EXPLORING POTENTIAL RISK FACTORS ASSOCIATED WITH INTERVAL COLORECTAL CANCER

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ABSTRACT

Background Colonoscopy has become the most commonly used screening test for colorectal cancer (CRC) with a 10-year interval recommended for those who are 50 years and older in the United States. There is new evidence that interval CRC occurs less than 5 years after a prior negative colonoscopy. The objective of this study was to assess potential risk factors associated with interval CRC.

Method To conduct this study, we reviewed approximately 64,000 colonoscopy records of patients who were 40 years and older and seen in the UPMC health system during 2013-2015. Demographic data, hospital locations, colonoscopy and pathology reports were abstracted from medical records. Patients diagnosed with CRC after 6 months but less than 5 years following the index negative colonoscopy procedure were defined as having interval CRC. Both bivariate analysis and logistic regression model were used to examine potential risk factors associated with interval CRC. Statistical significance level was set at 0.05. **S**tatistical analysis was performed using SAS Version 9.4.

Result We identified 323 patients diagnosed with invasive CRC. Among them, 88 patients had a prior colonoscopy. Among those with prior colonoscopy, 45 patients (51%) were diagnosed with interval CRC who were older at prior colonoscopy compared with those with non-interval

CRC (67 years vs. 62.6 years; p=0.035). Also, their sex, race, age and family history of CRC were not different from those with non-interval CRC. The results of logistic regression models showed that, compared to those with non-interval CRC, those with interval CRC were more likely to be older at prior colonoscopy and females ($p<0.05$).

Conclusion To reduce the risk of developing interval CRC, our findings suggest that the screening interval for CRC be shorter for female and older patients. Yet, this result should be interpreted with caution given the small sample in one health system. Further studies with larger study population in various geographical areas are necessary to fully explore risk factors associated with interval CRC and reduce the public health burden of interval CRC.

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PREFACE

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1.0 INTRODUCTION

1.1 EPIDEMIOLOGY OF COLORECTAL CANCER

Colorectal cancer (CRC) is the third most frequently diagnosed cancer in males (746,000 cases, 10.0% of the total) and the second in females (614,000 cases, 9.2% of the total) throughout the world, with 1.4 million cases and 693,900 deaths estimated in 2012.[1,2] The incidence of CRC varies by up to 10-fold across geographic regions,[2] with rates per 100,000 among males ranging from 4.1 in India (Karunagappally) to 59.1 in the Czech Republic.[3] The majority of countries with the highest incidence rates are located in Europe, North America, and Oceania, while the lowest rates are found in Asia, Africa, and South America.[3] Incidence rates have been increasing in regions that had historically low risk, such as Western Asia (Kuwait and Israel) and Eastern Europe (Czech Republic and Slovakia). Regions of high risk and high income have had more varied trends in CRC incidence rates, with increases in Finland and Norway, a stabilization in France and Australia, and a decline in the United States (U.S.),[1] but those rates may be confounded by screening utilization.

While CRC incidence rates vary greatly across regions, mortality rates have mostly decreased due to screening particularly in the U.S., as well as a reduction in the prevalence of risk factors and improved treatment.[1] Worldwide, there were 640,000 deaths in both males and females in 2012, which was 8.5% of the total cancer mortality.[2] Variability in mortality rates was

only six-fold in males and four-fold in females, with rates highest in Central and Eastern Europe (20.3 per 100,000 for males, 11.7 per 100,000 for females) and lowest in Western Africa (3.5 for males and 3.0 for females).[2] Mortality rates of CRC are still increasing in countries with rising incidence rates and limited resources, such as Brazil, Chile, Romania, and Russia.[1] Globally, there is a strong correlation between human development index (HDI) and CRC incidence rates (r=0.71) and between HDI and CRC standardized mortality rates (r=0.62).[4]

In the U.S., the incidence rate has been relatively high, with an annual age-standardized incidence rate of 40.7 per 100,000 persons between 2009 to 2013.[5] As a developed country with access to quality screening and treatment, the US has a relatively low mortality rate, with a rate of 14.8 per 100,000 persons from 2010 to 2014.[5]

1.2 RISK FACTORS FOR COLORECTAL CANCER

1.2.1 Age

In general, age is one of the most important risk factors for cancer. The incidence of most cancers increases with age. In 2009, more than 50% of all cancers occurred in adults aged older than 65 years old.[6] The risk of colorectal cancer also increases with age. The average age of diagnosis for colon cancer is 68 years for males and 72 years for females. For rectal cancer, the average age of diagnosis is 63 years for both males and females. The majority of CRC occurs in people older than 50 years old, with only about 11% of CRC being diagnosed in people younger than 50 years old.[7]

1.2.2 Sex

According to the estimates of American Cancer Society, the probability of developing CRC was about 4.49% for men and 4.15% for women in the US.[8] However, Ferlay et al. reported that females have been shown to have a higher incidence and mortality of CRC compared to males in populations over 65 years old, suggesting that CRC is a significant health risk among older women.[2] In particular, females are more likely to develop right-sided colon cancer, which is often diagnosed at a more advanced stage, than males. This was reported in a major cohort study involving 17,641 patients comparing left-sided colon cancer to right-sided colon cancer.[9,10] The higher incidence of right-sided colon cancer in older females may be explained by several factors, including hormones and genetics. A population-based case-control study of 4,246 patients suggested that estrogen acted as a protective factor against microsatellite instability (MSI), a condition that is commonly observed in right-sided colon cancer.[9,11] As women become older, their estrogen levels drop without hormone replace therapy which may result in increasing the risk of MSI, right-sided colon cancer, and mortality. This suggests that sex should be considered when assessing risk for CRC.

1.2.3 Race

Risk for CRC has been reported to vary among racial/ethnic groups, with African Americans having higher incidence and mortality rates in the U.S.,[12] although the role of race as a risk factor is inconclusive. Ollberding et al. examined the variation of CRC among 165,711 African Americans, Japanese Americans, Latinos, Native Hawaiians and Whites participating in the Multiethnic Cohort Study.[13] The study found that Japanese Americans (men, relative risk (RR) =

1.27, 95% CI = 1.09–1.48; women, RR = 1.49, 95% CI = 1.24–1.78) and African American women (RR = 1.48, 95% CI = 1.23–1.79) had an increased risk of CRC compared to Whites.[13] Another study analyzing the racial difference in CRC incidence and mortality in the Women's Health Initiative, a longitudinal study of postmenopausal women, reported that the risk for CRC was lower in Hispanics compared with Whites, (hazard ratio (HR) = 0.73, 95% CI: 0.54–0.97, p = 0.03), and was slightly higher in African Americans, (HR = 1.16, 95% CI: 0.99–1.34, p = 0.06).[12] However, once multivariable adjustment was performed, the difference in risk was not significantly different between African Americans and Whites (HR = 0.99, 95% CI: 0.82–1.20), while Hispanics were shown to have an even lower risk compared to Whites (HR = 0.68, 95% CI: 0.48–0.97).[12] The study concluded that the differences in risk of CRC between African Americans and Whites were likely due to sociodemographic and cultural factors other than race.[12]

1.2.4 Family History

A family history of CRC defined as a first degree relative (mother/father/siblings/children) with the disease has been associated with an increased risk of CRC.[14] A review of four meta-analyses and 12 original studies found that there is a two-fold increase in risk for CRC with at least one affected first-degree relative, with more than a three-fold increase in risk if a first-degree relative was diagnosed under the age of 50 years (pooled RR = 3.55; 95% CI: 1.84-6.83) and a two to three-fold increase if a first-degree relative is diagnosed under the age of 60 years (pooled RR = 1.81-3.30).[14] The review also found that having a first-degree relative with an adenoma, a benign tumor that may become malignant over time, was associated with an increased risk of CRC (RR ranging from 1.35-1.99), with the risk increasing even higher if the adenoma is larger than 10

mm in diameter (RR = 1.68; 95% CI: 1.29-2.18) or is considered advanced (RR = 3.90, 95% CI: 0.89-17.01).[14] However, other studies have shown that family history does not necessarily have a strong association with risk of CRC. In a retrospective cohort study of 431,153 individuals assessing the association between family history and CRC, the familial relative risk (family history defined as having ≥1 affected first-degree relative with CRC) ranged from 0.83 to 12.39.[15] The study concluded that family history on its own is not a strong predictor of CRC within 20 years.[15] Therefore, it is controversial that individuals with family history of adenoma might have higher risk of developing CRC.

