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ORIGINAL RESEARCH & CONTRIBUTIONS

Risk of Proximal Colonic Neoplasms in Asymptomatic Adults Older Than 50 Years Found to Have Distal Hyperplastic Polyps on Routine Colorectal Cancer Screening

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Abstract

Purpose: A retrospective case-control study was conducted to evaluate whether hyperplastic polyps (HPs) found in the lower 50 cm of colon could be used as indicators for synchronous proximal neoplasms (SPNs) in the large intestine. Additionally, other characteristics considered included age; sex; ethnicity; history of cancer, cholecystectomy, or appendectomy; current use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs); current use of estrogen or hormone replacement therapy (HRT) in women; current smoking status; and the size, number, and location of the distal HP if present.

Methods: Convenience sampling of medical charts and colonoscopy reports compiled during a ten-year period was used to glean the sample of 1792 participants.

Results: Distal HPs in the lower 50 cm of colon were not significantly associated with SPN when patients with HPs were compared with those without any distal polyps at all (odds ratio [OR] = 0.94; 95% confidence interval [CI] = 0.73–1.22). However, significant relationships with proximal neoplasms (adenomas, advanced adenomas, and colon cancer) were noted in patients with a prior diagnosis of cancer (OR = 1.62; 95% CI =1.25–2.11), advancing age (OR = 1.02; 95% CI = 1.01–1.03), non-Caucasian (men only) ethnicity (OR = 0.72; 95% CI = 0.55–0.96), a history (men only) of taking aspirin or NSAIDs (OR = 0.73; 95% CI = 0.56–0.95), and a history (women only) of taking estrogen or receiving HRT (OR = 1.51; 95% CI = 1.04–2.20).

Conclusion: Routinely recommending a colonoscopy for every patient with distal HPs found only by screening flexible sigmoidoscopy is neither justified nor necessary. Nevertheless, further investigation (ie, colonoscopy) may be warranted in the aforementioned subgroups.

Introduction

Although in the US colorectal cancer (CRC) remains the third most common type of cancer and the second leading cause of cancer death overall, it is one of the few malignancies for which effective secondary prevention methods are applicable and obtainable. Regrettably, CRC was diagnosed in more than 150,000 people in 2009 and 56,000 died because of it.[1] Furthermore, according to the World Health Organization (WHO), this disease resulted in an additional 655,000 deaths globally. Adenocarcinoma is by far the most prevalent type of CRC, accounting for nearly 95% of all cases, and 95% of all adenocarcinomas arise from specific growths called adenomatous polyps. As such, the array of contemporary screening methods now used for CRC prevention center on being able to successfully recognize and remove these precancerous neoplasms (adenomatous polyps) before they develop into cancer. Presently, there are five advocated options for elective screening in asymptomatic patients: 1) yearly stool testing for occult blood starting at age 50, 2) an air-contrast barium enema of the large bowel at age 50 and every five years thereafter if the findings are normal, 3) flexible sigmoidoscopy (FS) at age 50 and every five years thereafter if the findings are normal, 4) computed tomography colonography at age 50 and every five years thereafter if the findings are normal, and 5) colonoscopy at age 50 and every ten years thereafter if the findings are normal.[2,3]

The main focus of this analysis revolved around the use of FS within this asymptomatic screening population, and specifically, whether further evaluation (colonoscopy) should be considered in patients found to have distal hyperplastic

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polyps (HPs) only on these examinations. In addition, other potential risk factors for proximal neoplasms in those with and without distal HPs in the lower 50 cm of bowel were explored. Given that 60% to 70% of all polyps and cancers occur in this area of the colon, sigmoidoscopy is still frequently recommended as the initial screening examination for many asymptomatic individuals.

