ESTIMATES OF COMPLICATIONS AND CLINICALLY SIGNIFICANT FINDINGS IN SCREENING AND SURVEILLANCE COLONOSCOPY

By

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CERTIFICATE OF APPROVAL

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Abstract

Background and Aims: Colorectal cancer is the third most common cancer and the second most common cause of cancer death among Americans. Colonoscopic screening holds the potential to significantly reduce the amount of colorectal cancer death; however, the procedure is invasive and carries the risk of complications. This study aims to evaluate various patient characteristics that might predict both clinically significant findings and complications from colonoscopy. **Methods:** A cohort study following over 20,000 patients estimated the risk of serious complications within 30 days of colonoscopy. The present study utilizes those from that cohort with indication of screening or surveillance colonoscopy. Multivariate logistic regression models were constructed for two outcomes: (1) serious complication related to colonoscopy and (2) neoplasia (polyp or other mass) greater than 9 mm. The number needed to endoscope (NNE) in order to observe one instance of each outcome was estimated based on results from the multivariate logistic regression models. **Results:** Data from 21,302 participants were included in the present analysis. Sixty-eight participants experienced serious adverse events (0.31%), while 1866 had one or more polyps or other masses of size greater than 9 mm found on their exam (8.76%). Peri-procedural anticoagulation therapy was a significant risk factor for complication. Statistically significant predictors for neoplasia over 9 mm included male gender, increased patient age, ASA class of II or greater, and prior positive screening test as indication for exam. Among adults under 65, it would require an estimated 509 colonoscopies among males 607 among females before expecting to see 1 serious complication, compared to 332 for males older than 74 and 396 for similarly aged females. Use of anticoagulants appears to markedly increase risk of

complication without any increase in yield of the procedure. Increased ASA class may increase likelihood of complication, but has a corresponding increased yield of neoplasia. Regular use of aspirin and NSAIDs appears to protect against large neoplasia.

Conclusions: Male gender, increased age, and increased ASA class may be risk factors for complication from colonoscopy, though the present study is under-powered to detect moderate effects. Anticoagulation therapy is a risk factor for increased risk of complication, though it is not associated with clinically significant neoplasia. Screening may lose its benefit as procedure yield may plateau at older ages while risk of complication may continue to increase. Screening in females has lower yield, but may be somewhat safer.

Background and Significance

Colonoscopy is performed for a number of reasons, including diagnostic and therapeutic indications. However, the procedure is commonly used a tool for screening and surveillance of colorectal cancer and pre-cancerous polyps. While the procedure has great benefit in its ability to detect and – in the case of polyps – remove such growths, colonoscopy also carries possibility of harm to the patient. In understanding when and for whom colonoscopy is an appropriate tool for screening and surveillance, it is important to understand both the yield of the procedure as well as its potential for harm.

A number of studies have examined both the yield and harms of colonoscopy, but few have done so within the same cohort. Those that have looked at yield and harms have done so using small patient cohorts of 2,000 or fewer patients. Such numbers may be enough for a common outcome such as a large colon polyp, but for a rare event such as a major complication from colonoscopy, such numbers are unlikely to be sufficient to detect differences between groups of interest to the research question.

The present study addresses this concern by examining potential harms and clinically significant findings of colonoscopy within a larger cohort of over 21,000 participants. This study also addresses methodological concerns from prior studies by using patient interviews instead of relying solely on available records, as well as by including data from participants across the United States instead of limiting the study to only those in a specific region or clinic.

Colorectal Cancer Screening

Colorectal cancer (CRC) is defined as any malignancy that develops in the large intestine or rectum. Both prevalent and injurious, it is the third most common cancer in the United States, excluding skin cancers, and the second leading cause of cancer mortality[1]; in 2009, there were an estimated 146,970 new cases and 49,920 deaths from the disease in the United States[2]. Colorectal cancer's clinically unfortunate characteristics of pervasiveness and deadliness, along with the opportunity to detect and treat pre-clinical disease, make the condition amenable to screening tests, of which there are several.

Screening tests are used to detect pre-clinical disease – disease prior to onset of symptoms. In order for a test to be appropriate for use in screening, the disease should be serious, the prevalence of pre-clinical disease should be high in the screening population, and treatment of preclinical disease should result in improved prognosis compared to treatment of disease with clinically apparent signs and symptoms[3]. Given that CRC is the second leading cause of cancer mortality and third most common cancer in the United States, it certainly fits the criteria of prevalence and gravity for a screening test.

Prognosis for patients with colorectal cancer is related to a number of factors, one of which is tumor stage at the time of detection. This emphasizes the importance of early recognition. Additionally, colorectal cancer has a readily available precursor – adenomatous polyps – that is amenable to intervention. The majority of colorectal cancer is believed to develop from malignant transformation of such polyps, and the removal of such polyps has been demonstrated to prevent the majority of cancers[4]. Adenomatous polyps of the colon can be discovered and removed during some of the modalities

available for CRC screening – namely, colonoscopy and flexible sigmoidoscopy. The removal of such polyps, termed polypectomy, is therefore effective in reducing the incidence of colorectal cancer by preventing adenomatous polyps from developing into adenocarcinoma[5].

There are several different screening methods for CRC, each with its risks and benefits. Screening methods include: colonoscopy, sigmoidoscopy, fecal occult blood test (FOBT), double contrast barium enema, and CT colonography[1]. While each method has advantages, colonoscopy offers a significant benefit of the highest accuracy of detection with what is typically an acceptable risk. However, there is a paucity of studies to date evaluating both harms and benefits of this procedure among specific populations that may benefit or be harmed. This study looks to further investigate such patterns.

Screening Recommendations

In 2008, the U.S. Preventive Services Task Force (USPSTF) published recommendations for regular CRC screening via one of three modalities: colonoscopy, sigmoidoscopy and FOBT. These tests vary in their effectiveness in detecting pre-cancerous polyps and colorectal cancers. In general, colonoscopy is the most sensitive and specific of the tests, whereas FOBT has the least predictive ability, particularly in identifying pre-cancerous polyps[6]. On the other hand, the FOBT procedure itself carries essentially no risk, aside from false reassurance for false negative and unnecessary worry for false positives, whereas both sigmoidoscopy and colonoscopy carry inherent potential harms as detailed above, more so with the latter[7]. Sigmoidoscopy can only evaluate the distal portion of

the large intestine. As such, the procedure is by nature less invasive and results in fewer complications, though it does not allow for visualization of the proximal colon.

Estimates indicate that CRC deaths would decrease by 18,800 deaths annually should population-wide adherence to the general USPSTF guidelines among average-risk individuals occur. These recommendations include annual FOBT, sigmoidoscopy every 5 years, or colonoscopy every 10 years among average-risk individuals[8]. The 2008 USPSTF recommendations called for regular routine screening for individuals ages 50-74 years. For individuals ages 75 to 84 years, colonoscopic screening among those with a history of prior negative results is not recommended. Screening or surveillance colonoscopy is not recommended at all for those 85 and over.

Though the USPSTF recommendations cover multiple screening tests for CRC, the present study examines only colonoscopic screening. This is for two reasons: 1) patients with a positive FOBT will typically be referred for a follow-up endoscopy - either colonoscopy or flexible sigmoidoscopy; and 2) colonoscopy is substantially more heavily utilized in the United States than flexible sigmoidoscopy. Approximately 53% of all gastrointestinal endoscopic procedures performed in the United States Medicare population are colonoscopy, compared to just 10% for flexible sigmoidoscopy[9]. Results from a CDC survey of endoscopic CRC screening methods in 2002 indicated that approximately 2.8 million sigmoidoscopies were performed that year, compared with 14.2 million colonoscopies[10].

Risk Factors for Colorectal Neoplasia

Due to the risk of complication inherent in colonoscopy, consideration of patient characteristics that may affect the expected harms and benefit of the procedure is critically important when deciding whether colonoscopy is appropriate to optimize screening. Though complications of colonoscopy likely increase with age, colonoscopic yield – prevalent adenomatous polyps and colorectal adenocarcinoma – is also greater among older adults. Older patients carry a higher risk of pre-cancerous polyps and colorectal cancer compared to younger individuals[11, 12, 13].

In addition to patient age, gender is an important predictor of colorectal cancer and, in turn, colorectal neoplasia – polyps or other masses that can grow in the gastrointestinal system. The age-adjusted annual incidence of colorectal cancer in the United States is substantially greater in males (61.2 cases per 100,000) compared to females (44.8 per 100,000)[2]. Male gender has been demonstrated to be associated with increased risk of clinically significant findings on colonoscopy. In a 2005 study with a similar design to the currently proposed study, males were 1.6 times more likely than women to have a polyp or mass greater than 9 mm found during colonoscopy. Additionally, the number needed to endoscope (NNE) before seeing such a finding was lower for men than women in each age group, with findings indicating that prevalence of such findings in women tends to lag behind men by about one decade, such that the prevalence in women aged 60-70 is similar to that in men aged 50-60[11].

In a similar study from 2008, Lieberman and colleagues found that the gender difference in risk of clinically significant colonic neoplasia was particularly marked among whites.

Among blacks, the picture was somewhat less clear. The prevalence of such findings on colonoscopy for black women under 50 was comparable to that of all men (black and white) aged 50 to 59. The authors of that study indicated that this could be a chance result, and the finding should be confirmed with data from a larger cohort[14].

The results of a number of previous studies have shown an increased risk of colorectal neoplasia and increased need for colonoscopic screening among African-Americans compared to whites[15, 16]. The risk of colorectal cancer is estimated to be greater in African Americans compared to whites; age-adjusted annual incidence is greater in black males (71.2 per 100,000) than white males (58.9 per 100,000), as well as being greater in black females (54.5 per 100,000) than white females (43.2 per 100,000)[2]. One study indicated that the risk of clinically significant colonic neoplasia was greater for black patients undergoing colonoscopy compared to whites, among both men and women[14]. Black patients have elsewhere been shown to be at greater risk of polyp or mass greater than 9 mm compared to whites, while Asian / Pacific Islander patients were at reduced risk compared to whites and the risk in Hispanic and American Indian individuals was not significantly different from white patients[11].

Harms of Colonoscopy

Like most procedures in medicine, one must consider the potential harms of colonoscopy compared to the degree of potential benefit. Colonoscopy and other endoscopic procedures are certainly not without risk. Complications of some degree occur in about 10% of colonoscopies, though approximately 75% of these are minor in severity[17]. The

most common complications from colonoscopy are bloating and abdominal pain, and only 6% of individuals undergoing screening or surveillance colonoscopy report losing more than 2 days of productivity from the procedure[18]. Though rare, serious complications do occur, the most critical being bowel perforation. Estimates of the frequency of bowel perforations vary widely, from 19 perforations per 100,000 procedures to 190 per 100,000[19,20,21].

Patients with bowel perforation from colonoscopy have a large range of morbidity and mortality due to the complication. The proportion of patients experiencing further medical complications within 30 days of colonoscopic bowel perforation has been estimated to be as low as 21% and as high as 53%. Thirty day mortality estimates range from 0% to 26%, and estimated mean hospital stay length ranges from 1 to 3 weeks[22]. Despite the wide range in estimates, the severity and impact on the patient should not be underestimated.

Complications related to post-procedure bleeding are more common, occurring in about 640 per 100,000 (0.64%) colonoscopies[23]. A 1993 literature review found a range of 0.3% - 3.6% of patients undergoing colonoscopy with polypectomy experienced post-procedure hemorrhage[24]. Again, results from a recent study using the same cohort as the present study estimated GI bleeds to be less common than even the smallest estimate from the literature review, as incidence of GI bleed requiring hospitalization in that study was estimated to be 159 per 100,000, or just 0.16%[20].

Risk Factors for Complications

The basis for age categories in the USPSTF screening recommendations lies partly in research suggesting that patient age is a significant predictor of complication from colonoscopy, specifically bowel perforation[25-28], hemorrhage[19, 27-29], and complications in general[30]. However, the evidence for this is not wholly conclusive; a small number of studies have found no statistically significant association between age and risk of complication[13,20,31].

Polypectomy is a risk factor for gastrointestinal hemorrhage. Results of a study using the same cohort of the current project indicated that the risk of complication directly related to colonoscopy among those undergoing polypectomy with cautery was 6.7 times that of those who did not have polyps removed[20]. In an analysis of a hospital-based cohort of patients presenting with hemorrhaging after polyp removal during colonoscopy, 71.1% of patients had experienced cardiovascular comorbidities, 43.4% musculoskeletal comorbidities, 14.5% hematologic comorbidities, and 6.0% renal complications. There were no deaths related to the polypectomy. The median duration of hospital stay was 3 days[32]. In a study looking at anticoagulant use and postypolypectomy bleeding, 1% of control patients experienced some post-procedure bleeding, of which 40% experienced serious bleeding requiring hospitalization or transfusion. The mean length of stay for all hospitalized patients was 2.9 days, and no deaths were reported[33].

