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Risk factors for advanced sporadic colorectal neoplasia in persons younger than age 50

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Abstract

Background—Colorectal cancer (CRC) screening is recommended for average risk adults beginning at age 50. However, 7% of CRC occurs in persons younger than age 50, a group for which risk factors are not well defined. We sought to determine whether a retrospective case-control study could identify risk factors for sporadic CRC and advanced adenomatous polyps (together known as sporadic colorectal neoplasia [CRN]).

Methods—Using the cancer registry, medical records, and endoscopy and pathology reports from 6 local hospitals, we identified potentially eligible persons with CRN (cases) or controls who had no neoplasia on colonoscopy between 1/1/00 and 12/31/02. Consenting subjects completed a survey encompassing medical and family history, physical measures, lifestyle habits, and diet.

Results—Surveys were completed by 20 (15%) of 130 potentially eligible cases and by 54 (13%) of 408 potentially eligible controls. The following factors differed between cases and controls: living with a spouse/significant other (55% vs. 80%; P=0.034); prior pelvic irradiation (20% vs. 2%; P=0.019); having a first degree relative with CRC (25% vs. 7%; P=0.05); having had a prior sigmoidoscopy, colonoscopy, or barium enema (15% vs. 41%, P=0.038), and lightest weight since age 21 (155 lbs vs. 135 lbs; gender-adjusted P=0.049).

Conclusions—The low recruitment rate of this retrospective case-control study precludes its use for a larger, more definitive study. Several potential risk factors for advanced sporadic CRN were

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identified. It remains to be determined whether these factors represent an artifact of selection bias or true risk factors that may be used to stratify risk and target screening in persons under age 50.

Keywords

case-control studies; risk factors; colorectal cancer

INTRODUCTION

Screening for colorectal cancer (CRC) is recommended for average-risk adults beginning at age 50. This age was established largely because of a dramatic increase in disease incidence that occurs during the sixth decade of life. Between ages 45 and 49, the annual incidence of colorectal cancer is 24 cases per 100,000, whereas between the ages of 50 and 54, there are 48 new cases annually per 100,000 [1,2]. However, nearly 7 percent of colorectal cancer occurs in persons younger than 50 years, many of whom have no recognizable risk factors recognized prior to diagnosis[2]. In some studies, such younger persons present with more advanced disease and have a less favorable prognosis [3,4].

In a previous study of 906 persons aged 40 to 49 years who underwent first-time screening colonoscopy, no cancers were discovered (upper 95% CI of 0.4%) [5]. Further, advanced neoplasia[1] was uncommon and tended to be distal to the splenic flexure. The low yield of screening colonoscopy in this age group would appear to support current recommendations about when to begin screening for colorectal cancer. However, despite the low yield of colonoscopic screening for cancer in this study, the discovery of advanced colorectal cancer in young persons is particularly tragic and creates tension with these findings. Identification of risk factors for sporadic colorectal cancer and advanced proximal neoplasms prior to age 50 might be useful to target CRC screening for this age group. Thus, the objectives of this study were to: 1) determine the feasibility of using a retrospective case-control study design to conduct this type of research, and; 2) identify risk factors for advanced sporadic colorectal neoplasia (CRN) among average-risk persons under age 50.

MATERIALS AND METHODS

Study Design

We performed a retrospective case-control study of data assembled from 4 university-affiliated hospitals and two large community hospitals, all located in Indianapolis, IN. Cases and controls were identified based on clinical data collected between January 2000 and December 2002. Collection of survey data from selected cases and controls occurred between January 1, 2003 and June 30, 2004. The protocol was approved by institutional review boards at Indiana University and for each hospital.