As of now, it is debatable whether patients found to have distal HPs only by screening FS should undergo a colonoscopy for further evaluation of synchronous proximal neoplasms (SPNs). Largely, this is because the data surrounding the clinical utility of distal HPs as markers for SPNs are somewhat inconsistent, conflicting, and polarized. To date, 13 trials have been conducted on the proposed topic and target population.[4-17] Although the authors of seven[5-11] of these studies have concluded that distal HPs do predict the presence of SPNs and necessitate colonoscopy, the authors of the remaining six[12-17] have reported that no such increased risk exists, thus nullifying the need for colonoscopy. Moreover, beyond these visible discrepancies within the published literature, there are also tangible inconsistencies among the formal recommendations made for patients with distal HPs discovered by screening FS. Both the American College of Gastroenterology and the American Society of Gastrointestinal Endoscopy maintain that distal HPs do not significantly predict the presence of SPNs (when patients with distal HPs are compared with those without any distal polyps at all) and advise against habitually performing a colonoscopy.[18,19] In contrast, the American Cancer Society, the Agency for Health Care Policy and Research, and the US Preventive Services Task Force believe that there is not enough substantial evidence to make a sound recommendation either way; therefore, these organizations have offered no explicit suggestions for this subgroup of patients.[4] This unfortunately has culminated in an enduring and persisting knowledge gap. Consequently, many physicians and clinicians currently do not order any additional testing when HPs are the only significant finding on an FS. If however, distal HPs are indeed indicators of SPNs, not routinely performing colonoscopies in this unique faction of patients may mean that we are inadvertently and unduly missing an opportunity to identify and eradicate these precancerous or cancerous growths. This investigation was implemented to better elucidate these issues.

Methods

An unmatched retrospective case-control study design was used for this endeavor (Figure 1). The main independent variable was distal HPs, and the main dependent variable was proximal neoplasms. Cases included asymptomatic patients with proximal neoplasms (51 cm from rectum to cecum) found on screening colonoscopy, and control participants included asymptomatic patients without proximal neoplasms found on screening colonoscopy. From the selected sample, data were gathered on whether patients had distal HPs or no distal polyps (from rectum to 50 cm of colon). Other variables assessed included age, sex, ethnicity, current smoking status, current use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), current use of estrogen or hormone replacement therapy (HRT) in women, previous cholecystectomy or appendectomy, history of cancer other than CRC, and the size, number, and location of distal HPs if present. Information was amassed by reviewing medical charts and colonoscopy procedures performed by a private-practice, board-certified gastroenterologist during a ten-year span (1997 to 2007). A total of 1792 (896 in each group) patients were included. This study was approved by the institutional review board of TUI University (formerly Touro University International).

Study Population

The sampling pool was drawn from average-risk, asymptomatic individuals older than 50 years who underwent a baseline screening colonoscopy procedure between 1997 and 2007 at the Mountain View Surgery Center in Redlands, CA. To be considered for the study, all participants must have provided

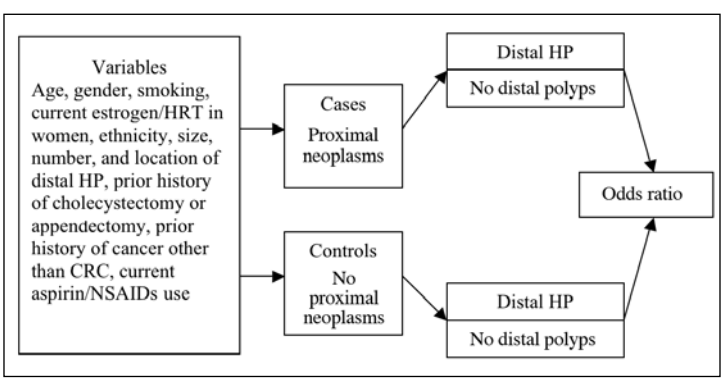

Figure 1. Flow diagram of research design.

CRC = colorectal cancer; HP = hyperplastic polyps; HRT = hormone replacement therapy; NSAIDs = nonsteroidal anti-inflammatory drugs

information for a complete medical history and undergone a physical examination prior to the colonoscopy. Patients were excluded if they had distal adenomas or distal colon cancer, a personal history of colon polyps or CRC, a history of colonoscopy or FS, a history of inflammatory bowel disease, a family history of CRC, an incomplete colonoscopy (cecum not reached or poor bowel preparation), or symptoms before colonoscopy such as rectal bleeding, abdominal pain, unexplained weight loss, or change in bowel patterns. Convenience sampling techniques were employed. The actual sampling process consisted of: 1) first identifying eligible medical charts by reviewing the daily register at the surgery center, which has chronicled every procedure performed there since 1997; 2) all colonoscopy examinations done in individuals older than 50 years for routine screening were pulled for further evaluation and review; 3) all charts meeting the specified inclusion and exclusion criteria were included in a consecutive fashion; and 4) began with procedures dated December 31, 2007, and worked backwards successively until the total number of required participants had been assembled. Participant recruitment was not a pressing issue, because this was a secondary data analysis. The WHO's standardized taxonomy for colonic polyps was used to histologically classify all polyps in the study.[20] This histologic determination was derived from official pathology reports from community-based pathologists (LabCorp, Caris Diagnostics [now Caris Life Sciences], and Quest Diagnostics).