Another factor that can increase risk of complication is patient use of anticoagulant therapies, such as warfarin, clopidogrel, dipyridamole, and ticlopidine. Anticoagulant therapy is a known risk factor for gastrointestinal hemorrhage[34]. Patients regularly

treated with clopidogrel with or without concomitant aspirin use and undergoing colonoscopy with polypectomy experience a higher incidence of post-procedure bleeding than those not taking any anticoagulant that undergo polypectomy. Furthermore, patients taking clopidogrel are more likely to experience delayed post-polypectomy bleeding that requires hospitalization and/or transfusion[33]. Few other studies have been conducted which can shed light on the role of anticoagulant therapy as a risk factor for colonoscopic complication. One prior study was conducted using data from the Clinical Outcomes Research Initiative (CORI), the same source as the current study. The authors found no evidence for increased risk of post-colonoscopic hemorrhage from such therapy, but indicated that the study was substantially under-powered to detect a reasonably sized effect[35].

Specific disease comorbidities that may play a role in increasing risk of complication from colonoscopy include hypertension[36], cardiovascular disease[29,30], and renal failure[29]. Among colorectal cancer patients, average life expectancy decreases as the number of chronic illnesses a patient has increases, a finding that argues against screening for colorectal cancer among those with numerous comorbid conditions[37]. Other studies have examined harms from colonoscopy based on overall health or comorbidity status, finding that this more general measure also predicts risk of complication[25,28,38]. Measures of general health and comorbidity status that have been used in these studies include, respectively, Charlson's comorbidity score, Deyo score, and the American Society of Anesthesiologists (ASA) Physical Status Classification Value, or ASA class.

Though the available evidence suggests an increased risk of significant colonic neoplasia

for men and black individuals, the evidence of any such race or gender risk factors for the risk of complications from colonoscopy is less clear. Only a small handful of studies have examined race as a predictor of colonoscopic complication, and those existing studies have found no association between race differences and increased risk of complication[20,26].

Compared with patient race, more studies have examined the role of patient gender in risk of complication; still, the results are both few and mixed. Some studies have demonstrated that females may be at increased risk of bowel perforation from colonoscopy[21,39]. Conversely, one study demonstrated an increased risk of post-polypectomy bleeding in males compared to females[40]. However, most studies examining patient gender and complications have found no such association[19,20,26].

Significance

This study shares conceptual and methodological similarities with prior studies examining CORI data. The study will use number needed to endoscope (NNE) as the primary frequency measure. This measure has been successfully used before by the research team in studying colonoscopy procedure reports stored in the National Endoscopic Database[11,14]. However, this study is unique in a few important ways. First, this study will examine the outcomes studied by Ko[20] and Lieberman[14] and their colleagues, measuring harms and benefit of the colonoscopic procedure within the same cohort. These prior studies have examined either harms or benefits - but not within the same population. Furthermore, complications data will be analyzed while keeping age guidelines suggested by the USPSTF in mind, which the original complications study by

Ko and her colleagues did not. Finally, this analysis will examine individuals undergoing screening or surveillance colonoscopy for the detection and prevention of colorectal cancer; the 2005 study by Lieberman and colleagues examined a more heterogeneous population, including many different procedure indications including diagnostic colonoscopy, while the 2008 Lieberman study looked only at screening colonoscopies. By including both screening and surveillance, and excluding colonoscopies performed for diagnostic or therapeutic indications, the study population more closely captures those individuals targeted in USPSTF guidelines.

The project attempts to answer the following research question: Which demographic characteristics are related to two outcomes: clinically significant neoplasia found on colonoscopy, and complication following colonoscopy? The study will shed light on this question by addressing three specific aims:

1) To estimate prevalence of and demographic characteristics associated with clinically significant colorectal neoplasia using data collected by Ko et al.;
2) To estimate risk of and demographic characteristics associated with colonoscopic complications among that cohort; and,
3) To estimate and compare race-, sex- and age-specific number needed to endoscope for both outcomes.

To determine the benefit conferred to an individual by colonoscopy as compared to the potential harms, we used the National Endoscopic Database to compare these outcomes by risk strata.

Methods

All data analyzed in this study come from two sources: 1) gastrointestinal procedure-reporting software developed by CORI; and, 2) seven- and thirty-day post-colonoscopy patient interviews conducted by CORI researchers.

Overview of CORI

The Clinical Outcomes Research Initiative was developed to study outcomes of gastrointestinal (GI) endoscopic procedures. CORI was founded in 1994 with help from the American Society of Gastrointestinal Endoscopists (ASGE) and is associated with Oregon Health and Science University (OHSU). Cross-sectional research is performed using CORI data, and these data also serve as a starting point for prospective research studies.

Physicians participating in this consortium use a specialty electronic health record software developed by CORI in order to produce their GI endoscopy reports. Software users document their endoscopic procedures, including personal and family history, physical examination, demographic information, American Society of Anesthesiologists (ASA) physical status classification score, indications for procedure, procedure findings, and performance of biopsy or polypectomy. Quality of patient bowel preparation, procedure completeness, medications used, and occurrence of any immediate complications are also recorded.

Each CORI procedure report is assigned a unique ID number, then removed of most personally identifiable health information and transmitted electronically to OHSU to be included in the National Endoscopic Database (NED), which is then used to answer questions about the practice and outcomes of endoscopy. Currently the NED contains data from over 2 million endoscopic procedures with data from as early as 2000. The CORI software is used at approximately 70 practice sites across the United States, and used by approximately 400 individual endoscopists.

For the present study, CORI procedure reports were used to examine procedure findings, indications, and other exam-related information from study participants. Specifically for the prospective cohort study, a separate file was transmitted daily to the CORI research offices consisting of the name, contact information and unique procedure ID number for individuals who consented to be contacted for prospective research studies and were qualified for the study.

Patient Eligibility

Study participants were those enrolled in a prospective cohort study conducted by Ko and colleagues[20]. Participants for that study were individuals having undergone colonoscopy at CORI practices.

The initial enrollment period extended from 2002 to 2005. An eligible patient was defined as being 40 years of age or older, and having a procedure indication (determined by the endoscopist) of one or more of the following: 1) average-risk screening; 2)

surveillance of colorectal polyps or cancer; 3) family history of CRC; or 4) positive FOBT, flexible sigmoidoscopy, or other test. Exclusion criteria included history of inflammatory bowel disease (IBD) or recent GI bleed.

Participant Recruitment

Of the 70 active practice sites using CORI procedure-reporting software during the enrollment period, 18 sites were recruited to enroll patients for the prospective cohort study. Immediately prior to their colonoscopy, patients seen at participating clinics were given the opportunity to consent to be contacted for the study. Patients with more than one screening colonoscopy during the enrollment period were recruited only at the first exam.

Eligible patients who had consented at the time of their colonoscopy to be contacted if eligible for research were contacted by phone at approximately 7 (range: 5 – 11) and 30 (range: 28-34) days after their colonoscopy. Those who agreed to participate were interviewed using a standardized questionnaire to assess symptoms, clinic visits, and hospitalizations since colonoscopy that might be related to the procedure. The full questionnaire can be found in Appendix A.

Measurement and Data Collection

The current analysis uses the complications data collected at the time of the procedure as well as at the last patient interview date (either 7 days or 30 days). The latest interview was conducted at 7 days post-colonoscopy for 14.5% of the study population, and at 30

days for 85.5%.

Main Predictor Variables

Patient age, gender, and race were the three main predictors of interest for all study aims. Patient age was categorized into four groups based upon cut-points described in the USPSTF guidelines for screening colonoscopy: under 65 years of age, 65-74 years, 75-84 years, and 85 years and over. The small number of events required combining the two oldest categories for analysis. Gender and race/ethnicity data were obtained from the NED. We categorized race and ethnicity into 6 groups: White, Black, American Indian/Alaska Native, Asian/Pacific Islander, Multiracial, and Hispanic. Patient race, ethnicity and gender are entered by the endoscopist or other clinic staff at the time of endoscopy and may not originate from patient self report.

Potential Confounding Variables

We also analyzed the following variables:

- Practice type (academic medical center, VA Medical Center, community hospital or ambulatory surgical center);
- Procedure indication (routine screening, family history of CRC, positive FOBT or other screening test; surveillance of colorectal polyps or carcinoma);
- Patient comorbidity (ASA class); and,
- Pre-procedure use of prescription anticoagulants (warfarin, ticlopidine, clopidogrel, dipyridamole), aspirin, or other non-steroidal anti-inflammatory medication, collected during patient phone interview.

Patient comorbidity was estimated by American Society of Anesthesiologists (ASA) Physical Status Classification, a value commonly assigned prior to surgery or other procedures. In colonoscopy and other gastrointestinal endoscopic procedures, this value is typically assigned by the endoscopist, or by an anesthesiologist if one is present. These data are available for approximately 96% of the cohort. The coding scheme for this variable is as follows:

1. A normal healthy patient.
2. A patient with mild systemic disease.
3. A patient with severe systemic disease.
4. A patient with severe systemic disease that is a constant threat to life.
5. A moribund patient who is not expected to survive without the operation.
6. A brain dead patient

No ASA class 5 and few class 4 (n=5) patients are in this dataset of screening and surveillance colonoscopies, as procedures for such patients are almost always emergent in nature due to the increased risk of morbidity and mortality as a result of any intervention. The sixth category is not relevant to this study. In order to minimize reliability concerns, ASA class values for Class III and Class IV were combined, creating a "severe systemic disease" category.

Outcome Variables

The first outcome of the study was clinically significant colorectal neoplasia. Because

pathology results are not available for days after the colonoscopy, the CORI software does not reliably contain these results; in fact, in less than 25% of retrieved polyps is the histopathology available. In the absence of pathology data, we will use a surrogate measure to approximate these outcomes. There is consistent evidence that approximately 90% of polyps greater than 9 mm in size are adenomas[41,42]. Therefore, we will define a polyp greater than 9 mm as evidence of colon neoplasia.

Because polyp size is estimated visually by endoscopists, such measures may not be exact. However, some studies have demonstrated that visual estimates of polyp size made by endoscopists are accurate more than 90% of the time, regardless of overall size[43,44]. Nonetheless, additional analyses were performed examining results using polyps > 8 mm and > 10 mm as endpoints, and those results were compared to those from the 9 mm outcome analysis.

In the CORI procedure reporting software, entering a size estimate for polyps is not required, though most users do document polyp size. For those exams in which no polyp has a size estimate, we assume that the size was not provided because the polyp was small. An additional analysis comparing results for a model that excludes all observations for any participant with a polyp lacking size information was conducted.

The second aim of this study is to examine the effect of the aforementioned independent variables on procedure complications. Complications related to colonoscopy are routinely reported in the CORI software when they occur within 24 hours of the

procedure. However, this may underestimate the true risk of complication from the procedure. As such, complications data were collected at the time of the procedure and by follow-up interview as part of the cohort study. The list of potential complications during colonoscopy that could be entered into the CORI procedure report is as follows: respiratory depression; cardiovascular complications (e.g. hypotension, bradycardia, vasovagal reaction, tachycardia, hypertension); GI bleeding; other GI complications (e.g. nausea, vomiting, abdominal pain); and hospitalization. Complications data are typically entered into the CORI procedure report by the endoscopist at the time of or immediately following the colonoscopy; however, the report can be edited at any point after the procedure.

We define complications of colonoscopy as including:

- Bowel perforation;
- Post-polypectomy syndrome (colonic burn, marked by localized abdominal pain without evidence of perforation);
- Gastrointestinal bleeding requiring hospitalization and/or transfusion; and,
- Diverticulitis requiring hospitalization.
- Angina requiring hospitalization;
- Myocardial infarction;
- Stroke;
- Transient ischemic attack; and,
- Other potentially related complications such as abdominal pain or sedation-related events requiring hospitalization.

Some participants may have had more than one complication; however, those participants would only be counted once.

In order to validate patient self-reports of complications leading to hospitalization, permission was received to review hospital records from participants (n = 52) at 9 of the 13 practice sites reporting hospitalizations. Specifically, investigators examined agreement between diagnoses leading to post-colonoscopy patient hospitalization and participants' self-reported diagnoses. Participants' self-report agreed with results from the medical record review over 80% of the time. Based on these results, patient self-report was deemed a suitable source of diagnoses and symptoms.