1.2.5 Smoking

There is strong evidence that smoking is associated with an increased risk for CRC.[16] A systematic review and meta-analysis of 36 studies found that current smokers had a 17% (95% CI: 0.97–1.40) higher risk of developing CRC and a 40% (95% CI: 1.06–1.84) higher risk of CRC mortality compared to never smokers.[17] Former smokers also showed an increased risk for CRC incidence (RR = 1.25, 95% CI: 1.05-1.51) and mortality (RR = 1.15, 95% CI: 0.90–1.48) compared to never smokers.[17] Boyle et al. reported similar results using the Western Australian Bowel Health Study (WABOHS), a population-based case-control study of CRC based in Western Australia from 2005-2007. A 24% higher risk of CRC (adjusted odds ratio (OR) = 1.24, 95% CI: 1.01-1.53) was found in former smokers compared to never smokers, with participants who smoked at least 20 pack-years showing a 26% higher risk of CRC relative to never smokers.[18]

1.2.6 Alcohol

Alcohol has been established as a significant risk factor for CRC. Boyle et al. reported that the consumption of beer for at least 5 days per week 10 years prior increased the risk of CRC compared to the consumption of beer less than once per week (adjusted OR = 1.50, 95% CI: 1.90-2.07).[18] A meta-analysis of nine cohort studies showed that heavy drinkers (>=50 g/day of ethanol) had a significant increase in risk (RR = 1.21, 95% CI: 1.01-1.46) compared with non-drinkers and occasional drinkers, with the risk being higher for males (RR=1.28, 95% CI, 1.13–1.46) than for females (RR=0.79, 95% CI, 0.40–1.54) when adjusting for smoking and other risk factors.[19] Based on the dose-response analysis, risk for CRC significantly increased at an exposure level of 56.5 g/day (RR=1.14, 95% CI, 1.00–1.30), with risk peaking at an exposure of 81.9 g/day (RR=1.29, 95% CI, 1.08–1.54).[19] Another meta-analysis found an association between alcohol and risk for colorectal adenomas, with significant increases in risk for the alcohol consumption of 50 g/day (RR = 1.16, 95% CI: 1.02-1.33) and 100 g/day (RR= 1.61, 95% CI: 1.42-1.84) when compared to no or occasional consumption.[20]

1.2.7 Obesity and Physical Activity

Obesity and the lack of physical activity have been associated with increasing the risk of CRC.[16] According to a systematic review of 20 meta-analyses, 5 reviews, 113 observational studies and 50 additional supporting articles on obesity and CRC, obesity is associated with a 30-70% increase in risk of colon cancer in men, with RR ranging from 1.37 (95% CI: 1.21-1.56) to 1.95 (95% CI: 1.59-2.39).[21] The review also found an association between obesity and an increased incidence of colorectal adenomas according to four meta-analyses.[21] A different meta-analyses

on body mass index (BMI), physical activity, and CRC showed similar results, finding a positive relationship between BMI and CRC for all colorectal subsites, including the distal colon (RR = 1.59, 95% CI: 1.34-1.89), proximal colon (RR = 1.24, 95% CI: 1.08-1.42), and rectum (RR = 1.23, 95% CI: 1.02-1.48).[22] The meta-analyses also found an inverse relationship between physical activity and the risk of CRC at the proximal (RR = 0.76, 95% CI: 0.70-0.83) and distal colon (RR = 0.77, 95% CI: 0.71-0.83).[22]

1.2.8 Diet

Diet plays a significant role in the risk of developing CRC.[16] A systematic review of diet and CRC found that red and processed meat (RR = 1.16, 95% CI: 1.04−1.30, per 100 g/day increase), fiber (RR = 0.90, 95% CI: 0.86−0.94, per 10 g/day increase), milk (RR = 0.91, 95% CI: 0.85−0.94, per 200 g/day increase), calcium (RR = 0.92, 95% CI: 0.89−0.95, per 300 mg/day increase), and whole grains (RR = 0.83, 95% CI: 0.78−0.89, per 3 servings/day increase) have been consistently linked to CRC in prospective cohort studies.[23] Bernstein et al. reported similar results for red and processed meat, with processed red meat having a positive association with the risk of CRC (HR = 1.15, 95% CI: 1.01-1.32, per 1 serving/day increase).[24] This relationship was even stronger with distal colon cancer (HR = 1.36, 95% CI: 1.09-1.69, per 1 serving/day increase).[24] Interestingly, unprocessed red meat was found to have an inverse relationship with the risk of distal colon cancer (HR = 0.75, 95% CI: 0.68-0.82, per 1 serving/day increase),[24] suggesting that reducing the intake of processed red meat should be prioritized over the intake of unprocessed red meat when it comes to CRC prevention.

1.3 SCREENING FOR COLORECTAL CANCER

Screening for CRC has been cited as one of the primary reasons for the decrease in CRC rates, particularly in the U.S.[3] Screening allows for the detection and removal of precancerous colorectal polyps resulting in a reduction in the incidence and mortality of CRC.[1] It also reduces the mortality of CRC by the detection of early-stage adenocarcinomas.[25] To evaluate the effectiveness of different screening methods, CRC screening studies tend to focus on measuring the detection rate of adenomatous polyps, the most common and clinically important polyps with an association for higher risk of CRC, and advanced adenomas, which are defined as polyps at least 10 mm in size or histologically having high-grade dysplasia or significant villous components.[25] Screening methods can be categorized as (1) stool tests, which include the guaiac-based fecal occult blood test, Fecal Immunochemical Test, and stool DNA test, as well as (2) structural exams, which include Flexible Sigmoidoscopy, Colonoscopy, and Computed Tomographic Colonography (CTC).[25]

The Affordable Care Act requires health plans to cover CRC screening once every 10 years. Medicare covers following CRC screening tests at no cost: fecal occult blood test once every 12 months, stool DNA test every 3 years, flexible sigmoidoscopy every 4 years, or colonoscopy once every 10 years for those with average risk. Medicaid coverage for CRC screening varies by state.[26] Based on 17 studies of CRC screening published during the period of 2007-2014,[27] the average costs of screening and range for each type of test were summarized in the Table 1. A description of each type of test used for CRC screening is described below.

1.3.1 Stool Blood Tests

Guaiac-Based Fecal Occult Blood Test (gFOBT). As a stool blood test, gFOBT is designed to detect occult blood in the stool using a guaiac-based test through the pseudoperoxidase activity of heme or hemoglobin, while immunochemical-based tests react to human globin. The protocol requires 2 samples from each of 3 consecutive bowel movements at home to be collected. Patients are instructed to avoid aspirin and other nonsteroidal anti-inflammatory drugs, vitamin C, and certain foods because of diet-test interactions that can increase the risk of both false-positive and false-negative results. The test is simple and puts patients in minimal harm. Annual testing with gFOBT has been reported to lower CRC incidence and mortality.[28,29] The main limitation of gFOBT is limited sensitivity even under the best conditions, which may be compromised further by low quality specimen collection and inadequate processing and interpretation of the test results. Testing for early detection of CRC for adults aged 50 years or older is recommended annually.[25]

Fecal Immunochemical Test. Fecal immunochemical test also detects occult human globin in the stool but has several advantages over gFOBT. Fecal immunochemical test directly detects human globin, a protein that makes up part of human hemoglobin, instead of relying on the detection of peroxidase in human blood. In addition, Fecal immunochemical test is not susceptible to false-negative results due to Vitamin C and diet-test interactions that gFOBT is. Furthermore, Fecal immunochemical test has a higher specificity for lower gastrointestinal bleeding, which improves specificity for the detection of CRC. Fecal immunochemical test is also easier on the patient due to requiring fewer stool samples and no diet restriction. Testing for early detection of CRC for adults aged 50 years or older is recommended annually in the U.S. and biennially in Europe.[25,30]