Data Analysis and Statistics

A number of bivariate and multivariate tests were generated to help highlight and clarify underlying relationships. The Statistical Package for the Social Sciences (SPSS) software (version 14.0; SPSS Inc, Chicago, IL) was used to conduct all χ^2 calculations, Student's τ-tests, and logistical regressions performed in this study. Forced-entry logistical regression models were run on the given variables to formulate the corresponding odds ratios (ORs) and 95% confidence intervals (CIs).

Results

Demographics

The baseline frequency counts for the selected variables are as follows. Roughly 17% (307 patients) of the total sample was found to have distal HPs. There were somewhat more men (55.9%) than women (44.1%) in the total sample. Current cigarette use was noted for 12.9% of the sample (231 patients), and the current usage of aspirin or NSAIDs was 37.0% (663 patients). Of the 791 women in the sample, 17.7% (140 patients) were taking estrogen or undergoing HRT. Regarding prior medical conditions and procedures, 9.6% of the total sample (172 patients) had had a cholecystectomy, 13.3% (238 patients) had had an appendectomy, and 17.0% (305 patients) had had a previous diagnosis of cancer other than CRC. For the type of cancer, the most frequent categories were skin (38.0%; 116 patients), prostate (21.6%; 66 patients), and breast (19.0%; 58 patients). For racial or ethnic background in the total sample, the most frequent categories were Caucasian (68.4%; 1226 patients), Hispanic (17.2%; 308 patients), and black (8.9%; 160 patients). Ages ranged from 50 to 89 years (mean = 61.76; SD = 8.84).

Multivariate Analysis

Table 1 displays the logistic regression model predicting the presence of proximal neoplasms on the basis of the total sample (n = 1792). The nine-variable model was statistically significant (χ^2 [9, n = 1.792] = 55.05; p = 0.001) and the base classification rate was 50.0%. The overall final classification rate was 57.5%. Specifically, the model correctly classified 62.3% of the cases in which there were no proximal neoplasms and 52.8% of the cases in which there were proximal neoplasms. Inspection of the ORs showed that proximal neoplasms were more frequently present in: 1) men (OR = 0.72; p = 0.001; 95% CI = 0.59–0.88), 2) nonusers of aspirin or NSAIDs (OR = 0.77; p = 0.009; 95% CI = 0.63–0.94), 3) those with previous cancer (OR = 1.62; p = .001; 95% CI = 1.25–2.11), and 4) older patients (OR = 1.02; p = 0.001; 95% CI = 1.01–1.03).

Table 1. Prediction of proximal neoplasms based on the total sample (n = 1792)

Variable	p value	OR	95% CI
Distal HP[a]	0.64	0.94	0.73-1.22
Women[a]	0.001	0.72	0.59-0.88
Smoking[a]	0.95	1.01	0.76-1.35
Use NSAIDs[a]	0.009	0.77	0.63-0.94
Gallbladder[a]	0.16	1.27	0.91-1.76
Appendectomy[a]	0.83	1.03	0.78-1.37
Non-Caucasian[a]	0.21	0.88	0.71-1.08
Previous cancer[a]	0.001	1.62	1.25-2.11
Age	0.001	1.02	1.01-1.03

[a] Coding: 0 = No; 1 = Yes
CI = confidence interval; NSAIDs = nonsteroidal anti-inflammatory drugs; OR = odds ratio

Table 2. Prediction of proximal neoplasms for sample of women only (n = 791)

Variable	p value	OR	95% CI
Distal HP[a]	0.39	0.83	0.55-1.27
Smoking[a]	0.81	0.94	0.57-1.54
Use NSAIDs[a]	0.28	0.85	0.63-1.14
Estrogen/HRT[a]	0.03	1.51	1.04-2.20
Gallbladder[a]	0.47	1.15	0.78-1.70
Appendectomy[a]	0.72	1.08	0.72-1.60
Non-Caucasian[a]	0.39	1.15	0.84-1.56
Previous cancer[a]	0.003	1.77	1.22-2.57
Age	0.01	1.02	1.00-1.04