Statistical analysis

Univariate logistic regression models were constructed comparing odds of each outcome (complication and clinically significant neoplasia) for each of the predictors of interest, as well as the various potential confounders under consideration. In the case of an inadequate number of events for one or more levels of a given variable, levels of the variable were either combined, or the variable was removed from consideration. Through this method, race was eventually dropped from consideration in the analysis. An explanation of this decision is found in Appendix B. Regardless of statistical significance, the remaining main predictor variables of age and sex were included in all final logistic regression models. Among the potential confounding variables, those with beta estimates with a p-value less than or equal to 0.25 were considered for inclusion in the multivariate model. Each qualifying variable was then entered into the multivariate

main effects model. Those factors that were significant at the 0.05 level remained in the multivariate model. Variables that did not meet these criteria for one outcome but did do so for the other were included in both models for ease of comparison.

The frequency measure of interest for the third aim of the study is number needed to endoscope before expecting to observe one event - either a complication from colonoscopy or a finding on exam of clinically significant neoplasia. The NNE for each of the two outcomes will be calculated, stratifying by all demographic variables (age, race and/or gender) that are included in the final multivariate logistic regression model for the respective outcome. In general, NNE can be described as being the inverse of a measure of relative frequency, such as an estimate of incidence or prevalence. Number needed to endoscope was calculated using the beta coefficients that result from the final multivariate logistic regression models built in Aims 1 and 2. The log-odds of the event are calculated for a given demographic profile through simple addition of beta coefficients. Taking the inverse of the natural log of that sum provides an odds estimate for a given demographic profile. The estimated probability of the outcome is then calculated as (odds/(1+odds)). Taking the inverse of this probability estimate produces the NNE

All data analyses were performed using SAS statistical software (SAS Institute, Inc, Cary, NC).

Results

There were 40,637 patients who fit study eligibility requirements and provided consent to be contacted for the study. Of those patients, 21,375 (53%) were successfully contacted via telephone up to 30 days post-colonoscopy, provided oral consent, and completed the phone interview. Of these participants from the initial analysis, we determined that the procedure indication for 73 individuals did not meet the study eligibility criteria although included in the inadvertently included in the larger cohort. Specifically, these 73 participants had indications of abdominal pain or bloating (n = 4), changes in bowel habits, constipation or diarrhea (n = 19), hematochezia or melena (n = 6), weight loss (n = 1), or some other unspecified indication (n = 43). This resulted in a final cohort of 21,302 patients. All observations from these participants were excluded from the current analysis, resulting in a final cohort of 21,302 participants.

Demographics

Demographic and other characteristics of the participants comprising this cohort are described in Table 1. The cohort is principally white, with black participants comprising the largest minority group and smaller numbers from the other race and ethnic groups (Asian, Hispanic, American Indian, Pacific Islander and multiracial). The cohort contains slightly more males than females, and the majority of patients were aged 65 or under.

Procedure Characteristics

Overall, the majority of colonoscopies included in the cohort were performed in a community setting as opposed to an academic or VA medical center. Over 95% of participants were classified as ASA class I (normal/healthy) or II (mild systemic disease).

Information on ASA class was unavailable for 3.8% of the cohort. The most common procedure indication was routine screening, followed by surveillance of prior colorectal adenocarcinoma or pre-cancerous polyps, family history of CRC, and prior positive screening test. Over 40% of participants were regular users of aspirin, with substantially smaller numbers of non-steroidal anti-inflammatory and prescription anticoagulant users.

Prevalence of Clinically Significant Colorectal Neoplasia

Among this cohort, clinically significant neoplasia was found on the exams of 1866 participants (8.76%). The unadjusted prevalence of clinically significant colorectal neoplasia – defined as a polyp or mass greater than 9 mm in size – is described in Table 2. The data are stratified by the two main predictors of interest that have an adequate number of events to be included in analyses – patient age and sex. The greatest prevalence of clinically significant neoplasia in this cohort is among males aged 65-74 and over 75 years of age – the two estimates are nearly identical. It is noteworthy that among females, prevalence increases with increasing age across all three age categories, while it appears to plateau for males aged 65 and older. Thus, while prevalence appears to increase with age in females, it may plateau with increased age among males. Furthermore, the highest prevalence among females – 81.7 per 1000 colonoscopies in those aged 75 and older – is estimated to be lower than the lowest among males – 88.2 per 1000 colonoscopies in those younger than 65 years old.

We built a multivariate logistic regression model in order to obtain adjusted odds ratio estimates as well as to provide the basis for the NNE calculation. The first step in the

model building process was to run univariate logistic regression analyses for each independent variable. Results of these univariate models are available in Table 3.

We constructed a multivariate model based on results of the univariate analyses. Both of the main predictors, age ($p < 0.0001$) and sex ($p < 0.0001$) were statistically significant effects. Four other covariates met criteria for inclusion in the multivariate neoplasia model – ASA class ($p < 0.0001$), pre-procedure aspirin use ($p = 0.0069$), pre-procedure NSAID use ($p = 0.009$), and procedure indication ($p < 0.0001$). Anticoagulant use was not statistically significant in this model ($p = 0.8013$); however, it was included in the final multivariate model because it was strongly associated with risk of complication. The number of observations analyzed in the final multivariate model for both study outcomes is 20,497 due to missing ASA class values for 805 participants.

The results of the multivariate logistic regression model are presented in Table 4. Because colorectal neoplasia exists in the colon prior to the procedure and is not necessarily detected at first onset, and because such neoplasia are not particularly rare, the odds ratio cannot serve as an estimate of relative risk for this outcome. The results indicate that the odds of a clinically significant neoplasia finding on colonoscopy among men are 1.65 times that of women. Increased age appears to be associated with greater odds of polyp or mass larger than 9 mm, as the odds for participants aged 65 – 74 and 75 and older are 1.50 and 1.46 times the odds of those under age 65, respectively. Patient comorbidity also is associated with increased odds of clinically significant neoplasia. While the overall effect for procedure indication was highly statistically significant ($p <$

0.0001), only one of the categories was statistically different from the reference category. Odds of clinically significant neoplasia among those with a prior positive screening test (such as a positive FOBT or prior flexible sigmoidoscopy) were 1.93 times the odds of those indicated for routine or average-risk screening colonoscopy. Family history of colorectal cancer (OR = 0.98) and personal history of colorectal cancer or pre-cancerous polyps (OR = 0.91) did not have statistically greater or lesser odds of neoplasia compared to those referred for routine screening.

Regular pre-procedure use of aspirin and non-steroidal anti-inflammatory medications were inversely associated with prevalent clinically significant colorectal neoplasia. Odds of a significant neoplasia finding on the colonoscopy of those who regularly used aspirin were 0.87 times the odds of those who were not on an aspirin regimen. There was an even more marked protective effect for those who regularly used NSAIDs, as the odds of a significant neoplasia finding among this group were 0.67 times the odds of those who did not regularly take such medications.

Incidence of Complication from Colonoscopy

In this cohort, there were 68 (0.32%) serious complications observed within 30 days of the participant's colonoscopy. The unadjusted incidence proportion of complication stemming from colonoscopy within 30 days of the procedure is described in Table 5. The data are stratified by the two main predictors of interest that have an adequate number of events to be included in analyses – patient age and sex. The highest incidence of complication within 30 days of colonoscopy is among women aged 75 years or older.

Among those in the less than 65 years and 65 to 74 years categories, incidence is somewhat higher in males than females.

In order to assess the association between each independent variable and the complication outcome we conducted univariate logistic regression analyses, results of which are found in Table 6. Based on our model selection criteria, the only covariate that met initial criteria for inclusion in the multivariate model for complications was use of prescription anticoagulants ($p < 0.0001$).

In addition to anticoagulant use, the two predictors of interest for the study – patient age and sex – were included in the final multivariate model, despite the fact that they were not statistically significant ($p = 0.138$ and $p = 0.319$, respectively). Other covariates that were included in the final multivariate model for complication despite not reaching statistical significance were patient ASA class, procedure indication, aspirin use and NSAID use. These 4 variables were included because they met criteria for inclusion in the multivariate model for the neoplasia outcome.

The results of the multivariate model are presented in Table 7. Because complications were collected prospectively and were incident events, and because the outcome is quite rare, we can use the adjusted odds ratio as an estimate of relative risk for this outcome. The results indicate that the adjusted risk of serious complication within 30 days of colonoscopy among those who were on a prescription anticoagulant regimen prior to their procedure is 3.4 times that of the risk among those not using such medications.

Examining the predictors of interest, patient age and gender, the results suggest that there is no increased risk of complication for male sex compared with females. Age of 65-74 years does not appear to be associated with increased risk of complication (OR = 1.02). Age of 75 years or older (OR = 1.54, 95% CI: 0.80 – 2.93) may be associated with increased risk of complication compared to those under age 65; however, this result is not statistically significant. Other covariates that suggest a possible – but not statistically significant – association with incident complication include aspirin use (OR = 1.50, 95% CI: 0.92 – 2.45) and ASA class of III or IV (OR = 2.14, 95% CI: 0.83 – 5.53).

Number Needed to Endoscope

The multivariate logistic regression models were used to calculate the NNE to observe 1 patient with a serious complication within 30 days of colonoscopy, as well as that required to observe 1 patient with a polyp or mass greater than 9 mm. The NNE and associated 95% confidence intervals are calculated based on the estimated beta coefficients (Tables 8-9) and covariance estimates from the logistic regression models. The NNE results for both outcomes are presented in Table 10.

The number needed to endoscope before expecting 1 major complication to occur among males is estimated to be 509 for those under 65, 498 for those aged 65-74, and 332 for those aged 75 and older. The number needed to endoscope before expecting to observe 1 major complication among females is 607 for those under 65, 594 for those 65-75, and 396 for those aged 75 and greater (Figure 1). As seen in the table, confidence intervals for all of these estimates are relatively wide.

Estimates for the clinically significant neoplasia outcome are more precise, likely due to a larger number of events compared to the complication outcome. For both men and women, there is a drop from patients younger than 65 compared with those older than 65 with regard to the number of patients a provider would need to endoscope before expecting to find an adenocarcinoma or polyp greater than 9 mm (Figure 2). Among males under 65, it would be expected to observe such a finding 1 time in every 18 exams, compared to approximately 1 per 12 exams for those older than 65. Among females under 65, it is estimated that an endoscopist would observe such a finding 1 time per every 28 exams, compared with 1 per 19 for those 65-74 and 1 per 20 for those 75 and older.

Additional analyses of NNE data were conducted to examine frequency estimates for individuals in higher-risk categories – namely, those who regularly used prescription anticoagulants prior to their procedure (Table 11, Figures 3 and 4) and those with ASA class III or IV (Table 12, Figures 5 and 6). With regard to complications, NNE point estimates for each profile appear substantially lower when anticoagulants are used regularly, suggesting that such usage is associated with increased risk of complication.

Results when ASA class is assigned to the highest level (class III or IV) indicate that the number needed to endoscope before seeing a serious complication may be much lower among those with high ASA class than those with low ASA class. Results for the neoplasia estimates indicated that the estimated NNE before seeing one exam with

clinically significant neoplasia is lower among those with high ASA class compared to those with the lowest ASA class.

Validity of Neoplasia Outcome Measurement

To check the validity of our definition of clinically significant neoplasia as any tumor or polyp greater than 9 mm, an analysis was conducted examining the outcome as either greater than 8 or 10 mm. The results of this analysis are found in Table 13. There were 1985 individuals with polyp or mass greater than 8 mm (9.32% of cohort), and 1139 participants with polyp or mass larger than 10 mm (5.35%), compared with 1866 (8.76%) with the original definition. Results of multivariate logistic regression models using the 8 mm and 10 mm outcomes and the same variables in the final 9 mm model demonstrates that the outcome is stable. Comparing the original outcome to the more liberal 8 mm cutoff point, the resulting odds ratios appear remarkably similar. When using size greater than 8 mm as a cutoff point, no odds ratio changes by more than 4.7%. However, when comparing the original outcome cutoff point to those polyps or tumors greater than 10 mm in size results in greater changes. Fiver variable levels change by more than 10%: gender (+15.2%); age greater than 75 years (+11.0%); NSAID use (-20.9%); anticoagulant use (-10.7%); and indication of prior positive screening test (+28.5%). Despite these shifts, the overall direction remains the same for all but two variables, anticoagulant use and indication of family history, which were both already not significantly different from an odds ratio of 1.0. In all, interpretations of results based on the use of either of the two cutoff points do not change substantially.