1.3.2 Stool DNA Test (sDNA)

sDNA tests stool for the presence of known DNA alterations in the adenoma-carcinoma sequence of colorectal carcinogenesis. This DNA comes from adenoma and carcinoma cells that are shed and passed in stool. A multitarget DNA stool assay identifies several gene mutations in the DNA linked with adenomas and carcinomas.[31] The benefits of sDNA include having acceptable sensitivity for CRC ranging from 52% to 91% in previous studies, not being reliant on the detection of occult bleeding that is intermittent, requiring only one stool sample, and being noninvasive to the patient. Limitations include higher unit cost per test compared to other stool tests and the dependence of test sensitivity on the panel of markers that identifies the majority but not all CRC. Testing interval for early detection of CRC for adults aged 50 years or older is still uncertain.[25]

1.3.3 Endoscopy Examinations of the Colon and Rectum

Flexible Sigmoidoscopy. Flexible sigmoidoscopy is a procedure that examines the lower half of the colon lumen using endoscopy performed with a range of instruments, including the standard 60-cm sigmoidoscope, colonoscope, an upper endoscope, and a pediatric colonoscope. The patient is not sedated during the procedure. The main benefit of flexible sigmoidoscopy is the simple preparation of only 2 Fleet enemas without the need for sedation. The main limitation of flexible sigmoidoscopy is that the procedure only examines the rectum, sigmoid, and descending colon but not the entire colon. Testing for early detection of CRC for adults aged 50 years or older is recommended every 5 years.[25]

Colonoscopy. Unlike flexible sigmoidoscopy, colonoscopy involves the direct inspection of the entire colon, including biopsy or polypectomy if a polyp is detected. Patients are required to adjust to a liquid diet a day or more prior to the examination along with the ingestion of oral lavage solutions or saline laxatives to clean out the bowel. Proper bowel preparation is extremely important in the accuracy and cost-effectiveness of colonoscopy. Sedation is often provided to patients before the procedure. The biggest advantage of colonoscopy is the examination of the entire colon and rectum, together with biopsy and polypectomy, in a single session. The thorough nature of the procedure makes it required as a second procedure for all other types of CRC screening showing a positive result. The limitations of colonoscopy include diet preparation, proper bowel cleansing and preparation, a day dedicated to the examination, a chaperone for transportation due to the sedation, the invasive nature of the procedure, dependence on operator skill and cost. Testing for early detection of CRC for adults aged 50 years or older is recommended every 10 years.[25]

1.3.4 Imaging Examinations of the Colon and Rectum

Computed Tomographic Colonography (CTC). Also known as virtual colonoscopy, CTC is a minimally invasive imaging examination of the entire colon and rectum. It uses a computed tomography (CT) to obtain images and display them in a 2-dimensional (2D) and 3-dimensional (3D) manner for interpretation. Proper bowel preparation and gaseous distention of the colon are required for an optimal examination. No sedation or recovery for the patient is needed, with the procedure taking only about 10 minutes. The benefits of CTC include being time-efficient, minimally invasive, and the examination of the entire colon. The limitations of CTC include being “imaging-only” and requiring a colonoscopy for polypectomy, being operator dependent,

having accuracy being dependent on polyp size. Testing for early detection of CRC for adults aged 50 years or older is recommended every 5 years.[25]

1.3.5 Colonoscopy as the "Gold Standard" for Screening

Colonoscopy is considered the "gold standard" and cornerstone of CRC screening programs, used either as the primary screening test or as a secondary follow-up to other screening tests.[3,32] Several medical authorities, such as the American College of Gastroenterology, have recommended it as the preferred initial screening test.[33] It has remained the dominant modality for CRC screening in the United States due to the advantages it has over other screening tests, including direct visualization of the entire colon, the ability to perform polypectomy and biopsy during the examination, allowing appropriate surveillance intervals to be determined based on the results of the index examination, longer intervals between recommended screening, and increasing acceptability and tolerability of sedation techniques.[34]

A wide range of studies and overwhelming evidence have shown the effectiveness of colonoscopy in reducing CRC incidence and mortality.[35] In a case-control study by Baxter et al., cases of CRC were less likely to have undergone colonoscopy compared to controls without CRC (OR = 0.40, 95% CI: 0.37 to 0.43).[36] The National Polyp Study reported a 76% reduction of CRC incidence and 53% reduction in CRC mortality in a cohort of patients with adenomas who were examined by colonoscopy.[34] The results of a meta-analysis of randomized control trials and observational studies involving CRC screening by sigmoidoscopy and colonoscopy suggested that screening by colonoscopy lowered the risk of CRC by 40-60%.[37] A study by Singh et al. provided evidence supporting the recommended 10 year interval between colonoscopy examinations, reporting that a negative colonoscopy was associated with

standardized incidence ratios (SIRs) of 0.69 (95% CI: 0.59-0.81) at 6 months, 0.66 (95% CI: 0.56-0.78) at 1 year, 0.59 (95% CI: 0.48-0.72) at 2 years, 0.55 (95% CI: 0.41-0.73) at 5 years, and 0.28 (95% CI: 0.09-0.65) at 10 years after the index colonoscopy which was a baseline colonoscopy used to compare with follow-up colonoscopies.[33] Together, the evidence strongly supports the use of colonoscopy as the standard for CRC screening.

1.4 INTERVAL COLORECTAL CANCER

Although CRC screening by colonoscopy has proven to be effective in lowering incidence and mortality of CRC, there are still a considerable number of individuals who are diagnosed with CRC relatively soon after a negative colonoscopy has indicated no evidence of CRC.[38] This is classified as interval CRC, which is defined as "CRC diagnosed after a screening or surveillance exam in which no cancer is detected, and before the date of the next recommended examination."[39] There is quite a large variation in the incidence rate of interval CRC within the literature, ranging from 2.9% to 9.6% of all CRC cases diagnosed in a population and from 1 in 130 to 1 in 1,000 colonoscopy examinations.[40] Recently, Ertem et al. has found the rate of interval CRC cases to be only 1 in 3,000 examinations.[41] This variation is likely due to differences in study designs, definitions of interval CRC, administrative data versus clinical data, study populations, or the specialty of practicing endoscopists.[42] Regardless, the incidence is expected to increase with the aging populations and widespread adoption of screening.[42]

Determining the causes of interval CRC is difficult due to the unknowns in tumor biology and the inability to discern whether a prior colonoscopy missed detecting CRC. However, the consensus is that the causes can be separated into three categories: missed neoplasia (either

cancer or significant polyps), incompletely resected lesions, and new lesions.[43] The majority of interval CRC is attributed to missed lesions, with 52% being attributed to missed lesions in a large pooled analysis that included eight large studies (>800 patients per study with a total N = 9,167) conducted in North America, including in the U.S.[43] The same pooled analysis estimated that incomplete resection of lesions resulted in 19% and new lesions resulted in about 25% of interval CRC cases, respectively.[43]

Previous studies have shown certain characteristics among patients with interval CRC. Erichsen et al. reported that cases of interval CRC compared to those without interval CRC were older (74 vs. 71 years), more likely to be female (54% vs. 48%), have comorbidities (CCI3+: 28% vs. 15%), have proximal tumors (38% vs. 22%), and have tumors with mucinous histology (9.1% vs. 7.0%), but cancer stage was similar (metastatic 23% vs. 24%).[44] Samadder et al. found that 57.2% of interval CRC cases had adenomas during the index colonoscopy compared to 36% of the patients who were diagnosed with CRC at the index colonoscopy and 26% of patients who did not develop cancer.[45] It was also found that interval CRCs tended to be earlier-stage tumors and more proximally located compared to CRCs diagnosed at the index colonoscopy (OR = 2.24, $p < 0.001$).[45] Patients with interval CRC tended to have a family history of CRC (OR = 2.27, $p = 0.008$) and a lower risk of death compared to patients diagnosed with CRC at the index colonoscopy (HR = 0.63, $p < 0.001$).[45] A meta-analysis of 12 studies reported similar results, with interval CRC cases being older (age >65-70 years vs. <65-70 years: OR = 1.15, 95% CI: 1.02-1.30), having more comorbidities (high Charlson comorbidity index: OR=2.00, 95% CI: 1.77-2.27), and having diverticular disease (OR = 4.25, 95% CI: 2.58-7.00).[46] Interval CRC cases were also less likely to present cancer at an advanced stage (OR = 0.79, 95% CI: 0.67-0.94), although there was no survival benefit for the patients.[46]

Colonoscopy has been proven to be effective as a screening method for CRC, yet interval CRC still occurs. The risk factors for interval CRC have not been fully established in the literature, with various studies reporting differing results, and therefore warrant further exploration.