[a] Coding: 0 = No; 1 = Yes
CI = confidence interval; NSAIDs = nonsteroidal anti-inflammatory drugs; OR = odds ratio

Table 2 displays the logistic regression model predicting the presence of proximal neoplasms on the basis of the full female sample (n = 791). The nine-variable model was statistically significant (χ^2 [9, n = 791] = 24.54; p = 0.004), and the base classification rate was 53.9%. The overall final classification rate was 59.2%. Specifically, the model correctly classified 75.6% of the cases in which there were no proximal neoplasms and 40.0% of the cases in which there were proximal neoplasms. Inspection of the ORs showed that proximal neoplasms were more frequently present in: 1) those taking estrogen or undergoing HRT (OR = 1.51; p = .03; 95% CI = 1.04–2.20), 2) those with previous cancer (OR = 1.77; p = 0.003; 95% CI = 1.22–2.57), and 3) older patients (OR = 1.02; p = .01; 95% CI = 1.00–1.04).

Table 3 displays the logistic regression model predicting the presence of proximal neoplasms on the basis of the full male sample (n = 1001). The eight-variable model was statistically significant (χ^2 [8, n = 1001] = 33.34; p = 0.001), and the base classification rate was 53.0%. The overall final classification rate was 57.5%. Specifically, the model correctly classified 47.9% of the cases in which there were no proximal neoplasms and 66.1% of the cases in which there were proximal neoplasms. Inspection of the ORs showed that proximal neoplasms were more frequently present in: 1) nonusers of aspirin or NSAIDs (OR = 0.73; p = 02; 95% CI = 0.56–0.95), 2) those who were Caucasian (OR = 0.72; p = 0.02; 95% CI = 0.55–0.96), 3) those with previous cancer (OR = 1.52; p = 0.03; 95% CI = 1.05–2.20), and 4) older patients (OR = 1.02; p = 0.005; 95% CI = 1.01–1.04).

Table 3. Prediction of proximal neoplasms for sample of men only (n = 1001)

Variable	p value	OR	95% CI
Distal HP[a]	0.93	1.02	0.73-1.41
Smoking[a]	0.68	1.08	0.75-1.55
Use NSAIDs[a]	0.02	0.73	0.56-0.95
Gallbladder[a]	0.16	1.62	0.83-3.13
Appendectomy[a]	0.82	0.95	0.64-1.42
Non-Caucasian[a]	0.02	0.72	0.55-0.96
Previous cancer[a]	0.03	1.52	1.05-2.20
Age	0.005	1.02	1.01-1.04

[a] Coding: 0 = No; 1 = Yes
CI = confidence interval; NSAIDs = nonsteroidal anti-inflammatory drugs; OR = odds ratio

Discussion

Above all, the results of this study helped confirm and substantiate current practice guidelines pertaining to patients with distal HPs found on baseline CRC screening. Accordingly, recommending a colonoscopy for every patient with distal HPs found only by FS is not necessary. As depicted in Tables 1 through 3, distal HPs were not associated with an increased occurrence of SPNs (even when stratified by sex). In fact, of the 307 patients with distal HPs, the incidence of these growths was nearly identical for those with (50.2%) and for those without (49.8%) proximal neoplasms. This finding concurs with the conclusions and outcomes of other investigators who have also reported on this topic.[12-17] In addition, this analysis demonstrated that there is a significant increase in odds of having a proximal neoplasm found on a routine screening examination if one is a Caucasian man, is a man not taking aspirin or NSAIDs, is of advancing age, has a history of cancer other than CRC, or is a woman actively taking estrogen. With the exception of the latter two variables, these factors too have been documented by other researchers to be associated with neoplasms in the large intestine.[21-29] What was unique to this particular study was the identification of potentially two new risk factors for proximal neoplasms within the asymptomatic screening population (use of estrogen and a history of cancer other than CRC). Although it would have been both provocative and insightful to be able to compare and contrast the outcomes of this investigation with the outcomes of others mentioned in this article, this was not realistically feasible because of diverse study designs, inclusion and exclusion criteria, operational definitions for the distal colon, applications of multivariate and statistical techniques, sample sizes, baseline demographic characteristics, and control or reference groups. It was the intent of this inquiry to answer the posed research question, by using the specified sample and target population in mind, to mirror present clinical climates and situations.