An additional analysis was conducted excluding any participant with a polyp or mass for whom no neoplasia size information was available. There were 449 participants flagged as having one or more colorectal polyps or tumors on their exam, but with no size information entered. In the main analysis, such neoplasia were treated as being 9 mm or smaller in size. To check this assumption, a multivariate logistic regression model including only sized polyps or tumors was run. Results of this model compared with the original model are presented in Table 14. Examining the comparison we see little difference between the two models. No odds ratio in the more conservative approach is changed by more than 2.2% from the original study results.

Discussion

The present study differs from other studies looking at colonoscopic yield and complications in a number of important ways. First, this study comes from a relatively large cohort of over 21,000 individuals. There have been prior studies that have examined both potential harms and yield of colonoscopy, all of which had substantially smaller samples, of 2000 or fewer participants[13,45,46]. Many studies examining only colonoscopic complications have been substantially smaller than the present study[19,27,31]. Other such studies have had similar or even greater power to detect this relatively rare event, but have looked only at medical or administrative records[25,26,28,30]. Of these studies, just one examined only screening or surveillance procedures[28], and most used data from only one location or region[13,25,27,31]. The present study benefits from having a relatively large cohort, from multiple sites across the United States. This study focuses on screening and surveillance procedures relevant to the USPSTF recommendations, and

uses data acquired directly from patients or family members answering on their behalf.

This study examines the frequency of two outcomes – clinically significant neoplasia found on colonoscopy and serious complication following colonoscopy. Serious complications are rare events, with age- and sex-stratified NNE estimates suggesting a range from 1 event per 607 colonoscopies to 1 per 332 colonoscopies. Complications appear to be more common among men than women, as well as more common as patient age increases. However, these age and sex effects are not statistically significant, possibly due to relatively few events observed in the study cohort. The finding of clinically significant colonic neoplasia – as defined as any polyp or mass greater than 9 mm found on exam – is much more common. The range of age- and sex-stratified NNE estimates observed in this cohort extends from 1 clinically significant finding per 12 colonoscopies to 1 per 28 colonoscopies. Similar to the complication outcome, polyps or masses over 9 mm are more commonly found in exams performed on males and in older patients. The effect of age in increasing the odds of having a large polyp or mass appears to plateau somewhere after age 65; the estimated NNE to find 1 large polyp or mass actually increases slightly between the 65-74 year category and the 75 and older category. The NNE estimates for both men (12 for all those 65 and older) and women (19 for those between 65 and 74; 20 for those 75 and older) suggest that the odds of finding such a polyp or mass among patients in these two age groups are essentially equal. It is important to note, of course, that this effect may not be because growth of neoplasia actually slows or stops with increased age, but rather this may be an effect of older patients having a greater likelihood of previously undergoing polypectomy during a prior

endoscopic procedure.

Further examination of complications NNE data when other risk factors are taken into consideration demonstrates that screening may not be beneficial for patients who regularly take prescription anticoagulants such as warfarin. When anticoagulants are regularly used, NNE estimates range between 98 and 179 depending on demographic characteristic, a far cry from the range of 332-607 observed when anticoagulants are not used, a finding consistent with the statistically significant odds ratio of 3.40 for anticoagulant use observed in the complications logistic regression model. A similar drop in NNE for clinically significant neoplasia is not observed, which again is confirmed by the observed odds ratio of 1.03 for anticoagulant use in that logistic regression model. If reflective of the true risk of colonoscopic complication and findings, this relationship between the procedure's benefits and harms among users of anticoagulants may not be acceptable, and the question of whether such screening is appropriate in this population should be further scrutinized.

Compared to anticoagulant use, the role of patient comorbidity may not be of as much importance when considering appropriateness of CRC screening with colonoscopy. While the risk of complication is elevated among patients with ASA class of III or IV, the odds of finding clinically significant neoplasia are similarly elevated. So while the risk of serious complication among those with ASA class of III or IV may be lower than those with ASA class I, the corresponding increase in risk for significant neoplasia may indicate that the increase in likelihood of harm is concurrent with an increase in

procedure benefit. This is not to say that colonoscopic screening is thus appropriate among those patients with serious medical conditions; the increased yield of screening may not justify the increased risk to the patient. And with all of these conclusions, further examination of other potential harms and benefits associated with CRC screening with colonoscopy is necessary.

Nonetheless, the results of the present study do suggest that guidelines for the use of colonoscopy in CRC screening could incorporate more information than being solely based on patient age. Specifically, screening guidelines may be improved by incorporating patient gender into the criteria used to determine when and if colonoscopic screening is appropriate for a particular patient. Across all age categories examined, the number needed to endoscope in order to observe one patient with a large polyp or mass was significantly greater for males compared to females. This is not the first study to observe such an effect.

Other patient habits and characteristics should be considered when recommending an appropriate colonoscopic screening regimen. Specifically, routine colonoscopic CRC screening of patients who regularly use prescription anticoagulants such as warfarin should be carefully considered. Results from this study indicate that while use of such medications increases the risk of serious complications more than three-fold (OR = 3.40, 95% CI: 1.78 – 6.48), there is no increase in clinically significant neoplasia findings among such patients (OR = 1.03, 95% CI: 0.84 – 1.25). While providers make efforts to safely manage anticoagulants in the peri-endoscopic period, it is a difficult task and

adherence to management guidelines is not perfect[35]. As such, routine screening with colonoscopy may not be appropriate for such patients, and increased utilization of more conservative methods may be more appropriate for this subset of the population.

In addition to patient age, gender, and ASA class of III or IV, there are a number of other variables that are associated with clinically significant neoplasia on screening colonoscopy. Even a slightly elevated ASA score (class II vs. I) is related to increased odds of neoplasia. Additionally, procedure indication of prior positive screening test, such as positive FOBT or flexible sigmoidoscopy, was strongly associated with increased odds of clinically significant neoplasia, compared to those with indication of routine screening. This makes sense, given that these patients are sent to colonoscopy for polyp removal (sigmoidoscopy) or suspected polyps or masses (FOBT).

Despite the fact that family history of CRC and personal history of CRC or precancerous polyps are considered to be risk factors for incident CRC, neither of those procedure indications were associated with increased odds of large polyp or mass when compared to patients with indication of routine screening. This may be because screening practice is so effective for individuals in these categories – such patients are screened more aggressively than others, and in the cases of those with family history of the disease, screening is recommended at a younger age. Any follow-up exams may not have clinically significant neoplasia because that finding was observed – and the polyp or mass removed – during or immediately after an earlier procedure. Any new growths since that procedure may not have had ample time to exceed 9 mm in size, even if they are

relatively aggressive in their growth.

In addition to risk factors for neoplasia, this study identified two variables that may protect against neoplasia. Specifically, both aspirin use and NSAID use are associated with decreased odds of having a large polyp or mass found on colonoscopy. This finding is consistent with the available literature. In a 1991 case-control study, Rosenberg and colleagues demonstrated that non-steroidal anti-inflammatory medications, or NSAIDs, have a protective effect against colorectal cancer[47], a finding later confirmed in various studies[48,49]. Traditional anti-inflammatory medications such as aspirin non-selectively inhibit the production of cyclooxygenase-1 and cyclooxygenase-2 enzymes; the former is associated with maintaining the gastrointestinal tract, while the latter is associated with inflammation and pain. In recent years, a new class of NSAIDs called COX-2 inhibitors was developed and introduced to the market. These drugs selectively inhibit COX-2, alleviating pain and inflammation without the gastrointestinal side effects[50]. Unfortunately, COX-2 inhibitors are not without their own set of side effects, most notably the increased risk of cardiovascular events[51], and because of this the only such drug that remains on the market today is celecoxib (Celebrex).

While it is tempting to recommend the use of aspirin or COX-2 inhibitors in chemoprevention of CRC, this type of therapy does carry a risk. The risk of gastrointestinal side effects from NSAID may outweigh the benefit to CRC risk reduction[52]. Specifically, NSAIDs carry an increased risk of development of peptic ulcers and gastrointestinal bleeding[53].

Because aspirin and NSAID use appear to protect against development of clinically significant neoplasia, and because they may be associated with increased risk of complication, further examination of screening among patients who use such medication is required. Specifically, a study that is adequately powered to observe a sufficient number of procedure-related complications among aspirin and NSAID users would be ideal.

Strengths and Weaknesses

The present study has a number of strengths when compared to prior research on the topic. The NED is large enough to study rare GI endoscopy outcomes, and the data are representative of endoscopy practice in the United States[9]. As such, results from this study are more generalizable than those from studies based in one academic medical center or geographic region. Furthermore, the NED data come not just from all over the country, but also come from a variety of practice settings, such as community-based practices, VA hospitals, and academic medical centers.

Another advantage of the present study is the use of prospectively collected data. Other studies that have examined GI endoscopy complications have exclusively used medical records abstraction to collect complications information, or relied on data from immediately following the colonoscopy. Complete collection of such information from records alone is difficult, and harms may occur well beyond 1 day post-colonoscopy. Though the use of patient interviews certainly comes with its own set of methodological

concerns, such as recall bias, a memorable event of such magnitude that it requires a hospitalization likely lends itself well to reliance on patient recall.

Despite these strengths, this study is not without a number of weaknesses that must be considered when evaluating the study's results. The primary limitation of this study is the low proportion of eligible individuals who participated. The 21,375 who did participate constituted just 53% of those who were deemed eligible to participate. It is possible that non-participation in the study might be related to adverse events, as well as potential risk factors for those events. Non-participation could also be related to increased risk of neoplasia, possibly if non-participation is associated with poorer overall health. However, Ko and her colleagues examined demographic and clinical characteristics of those who were eligible but did not participate, and found that participants and non-participants did not differ substantially based on age or ASA class, as well as other potential confounders[20].

Though the NED is used for research purposes, its data is collected by consortium members primarily for medical care, and serves as the legal medical record of the endoscopic procedure. Procedure data are input by practicing physicians who have limited or no knowledge of ongoing CORI research studies, and likely do not have data reliability results in mind when creating reports. Thus, data are at times missing, as is the case in this study with a small proportion of race and ASA class values. Demographic data, such as patient race, ethnicity and gender, are determined by the endoscopist or other clinic staff at the time of their first endoscopic procedure. Methods of obtaining this information vary by clinic; some may take the information from patient records,

while others may simply use their own best guess. However, such misclassification would be virtually non-existent for gender, and any race misclassification is not an issue with this study as we eventually excluded race and ethnicity from consideration.

As mentioned above, this study relies greatly on self-report information for the outcome of harms from colonoscopy and medication usage. Such a method of data collection has both advantages and disadvantages. The primary concern with such a method is accuracy of patient recall. In the original study of this cohort, the researchers conducted an analysis of a subset of the study data, comparing participants' self-report questionnaire data to medical records. In this analysis, the self-report data agreed with results from the medical record review over 80% of the time, a figure which the researchers deemed suitable for a source of diagnoses and symptoms.

Potentially important predictors of harms from colonoscopy also include factors related to the patient's general health. CORI procedure reports do not reliably and systematically contain information on specific co-morbid conditions (e.g. diabetes), physical characteristics (e.g. presence of obesity or overweight), or behaviors (e.g. smoking) that may be associated with harms from procedures such as colonoscopy. Instead we include ASA class in this study as a surrogate for such characteristics, conditions and behaviors. While ASA class may be a useful measure of overall patient health, there are some reliability concerns with its measurement. The measure is very subjective in nature, and studies have shown that it is somewhat imprecise and lacks strong inter-rater reliability[54-56]. It is reasonable to assume that such characteristics and behaviors associated with poor overall health may be related to one or more of the predictors of interest in this study

(race, age or sex); as such, it would be an important potential confounding factor to control for statistically. However, using such a broad measure of health may not be a particularly effective surrogate. Should ASA class not be an accurate measure of such conditions, characteristics and behaviors, this may result in residual confounding.

Another potential limitation of this study is in the relative homogeneity of race among patients included in this study. Though practices that participate in CORI come from all regions of the country, in urban, suburban and rural populations, the dataset is predominantly composed of white individuals. Just over 90% of patients in this cohort are white, compared with an estimated 75.1% in the United States in 2000 [57]. It is unclear at this time if this is because sites using the CORI procedure reporting software are fundamentally different from other sites with regard to race or if it is a reflection of racial and ethic inequity in utilization of colonoscopic screening for colorectal cancer. While this would not limit the implications of this study for white populations, it may reduce ability to generalize results to the U.S. population as a whole.