Study Procedures

We defined cases as patients aged 35 to 49 years who were diagnosed between January 2000 and December 2002 with advanced colorectal neoplasia, defined as adenocarcinoma, a polyp with high-grade dysplasia, villous histology, or a tubular adenoma 1 cm or larger. Controls

[1]During the past several years, the phrase “advanced neoplasia” has been used in several studies [6-10] to refer to the combination of adenocarcinoma and certain types of pre-malignant polyps, which include tubular adenomas 1 cm or larger, polyps with villous histology, and polyps with high-grade dysplasia. As such, “advanced neoplasia” is now, for better or for worse, the outcome by which studies of screening and surveillance are measured. Whether the pre-malignant components of this composite outcome measure are as sinister as adenocarcinoma is not known, though it is believed that advanced, pre-malignant polyps are at high risk to evolve to invasive carcinoma in the short-term.

were defined as patients from the same age range who underwent colonoscopy during the same time interval and were found to have no neoplasia.

To identify cases, we examined each hospital's cancer registry and pathology files, and verified tissue diagnosis by reviewing each patient's pathology report and medical records. Control patients were identified by examining each hospital's endoscopy databases. Our goal was to enroll 5-10 cases and 15-30 controls per hospital, matched for age within two years, hospital, and year of diagnosis and/or colonoscopy. Per institutional review board stipulation, a letter from potential subjects' primary care provider or other physician involved in their care relevant to the diagnosis or procedure was sent to patients to request study participation. Potential subjects were to respond to the letter by indicating their interest, and, if interested in participating, answer a few screening questions to determine their final eligibility. Those potential subjects for whom a current primary care physician or physician who participated in the patient's care could not be identified were sent a letter of introduction that was signed by the principal investigator. Potential subjects who did not respond to the physician's letter of invitation were telephoned when possible by a research assistant to determine their willingness to participate. We intended to exclude persons with a hereditary colorectal cancer syndrome (Familial Adenomatous Polyposis or Hereditary Non-Polyposis Colon Cancer) and inflammatory bowel disease. Eligible interested subjects were mailed a comprehensive survey on risk factors including personal health information, physical measurements, non-dietary lifestyle habits, and family history, along with the 1998 Block food frequency survey [11].

Data collection and analysis—Surveys completed by subjects were reviewed to ensure complete responses. Subjects with missing responses were telephoned by a research assistant and the missing data were collected over the telephone. Variables included for analysis were height, weight, self-measured waist and hip circumferences, waist-to-hip ratio, physical activity, cigarette smoking, red meat consumption, prior cholecystectomy, occupation, family history of colorectal and other malignancies, multivitamin use, ethanol consumption, post-menopausal hormone use, diabetes mellitus, use of aspirin and noon-steroidal anti-inflammatory drugs, and sociodemographic features (age, sex, race, education level, marital status, and countries of residence). The data were managed and analyzed by personnel in the Division of Biostatistics.

For analysis, response distributions for items on the comprehensive survey were measured and compared between cases and controls. From review of responses to the items on the Block food frequency survey, 28 items were compared, including total calories, daily fat consumption in grams per day, folate consumption in micrograms per day, and percent of calories from fat, protein, and carbohydrates. For categorical variables, either the Chi-square test or Fisher's exact test was used to test for differences between cases and controls. For continuous variables with normal distributions, Student's t-test was performed to detect such differences. For variables with non-normal distributions, the Wilcoxon rank sum test was used. For all statistical testing, the two-sided α level was set at 0.05. Odd ratios (OR) and 95% confidence limits were calculated for dichotomous variables using logistic regression. For continuous variables that may be gender dependent (such as weight, body mass index [BMI], amount of weight gained since age 21, etc), analysis of variance models were generated to test for differences between cases and controls, with the estimates adjusted for gender. DIETSYS+plus (version 5.9 Block Dietary Data Systems, Berkeley, CA, 1999) was used to perform dietary analysis. All other analyses were done with SAS, version 9.1 (SAS Institute, Cary, North Carolina).