1.5 PUBLIC HEALTH SIGNIFICANCE

Colorectal cancer, as the third most commonly diagnosed cancer and the second leading cause of cancer mortality in the U.S., remains a major public health issue that affects the lives of many. Dubé pointed out that CRC screening is one of the most cost-effective interventions and good evidence has supported the reduction of CRC incidence and CRC-related mortality (ranging from 12% to 43% reductions in mortality).[47] As the incidence of interval CRC will likely rise due to the aging population and increased adoption of CRC screening, the urgency to determine the underlying causes for interval CRC grows stronger as well. Even a single failure of colonoscopy screening to identify CRC may be devastating, affecting not only the patient but family members and friends. The identification of risk factors associated with interval CRC are of utmost importance for the creation of modified CRC screening strategies that would minimize the incidence of interval CRC and therefore improve public health in the future.

2.0 OBJECTIVE

The goal of this study is to assess potential risk factors for developing interval CRC which may positively impact future efforts to prevent interval CRC and improve public health.

3.0 METHODS

3.1 STUDY POPULATION AND DATA SOURCES

We retrospectively reviewed approximately 64,000 colonoscopy records of patients (aged 40 years and older) seen in the UPMC health system during the period of 2013 through 2015 and identified patients who were diagnosed with invasive CRC at the time of their colonoscopy (n=323). We subsequently reviewed their medical records for evidence of a previous colonoscopy in the system going back to 1990, identifying patients with at least one prior colonoscopy (n=88). Demographic characteristics (age, sex, race, etc.), hospital locations, and clinical characteristics were abstracted from medical records, including colonoscopy and pathology reports. In this study, ***Interval CRC*** is the key outcome variable which is defined as CRC diagnosed at least 6 months but less than 5 years after a previous examination in which no cancer was detected.

3.2 EXAMINATION CHARACTERISTICS

Demographic and hospital location data were collected for all 323 patients who were diagnosed with CRC. Clinical characteristics for the index colonoscopy (examination that diagnosed the patient with CRC) and prior colonoscopy (most recent examination before the index

colonoscopy) were collected for the 88 patients with at least one prior colonoscopy in the UPMC system since 1990. These clinical characteristics include: indication for examination (screening, surveillance, or diagnostic); family history of CRC; quality of bowel preparation; examination completeness (whether endoscopist reached the cecum, appendiceal orifice, and ileocecal valve); whether the examination procedure was aborted; whether polyps were removed; whether a polyp > 1 cm, advanced adenoma, or carcinoma was found; the largest size of polyps and adenomas found; and the location of polyps found by colon segment. These data were not collected for patients who did not have a prior colonoscopy because we were primarily interested in clinical characteristics that were present in the most recent prior colonoscopy that are associated with interval CRC and may have been overlooked during the examination, causing the interval CRC to occur. Detailed descriptions of the variables of interest will be summarized in Table 2.

3.3 STATISTICAL ANALYSIS

To identify risk factors associated with developing interval CRC, we first compared demographic characteristics of all patients with non-interval CRC (n=278) with those with interval CRC (n=45). To examine whether hospital location and academic role might be related to the development of interval CRC, we categorized 14 hospitals in our study into academic, suburban, and rural groups. We defined a hospital that is affiliated with a medical school and provides professional medical training as academic. The rest of hospitals that are not academic were categorized as suburban or rural hospital by the location of the facility. Furthermore, we focused on 88 patients who had at least one prior colonoscopy.

One-way ANOVA (analysis of variance) for continuous variables and chi-square tests or Fisher's exact tests for categorical variables were used to compare whether there were differences between patients with interval CRC vs non-interval CRC. If the continuous variables were not normally distributed according to the Shapiro-Wilk test of normality, then the Wilcoxon Rank Sum non-parametric test was used for analysis. Finally, for those patients with prior colonoscopies, we performed stepwise logistic regression to further examine any risk factors that may be identified in the regression model. The outcome variable is "with interval CRC" vs. "with non-interval CRC." The independent variables included in the regression were demographic variables and variables with p-values < 0.20 in the bivariable analyses comparing colonoscopy characteristics by interval CRC vs. non-interval CRC. We were also interested in the potential relationship of family history of cancer and hospital character (academic/suburban/rural) with the outcome of interest so these two variables were included in the regression model as well. Odds ratios (OR) and corresponding 95% confidence intervals (95% CI) were calculated. Statistical significance level was set at 0.05. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for statistical analyses.

4.0 RESULTS

Out of the approximately 64,000 colonoscopies performed in the UPMC health system between 2013-2015, 323 patients were identified with colon cancers. Eighty-eight (27.2%) out of 323 patients had prior colonoscopies before being diagnosed with CRC. Of the patients with any prior colonoscopies, 45 out of 88 patients (51.1%) were classified as having interval CRC. Among 323 patients with CRC during the study period, 13.9% had interval CRC.

The demographic characteristics were categorized by patients without a prior colonoscopy and patients with a prior colonoscopy, which was then further categorized by patients who had interval CRC and non-interval CRC (Table 3). Among 323 patients, 41.5% were female and 87.6% were white race. Their average age when the CRC was diagnosed was 68.3 years old. Out of the patients without a prior colonoscopy, 40.9% (96/235) were female and 90.6% (213/235) were white race. Out of the patients with a prior colonoscopy, 43.2% (38/88) were female and 79.5% (70/88) were white race. There was a significant difference in race ($p=0.007$) between patients with and without prior colonoscopy but there were no significant differences in sex and age (see p values at the column ** of Table 3).

Among patients with prior colonoscopies (n=88), compared to those with non-interval CRC, a higher proportion of patients of those with interval CRC were females (51.1% (23/45) vs. 34.9% (15/43)), white (84.4% (38/45) vs. 74.4% (32/43)), and had a family history of CRC (13.3% (6/45) vs. 7.0% (3/43)) (Table 3). Furthermore, we examined proportion of patients with

interval CRC and non-interval CRC within sex, race, and family history of CRC. Compared to their counterparts, greater proportions of those who were female (60.5% female vs. 44.0% male), white (54.3% white vs. 38.9% non-white), or with family history of CRC had interval CRC (66.7% with family history vs. 49.4% without family history of CRC) (Figure 2). Overall, patients with interval CRC and non-interval CRC were not significantly different in these demographic characteristics (see p values at the column * in Table 3). Among those with prior colonoscopies, patients who were diagnosed with interval CRC were older at prior colonoscopy compared to those with non-interval CRC (67.0 vs. 62.6 years; p=0.035), but their average age at the diagnosis of CRC was similar (69.8 vs. 68.1 years; p=0.658). For those with interval CRC, the mean number of years between prior and index colonoscopies was 2.8 years (range: 0.6 – 4.9 years) while it was 6.2 years (range: 0.03 – 22.6 years) for those with non-interval CRC ($p < 0.0001$).

The number and proportion of patients with interval CRC and non-interval CRC for each hospital are summarized in Table 4. The hospitals were categorized as academic, suburban, or rural. Three hospitals were categorized as academic because they are teaching hospitals, while six hospitals were located in suburban areas and five hospitals were located in rural areas. The distribution of patients with interval CRC or non-interval CRC varied significantly by hospitals' academic/suburban/rural location ($p < 0.001$) (Figure 3). Academic hospitals had the largest proportion of patients with interval CRC (18.7%), compared with suburban hospitals (12.2%) and rural hospitals (11.5%) ($p = 0.301$). Of 88 patients with prior colonoscopy, academic hospitals had the lowest proportion of patients with interval CRC (46.0%), hospitals in the suburban locations had the highest proportion (56.4%), while rural hospitals had the 2nd highest proportion (50.0%) ($p = 0.657$) (Table 5).