This issue of patient race is still important for purposes of generalizability, despite the fact that we had to drop race from consideration in the analysis of these data. That we had to drop race from our study is another weakness of this study. Due to small cell counts, it was necessary to remove race from consideration, as there were too few events for all races except black and white to draw any valid conclusions. This was problematic particularly for the neoplasia outcome, as race has been demonstrated to be associated with increased odds of having clinically significant neoplasia on exam. One alternative would have been to limit the study to white and black participants only, as these two

races comprised approximately 97% of the study sample. However, it was decided to avoid doing that, as it would limit the study's validity. By including all races in this analysis, the study remains generally representative of GI endoscopy practice in the United States.

The definition used for the complication outcome in this study is somewhat heterogeneous. In the current analysis, we have combined events that Ko and her colleagues defined as events potentially related to colonoscopy and events directly related to colonoscopy into one outcome of adverse events[20]. Thus, if for example male sex is related to one kind of adverse event and female sex is related to a different kind, but both events were treated identically, this may obscure effects for sex on those event types. However, of primary concern in this study is not the type of event that occurred, but whether or not any serious complication occurred that can be attributed to the procedure. While some events may be graver than others, the outcome as defined contains events serious enough in nature that all should be avoided. Of greater concern is if some of the "potentially related" complications are truly related to the colonoscopy. If some of these events are not actually related to the procedure this would lead to an overestimate of the incidence of complication. Furthermore, if any of the predictors of interest are associated with increased (or decreased) likelihood of these health problems unrelated to colonoscopy, this could lead to a number of spurious findings. While it would be ideal to look at only direct complications, the overall paucity of adverse events in this cohort (despite its size at over 21,000 participants) makes combining this more heterogeneous outcome a necessity in order to maximize the study's statistical power to detect a true

effect.

Future Studies

In order to address these concerns further research on the topic is needed. Future studies of the potential harms associated with colonoscopy will need to address issues of statistical power due to the rarity of the event under study. However, a study of such size may be cost-prohibitive, and devoting such resources to a relatively rare event may not be justified.

The present analysis primarily examined the role of patient demographics in predicting complication and neoplasia. Patient race and ethnicity were excluded due to statistical concerns, but our understanding of the potential harms and benefits associated with colonoscopy would be improved by examining the role played by race. Future research should involve a greater number of non-white and non-black patients in order to enable valid conclusions to be drawn regarding patients of other races. This could be done by conducting research in regions that have greater proportion of Asian, Pacific Islander, American Indian, and Hispanic inhabitants, and by over-sampling among patients of these races.

This study examined ASA class as a surrogate for patient comorbidity. However, this classification is very subjective, and an imperfect measure of a patient's overall well-being. Furthermore, the measure is by nature very imprecise and heterogeneous; any number of conditions could lead to a provider assigning a patient a higher ASA

classification. Future research should focus on measuring actual comorbidities that researchers deem to be of particular interest, and their association with both complications and findings on exam. Collecting such information would improve the ability to assess whether a patient is a good candidate for colonoscopic screening based on a specific condition, rather than relying on a measure of general well-being.

Despite this study's limitations and the need for further improved research, the present study is valuable in identifying harms and benefits from colonoscopy for patients in specific demographic profiles. It is, to our knowledge, the largest and most representative study of harms and outcomes of surveillance and screening colonoscopy performed to date. The findings of this study provide valuable insight into which patients may be most appropriate to receive colorectal cancer screening and surveillance via colonoscopy.

References

1. National Cancer Institute. SEER Cancer Statistics Review, 1975-2005, based on November 2007 SEER data submission, posted to the SEER web site. Bethesda, MD: National Cancer Institute; 2008.
2. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer Statistics, 2009. *CA: Cancer Journal for Clinicians.* 2009;59:225-49.
3. Hennekens CH, Buring JE. *Epidemiology in Medicine.* 1st ed. Philadelphia, Pa: Lippincott Williams and Wilkins, 1987.
4. Cornett Patricia A, Dea Tiffany O, "Chapter 39. Cancer" (Chapter). McPhee SJ, Papadakis MA: CURRENT Medical Diagnosis & Treatment 2011: http://www.accessmedicine.com.liboff.ohsu.edu/content.aspx?aID=8950897.
5. Winawer SJ, Zauber AG, Ho MN, O'Brien MJ, Gottlieb LS, Sternberg SS, Waye JD, Schapiro M, Bond JH, Panish JF, Ackroyd F, Shike M, Kurtz RC, Hornsby-Lewis L, Gerdes H, Stewart ET, and The National Polyp Study Workgroup. Prevention of Colorectal Cancer by Colonoscopic Polypectomy. *New England Journal of Medicine,* 1993*;329*:1977-1981.
6. Lieberman DA. Screening for colorectal cancer. *New England Journal of Medicine.* 2009;361:1179-87.
7. U.S. Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Annals of Internal Medicine.* 2008;149:627-37.
8. Maciosek MV, Solberg LI, Coffield AB, Edwards NM, Goodman MJ. Colorectal cancer screening: health impact and cost effectiveness. *American Journal of*

Preventive Medicine. 2006;31:80-89.

9. Sonnenberg A, Amorosi SL, Lacey MJ, Lieberman DA. Patterns of endoscopy in the United States: analysis of data from the Centers for Medicare and Medicaid Services and the National Endoscopic Database. *Gastrointestinal Endoscopy.* 2008;67:489-96.
10. Seeff LC, Richards TB, Shapiro JA, Nadel MR, Manninen DL, Given LS, Dong FB, Winges LD, McKenna MT. How many endoscopies are performed for colorectal cancer screening? Results from CDC's survey of endoscopic capacity. *Gastroenterology.* 2004;127:1670-77.
11. Lieberman DA, Holub J, Eisen G, Kraemer D, Morris CD. Prevalence of polyps greater than 9 mm in a consortium of diverse clinical practice settings in the United States. *Clinical Gastroenterology and Hepatology.* 2005;3(8):798-805.
12. Lin OS, Kozarek RA, Schembre DB, Ayub K, Gluck M, Drennan F, Soon M, Rabeneck L. Screening colonoscopy in very elderly patients: prevalence of neoplasia and estimated impact on life expectancy. *JAMA.* 2006;295(20):2357-65.
13. Karajeh MA, Sanders DS, Hurlstone DP. Colonoscopy in elderly people is a safe procedure with a high diagnostic yield: a prospective comparative study of 2000 patients. *Endoscopy.* 2006;38(3):226-30.
14. Lieberman DA, Holub JL, Moravec MD, Eisen GM, Peters D, Morris CD. Prevalence of colon polyps detected by colonoscopy screening in asymptomatic black and white patients. *JAMA*, 2008;300(12):1417-22.
15. Theuer CP, Wagner JL, Taylor TH, Brewster WR, Tran D, McLaren CE, Anton-

Culver H. Racial and ethnic colorectal cancer patterns affect the cost-effectiveness of colorectal cancer screening in the United States. *Gastroenterology.* 2001;120:848-56.

16. Nelson RL, Dollear T, Freels S, Persky V. The relation, age, race, and gender to the subsite location of colorectal carcinoma. *Cancer*. 1997;80:193-7.
17. Heldwein W, Dollhopf M, Rosh T, Meining A, Schmidtsdorff G, Hasford J, Hermanek P, Burlefinger R, Birkner B, Schmitt W. The Munich Polypectomy Study (MUPS): Prospective analysis of complications and risk factors in 4000 colonic snare polypectomies. *Endoscopy. 37 (11):*1116-22.
18. Ko CW, Riffle, S, Shapiro JA, Saunders MD, Lee SD, Tung BY, Kuver R, Larson AM, Kowdley KV, Kimmey MB. Incidence of minor complications and time lost from normal activities after screening or surveillance colonoscopy. *Gastrointestinal Endoscopy.* 2007;65(4):648-56.
19. Lohsiriwat V, Sujarittanakarn S, Akaraviputh T, Lertakyamanee N, Lohsiriwat D, Kachinthorn U. What are the risk factors of colonoscopic perforation? *BMC Gastroenterology.* 2009;9:71.
20. Ko CW, Riffle S, Michaels L, Morris C, Holub J, Shapiro JA, Ciol MA, Kimmey MB, Seeff LC, Lieberman D. Serious complications within 30 days of screening and surveillance colonoscopy are uncommon [published online ahead of print October 20 2009]. *Clinical Gastroenterology and Hepatology.* 2009.
21. Anderson ML, Pasha TM, Leighton JA. Endoscopic perforation of the colon: Lessons from a 10-year study. *American Journal of Gastroenterology.* 2000;95(12):3418-22.

22. Lohsiriwat, V. Colonoscopic perforation: Incidence, risk factors, management and outcome. *World Journal of Gastroenterology.* 2010;16(4):425-30.

23. Singh H, Penfold RB, DeCoster C, Kaita L, Proulx C, Taylor G, Bernstein CN, Moffatt M. Colonoscopy and its complications across a Canadian regional health authority. *Gastrointestinal Endoscopy.* 2009;69:665-71.

24. Rosen L, Bub DS, Reed III JF, Nastasee SA. Hemorrhage following colonoscopic polypectomy. *Disease of the Colon and Rectum.* 1993;36:1126-31.

25. Arora G, Mannalithara A, Singh G, Gerson LB, Triadafilopoulos G. Risk of perforation from a colonoscopy in adults: a large population-based study. *Gastrointestinal Endoscopy, 2009; 69:*654-64.

26. Gatto NM, Frucht H, Sundararajan V, Jacobson JS, Grann VR, Neugut AI. Risk of perforation after colonoscopy and sigmoidoscopy: A population-based study. *Journal of the National Cancer Institute*. 2003;95:230-6.

27. Levin TR, Zhao W, Conell C, Seeff LC, Manninen DL, Shapiro JA, Schulman J. Complications of colonoscopy in an integrated health care delivery system. *Annals of Internal Medicine.* 2006;145:880-886.

28. Rabeneck L, Paszat LF, Hilsden RJ, Saskin R, Leddin D, Grunfeld E, Wai E, Goldwasser M, Sutradhar R, Stukel TA. Bleeding and perforation after outpatient colonoscopy and their risk factors in usual clinical practice. *Gastroenterology.* 2008;135:1899-1906.

29. Kim HS, Kim TI, Kim WH, Kim Y, Kim HJ, Yang S, Myung S, Byeon J, Lee MS, Chung IK, Jung S, Jeen YT, Choi JH, Choi KY, Choi H, Han DS, Song JS. Risk factors for immediate 47ostypolypectomy bleeding of the colon: a

multicenter study. *American Journal of Gastroenterology.* 2006;101:1333-1341.

30. Warren JL, Klabunde CN, Mariotto AB, Meekins A, Topor M, Brown ML, Ransohoff DF. Adverse events after outpatient colonoscopy in the Medicare population. *Annals of Internal Medicine.* 2009;150:849-57.
31. Dobrowolski S, Dobosz M, Babicki A, Glowacki J, Nalecz A. Blood supply of colorectal polyps correlates with risk of bleeding after colonoscopic polypectomy. *Gastrointestinal Endoscopy.* 2006;63(7):1004-1009.
32. Sorbi D, Norton I, Conio M, Balm R, Zinsmeister A, Gostout CJ. Postpolypectomy lower GI bleeding: Descriptive analysis. *Gastrointestinal Endoscopy.* 2000;51(6):690-6.
33. Singh M, Mehta N, Murthy UK, Kaul V, Arif A, Newman N. Postpolypectomy bleeding in patients undergoing colonoscopy on uninterrupted clopidogrel therapy. *Gastrointestinal Endoscopy.* 2010;71:998-1005.
34. Kaplan RC, Heckbert SR, Koepsell TD, Furberg CD, Polak JF, Schoen RE, Psaty BM. Risk factors for hospitalized gastrointestinal bleeding among older persons. *Journal of the American Geriatrics Society.* 2001;49(2):126-33.
35. Gerson LB, Michaels L, Ullah N, Gage B, Williams L. Adverse events associated with anticoagulation therapy in the periendoscopic period. *Gastrointestinal Endoscopy.* 2010;71:1211-7.
36. Watabe H, Yamaji Y, Okamoto M, Kondo S, Ohta M, Ikenoue T, Kato J, Togo G, Matsumura M, Yoshida H, Kawabe T, Omata M. Risk assessment for delayed hemorrhagic complication of colonic polypectomy: polyp-related factors and patient-related factors. *Gastrointestinal Endoscopy.* 2006;64:73-8.

37. Gross CP, McAvay GJ, Krumholz HM, Paltiel AD, Bhasin D, Tinetti ME. The effect of age and chronic illness on life expectancy after a diagnosis of colorectal cancer: implications for screening. *Annals of Internal Medicine.* 2006;145:646-53.

