Published in final edited form as:

Am J Gastroenterol. 2008 October ; 103(10): 2577–2584. doi:10.1111/j.1572-0241.2008.02019.x.

Colonic Adenoma Risk in Familial Colorectal Cancer – a Study of Six Extended Kindreds

Deborah W. Neklason, Ph.D.^{*,†}, Brett L. Thorpe, M.D.[^], Angel Ferrandez, M.D.^{*}, Anil Tumbapura, M.D.[^], Kenneth Boucher, Ph.D.^{*,†}, Gilda Garibotti, M.S.^{*}, Richard A. Kerber, Ph.D.^{*,†}, Cindy H. Solomon, M.S.-G.C.^{*}, Wade S. Samowitz, M.D.⁺, John C. Fang, M.D.[^], Geraldine P. Mineau, Ph.D.^{*,†}, Mark F. Leppert, Ph.D.[#], Randall W. Burt, M.D.^{*,^}, and Scott K. Kuwada, M.D.^{*,^,@,†,‡}

^{*}Huntsman Cancer Institute, Salt Lake City, Utah

[‡]Oncological Sciences, Salt Lake City, Utah

[^]Dept. of Medicine, Salt Lake City, Utah

⁺Dept. of Pathology, Salt Lake City, Utah

[#]Dept. of Genetics Salt Lake City, Utah

[@]University of Utah and Veterans Administration Health Care System, Salt Lake City, Utah

Abstract

Objectives—Most colorectal cancers arise from adenomatous polyps, but the effects of colorectal cancer 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 colorectal cancer.

Methods—Colonoscopies were performed in 236 first-, second-, and third- degree relatives of 40 index colorectal cancer cases from 6 large kindreds selected from a large population database. The kindreds were selected for significantly increased risk of colorectal cancers compared with the overall population. Known hereditary colon cancer syndromes were clinically and genetically excluded.

Results—37% of relatives were found to have adenomas on colonoscopy. The average age of diagnosis for colon cancer was 63 years and advanced adenomas 56 years. 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 colorectal cancer 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.

[†]To whom correspondence should be sent: Scott Kuwada, M.D. Huntsman Cancer Institute 2000 Circle of Hope Salt Lake City, Utah 84112-5550 (801)585-0303 phone Scott.kuwada@hci.utah.edu.

Author Contributions: Dr. Kuwada is the guarantor of the paper, 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.

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

Competing interests and financial disclosure: None

Conclusions—These data support the current recommendations for colonoscopy starting before the age of 50 years in individuals with a strong family history of colorectal cancer.

Introduction

Approximately 10% of the U.S. population has at least one first-degree relative with colorectal cancer (CRC) ¹, and approximately 25% of CRC cases meet the criteria of “high risk”, defined as two first degree relatives with CRC or CRC diagnosed at age 50 or younger². Previous studies demonstrated a common autosomal dominant inheritance pattern for colon adenomas and cancers ³, with a gene frequency of 0.19 for adenomas and colorectal adenocarcinomas ⁴. A large study of mono- and di-zygotic twins revealed that 35% of the risk for colorectal adenocarcinoma was attributable to heredity ⁵. In individuals with more than one first-degree relative with colorectal cancer or a single first-degree relative with colorectal cancer diagnosed at age 50 or younger (defined as a strong family history), the relative risk of colorectal cancer is approximately 3-6-fold greater than those with no family history of colorectal cancer ^{6,7}. Clearly there is a hereditary component to these “high-risk” colorectal cancer cases. Families which fulfill Amsterdam criteria (3 relatives with a Lynch Syndrome- associated cancer (primarily CRC), 2 who are first-degree relatives, and one diagnosed ≤ 50 years) demonstrate a more intense familial clustering and are estimated to contribute 2.3% of all CRC cases². The majority of these families lack microsatellite unstable cancers, a hallmark feature of defects in mismatch repair genes and Lynch Syndrome. Recently two studies have effectively distinguished these familial high-risk CRC from the more penetrant Lynch Syndrome. In these studies, familial colorectal cancer families that fulfill Amsterdam criteria for Lynch Syndrome but lack microsatellite unstable cancers, the average age of colorectal cancer diagnosis is 61 ⁸ and 55 years ⁹, which is more than 10 years later than Lynch Syndrome (44 years) and earlier than the general population (70 years). These high-risk CRC kindreds appear to constitute a definable set of unknown genetic etiology which require more aggressive and earlier colon cancer prevention than the general population. Based on these types of studies, the American Cancer Society and U.S. Preventive Services Task Force recommended that individuals with a strong family history of colorectal cancer undergo colorectal cancer screening, preferably with colonoscopy, and earlier than the recommended age of 50 years for the general population.