Indication for colonoscopy examination and colonoscopy characteristics were investigated and summarized in Tables 6 and 7. Only indications categorized under "surveillance" were significantly different between patients with and without interval CRC (p = 0.036), with patients that have a colonoscopy due to surveillance reasons having a higher risk for interval CRC (44.4% (20/45) vs. 23.3% (10/43), p = 0.036). None of the patients with interval CRC had an aborted procedure while 6 patients (14.0%, 6/43) with non-interval CRC had aborted procedures (p = 0.011). A lower proportion of patients with interval CRC were reported to have inadequate quality of preparation compared to those without interval CRC (8.9% (4/45) vs. 20.9% (9/43), p = 0.140). The rest of the colonoscopy procedure data indicated that, compared to patients with non-interval CRC, those with interval CRC were less likely to have polyps > 1 cm (22.2% (10/45) vs. 25.6% (11/43)) and an advanced adenoma (22.2% (10/45) vs. 27.9% (12/43)), while being more likely to have an examination that reached the cecum (93.3% (42/45) vs. 79.1% (34/43)), saw the appendiceal orifice (93.3% (42/45) vs. 81.4% (35/43)), saw the ileocecal valve (91.1% (41/45) vs. 81.4% (35/43)), had a polyp removed (64.4% (29/45) vs. 48.8% (21/43)), had a proximally located polyp (42.2% (19/45) vs. 39.5% (17/43)), had a distally located polyp (40.0% (18/45) vs. 25.6% (11/43)), and had at least one polyp identified (62.2% (28/45) vs. 48.8% (21/43)). On average, for patients with polyps (n = 49), the largest Adenoma size (mm) identified was comparable for patients with interval CRC (6.13 mm vs. 6.15 mm, p = 0.606) while the largest polyp size (mm) identified was smaller for patients with interval CRC (11.08 mm vs. 14.83 mm, p = 0.202). However, none of these examination characteristics were significantly different between patients with and without interval CRC.

The results of the stepwise logistic regression analysis are presented in Table 8. In Model 1, the odds ratio estimates showed that older age at prior colonoscopy (p = 0.0090) and having an

examination that reached the cecum (p = 0.0310) were factors that increased the likelihood of developing interval CRC. Model 1 also showed that males (p = 0.0268) were significantly less likely to have interval CRC. In Model 2, when we replaced the continuous variable of age at prior colonoscopy with a binary variable of age at least 65 years vs. under 65 years, the results of significant risk factors were comparable to those in the Model 1 except the p-value of age became much smaller (p = 0.0046). It showed that those who were 65 years and older are significantly more likely to have interval CRC.

In summary, interval CRC patients were more likely to be female (51.1% vs. 34.9%, p = 0.125), white (84.4% vs. 74.4%, p = 0.244), older at prior colonoscopy (67.0 years vs. 62.6 years; p = 0.035), have a family history of CRC (13.3% vs. 7.0%, p = 0.485), and have a surveillance indication (44.4% vs 23.3%, p = 0.036), in addition to having an examination that reached the cecum (93.3% vs. 79.1%, p = 0.066), saw the appendiceal orifice (93.3% vs. 81.4%, p = 0.114), saw the ileocecal valve (91.1% vs. 81.4%, p = 0.224), removed a polyp (64.4% vs. 48.8%, p = 0.140), had a proximally located polyp (42.2% vs. 39.5%, p = 0.798), had a distally located polyp (40.0% vs. 25.6%, p = 0.150), and had at least one polyp identified (62.2% vs. 48.8%, p = 0.206) compared non-interval CRC patients. Interval CRC patients were less likely to have an examination that had an aborted procedure (0.0% vs. 14.0%, p = 0.011), inadequate preparation (8.9% vs. 20.9%, p = 0.140), a polyp > 1 cm (22.2% vs. 25.6%, p = 0.805), and an advanced adenoma (22.2% vs. 27.9%, p = 0.538), in addition to having a smaller largest adenoma size (6.13 mm vs. 6.15 mm, p = 0.606) and smaller largest polyp size (11.08 mm vs. 14.83 mm, p = 0.202) compared to non-interval CRC patients. In the logistic regression models, older age at the prior colonoscopy remained significant, with female sex and a prior examination reaching the cecum also shown as significantly increasing the risk of interval CRC.

5.0 DISCUSSION

Using data from medical records in the UPMC Health System from 2013 to 2015, we conducted a retrospective review to identify possible risk factors associated with interval CRC in order to help predict which patients may benefit from more frequent or modified screening strategies. The main findings of our study include: (a) interval CRC patients had a significantly older age at the most recent prior colonoscopy compared to non-interval CRC patients, (b) rates of interval CRC vary among academic, suburban, and rural hospitals, with the lowest rates in academic hospitals, (c) patients having an indication for examination classified under surveillance were significantly more likely to have interval CRC, and (d) females having a significantly higher risk of interval CRC compared to males.

Our study showed that the increased age is associated with interval CRC, with the average age at the prior colonoscopy being 4.4 years older for patients with interval CRC compared to non-interval CRC patients ($p = 0.035$). Older age as a risk factor for interval CRC has been widely reported in other studies. Both Baxter et al. and Cooper et al. reported that patient with interval CRC were more likely to be older.[48,49] Stoffel et al. found that older age was more common in interval CRC cases.[50] A meta-analysis by Singh et al also showed that older age (>65-70 years), along with having more comorbidities, was significantly associated with interval CRC.[46] Comorbidities, which are positively correlated with age, may cause increased difficulty during colonoscopy examinations, resulting in increased risk for missed polyps and

adenomas, eventually leading to a greater likelihood of interval CRC. As cancer is considered a disease of aging, this result was expected.

Because a previous study by Simon et al. concluded that the difference in risk of interval CRC between whites and African Americans was not due to race itself but rather due to other cultural or sociodemographic reasons, we used hospital location as a proxy of patients' sociodemographic factors.[12] In our analysis, we found that patients who attended rural hospitals were more likely to have interval CRC compared to those patients who attended academic hospitals while less likely to have interval CRC compared to those who were seen in the suburban hospitals. This result matches what was reported by Singh et al. in which patients who were seen in rural hospitals had an OR = 2.11 compared to urban hospitals as a reference group.[51] This may be related to the higher prevalence of obesity, alcohol consumption, and smoking in rural areas, all of which are considered risk factors for CRC.[52,53] Although our findings in the regression models were not statistically significant, they are consistent with previous research.

In our bivariate analysis, we identified that patients with an examination indication categorized as surveillance were significantly more likely to have interval CRC ($p = 0.036$). This is also consistent with previous findings, with Richter et al. reporting that patients with interval CRC had a significantly larger proportion (34.0%) of examinations that were indicated for surveillance purposes compared to the reference group (21.7%).[54] This makes logical sense because patients with examinations indicated for surveillance have some type of history with polyps or lesions and therefore would be at higher overall risk for interval CRC.

Although inconsistent with the Siegel and her colleagues' finding using SEER data in the U.S.,[8] Ferlay et al. and Kim et al. reported that there is a higher incidence and mortality of CRC

in females compared to men among populations over 65 years old in the world.[2,9] They suggested that older females may also be more susceptible to interval CRC. From the results of our logistic regression models, we found that males had a lower risk of interval CRC (Model 1: OR = 0.247, p = 0.024; Model 2: OR = 0.211, p = 0.018). This finding is consistent with several other studies involving interval CRC. Brenner et al. reported that female sex had an OR = 2.28 compared to male sex as the reference group.[55] Similarly, Baxter et al. found that female sex was significantly associated with interval CRC for patients with distal CRC.[48] However, these findings are somewhat inconsistent in the literature, with a pooled multicohort analysis of eight large North American studies by Robertson et al. showing that male sex was associated with an increased risk of interval CRC.[56]

Although the covariates mentioned above were the only ones found to be statistically significant in our study, other covariates that were not found to be significant may still provide some clinical insight into possible risk factors for CRC. For race, it was somewhat unexpected that there was a larger proportion of whites in the interval CRC group compared to the non-interval CRC group based on reports of African Americans having higher incidence and mortality rates in the U.S.[12] However, this is probably due to the small sample size of our study since only 18 of the 88 patients with a prior colonoscopy were non-white. Differences in risk between races was also reported to be likely due to sociodemographic and cultural factors.[12] For family history of CRC, the data showed that interval CRC patients were more likely to have had a family history of CRC compared to non-interval CRC patients. This was expected since having a family member with CRC means that a person may be at higher risk for CRC due to genetic factors.