38. Teoh AYB, Poon CM, Lee JFY, Leong HT, Ng SSM, Sung JJY, Lau JYW. Outcomes and predictors of mortality and stoma formation in surgical management of colonoscopic perforations. *Archives of Surgery.* 2009;144(1):9-13.

39. Korman LY, Overholt BF, Box T, Winker CK. Perforation during colonoscopy in endoscopic ambulatory surgical centers. *Gastrointestinal Endoscopy.* 2003;58:554-7.

40. Witt DM, Delate T, McCool KH, Dowd MB, Clark NP, Crowther MA, Garcia DA, Ageno W, Dentali F, Hylek EM, Rector WG. Incidence and predictors of bleeding or thrombosis after polypectomy in patients receiving and not receiving anticoagulation therapy. *Journal of Thrombosis and Haemostasis.* 2009;7:1982-9.

41. Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chefject G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. *NEJM.* 2000;343(3)162-8.

42. Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. *New England Journal of Medicine.* 2000;343:169-74.

43. Schoen RE, Gerber LD, Margulies C. The pathologic measurement of polyp size

is preferable to the endoscopic estimate. *Gastrointestinal Endoscopy.* 1997;46(6):571-4.

44. Gopalswamy N, Shenoy VN, Choudhry U, Markert RJ, Peace N, Bhutani MS, Barde CJ. Is in vivo measurement of size of polyps during colonoscopy accurate? *Gastrointestinal Endoscopy.* 1997;46(6):497-502.
45. Arora A, Singh P. Colonoscopy in patients 80 years of age and older is safe, with high success rate and diagnostic yield. *Gastrointestinal Endoscopy, 2000; 60:* 408-13.
46. Duncan JE, Sweeney WB, Trudel JL, Madoff RD, Mellgren AF. Colonoscopy in the elderly: low risk, low yield in asymptomatic patients. *Diseases of the Colon and Rectum.* 2006;49:646-51.
47. Rosenberg L, Palmer JR, Zauber AG, Warshauer ME, Stolley PD, Shapiro S. A hypothesis: Nonsteroidal anti-inflammatory drugs reduce the incidence of large-bowel cancer. *Journal of the National Cancer Institute.* 1991;83(5):355-8.
48. Flossmann E, Rothwell PM. Effect of aspirin on long-term risk of colorectal cancer: consistent evidence from randomised and observational studies. *Lanc*et. 2007 May 12; 369(9573): 1603-13.
49. Cooper K, Squires H, Carroll C, Papaioannou D, Booth A, Logan RF, Maguire C, Hind D, Tappenden P. Chemoprevention of colorectal cancer: systematic review and economic evaluation. *Health Technology Assessment.* 2010;14(32).
50. Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowith JB, Verburg KM, Geis GS. Gastrointestinal toxicity with celecoxib versus non-

steroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *JAMA*. 2000; 284: 1247-1255.

51. Krotz F, Schiele TM, Klauss V, Sohn HY. Selective COX-2 inhibitors and risk of myocardial infarction. *Journal of Vascular Research*. 2005; 42: 312-324.
52. United States Preventative Services Task Force. *Routine aspirin or nonsteroidal anti-inflammatory drugs for the primary prevention of colorectal cancer*. http://www.ahrq.gov/clinic/uspstf/uspsasco.htm. 2007. Retrieved 3/14/2009.
53. Traversa G, Walker AM, Ippolito FM, Caffari B, Capurso L, Dezi A, Koch M, Maggini M, Alegiani SS, Raschetti R. Gastroduodenal toxicity of different nonsteroidal anti-inflammatory drugs. *Epidemiology*. 1995 Jan; 6(1): 49-54.
54. Owens WD, Felts JA, Spitznagel EL Jr. ASA physical status classifications: a study of consistency of ratings. *Anesthesiology.* 1978;49(4):239-43.
55. Mak PH, Campbell RC, Irwin MG, American Society of Anesthesiologists. The ASA Physical Status Classification: inter-observer consistency. American Society of Anesthesiologists. *Anaesthesiology Intensive Care.* 2002;30(5):633-40.
56. Ranta S, Hynynen M, Tammisto T. A survey of the ASA physical status classification: significant variation in allocation among Finnish anaesthesiologists. *Acta Anaesthesiol Scand.* 1997; 41(5):629-32.
57. U.S. Census Bureau. QT-P5. Race alone or in combination: 2000. *American FactFinder.* 2000. Bureau of the Census. Web. 21 November 2009.

Tables

Table 1

Patient Demographics (n = 21,302)					
Variable	**Level**	**% of total w/out neoplasia (n = 19,436)**	**% of total with neoplasia (n = 1,866)**	**% of total w/out complication (n = 21,234)**	**% of total with complication (n = 68)**
Gender	Female	46.19	31.94	44.97	36.76
	Male	53.81	68.06	55.03	63.24
Age	<65	59.76	48.39	58.80	47.06
	65-74	26.63	33.65	27.24	27.94
	75-84	12.44	16.35	12.75	23.53
	85+	1.18	1.61	1.22	1.47
Practice Type	Community/HMO	77.32	68.22	76.54	69.12
	Academic	9.08	8.25	9.00	13.24
	VA	13.60	23.53	14.46	17.65
ASA	I	25.33	13.67	24.32	19.12
	II	67.19	76.37	67.99	69.12
	III	3.66	6.38	3.87	11.76
	IV	0.02	0.05	0.02	0.00
	Unknown	3.80	3.54	3.79	0.00
Indication	Routine / Average Risk	41.93	34.46	41.31	32.35
	Family History	16.94	12.70	16.58	14.71
	Positive Screening Test	12.99	25.88	14.11	14.71
	Surveillance	28.14	26.96	28.00	38.24
Aspirin Use	Yes	40.76	42.18	40.85	51.47
	No	59.24	57.82	59.15	48.53
NSAID Use	Yes	4.01	2.68	3.89	4.41
	No	95.99	97.32	96.11	95.59
Prescription Anticoagulant Use	Yes	5.27	7.29	5.41	19.12
	No	94.73	92.71	94.59	80.88

Table 2

Prevalence of Clinically Significant Neoplasia, by Age and Gender

Gender	Age (years) < 65 (n = 12517)	65 - 74 (n = 5803)	≥ 75 (n = 2982)
Female (n = 9574)	310/5796 53.5 per 1000	182/2505 72.7 per 1000	104/1273 81.7 per 1000
Male (n = 11728)	593/6721 88.2 per 1000	446/3298 135.2 per 1000	231/1709 135.2 per 1000

Table 3

Univariate Logistic Regression Results - Clinically Significant Neoplasia					
Variable	**Level**	**Beta**	**OR**	**95% CI**	**p**
Gender	Male	0.6039	1.829	1.653 - 2.024	**<0.0001**
Age	65-74	0.4452	1.561	1.402 - 1.737	**<0.0001**
	75+	0.4872	1.628	1.426 - 1.858	
ASA (Unknown = 805)	II	0.7451	2.107	1.836 - 2.416	**<0.0001**
	III and IV	1.1756	3.240	2.573 - 4.081	
Aspirin	Yes	0.0584	1.060	0.963 - 1.167	**0.2346**
NSAIDs	Yes	-0.4164	0.659	0.493 - 0.881	**0.0049**
RX Anticoagulants	Yes	0.3450	1.412	1.173 - 1.700	**0.0003**
Indication	Family Hx	-0.0919	0.912	0.782 - 1.064	**<0.0001**
	Surveillance	0.1534	1.166	1.032 - 1.316	
	Prior + Test	0.8861	2.426	2.138 - 2.752	
Practice Type	Academic	0.0295	1.030	0.865 - 1.226	**<0.0001**
	VA	0.6729	1.960	1.745 - 2.201	

*** Criteria for Consideration in Multivariate Model: alpha ≤ 0.25**

*** P-values indicate variable's overall significance, not significance of specific level (for variables with >2 levels)**

Table 4

Adjusted Odds Ratio Estimates for Clinically Significant Neoplasia (n = 20,497)	
Variable	**Odds Ratio (95% CI)**
Gender	
Female	1 (Reference)
Male	**1.65 (1.48 - 1.84)**
Age, years	
< 65	1 (Reference)
65 - 74	**1.50 (1.34 - 1.68)**
≥ 75	**1.46 (1.27 - 1.69)**
Aspirin Use	
No	1 (Reference)
Yes	**0.87 (0.78 - 0.96)**
NSAID Use	
No	1 (Reference)
Yes	**0.67 (0.49 - 0.90)**
Anticoagulant Use	
No	1 (Reference)
Yes	1.03 (0.84 - 1.25)
ASA Class	
I	1 (Reference)
II	**1.72 (1.49 - 1.98)**
III & IV	**2.33 (1.83 - 2.97)**
Indication	
Routine / Average Risk	1 (Reference)
Family History	0.98 (0.84 - 1.15)
Surveillance of Polyps / CRC	0.91 (0.80 - 1.04)
Prior Positive Screening Test	**1.93 (1.69 - 2.21)**

Table 5

Incidence Proportion of Colonoscopic Complications within 30 days, by Age and Gender

Gender	Age (years) < 65 (n = 12517)	65 - 74 (n = 5803)	≥ 75 (n = 2982)
Female (n = 9574)	12/5796 2.1 per 1000	5/2505 2.0 per 1000	8/1273 6.3 per 1000
Male (n = 11728)	20/6721 3.0 per 1000	14/3298 4.2 per 1000	9/1709 5.3 per 1000

Table 6

Univariate Logistic Regression Results - Complications					
Variable	**Level**	**Beta**	**OR**	**95% CI**	**p**
Gender	Male	0.3403	1.405	0.858 - 2.302	**0.1766**
Age	65-74	0.2481	1.282	0.726 - 2.263	**0.0276**
	75+	0.8053	2.237	1.241 - 4.034	
ASA (Unknown = 805)	II	0.2573	1.293	0.699 - 2.392	**0.0073**
	III and IV	1.3468	3.845	1.589 - 9.304	
Aspirin	Yes	0.4290	1.535	0.954 - 2.473	**0.0775**
NSAIDs	Yes	0.1313	1.140	0.358 - 3.636	0.8243
RX Anticoagulants	Yes	1.4196	4.136	2.253 - 7.591	**<0.0001**
Indication	Family Hx	0.1245	1.133	0.536 - 2.394	0.2695
	Surveillance	0.5558	1.743	0.987 - 3.079	
	Prior + Test	0.2854	1.330	0.629 - 2.812	
Practice Type	Academic	0.4883	1.629	0.797 - 3.330	0.3197
	VA	0.3010	1.351	0.716 - 2.550	

*** Criteria for Consideration in Multivariate Model: alpha ≤ 0.25**

*** P-values indicate variable's overall significance, not significance of specific level (for variables with >2 levels)**

Table 7

Adjusted Odds Ratio Estimates for Complication within 30 Days (n = 20,497)	
Variable	**Odds Ratio (95% CI)**
Gender	
Female	1 (Reference)
Male	1.19 (0.71 - 1.99)
Age, years	
< 65	1 (Reference)
65 - 74	1.02 (0.56 - 1.86)
≥ 75	1.54 (0.80 - 2.93)
Aspirin Use	
No	1 (Reference)
Yes	1.50 (0.92 - 2.45)
NSAID Use	
No	1 (Reference)
Yes	1.33 (0.42 - 4.25)
Anticoagulant Use	
No	1 (Reference)
Yes	**3.40 (1.78 - 6.48)**
ASA Class	
I	1 (Reference)
II	0.98 (0.51 - 1.87)
III & IV	2.14 (0.83 - 5.53)
Indication	
Routine / Average Risk	1 (Reference)
Family History	1.22 (0.58 - 2.60)
Surveillance of Polyps / CRC	1.34 (0.74 - 2.44)
Prior Positive Screening Test	1.06 (0.49 - 2.28)

Table 8

Multivariate Logistic Regression Results - Clinically Significant Neoplasia (n = 20,497)						
Parameter		**Estimate**	**SE**	**OR**	**95% CI**	**Pr > ChiSq**
Intercept		-3.3063	0.0786			<0.0001
Gender	**Male**	0.5013	0.0551	**1.651**	**1.482 - 1.839**	**<0.0001**
Age	**65-74**	0.4046	0.0586	**1.499**	**1.336 - 1.681**	**<0.0001**
	75+	0.3809	0.0736	**1.464**	**1.267 - 1.691**	**<0.0001**
ASA Class	**II**	0.5394	0.0731	**1.715**	**1.486 - 1.979**	**<0.0001**
	III and IV	0.8472	0.1235	**2.333**	**1.832 - 2.972**	**<0.0001**
Aspirin Use	**Yes**	-0.1407	0.0521	**0.869**	**0.784 - 0.962**	**0.0069**
NSAID Use	**Yes**	-0.4029	0.1543	**0.668**	**0.494 - 0.904**	**0.0090**
Anticoagulant Use	**Yes**	0.0250	0.0994	1.025	0.844 - 1.246	0.8013
Indication	**Family Hx**	-0.0171	0.0812	0.983	0.838 - 1.153	0.8337
	Surveillance	-0.0919	0.0658	0.912	0.802 - 1.038	0.1626
	Prior + Test	0.6588	0.0680	**1.932**	**1.691 - 2.208**	**<0.0001**

