adenomas in the 6th decade of life in close relatives of CRC cases supports current recommendations for the initiation of colon screening in individuals with a strong family history of CRC before the age of 50 yr. Our study provides long-needed evidence in support of the current guidelines issued by the American Cancer Society, U.S. Preventive Services Task Force, American College of Gastroenterology, and American Gastroenterological Association for earlier and more rigorous CRC screening for those with a strong family history of CRC (cancer or polyps in a first-degree relative (parent, sibling, or child) younger than 60 or in 2 first-degree relatives of any age).

**ACKNOWLEDGMENTS**

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What Is New Here

- Family history, specifically the degree of relation to CRC, increases adenoma risk.
- Adenoma-carcinoma progression appears stronger in women than men with a strong family history of CRC.
- Undefined genetic and environmental factors are responsible for common familial CRC; known colon cancer genes are not involved.

REFERENCES


CONFLICT OF INTEREST

Guarantor of the article: Scott K. Kuwada, M.D. is the guarantor of the article, had full access to all of the data in the study, and takes responsibility for the integrity of the data and accuracy of the data analysis.

Specific author contributions: Study concept and design: Neklason, Thorpe, Burt, Kuwada; Acquisition of data: Neklason, Solomon, Samowitz, Fang, Burt, Kuwada; Analysis and interpretation of data: Neklason, Thorpe, Ferrandez, Tumbapura, Kuwada; Statistical analysis: Boucher, Garibotti, Kerber; Drafting of manuscript: Neklason, Kuwada; Obtained funding: Burt, Mineau; Study supervision: Burt, Leppert, Mineau.

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