Given that this investigation in essence dealt with a cohort of individuals who would otherwise not be advised to undertake a colonoscopy (those with distal HPs or no distal polyps found by screening FS), these findings are relevant to this group as well. Hence, it may be judicious to advocate a diagnostic colonoscopy procedure for patients meeting any of the subsequent criteria: 1) older than 65 years of age; 2) positive history of cancer, particularly kidney, lung, leukemia, lymphoma, testicular, or thyroid; 3) men who are Caucasian; 4) men who are not taking aspirin or NSAIDs; and 5) women who are actively taking estrogen or undergoing HRT. With this being said, it is important to remain aware that there was a large amount of unexplained variance in the specified regression models. Therefore, additional research in this arena is mandatory to clearly define these variables and to determine their potential impact on clinical practice.

Limitations

It must be emphasized that because a temporal association between an individual variable assessed in this investigation and the outcome of interest could not be firmly established, assertions concerning a direct cause-and-effect relationship could not be made. However, it should be noted that the results of a case-control study such as this can provide reasonable estimates that, when taken with other evidence, may support causal links between a specific risk factor and the presence or absence of disease.[30]

Constraints also surround the overall generalizability and external validity of these findings, as convenience sampling was chosen to amass the respective sample. In this setting, the probability of selection was not readily known and the amount of sampling error could not be reasonably predicted. Thus, the ability to disseminate these findings beyond the sample studied is somewhat hindered; it cannot be assumed that the sample represents the target population. Conceding this, the principle investigator made efforts to reduce the restraints placed on the data by this issue. Largely, this entailed making mindful and impartial sample selections in a manner that was void of influence from exposure histories and distal colonoscopy findings.

The only major threat to the internal validity of this undertaking identified was that of history. Fortunately, as dictated by the research design protocol, the rest of the main internal threats were not a dominant concern. Because this study incorporated medical charts and procedures dating back to 1997, it is plausible that the coercive effects of history could have affected some of the independent variables analyzed (current use of estrogen or HRT). Until late 2002, roughly seven million women in the US regularly took some form of estrogen or were receiving HRT, as these medications were heralded to be beneficial and protective. Yet after the landmark results from the highly publicized National Institutes of Health study of HRT describing the dangers of these products were made public in July 2002, the use of estrogen and HRT plummeted precipitously. Therefore, this event might have affected this variable (use of estrogen or HRT) in the women included from 2002 to 2007.

In conjunction with these limitations, it is also recognized that this retrospective inquiry was inherently and fundamentally predisposed to various forms of bias—namely, selection, misclassification, and observation. In response to this, safeguards were put into place. As alluded to earlier, the diffusion of selection bias centered on meticulously selecting the sample without prior knowledge of exposure histories or distal colonoscopy findings. Given the gravity of correctly classifying cases and controls, efforts to effectively manage misclassification took precedence. Case and control participants were operationally defined within the research protocol according to and abiding by set community standards (based on the WHO taxonomy for colonic polyps). To guarantee that there were no systematic differences in the way information was obtained from the study groups (observation bias), all data inspection, extraction, and documentation was done exclusively by the principle investigator.

Of note, other additional drawbacks of this protocol included not performing FS for all patients before the colonoscopy, not using one central pathologist to review the biopsy specimens, not requiring biopsies to be done by cold snare to ensure accurate tissue analysis, not recruiting from a variety of clinical settings, and not accumulating a larger and more ethnically diverse sample of patients with distal HPs.

Future Research

It is anticipated that FS will continue to be used as a viable screening modality for the prevention of CRC for years to come (both in the US and abroad), so ongoing investigation regarding this procedure seems prudent. Why did a history of cancer other than CRC increase the odds of having a proximal neoplasm in the asymptomatic screening population? Why did taking estrogen or HRT-related medications heighten the risk of proximal neoplasms in women? Why was current use of aspirin or NSAIDs protective against proximal lesions in men but not in women? Why did Caucasian men have a higher incidence of proximal growths? These are compelling questions that require future scientific inquiry. ❖

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Disclosure Statement

The author discloses that he is on the Advisory Board and Speaker Bureau for Three Rivers Pharmaceuticals.

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