Colonoscopy is very effective in decreasing the incidence of colorectal cancer 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 colorectal cancer 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 colorectal cancer

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 colorectal cancer 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 colorectal cancer. FSIR is calculated as the ratio of observed to expected colorectal cancers as previously described 12. P-values for the families are calculated under the assumption of no familial aggregation of colorectal cancer 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 colorectal cancer along with uterine cancer were not included as they most likely represented a HNPCC family.

Colorectal cancer 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 colorectal cancer 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 their late 50's and went on to have 14 cumulative adenomas over 18 years, 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 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 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 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. Colorectal cancer 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 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 was 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 was 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

Colorectal cancer risk in male and female family members was calculated using survival analysis with Kaplan-Meier and proportional hazards methods²¹. Analysis included UPDB data from all descendents and UPDB recorded colorectal cancer cases of the 6 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 was 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 specified²⁴. 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

Colorectal cancer 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 colorectal cancer 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 males and 18 females. Data from UPDB was used to calculate the cumulative risk of developing colorectal cancer in males versus females in all six families (Table 2). The four spouse CRC and one child-reported CRC were not included in the analysis. By age 90, males had a cumulative risk of 15% (95% CI: 9-25%) and females 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 years (range: 35-90) overall, and was not statistically different between men and women ($p=0.47$ ANOVA; 64.0 ± 13.9 years in men; 61.8 ± 14.1 years in women). Location of the colorectal cancers 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 was 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 Center. The cecum was reached in 97% of colonoscopies. The mean age at colonoscopy was 50.2 ± 11.5 years (range = 25-82 years). Of these 236 individuals, 131 men underwent colonoscopy at a mean age of 50.0 ± 11.0 years and 105 women underwent colonoscopy at a mean age of 50.5 ± 12.1 years. 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 ($\pm$ 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 colorectal cancer. 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 colorectal cancer. The third-degree relative group is composed of individuals with no affected first- or second- degree relative but a third-degree relative affected with colorectal cancer. 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 colorectal cancer 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 colorectal cancer cases ($p=0.007$). Although men and women did not differ in their development of colorectal cancer, women did have significantly fewer adenomas ($p=0.001$; Table 3 and Figure 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 Generalized Estimating Equation (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 are 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 >10mm in size; 10% had villous histology alone; 60% were >10mm alone; and none had high-grade dysplasia. The degree of relationship to colorectal cancer 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 right-sided colonic adenomatous polyps in first-degree relatives of colorectal cancer cases²⁵. 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 colorectal cancer 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 known¹³. 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 colorectal cancers. This enabled not only analysis of adenoma risk in first-degree relatives of the colorectal cancers, 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 colorectal cancer cases.

The colonoscopies revealed important risk factors for adenomatous polyps in relatives of colorectal cancer 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 colorectal cancer case were independently and significantly associated with an increased 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 colorectal cancers is significantly related to the number and age of first-degree relatives of colorectal cancer cases²⁶. However, accurate assessment of the effects of degree of relation to colorectal cancer cases on the risk for simple and advanced adenomatous polyps has been lacking. Our finding that the degree of relation to colorectal cancer 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 colorectal cancer. The similar incidence of adenomas in the right or left colon in first-degree relatives of colorectal cancer 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 2.4-fold fewer adenomas than men, yet had a similar incidence of colorectal cancer as men. This effect of gender was not due to age or degree of relation, as these were accounted for in the analyses, nor were they due to differences in colonoscopy

completion rates. These results suggest that while adenoma initiation events may be less common in women, adenoma-carcinoma progression is strongly influenced by female gender. Previous studies have shown a protective effect of estrogens in colonic tumorigenesis²⁷ and it is possible that adenoma-carcinoma progression is accelerated in post-menopausal women who are not on estrogen replacement. We were unable to retrospectively analyze this factor in our data set. However, this observation is supported by a study of polyps in the colons of 445 consecutive autopsies²⁸ whereby adenomas were fewer in women than men, but showed more atypia, villous histology, and larger size in women. Additionally, in a retrospective study of 12,960 individuals who underwent flexible sigmoidoscopy screening, distal colonic adenomas were 1.6-fold less common in women than men²⁹. Thus, several studies, including ours, suggest that adenomas are less common in women than men, but that adenoma-carcinoma progression is more likely in women than men.