RESULTS

Based on review of the cancer registries, pathology databases, medical records, and endoscopy and pathology reports from the 6 hospitals, we identified 130 candidate cases with advanced

colorectal neoplasia and 408 candidate controls with no colorectal neoplasia as determined by colonoscopy. We were unable to identify a mailing address for 34 potential subjects. Of 504 letters mailed to potential subjects, we received responses indicating interest in the study from 132 (26%). Of 132 surveys mailed, 78 (59%) were returned. Four patients were excluded post-hoc because of violation of case or control definitions. The final study group included 20 cases and 54 controls. By case-control status, surveys were completed by 20 (15%) of 130 potentially eligible cases and by 54 (13%) of 408 potentially eligible controls. Given the low response rates and resulting small sample sizes, we were unable to match cases and controls for age, hospital site, and year of diagnosis.

Mean age between cases and controls was comparable: 43.9 (range, 28 to 49 years) vs. 43.1 (range, 25 to 49 years) (P=0.62), as was gender distribution (55% vs. 35% were men; P=0.12). The 20 cases included 11 subjects with colorectal cancer, 2 subjects with polyps containing high-grade dysplasia, 3 with tubulovillous adenomas, and 4 with tubular adenomas larger than 1 cm. Indications for colonoscopy for both cases and controls are listed in Table 1.

With regard to the Block food frequency survey, there were no differences in any of 28 pre-selected dietary factors, including total calories; proportion of calories from protein, fat, and carbohydrates; folate; fiber; or vitamin and mineral supplements. Among categorical variables, there were no differences between cases and controls in alcohol use, diabetes mellitus, cigarette smoking, or previous cholecystectomy. While the proportions of persons who were college graduates, exercised on a regular basis, and used aspirin or NSAIDs at least twice a week were higher among controls, the differences were not statistically significant (Table 2). Categorical exposure factors that differed significantly between cases and controls were: having a first degree relative with CRC (25% vs. 7%; P=0.05; OR=4.17; 95% CI, 1.00-17.5); prior pelvic irradiation (20% vs. 2%; OR=12.8; 95% CI, 1.33-122); living with a spouse or significant other (55% vs. 80%; OR=0.31; 95% CI, 0.10-0.94); and a reported prior test to evaluate large bowel structure (i.e., colonoscopy, sigmoidoscopy, or barium enema) (15% vs. 41%; OR=0.27; 95% CI, 0.07–0.98).

Continuous variables that differed between cases and controls are shown in Table 3. In univariate analysis, reported weight at age 21, reported waist circumference at age 21, lightest weight since age 21, and smallest waist circumference since age 21 were all greater in cases than in controls. However, when these differences were adjusted for gender, only the lightest weight since age 21 remained statistically difference (P=0.049) for the nearly 20 pound difference between cases and controls (Table 3). There were no differences in BMI, in heaviest weight, or in largest reported waist circumference.

DISCUSSION

Screening for colorectal cancer is recommended by several professional organizations beginning at age 50 for average-risk persons [12]. The most likely reason for the choice of age 50 as the primary age threshold for screening is the dramatic increase in disease incidence around that age[1,2]. The simplicity and convenience of this single age threshold for “average-risk” persons may give the impression that the risk of colorectal cancer is dichotomous. Yet we know that the risk increases continuously with age, and that the age 50 threshold will miss nearly one in 15 colorectal cancers occurring in persons who are younger than age 50.

Perhaps the age threshold for screening should be lower. An analysis of the association between screening, subject characteristics, and stage of colorectal cancer found that age less than 45 at diagnosis was a risk factor for late-stage presentation[4]. However, lowering the age threshold for screening for everyone would be impractical, as the yield would be low and would come with a high cost, both in monetary and in clinical terms, as procedure-related complications

could well exceed any benefit from screening. If we understood more about which factors affected risk and how to use the factors in a quantitative way to estimate risk, then we could extend screening recommendations to selected persons younger than 50, based on an individualized assessment of risk.