During the data analysis, we noticed that none of the patients with interval CRC had their procedure aborted while six patients with non-interval CRC did have their procedures aborted. We further examined the records of procedure aborted for 12 patients who were diagnosed with CRC but did not meet the criteria of interval CRC because they were diagnosed with CRC within 6 months after prior colonoscopy. Out of those 12 patients, five had their colonoscopy procedure aborted. It was possible that they were asked by their colonoscopists to return soon after their prior colonoscopy because of potential complications during the examination which resulted in the procedure being aborted. While those patients would not meet the criteria for interval CRC, this may justify why there were no procedure aborted among those with interval CRC.

The quality of preparation for the colonoscopy examination also had an unexpected outcome, with a lower proportion of patients in the interval CRC group having inadequate preparation compared to the non-interval CRC group. An inadequate preparation for the examination would mean that the colonoscopist would have a more difficult time performing a thorough examination, resulting in an increased likelihood of missed polyps or adenomas and an increased risk for CRC. However, this was not observed in our data, which we may be due to the non-interval CRC patients who were diagnosed with CRC within 6 months after a prior colonoscopy having inadequate preparation for their colonoscopy examinations. These patients may also have been the same patients who had their procedures aborted.

Despite not being statistically significant in our analysis, several other covariates from the colonoscopy's pathology report also had somewhat unexpected outcomes. A slightly smaller proportion of interval patients had a polyp > 1 cm and advanced adenomas compared to non-interval patients, which were most likely due to random chance and a small sample size since the differences were quite small ($p > 0.500$). Examinations that reached the cecum, saw the

appendiceal orifice, and saw the ileocecal valve would be expected to be more common among non-interval CRC patients because that would indicate a more thorough examination, however they were more common among interval CRC patients. This again may be due to non-interval CRC patients who were diagnosed with CRC within 6 months after a prior colonoscopy because five of the 12 patients had their examination procedures aborted and therefore would not have had the examination reach those areas of the colon. In particular, six of these 12 patients had examinations that did not reach the cecum, which may have caused the covariate of the examination reaching the cecum to appear as a significant risk factor for interval CRC in the logistic regression models.

In addition to the covariates with unexpected outcomes from the colonoscopy's pathology report, there were also a few covariates with outcomes that were expected. Interval CRC patients were expected and were found to have more polyps identified and removed since that means they are more likely to develop polyps, resulting in an increased risk for CRC in general and interval CRC by extension. Interval CRC patients were also found to have more proximally-located and distally-located polyps compared to non-interval CRC patients. This is to be expected, especially for distally-located polyps, since interval CRC is more likely to occur on the right or distal side of the colon because the colonoscopist must go deeper into the colon to reach it, increasing the chances of missing polyps due to the increased difficulty of going deeper.[54] Finally, interval CRC patients were expected to have had a larger largest adenoma size and largest polyp size compared to non-interval CRC patients since larger size would indicate growths more advanced in their development into cancer, with our findings showing this.

The strengths of our study include the use of a data set from the UPMC Health System, which is the largest health provider in the Western Pennsylvania region and therefore has access

to a very sizeable population, as well as a comprehensive electronic medical record that goes back many years and allows us to more accurately identify patients with interval CRC. The data was abstracted by one person so there is no variation in the interpretation of the medical record. We also were not missing any medical records for the 88 patients with a prior colonoscopy, increasing the quality of the data. However, our study did have some noticeable limitations. Despite having access to data from a large health system, we were still limited to data from the Western Pennsylvania region which is not very racially diverse, being primarily white. Although the data came from one health system, the multiple hospitals that make up the system may have not had a completely uniform way of reporting the data, resulting in more variability in the data. We also had a relatively small sample size of patients who had prior colonoscopies, which may have decreased the power in our statistical analyses.

The regression results of our study show that older age and female sex are significantly associated with developing interval CRC and should be taken into consideration when determining the level of risk a patient may have for getting interval CRC. However, these associations may be linked to other underlying reasons that might not be as apparent, such as socioeconomic, cultural, and procedural factors. These results should be interpreted with caution given the small sample in one health system. More research is needed to definitively determine the risk factors for interval CRC in order to create modified screening strategies for patients at high risk. Further studies with larger study populations in various geographical areas are necessary to fully explore risk factors associated with interval CRC and reduce the public health burden of interval CRC.

APPENDIX A: TABLES

Table 1. Costs of Colorectal Cancer Screening Tests (2012 US $)

CRC Screening Tests	Costs ($)	Range ($)
Fecal Occult Blood Test	14.70	(5.54-24.22)
Fecal Immunochemical Test	24.10	(22-25.05)
Stool DNA Test	245.83	(150-341.66)
Sigmoidoscopy	297.20	(161-485.39)
Colonoscopy	786.82	(498-1218.05)
Computed Tomographic Colonography	637.68	(540.37-901.36)

Source: Patel SS and Kilgore L. Cost Effectiveness of Colorectal Cancer Screening Strategies. Cancer Control, 2015; 22(2):248-258.

Table 2. Examination Characteristics

Parameters	Description/Definition
Indication of Examination	
Screening	• Screening for colon cancer - no history of polyps • Screening in patients with significant family history
Surveillance	• Screening/surveillance among those with a history of polyps • Colonoscopy to remove synchronous neoplastic lesions at or around time of curative surgery or f/u co • Evaluation of abnormality on barium enema, CT, or other previous study • Excision of colonic polyp
Diagnostic	• Abdominal pain • Change in bowel habits • Clinically significant diarrhea of unexplained origin / chronic diarrhea • Evaluation of unexplained gastrointestinal bleeding • Unexplained iron deficiency anemia • Weight loss
Examination Report	
Procedure Aborted	Reported "Yes" if the colonoscopy was aborted during the most recent prior colonoscopy.
Quality of Preparation	Reported "Yes" if there was inadequate colon preparation during the most recent prior colonoscopy.
Polyp > 1 cm	Reported that a polyp > 1 cm was found during the most recent prior colonoscopy.
Advanced Adenoma	Reported that there was an advanced adenoma found during the most recent prior colonoscopy.
Reached the Cecum	Reported that reached the cecum was found during the most recent prior colonoscopy.
Saw Appendiceal Orifice	Reported that saw appendiceal orifice was found during the most recent prior colonoscopy.
Saw Ileocecal Valve	Reported that saw ileocecal valve was found during the most recent prior colonoscopy.
Any Polyp Removed	Reported that there was an advanced adenoma found during the most recent prior colonoscopy.
Polyp locations	Polyp locations of ascending, cecum, hepatic flexure, mid ascending, mid transverse, transverse, proximal ascending, proximal descending, proximal transverse were categorized as 'proximal'; while locations of descending, mid-descending, sigmoid, recto-sigmoid, rectum, distal ascending and distal rectum were categorized as 'distal'.
Largest Adenoma size (mm)	Adenoma size recorded in the pathological report.
Largest polyp size (mm)	Polyp size recorded in the pathological report.

Table 3. Demographic Characteristics of Study Population

	Total Patients with CRC (1) = 2+3+4	Without Prior Colono-scopy (2)	With Prior Colonoscopy		p-value		
			Non-Interval CRC (3)	Interval CRC (4)	2 vs. 3+4 **	2+3 vs. 4 #	3 vs. 4 *
N (%)	323	235 (72.8)	43 (13.3)	45 (13.9)			
Sex, n (%)					0.705	0.158	0.125
Female	134 (41.5)	96 (71.6)	15 (11.2)	23 (17.2)			
Male	189 (58.5)	139 (73.5)	28 (14.8)	22 (11.6)			
Race, n (%)					**0.007**	0.486	0.244
White	283 (87.6)	213 (75.3)	32 (11.3)	38 (13.4)			
Non-white	40 (12.4)	22 (55.0)	11 (27.5)	7 (17.5)			
Age with CRC (years)					0.339	0.360	0.658
Mean (SD)	68.3 (11.3)	68.0 (11.9)	68.1 (11.6)	69.8 (9.3)			
Range	40-96	40-96	40-96	52-86			
Age at prior colonoscopy screening (years) (n= 88)							**0.035**
Mean (SD)	64.9 (9.8)	---	62.6 (10.2)	67.0 (9.0)	---	---	
Range	41-86	---	41-81	49-86	---	---	
Years between CRC diagnosed and prior colonoscopy							**<0.001**
Mean (SD)	---	---	6.2 (5.0)	2.8 (1.2)	---	---	
Range	---	---	0.03-22.6	0.6-4.9	---	---	
Family History of CRC							0.485
Yes	---	---	3 (33.3)	6 (66.7)	---	---	
No/No Report	---	---	40 (50.6)	39 (49.4)	---	---	

** Compare difference in demographics between (2) without prior vs. (3)+(4) with prior colonoscopy

Compare difference in demographics between those without (2) + (3) vs. with interval CRC (4). * Among those with prior screening of CRC, compare difference in demographics between without (3) and with (4) interval CRC. One-way ANOVA was used for age comparison while Wilcoxon test was used for comparing years between index CRC and prior screening.