Other studies have suggested that adenoma-carcinoma progression, rather than adenoma initiation is influenced strongly by degree of relation to colorectal cancer cases. Pariente et al. found that adenomas occurred with similar frequency in first-degree relatives of colorectal cancer cases and matched controls with no family history of colorectal cancer³⁰. However, advanced adenomas ($\geq 10\text{mm}$ in diameter and/or villous histology) were significantly (odds ratio = 2.5, $p < 0.01$) more frequent in the first-degree relatives than the sex- and age- matched controls. Lindgren et al. found that non-Lynch Syndrome colorectal cancer family members demonstrated significantly higher colorectal cancer risk on a per adenoma basis than controls²⁵. Almendigen et al. found that a family history of colorectal cancer was associated with an adjusted odds ratio = 3.9 (95% C.I. = 1.2-13.4) for net adenoma growth but not baseline adenoma occurrence compared with sex- and age-matched controls³¹. Our results showed a significant relationship between the degree of relation to colorectal cancer cases and the incidence of simple adenomas. Furthermore, the incidence of advanced adenomas was significantly associated with degree of relation to colorectal cancer cases in our study as well. These results suggest that both initiation of adenomas and progression to advanced adenomas are related to the degree of relation to colorectal cancer cases.

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

Since up to one-third of one's risk for colorectal cancer can be attributed to heredity²⁵, it is important to seek out a family history of colorectal cancer. Although most regions in our country do not have the large families represented here, it is still imperative that a careful family history of colorectal cancer 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 colorectal cancer receive counseling for colorectal cancer screening.

In conclusion, the significant association between simple and advanced adenomatous polyps and the degree of relation to colorectal cancer cases provides important support of the current recommendations for earlier and colonoscopic colorectal cancer screening for those with a strong family history of colorectal cancer. The lack of differences in the distribution of colonic adenomatous polyps between the right and left colon in first-degree relatives of

colorectal cancer cases supports the current recommendations for using colonoscopy to screen those with a strong family history of colorectal cancer. The average age of detection of advanced adenomas in the 6th decade of life in close relatives of colorectal cancers supports current recommendations for the initiation of colon screening in individuals with a strong family history of colorectal cancer before the age of 50 years. 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 colorectal cancer screening for those with a strong family history of colorectal cancer (cancer or polyps in a first-degree relative (parent, sibling, or child) younger than 60 or in 2 first-degree relatives of any age).

STUDY HIGHLIGHTS

1) What is current knowledge

- Colon cancer risk is increased in individuals with a strong family history.
- The effect of family history of colorectal cancer on adenoma risk is not well known.

2) What is new here

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to Jared Cox and Ryan Turner for generating the pedigrees and Michelle Condie and Xiufen Li for technical assistance.

Funding/support: Supported by National Cancer Institute grants R01-CA40641 and P01-CA73992; additional support was provided by a Cancer Center Support Grant P30-CA42014, General Clinical Research Center Grant M01-RR00064 and N01-PC-67000, Utah Cancer Registry grant N01-PC-35141 from the National Cancer Institute's SEER program with additional support from the Utah State Department of Health and the University of Utah, and by the Huntsman Cancer Foundation. Database support to the Utah Population Database is provided by the Huntsman Cancer Foundation.

References

1. Ivanovich JL, Read TE, Ciske DJ, et al. A practical approach to familial and hereditary colorectal cancer. *Am J Med* 1999;107:68–77. [PubMed: 10403355]
2. Kerber RA, Neklason DW, Samowitz WS, et al. Frequency of familial colon cancer and hereditary nonpolyposis colorectal cancer (Lynch syndrome) in a large population database. *Fam Cancer* 2005;4:239–244. [PubMed: 16136384]
3. Burt RW, Bishop DT, Cannon LA, et al. Dominant inheritance of adenomatous colonic polyps and colorectal cancer. *N Engl J Med* 1985;312:1540–1544. [PubMed: 4000184]