In this study, we attempted to identify risk factors for sporadic advanced colorectal neoplasia among persons younger than age 50. Among many factors measured, we found that prior pelvic irradiation, a first degree relative with colorectal cancer, and a heavier lightest weight since age 21 were associated with an increased risk for advanced colorectal neoplasia, while living with a spouse or significant other and a prior diagnostic sigmoidoscopy, colonoscopy, or barium enema; were associated with a lower risk. Further, trends for decreased risk were found for other factors, including a college-level education; reporting of regular exercise; use of aspirin or NSAIDs at least twice weekly; a second-degree relative with colorectal cancer; and smaller waist circumference and lighter reported weight since age 21. In contrast, male gender and having a second-degree relative with colorectal cancer showed trends toward increased risk for advanced neoplasia.

Previous research from studies involving older adults supports our findings. Previous studies have found pelvic irradiation to be a risk factor for colorectal cancer in both men and women [13-14]. Several studies support the association of a positive family history of colorectal cancer and increased risk for neoplasia [15-19]. In our study, having a first degree relative with CRC increased the risk for advanced neoplasia, while having a second degree relative showed a trend toward increased risk. Despite the fact that three cases had both a first-degree relative and a second-degree relative with colorectal cancer, our analysis indicated that the test for association between first and second degree relatives was not significant (P=0.35), suggesting that these two risk factors were independent from a statistical perspective; however, the ability to detect statistical dependence was limited because of the small sample size.

Obesity is a risk factor for several cancers, including colorectal cancer [20-23]. Although current BMI was no different between cases and controls, there was a difference in lightest weight (presumably at a younger age) between cases and controls. In support of this lightest weight having occurred at a younger age were strong trends for differences in weight at age 21 (a 10 kilogram difference between cases and controls) and in waist circumference at age 21 (nearly a three inch difference).

We found that current living with a spouse or significant other was associated with a reduced risk of advanced colorectal neoplasia, as it was more common among controls. As we compared many factors between cases and controls, it is possible that this was a chance finding. However, it is also possible that living with a spouse or significant other is a marker for a more health-conscious lifestyle. Literature about social support and health behaviors suggests that social support and social ties are associated with adopting and maintaining positive health behaviors such as regular physical activity and consuming a low fat diet [24-25].

We found no differences between cases and controls for all 28 pre-selected dietary factors (which included dietary components as well as vitamins and minerals), cigarette smoking, and alcohol use. There are several possible explanations for the lack of differences for these variables, one of which is the small sample size. The power to detect differences was limited, especially for dichotomous and categorical factors. Another possible reason is that the time frame we queried for exposure was limited to the ten years or so prior to the diagnosis for cases and prior to the index colonoscopy for controls. It is possible that dietary factors, cigarette smoking, and alcohol use require a longer time frame to affect risk for neoplasia or that behavior changed over time. A third explanation, related to duration of exposure, is that these factors interact with age to affect risk. Studies that have associated these factors with colorectal

adenomas and cancer have involved persons older than those in the current study. Were these exposures to continue into the next decade or two, the effect on risk for neoplasia might become apparent.

There are several limitations to this study, the most important of which is the low recruitment rate of both cases and controls. The concern here is that those cases and controls who were recruited may be different in their exposure status to the factors we measured than the non-recruits, with the potential for biased estimates for certain factors. We attribute our low recruitment rate to a few reasons. First, we were limited in how and under what conditions we could contact eligible persons. We were required initially to identify a physician who had provided care to the patient around the time of the diagnosis of cancer or the colonoscopy, and to obtain their permission and signature on a letter addressed to the patient. Frequently, we were unable to identify a physician that the patient recognized as a current or former provider. The institutional review board eventually allowed us to modify our contact procedures to send a letter directly from the study investigators, but between 9 and 12 additional months had lapsed between diagnosis or procedure and our contact, on top of the year or two resulting from the retrospective design of the study. Second, the low response rate to our letter of invitation was likely due to cases having moved on from their diagnosis or colonoscopy and perhaps no longer recognizing their provider, especially when he or she was a subspecialist. Of the 132 patients who were interested in the study, 78 (59%) completed the surveys.