Note: Column (1) showed column percentage while columns (2)-(4) showed row percentage

Table 4. Number of Patients with Non-Interval CRC vs. Interval CRC by Hospital

	Total Patients with CRC (1) = (2)+(3)+(4)	Without prior Colonoscopy (2)	With prior Colonoscopy	
			Non-interval CRC(3)	Interval CRC (4)
Total N	N=323	N=235	N=43	N=45
	N	n (%)	n (%)	n (%)
Academic				
Shadyside (SHY)	51	28 (54.9)	12 (23.5)	11 (21.5)
Magee (MWH)	12	7 (58.3)	1 (8.3)	4 (33.3)
Presbyterian (PUH)	28	19 (67.9)	7 (25.0)	2 (7.1)
Suburban				
Passavant (PAS)	67	56 (83.6)	5 (7.5)	6 (9.0)
McKeesport (MCH)	19	9 (47.4)	3 (15.8)	7 (36.8)
St. Margaret (SMH)	62	47 (75.8)	8 (12.9)	7 (11.3)
Mercy (MER)	15	14 (93.3)	1 (6.7)	0 (0.0)
East (EAS)	12	12 (100.0)	0 (0.0)	0 (0.0)
South Side (SSH)	5	3 (60.0)	0 (0.0)	2 (40.0)
Rural				
Bedford (BMC)	20	16 (80.0)	0 (0.0)	4 (20.0)
Horizon–Greenville (HHG)	20	14 (70.0)	4 (20.0)	2 (10.0)
Altoona (ARH)	2	1 (50.0)	1 (50.0)	0 (0.0)
Horizon- Shenago (HHS)	5	4 (80.0)	1 (20.0)	0 (0.0)
North West (NWH)	5	5 (100.0)	0 (0.0)	0 (0.0)

Note: % in parenthesis shows row percentage for each hospital,

Table 5. Number and Distribution of Patients by Hospital Category

	N	Hospital Category			P value
		Academic	Suburban	Rural	
		n (%)	n (%)	n (%)	
Non-interval CRC (with & without Prior Colonoscopy)	278	74 (81.3)	158 (87.8)	46 (88.5)	0.301
Interval CRC	45	17 (18.7)	22 (12.2)	6 (11.5)	
Total	323	91 (28.2)	180 (55.7)	52 (16.1)	
Non-interval CRC (with Prior Colonoscopy)	43	20 (54.0)	17 (43.6)	6 (50.0)	0.657
Interval CRC	45	17 (46.0)	22 (56.4)	6 (50.0)	
Total	88	37 (42.1)	39 (44.3)	12 (13.6)	

Table 6. Indication for Colonoscopy Examination (N=88)

	Total	Non-Interval CRC		Interval CRC		
	N	**N**	**%**	**n**	**%**	**p-value**
Number of Patients	88	43	48.9	45	51.1	
Indication						
Screening						0.389
Yes	22	9	40.9	13	59.1	
No	66	34	51.5	32	48.5	
Surveillance						**0.036**
Yes	30	10	33.3	20	66.7	
No	58	33	56.9	25	43.1	
Diagnostic						0.136
Yes	44	25	56.8	19	43.2	
No	44	18	40.9	26	59.1	

Note: % columns showed row percentage; chi-square and Fisher's exact tests were used.

Table 7. Colonoscopy Characteristics (N=88)

	Total	Non-Interval CRC		Interval CRC		
	N	N	%	N	%	p-value
Number of Patients	88	43	48.9	45	51.1	
Procedure Aborted						**0.011**
Yes	6	6	100.0	0	0.0	
No/No Report	82	37	45.1	45	54.9	
Quality of Preparation						0.140
Not adequate	13	9	69.2	4	30.8	
Adequate/No Data	75	34	45.3	41	54.7	
Polyp > 1 cm						0.805
Yes	21	11	52.4	10	47.7	
No	67	32	47.8	35	52.2	
Advanced Adenoma						0.538
Yes	22	12	54.6	10	45.4	
No/No Report	66	31	47.0	35	53.0	
Reached the Cecum						0.066
Yes	76	34	44.7	42	55.3	
No/No Data	12	9	75.0	3	25.0	
Saw Appendiceal Orifice						0.114
Yes	77	35	45.5	42	54.5	
No/No Data	11	8	72.7	3	27.3	
Saw Ileocecal Valve						0.224
Yes	76	35	46.1	41	53.9	
No/No Data	12	8	66.7	4	33.3	
Any Polyp Removed						0.140
Yes	50	21	42.0	29	58.0	
No	38	22	57.9	16	42.1	
Polyp location						
Proximal						0.798
Yes	36	17	47.2	19	57.8	
No	52	26	50.0	26	50.0	
Distal						0.150
Yes	29	11	37.9	18	62.1	
No	59	32	54.2	27	45.8	
Unspecific						1.000
Yes	1	0	0.0	1	100.0	
No	87	43	49.4	50.6		
Number of polyps						0.206
≥ 1	49	21	42.9	28	57.1	
0	39	22	56.4	17	43.6	
Largest Adenoma Size for Patients with Polyps (n=49)						0.606
Mean **(mm)** (SD)		6.2 (3.8)		6.1 (5.2)		
Range		3-16		3-25		
Largest Polyp Size for Patients with Polyps (n=49)						0.202
Mean (SD)		14.8 (12.8)		11.1 (11.5)		
Range		4-50		2-50		

Table 8. Results of Stepwise Logistic Regression Model

	Model 1				Model 2			
Parameter	**Odds Ratio**	**95% C.I.**		**P-value**	**Odds Ratio**	**95% C.I.**		**P-value**
Age at prior colonoscopy (years)	1.070	1.017	1.126	**0.0090**	---	---	---	---
Age at prior colonoscopy ≥ 65 (Reference: < 65)	---	---	---	---	4.276	1.566	11.675	**0.0046**
Male (Reference: Female)	0.331	0.125	0.881	**0.0268**	0.296	0.107	0.821	**0.0193**
Reached the cecum (Reference: No)	5.349	1.165	24.554	**0.0310**	5.179	1.125	23.838	**0.0348**