4. Cannon-Albright LA, Skolnick MH, Bishop DT, et al. Common inheritance of susceptibility to colonic adenomatous polyps and associated colorectal cancers. *N Engl J Med* 1988;319:533–537. [PubMed: 2841598]
5. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 2000;343:78–85. [PubMed: 10891514]
6. Fuchs CS, Giovannucci EL, Colditz GA, et al. A prospective study of family history and the risk of colorectal cancer. *N Engl J Med* 1994;331:1669–1674. [PubMed: 7969357]
7. Slattery ML, Kerber RA. Family history of cancer and colon cancer risk: the Utah Population Database. *J Natl Cancer Inst* 1994;86:1618–1626. [PubMed: 7932826]
8. Lindor NM, Rabe K, Petersen GM, et al. Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. *JAMA* 2005;293:1979–1985. [PubMed: 15855431]
9. Mueller-Koch Y, Vogelsang H, Kopp R, et al. Hereditary non-polyposis colorectal cancer: clinical and molecular evidence for a new entity of hereditary colorectal cancer. *Gut* 2005;54:1733–1740. [PubMed: 15955785]
10. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993;329:1977–1981. [PubMed: 8247072]
11. Kerber RA, O'Brien E. A cohort study of cancer risk in relation to family histories of cancer in the Utah population database. *Cancer* 2005;103:1906–1915. [PubMed: 15779016]
12. Kerber RA. Method for calculating risk associated with family history of a disease. *Genet Epidemiol* 1995;12:291–301. [PubMed: 7557350]
13. Ziogas A, Anton-Culver H. Validation of family history data in cancer family registries. *Am J Prev Med* 2003;24:190–198. [PubMed: 12568826]
14. Wang L, Baudhuin LM, Boardman LA, et al. MYH mutations in patients with attenuated and classic polyposis and with young-onset colorectal cancer without polyps. *Gastroenterology* 2004;127:9–16. [PubMed: 15236166]
15. Boland CR. Molecular genetics of hereditary nonpolyposis colorectal cancer. *Ann N Y Acad Sci* 2000;910:50–59. discussion 59–61. [PubMed: 10911905]
16. Iino H, Simms L, Young J, et al. DNA microsatellite instability and mismatch repair protein loss in adenomas presenting in hereditary non-polyposis colorectal cancer. *Gut* 2000;47:37–42. [PubMed: 10861262]
17. Spirio LN, Samowitz W, Robertson J, et al. Alleles of APC modulate the frequency and classes of mutations that lead to colon polyps. *Nat Genet* 1998;20:385–388. [PubMed: 9843214]
18. Boland CR, Thibodeau SN, Hamilton SR, et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. *Cancer Research* 1998;58:5248–5257. [PubMed: 9823339]
19. Cottingham RW Jr, Idury RM, Schaffer AA. Faster sequential genetic linkage computations. *Am J Hum Genet* 1993;53:252–263. [PubMed: 8317490]
20. Lathrop GM, Lalouel JM, White RL. Construction of human linkage maps: likelihood calculations for multilocus linkage analysis. *Genet Epidemiol* 1986;3:39–52. [PubMed: 3957003]
21. Hosmer, DW.; Lemeshow, S. *Applied survival analysis: regression modeling of time to event data*. Wiley; New York: 1999.
22. Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* 1986;73:13–22.
23. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121–130. [PubMed: 3719049]
24. Fahrmeir, L.; Tutz, G. *Multivariate Statistical Modeling Based on Generalized Linear Models*. Springer-Verlag; New York: 2001.
25. Lindgren G, Liljegren A, Jaramillo E, et al. Adenoma prevalence and cancer risk in familial non-polyposis colorectal cancer. *Gut* 2002;50:228–234. [PubMed: 11788565]

26. Burt RW. Colon cancer screening. *Gastroenterology* 2000;119:837–853. [PubMed: 10982778]
27. Crandall CJ. Estrogen replacement therapy and colon cancer: a clinical review. *J Womens Health Gend Based Med* 1999;8:1155–1166. [PubMed: 10595328]
28. Vatn MH, Stalsberg H. The prevalence of polyps of the large intestine in Oslo: an autopsy study. *Cancer* 1982;49:819–825. [PubMed: 7055790]
29. Gondal G, Grotmol T, Hofstad B, et al. Lifestyle-related risk factors and chemoprevention for colorectal neoplasia: experience from the large-scale NORCCAP screening trial. *Eur J Cancer Prev* 2005;14:373–379. [PubMed: 16030428]
30. Pariente A, Milan C, Lafon J, et al. Colonoscopic screening in first-degree relatives of patients with ‘sporadic’ colorectal cancer: a case-control study. The Association Nationale des Gastroenterologues des Hopitaux and Registre Bourguignon des Cancers Digestifs (INSERM CRI 9505). *Gastroenterology* 1998;115:7–12. [PubMed: 9649451]
31. Almendingen K, Hofstad B, Vatn MH. Does a family history of cancer increase the risk of occurrence, growth, and recurrence of colorectal adenomas? *Gut* 2003;52:747–751. [PubMed: 12692063]

Figure 1.
Number of adenomas per subject by gender (n=236)

Table 1

Characteristics of Familial Colon Cancer Kindreds

Kindred	P-value	FSIR	Youngest CRC	Total CRC (spouse)	AC	No. Examined by Colonoscopy
4562	0.001	4.6	45 yr	6 (1)	No	56
4586	0.035	4.2	45 yr	4 (1)	Yes	54
4853	0.028	7.8	65 yr	3 (1)	No	24
5234	0.005	2.3	53 yr	11 (1)	No	53
5275	0.002	12.4	35 yr	5	No	12
6694	0.0002	6.2	40 yr	7	Yes	37

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.