Table 9

Multivariate Logistic Regression Results - Complications (n = 20,497)						
Parameter		**Estimate**	**SE**	**OR**	**95% CI**	**Pr > ChiSq**
Intercept		-6.4068	0.3593			< 0.0001
Gender	**Male**	0.1767	0.2618	1.193	0.714 - 1.993	0.4999
Age	**65-74**	0.0214	0.3046	1.022	0.562 - 1.856	0.9440
	75+	0.4285	0.3305	1.535	0.803 - 2.934	0.1949
ASA	**II**	-0.0209	0.3311	0.979	0.512 - 1.874	0.9497
	III or IV	0.7591	0.4850	2.136	0.826 - 5.527	0.1176
Aspirin Use	**Yes**	0.4050	0.2499	1.499	0.919 - 2.447	0.1050
NSAID Use	**Yes**	0.2832	0.5938	1.327	0.415 - 4.250	0.6334
Anticoagulant Use	**Yes**	1.2234	0.3291	**3.399**	**1.783 - 6.479**	**0.0002**
Indication	**Family Hx**	0.2021	0.3841	1.224	0.577 - 2.598	0.5988
	Surveillance	0.2951	0.3042	1.343	0.740 - 2.438	0.3319
	Prior Screening	0.0567	0.3925	1.058	0.490 - 2.284	0.8851

Table 10

Number Needed to Endoscope for One Complication / One Significant Neoplasia Finding*				
	Complication		Neoplasia	
Age	Male	Female	Male	Female
<65	508.8 (250.1 - 1036.2)	607.0 (300.7 - 1226.4)	17.5 (15.2 - 20.2)	28.3 (24.4 - 32.8)
65-74	498.1 (209.1 - 1188.2)	594.1 (253.1 - 1396.6)	12.0 (10.2 - 14.2)	19.3 (16.2 - 22.7)
≥75	331.8 (130.5 - 845.9)	395.8 (159.7 - 982.8)	12.3 (10.2 - 14.8)	19.6 (16.2 - 23.8)

*Values for ASA class, aspirin use, NSAID use, anticoagulant use, and procedure indication set to reference level

Table 11

Number Needed to Endoscope for One Complication / One Significant Neoplasia Finding Given Anticoagulant Use*				
	Complication		Neoplasia	
Age	Male	Female	Male	Female
<65	150.4 (60.7 - 375.0)	179.3 - (70.3 - 459.6)	17.1 (13.7 - 21.5)	27.6 (21.7 - 35.1)
65-74	147.3 (54.3 - 402.2)	175.5 (63.5 - 488.4)	11.8 (9.35 - 14.9)	18.8 (14.7 - 24.0)
≥75	98.3 (35.4 - 276.4)	117.2 (41.8 - 331.7)	12.0 (9.4 - 15.4)	19.2 (14.9 - 24.8)

*Values for ASA Class, Aspirin Use, NSAID Use, and Procedure Indication set to Reference Level

Table 12

Number Needed to Endoscope for 1 Complication / 1 Significant Neoplasia Finding Given ASA Class III or IV*

	Complication		Neoplasia	
Age	Male	Female	Male	Female
<65	238.7 (92.9 - 616.1)	284.6 (108.7 - 747.7)	8.1 (6.6 - 9.9)	12.7 (10.2 - 15.8)
65-74	233.7 (87.2 - 628.9)	278.6 (102.9 - 757.2)	5.7 (4.7 - 7.0)	8.8 (7.2 - 10.9)
≥75	155.9 (56.7 - 431.9)	185.8 (67.6 - 514.0)	5.8 (4.8 - 7.2)	9.0 (7.2 - 11.3)

*Values for Aspirin Use, NSAID Use, Anticoagulant Use, and Procedure Indication set to Reference Level

Table 13

Neoplasia OR Comparisons - +/- 1 mm Criterion Change (n = 20,497)						
Variable	**Level**	**Original Neoplasia Cutoff: > 9 mm**	**Neoplasia Cutoff: > 8 mm**	**% Change**	**Neoplasia Cutoff: > 10 mm**	**% Change**
Gender	Male	1.65 (1.48 - 1.84)	1.62 (1.46 - 1.80)	-1.8%	1.90 (1.65 - 2.19)	+15.2%
Age	65-74	1.50 (1.34 - 1.68)	1.47 (1.32 - 1.65)	-2.0%	1.64 (1.42 - 1.89)	+9.3%
	75+	1.46 (1.27 - 1.69)	1.43 (1.24 - 1.64)	-2.1%	1.62 (1.36 - 1.94)	+11.0%
ASA	II	1.72 (1.49 - 1.98)	1.64 (1.43 - 1.88)	-4.7%	1.56 (1.30 - 1.87)	-9.3%
	III and IV	2.33 (1.83 - 2.97)	2.22 (1.76 - 2.81)	-4.7%	2.21 (1.64 - 2.97)	-5.2%
Aspirin	Yes	0.87 (0.78 - 0.96)	0.88 (0.79 - 0.97)	+1.1%	0.83 (0.73 - 0.94)	-4.6%
NSAIDs	Yes	0.67 (0.49 - 0.90)	0.65 (0.49 - 0.88)	-3.0%	0.53 (0.35 - 0.81)	-20.9%
Anticoagulants	Yes	1.03 (0.84 - 1.25)	1.04 (0.86 - 1.25)	+1.0%	0.92 (0.72 - 1.17)	-10.7%
Indication	Family Hx	0.98 (0.84 - 1.15)	0.95 (0.81 - 1.11)	-3.1%	1.06 (0.86 - 1.30)	+8.2%
	Surveillance	0.91 (0.80 - 1.04)	0.93 (0.82 - 1.05)	+2.2%	0.93 (0.78 - 1.09)	+2.2%
	Prior + Test	1.93 (1.69 - 2.21)	1.87 (1.64 - 2.13)	-3.1%	2.48 (2.11 - 2.91)	+28.5%

Table 14

Neoplasia OR Comparisons - Sized vs. Unsized Polyps				
Variable	**Level**	**OR w/ Unsized Polyps (n = 20,497)**	**Only Sized Polyps (n = 20,050)**	**% Change**
Gender	Male	1.65 (1.48 - 1.84)	1.66 (1.49 - 1.85)	+0.6%
Age	65-74	1.50 (1.34 - 1.68)	1.50 (1.34 - 1.69)	--
	75+	1.46 (1.27 - 1.69)	1.47 (1.27 - 1.70)	+0.7%
ASA	II	1.72 (1.49 - 1.98)	1.75 (1.51 - 2.01)	+1.7%
	III and IV	2.33 (1.83 - 2.97)	2.38 (1.87 - 3.04)	+2.1%
Aspirin	Yes	0.87 (0.78 - 0.96)	0.86 (0.78 - 0.95)	-1.1%
NSAIDs	Yes	0.67 (0.49 - 0.90)	0.68 (0.50 - 0.92)	+1.5%
Anticoagulants	Yes	1.03 (0.84 - 1.25)	1.03 (0.84 - 1.25)	--
Indication	Family Hx	0.98 (0.84 - 1.15)	1.00 (0.85 - 1.25)	+2.0%
	Surveillance	0.91 (0.80 - 1.04)	0.93 (0.82 - 1.06)	+2.2%
	Prior + Test	1.93 (1.69 - 2.21)	1.94 (1.69 - 2.21)	+0.5%