A second important limitation is the potential for chance associations (i.e., a type I error), given the number of factors that were tested. However, as we acknowledged *a priori*, our goal was more focused on determining feasibility of a retrospective study design, the effort required, and acquiring data with which to estimate more precisely the minimal sample size than it was on generating definitive results. As such, we consider our findings to be hypothesis generating.

This study has been useful for clarifying logistical issues and for refining our sample size estimates for a more definitive study. In subsequent efforts, we plan to use a prospective case-control design with a city-wide surveillance system to identify cases and controls. This type of prospective approach was used successfully to study the association of Reye's syndrome and aspirin use [26]. Based on exposure rates of the variables in Table 2, we estimate requiring 70- 80 cases and 210-240 controls. A study of this size would allow the use of multivariate analysis to determine which factors are independently associated with advanced colorectal neoplasia.

In conclusion, while it was feasible to use a retrospective case-control study design, the low recruitment rate precludes use of this method for a more definitive study. Several potential risk factors for advanced sporadic colorectal neoplasia were identified. It remains to be determined whether these factors represent an artifact of selection bias or true risk factors that may be used to stratify risk and target colorectal cancer screening in persons younger than 50 years old.

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Table 1

Indications for colonoscopy among cases and controls

Indication	Cases, n (%)	Controls, n (%)
Hematochezia	12 (60)	18 (31)
Hemoccult positive	1 (5)	5 (9)
Iron deficiency anemia	2 (10)	6 (10)
Abdominal pain	1 (5)	11 (19)
Chronic diarrhea	1 (5)	10 (17)
Screening	1 (5)	3 (5)
Recent diverticulitis	0 (0)	2 (3)
Change in bowel habits	0 (0)	2 (3)
Weight loss	0 (0)	1 (2)
Unknown	2 (10)	0 (0)

Table 2

Comparison of Dichotomous Factors Between Cases and Controls

	n (%)			
Factor	**Cases (n= 20)**	**Controls (n = 52)**	**Odds Ratio (95% CI)**	**P-value**
Living with spouse or significant other	11 (55)	43 (80)	0.31 (0.10-0.94)	0.034
Pelvic irradiation	4 (20)	1 (2)	12.8 (1.33-122)	0.019
First-degree relative with colon cancer	5 (25)	4 (7.4)	4.17 (1.0-17.5)	0.05
Second-degree relative with colon cancer	6 (30)	6 (11)	3.43 (0.96-12.3)	0.07
Previous non-screening sigmoidoscopy, colonoscopy, or barium enema	3 (15)	22 (41)	0.26 (0.07-0.98)	0.038
Male gender	11 (55)	19 (35)	2.25 (0.79-6.39)	0.123
College graduate	4 (20)	21 (39)	0.39 (0.12-1.34)	0.127
Regular exercise	4 (20)	21 (39)	0.39 (0.12-1.34)	0.127
Aspirin or NSAID use at least twice weekly	5 (25)	24 (44)	0.42 (0.13-1.31)	0.128

Table 3

Comparison of Continuous Variables Between Cases and Controls

Variable	Cases	Controls	Unadjusted P-Value	Adjusted P-Value†
Reported weight at age 21 (lbs)	163 ± 36	142 ± 31	0.018	0.073
Reported waist circumference at age 21 (in)	32.2 ± 3.5	29.5 ± 5.2	0.045	0.158
Lightest weight (lbs) since age 21	154.8 ± 35	135.4 ± 26	0.012	0.049
Smallest waist circumference since age 21 (in)	31.1 ± 2.9	28.6 ± 4.3	0.019	0.076

*All values are means ± standard deviations

†Adjusted for differences in gender