Table 2

Colon cancer risk in six kindreds by age and gender

Age	Male			Female		
	Total number	Colon Cancers	Cumulative Risk (95% CI)	Total number	Colon Cancers	Cumulative Risk (95% CI)
50	325	2	0.00 (0.00-0.02)	299	3	0.01 (0.00-0.03)
60	177	2	0.01 (0.00-0.04)	168	3	0.02 (0.01-0.06)
70	101	10	0.09 (0.05-0.16)	110	4	0.06 (0.03-0.11)
80	40	4	0.15 (0.09-0.25)	62	3	0.09 (0.05-0.17)
90	8	0	0.15 (0.09-0.25)	17	4	0.19 (0.11-0.36)

Table 3

Predictors of Total Adenomatous Polyps

		N	Total Adenomas Mean ± Std Dev	I+ Adenomas N (%)	Univariate * p-value	Multivariate Logistic Regression ** p-value	GEE model p- *** value
Age	25-34	10	0.10 ± 0.32	1 (10)	0.000002	0.000080	6.8 e-11
	35-44	77	0.30 ± 0.56	19 (25)			
	45-54	72	0.53 ± 1.05	22 (31)			
	55-64	46	1.33 ± 1.56	30 (65)			
	65-82	31	0.90 ± 1.11	17 (55)			
Gender	male	131	0.86 ± 1.31	61 (47)	0.000471	0.000913	0.000026
	female	105	0.36 ± 0.70	28 (27)			
Nearest CRC relative	1st degree	102	0.86 ± 1.23	51 (50)	0.003907	0.007130	0.004632
	2nd degree	104	0.57 ± 1.07	34 (33)			
	3rd degree	30	0.13 ± 0.35	4 (13)			
Kindred	4562	56	0.53 ± 1.04	16 (29)	0.54		
	4586	54	0.83 ± 1.51	23 (43)			
	4853	24	0.83 ± 1.13	11 (46)			
	5234	53	0.49 ± 0.78	19 (36)			
	5275	12	0.75 ± 0.87	6 (50)			
	6694	37	0.57 ± 0.93	14 (38)			

* The univariate p-value are from Kruskal-Wallis nonparametric analysis of variance for total adenomas.

** The multivariate p-values are from likelihood ratio tests from a logistic regression model with age, gender and nearest CRC relatives as predictors and binary response presence/absence of one or more adenomatous polyps. Because "Kindred" was not a significant predictor, it was not used in the multivariate analysis.

*** The GEE model p-values are from robust Z-scores from a logistic model for binary response presence/absence of one or more adenomatous polyps, with exchangeable correlation structure within kindreds. N represents the number of subjects in the respective category.

Table 4

Degree of relationship to colorectal cancer case as a predictor of polyps

Nearest CRC Relative	1 st Degree	2 nd Degree	3 rd Degree	p-value
Number subjects	102	104	30	
Zero simple adenoma (%)	59 (58)	73 (70)	26 (87)	0.046
1+ simple adenoma (%)	43 (42)	31 (30)	4 (13)	
Zero advanced adenoma (%)	88 (86)	98 (94)	30 (100)	0.029
1+ advanced adenoma (%)	14 (14)	6 (6)	0 (0)	
Zero hyperplastic polyp (%)	71 (70)	76 (73)	22 (73)	0.65
1+ hyperplastic polyp (%)	31 (30)	28 (27)	8 (27)	

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.

Table 5

Distribution of polyp categories and average age by gender

	Zero Adenomas		Simple Adenomas		Advanced Adenomas	
	N (%)	mean age ± sd	N (%)	mean age ± sd	N (%)	mean age ± sd
Male	70 (53)	45.6± 9.6	47 (36)	53.9 ±10.9	14 (11)	58.4 ±8.8
Female	77 (73)	49.1 ± 11.5	22 (21)	55.2 ±13.0	6 (6)	51.8 ± 15.7