APPENDIX B: FIGURES

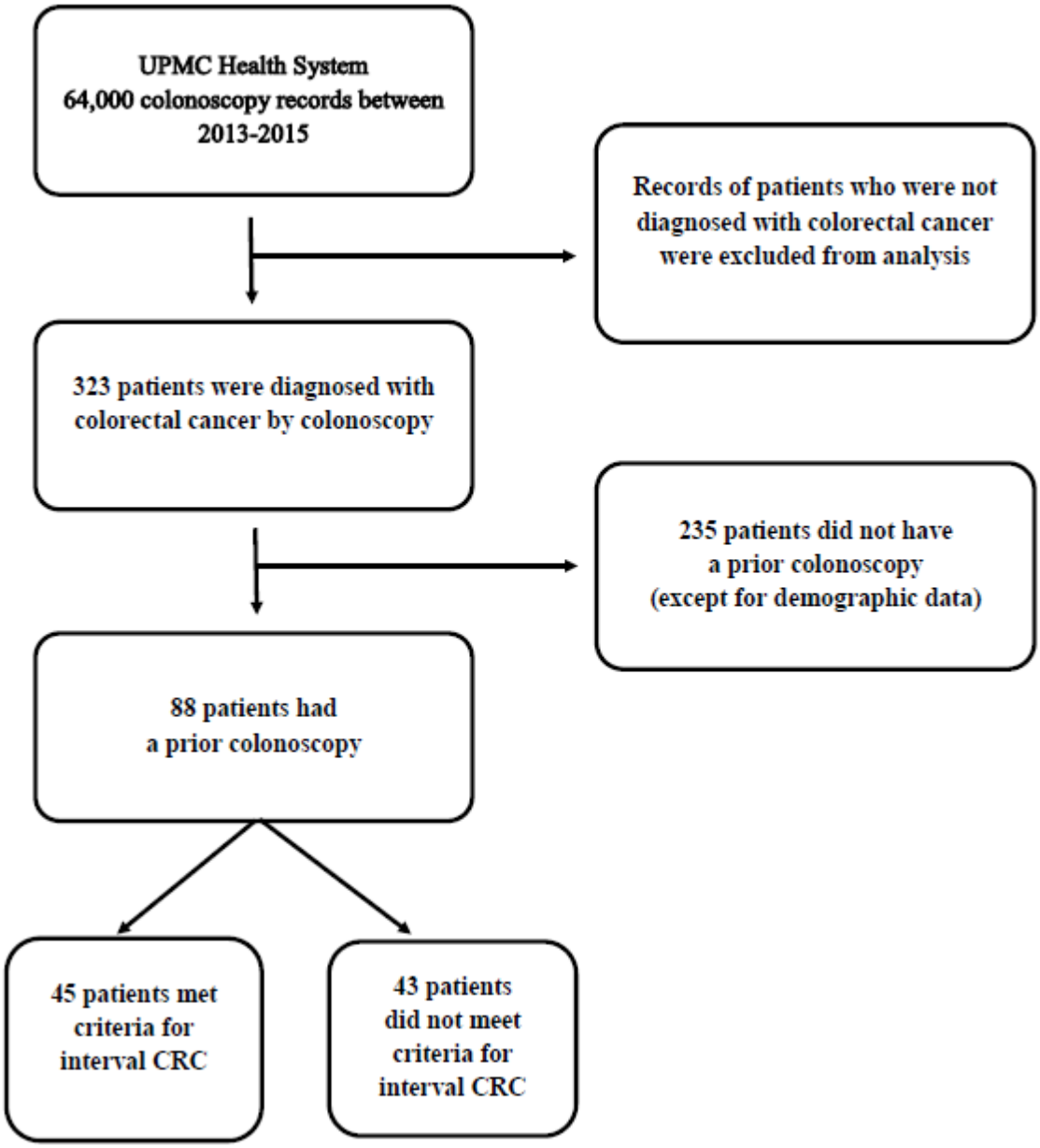

Figure 1. Data Sources and Data Extraction Flow

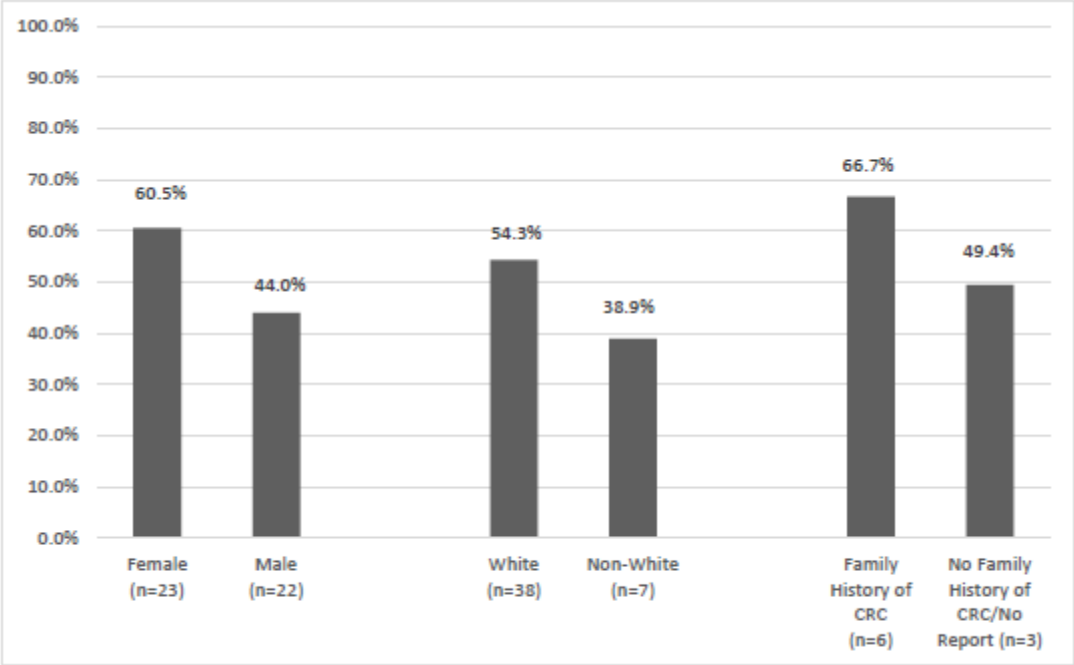

Figure 2. Proportions of Patients with Interval CRC among Those with Prior Colonoscopy (N=88) by Sex, Race, and Family History of Colorectal Cancer

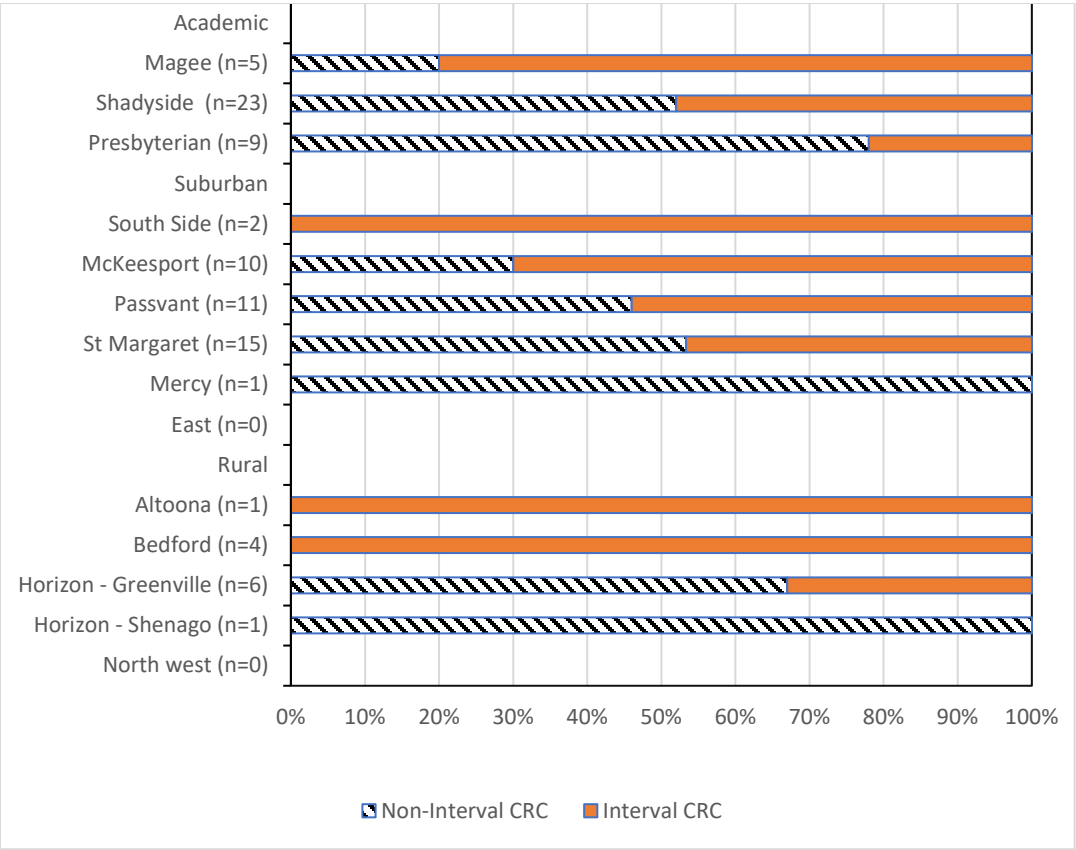

Figure 3. Distribution of Patients with vs. without Interval CRC by Hospital (N=88)

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