Figures

Figure 1

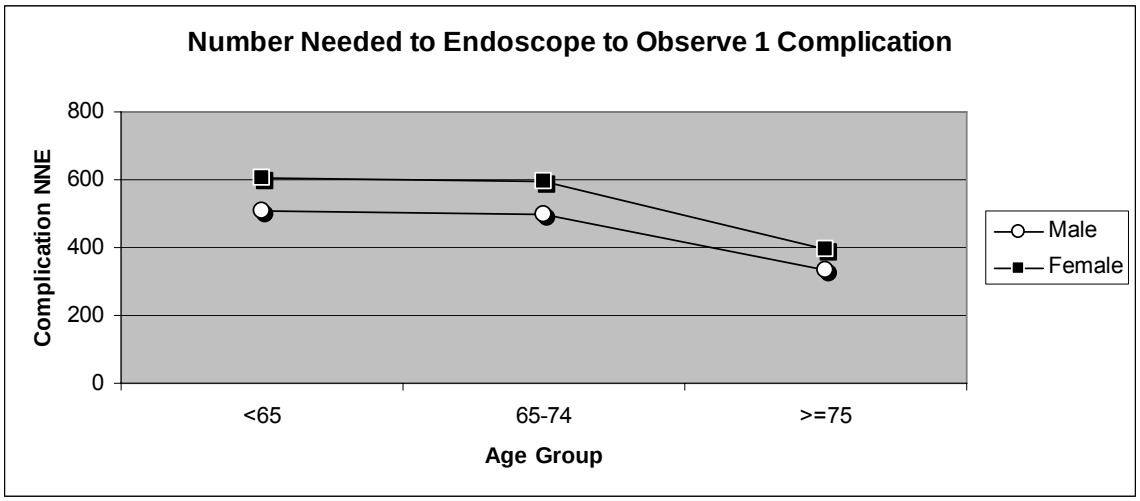


Figure 2

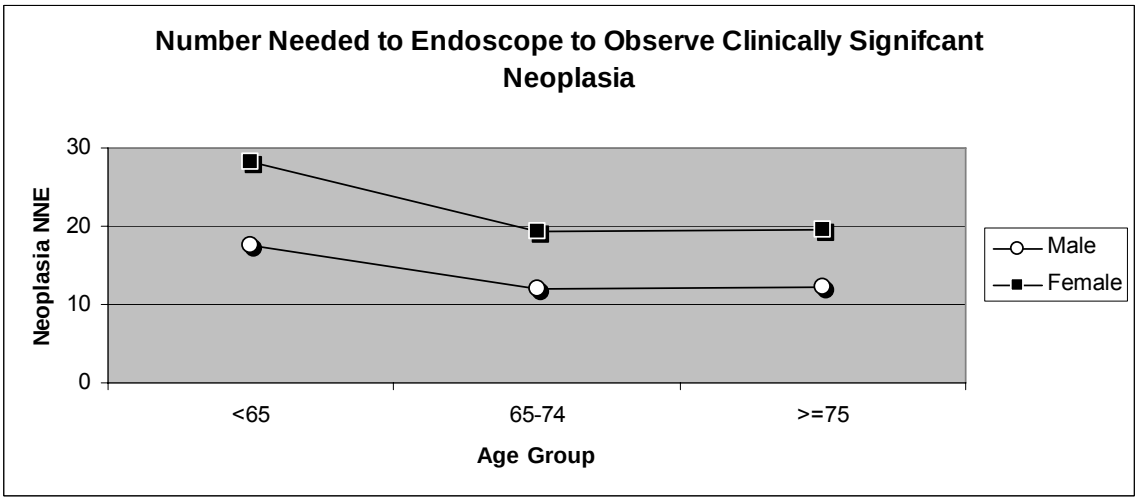


Figure 3

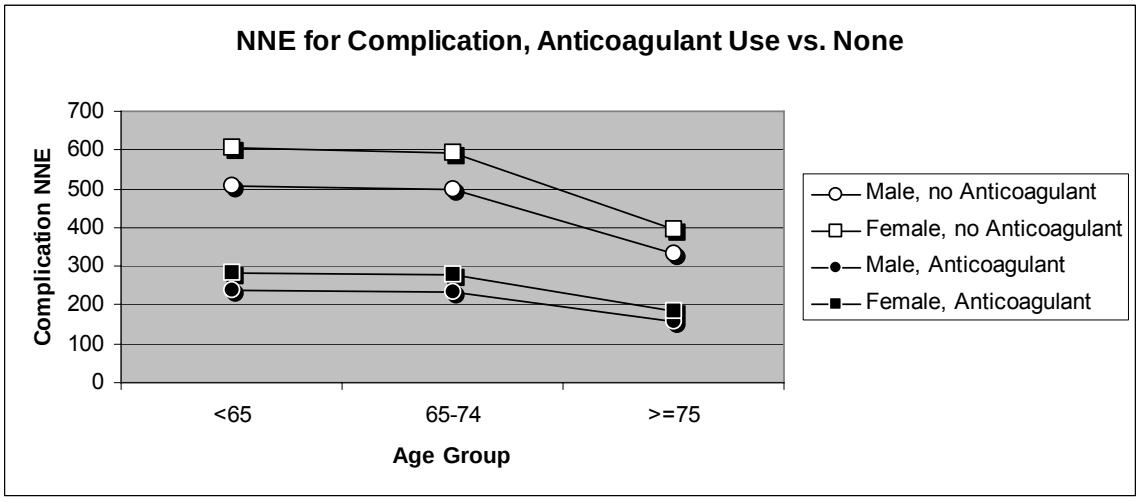


Figure 4

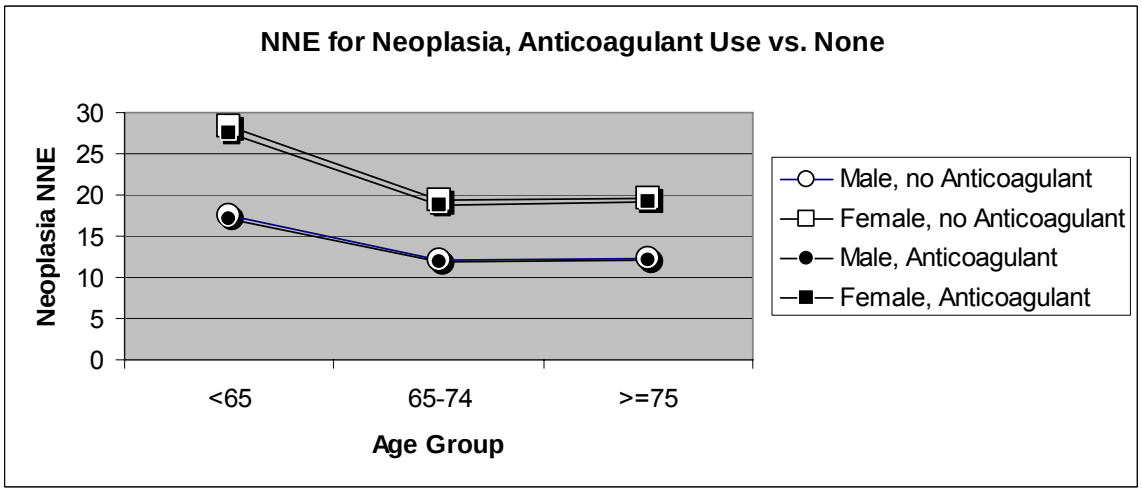


Figure 5

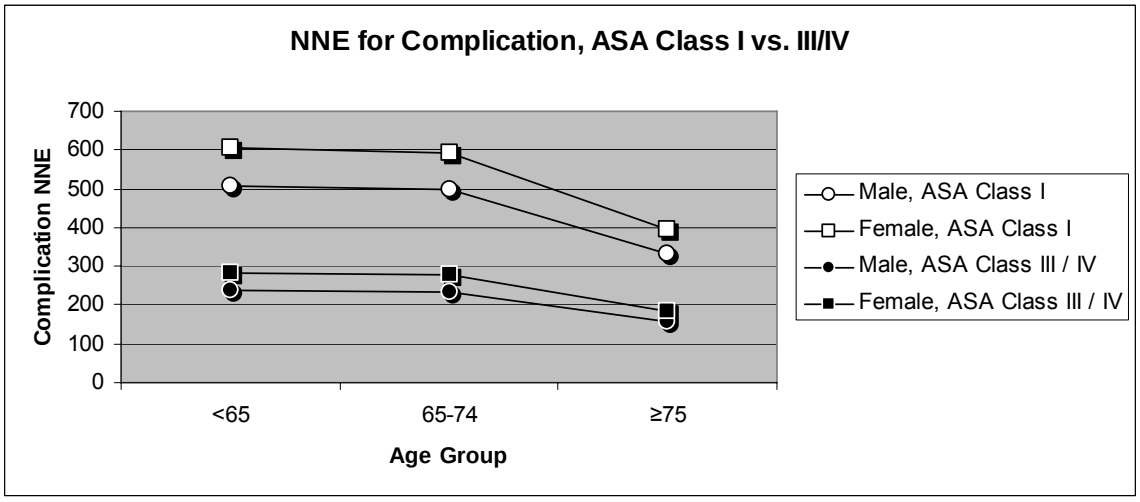
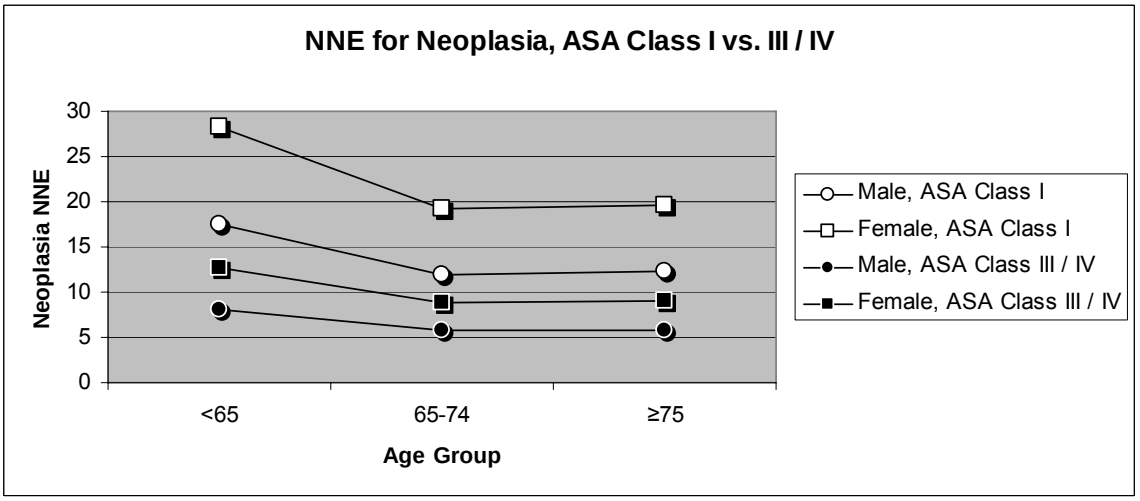


Figure 6



Appendix A

Questions to Ascertain Delayed Complications in CORI

1. Since your colonoscopy, have you had any new abdominal pain? Yes No

If Yes

Where was this pain located?

a. upper right abdomen
b. upper left abdomen
c. lower right abdomen
d. lower left abdomen
e. upper middle abdomen
f. lower middle abdomen
g. all over

How severe was the pain?

a. mild b. moderate c. severe

About what date did the pain start? _____

2. Since your colonoscopy, have you had any new shoulder pain? Yes No

If Yes

Where was this pain located?

a. right shoulder
b. left shoulder
c. both shoulders

How severe was the pain?

a. mild b. moderate c. severe

About what date did the pain start? _____

3. Since your colonoscopy, did you have any new chest pain or a change in your usual pattern of chest pain? Yes No

If Yes

Where was this pain located?

a. right side

b. left side

c. middle

How severe was the pain?

a. mild b. moderate c. severe

About what date did the pain start? _____

4. Since your colonoscopy, did you pass any blood in your stools? Yes No

If Yes

What was the color of the blood?

a. bright red

b. maroon or dark red

c. black

What was the total number of times you passed blood? ____ number

About what date did you start passing blood?

5. Did you have any change in your bowel patterns, such as constipation or diarrhea?

Yes No

If Yes –

What type of change did you have?

a. infrequent stools

b. frequent stools

c. hard stools

d. loose stools

6. Since your colonoscopy, did you have any unexpected visits to a physician or nurse, visit an urgent care clinic or emergency room, or been hospitalized? Yes No

If Yes

Which type of visit did you have?

a. Clinic or physician visit

b. Urgent care or emergency room

c. Hospitalization (>24 hours)

About what date was your visit or hospitalization?

What type of problem were you having?

a. abdominal/belly pain

b. chest pain

c. shoulder pain

d. fever

e. passing blood in stool

f. other. Describe_____.

If hospital admission –

How many days were you in the hospital?

How many days did you spend in an intensive care unit?

7. What were you told was the problem? (choose one or more of the following)

a. hole or tear in my colon

b. bleeding from where a polyp was taken out

c. bleeding from a different place in the intestines

d. infection in the colon (diverticulitis)

e. burn in the lining of the colon where a polyp was taken out (post-polypectomy syndrome)

f. angina/heart pains

g. heart attack

h. stroke or mini-stroke

i. problem with IV site

j. other. Describe:

8. Did you have any blood transfusions after your colonoscopy? Yes No

If yes – how many pints (units) of blood did you receive?

9. Did you have unexpected surgery after your colonoscopy? Yes No

10. Were you taking any of the following medications before your colonoscopy?

a. aspirin- Yes No

b. arthritis or pain medications such as ibuprofen, motrin, aleve, or naproxen – Yes No

c. coumadin or warfarin – Yes No

d. ticlopidine or ticlid – Yes No

e. clopidogrel or plavix – Yes No

f. dipyridamole or persantine – Yes No

If yes –

About what date did you begin taking these medications again after your colonoscopy?

Appendix B

Outcome Frequency

A table examining outcome frequency for both complications and clinically significant neoplasia stratified by the three predictors of interest (age, sex and race) was constructed to examine the feasibility of the analysis plan. In the case of an inadequate number of events for one or more levels of a given variable, levels of the variable were either combined, or the variable was removed from consideration, particularly because it is assumed that at least 5 events must be present in any given cell in order to draw valid conclusions regarding that group.

This was of particular concern with regard to colonoscopic complications. Because so few complications were observed (n = 68), stratifying results even on the three predictors of interest (age, race and sex) led to an inadequate number of events in many cells.

Colonoscopic Complications, by Age, Race and Gender

Race	Gender	Age (years) < 65	65 - 74	75 - 84	≥ 85
American Indian	Female	0	0	0	0
	Male	0	0	0	0
Asian	Female	0	0	0	0
	Male	1	0	0	0
Black	Female	0	1	0	0
	Male	5	0	0	0
Hispanic	Female	0	0	0	0
	Male	1	0	1	0
Multi-Racial	Female	0	0	0	0
	Male	0	0	0	0
White	Female	12	4	7	1
	Male	13	14	8	0
Pacific Islander	Female	0	0	0	0
	Male	0	0	0	0
Unknown	Female	0	0	0	0
	Male	0	0	0	0
Total (n = 68)		32	19	16	1

There are an inadequate number of events for the complication outcome for all

demographic profiles aside from white patients under age 85. Combining the oldest age group with the 75-84 group does not change this conclusion.

With regard to the neoplasia outcome, there are an adequate number of events for all white profiles, all black participants under age 85, and Hispanic and Asian profiles in the youngest (< 65 years) age group. Again, combining the oldest age group with the 75-84 group leaves this conclusion unchanged.

Clinically Significant Neoplasia, by Age, Race and Gender

		Age (years)			
Race	Gender	< 65	65 - 74	75 - 84	≥ 85
American Indian	Female	3	1	0	0
	Male	0	1	1	0
Asian	Female	6	2	0	0
	Male	5	3	2	0
Black	Female	47	17	7	0
	Male	60	27	5	0
Hispanic	Female	5	2	0	0
	Male	7	6	1	0
Multi-Racial	Female	3	0	0	0
	Male	2	0	0	0
White	Female	246	160	87	10
	Male	516	409	201	20
Pacific Islander	Female	0	0	0	0
	Male	1	0	1	0
Unknown	Female	0	0	0	0
	Male	2	0	0	0
Total (n = 1,866)		903	628	305	30

Because there is no clinical justification for combining racial groups (e.g. black vs. white vs. other race), and because this study is designed to be a representative of gastrointestinal endoscopy practice in the United States, we decided to eliminate patient race from consideration in the data analysis.

Disregarding race and combining the ≥ 85 and 75 – 84 age groups into a ≥ 75 group leaves all demographic profiles for both outcomes with adequate numbers of events in order to draw conclusions.

Colonoscopic Complications, by Age and Gender

	Age (years)		
Gender	< 65	65 - 74	≥ 75
Female	12	5	8
Male	20	14	9
Total (n = 68)	32	19	17

Clinically Significant Neoplasia, by Age and Gender

	Age (years)		
Gender	< 65	65 - 74	≥ 75
Female	310	182	104
Male	593	446	231
Total (n = 1,866)	903	628	335