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Frequency of Colonoscopy Surveillance in Average-Risk Adults Relative to Guideline Recommendations

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FREQUENCY OF COLONOSCOPY SURVEILLANCE IN AVERAGE-RISK ADULTS RELATIVE TO GUIDELINE RECOMMENDATIONS

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ABSTRACT

Colorectal cancer (CRC) is the third leading cancer in the United States with an estimated 132,700 new cases and 49,700 deaths in 2015. Well-performed screening colonoscopies prevent cancer by allowing visualization of the entire colon and removal of precancerous polyps (adenomas). Persons with high-risk polyps at screening are therefore advised to undergo periodic surveillance colonoscopy. Screening and surveillance colonoscopy guidelines were updated by the U.S. Multi-society Task Force (USMSTF) in 2006, which emphasized risk stratification by polyp features at screening colonoscopy.

This is a retrospective cohort study of patients with screening colonoscopy at an endoscopy center in South Carolina between September 2001 and February 2010, followed through February 2011. The aims of the study are to: (a) assess the impact of the 2006 USMSTF guidelines on CRC surveillance and re-screening timing, and, (b) identify the predictors of guideline-concordant surveillance colonoscopy recommendations, overuse or underuse.

We compared patients with screening colonoscopy in the pre- and post-2006 periods for appropriate use (surveillance interval as per guideline), overuse (premature relative to guideline) and underuse (delayed or not done). We classified patients by cancer risk, and comparisons were made using chi-square tests, Kaplan-Meier (KM) approach with log-rank test, and multiple regression modeling to identify factors associated with appropriate surveillance.

Of 16,897 study patients, 4,234 had adenomatous polyps (surveillance-eligible), of whom 2,195 (51.4%) had a surveillance colonoscopy, 91.8% with inappropriate surveillance timing. We observed underuse among ≤1-, and 3-year surveillance groups ($p<0.001$), and overuse among 5-year recommended surveillance ($p<0.001$). Among those without adenomas at initial colonoscopy, 14.3% (1,793 of 12,571 pre-period patients) had premature second colonoscopy after a mean of 4.65 years. In multivariate analysis, patients with large adenoma (≥ 10 mm) (OR: 1.81; 95%CI: 1.25-2.63), and ≥2 advanced characteristics (OR: 2.26; 95%CI: 1.30-3.93), and post-guideline period (OR: 1.73; 95%CI: 1.30-2.31) were associated with overuse. Delayed surveillance was more likely in patients with the largest adenoma found in the right colon (OR: 1.49; 95%CI: 1.12-1.98) and Medicaid beneficiaries (OR: 3.22; 95%CI: 1.14-9.09).

Minimizing overuse among low-risk patients will spare provider time for high-risk patients and reduce colorectal cancer incidence at no extra cost.

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CHAPTER 1

INTRODUCTION

This chapter describes background information on colorectal cancer (CRC) and significance of the study objectives. There are four sections: (1) background, (2) objectives, (3) significance of the study, and (4) limitations.

1.1 Background

Colorectal cancer (CRC) is the third leading cancer in the United States with an estimated 132,700 new cases and 49,700 deaths in 2015(ACS, 2015). Incidence and mortality rates vary by gender, age, and race/ethnicity. There has been an annual 4.3% decline in CRC incidence among adults aged over 50, but there has been an increase of 1.8% per year in the below 50-age group from 2007 to 2011(ACS, 2015). Younger CRC patients aged < 40 years typically have more advanced disease, estimated at more than one-tenth of CRC cases (Ahnen et al., 2014; Bailey et al., 2015). However, patients in this age group account for 6.5% of CRC-related deaths (Fairley, Li, Komar, Steigerwalt, & Erlich, 2014; Siegel, Desantis, & Jemal, 2014).

Adenomatous polyps are the most frequent neoplasm found during colorectal screening (Imperiale et al., 2000; Schoenfeld et al., 2005). At least ≥30% of men and ≥20% of women who undergo colonoscopic screening by experienced endoscopists

are found to have ≥ 1 adenomas (Levine & Ahnen, 2006; Rex et al., 2015). Well-performed screening colonoscopies prevent cancer by enabling visualization and removal of precancerous polyps (adenomas). Therefore, the presence of adenomas on the most recent colonoscopy can be an indicator for subsequently advanced adenomas (Imperiale et al., 2014; Laiyemo et al., 2009; Pinsky et al., 2009; Robertson et al., 2009). Screening colonoscopy can achieve 76-90% reduction in CRC incidence and mortality can be reduced by 53-89% after colonoscopic polypectomy (Winawer et al., 1993; Xirasagar et al., 2015; Zauber et al., 2012).

Persons with high-risk polyps at screening are advised to undergo periodic surveillance colonoscopy. Surveillance guidelines have been updated by the U.S. Multisociety Task Force (USMTF) Colorectal Cancer and the American Cancer Society (ACS) in 2006. Risk stratification is a strategy to markedly reduce the intensity of follow-up evaluation in a substantial proportion of patients. The guidelines recommend the following surveillance intervals post baseline screening: 2-6 months for patients with sessile adenomas that are removed piecemeal; at 1 year for patients with hyperplastic polyposis syndrome or > 10 adenomas; at 3 years for patients with 3-10 adenomas, ≥ 1 cm adenoma, or any adenoma with villous features, or high-grade dysplasia; at 5 years for patients with 1 or 2 small tubular adenomas or any adenoma without advanced features; and no surveillance (i.e., resume 10 year screening interval) for patients with small rectal hyperplastic polyps or normal tissues(Winawer et al., 2006).

However, many studies reported that time to re-examination varied in clinical practice (Kahn et al., 2015; Schoen et al., 2010; Sint Nicolaas et al., 2013). Many related factors should be explored, including baseline polyp, patient, and/or colonoscopy

procedure characteristics. A possible reason is that very few data sources are available that are validated to have achieved polyp clearance at surveillance. Most of surveillance studies focused on surveillance use among patients with polyps found at screening examination but not those with no polyps found. (Laiyemo et al., 2009; Morelli, Glowinski, Juluri, Johnson, & Imperiale, 2013; Pinsky et al., 2009; Robertson et al., 2009) . Documenting timely surveillance and the rate of new polyp development may increase the efficiency of surveillance use while decreasing the subsequent risk of cancer for high-risk individuals (de Jonge et al., 2012; Winawer et al., 2006). Therefore, this study explores the relationship between timely surveillance colonoscopy and baseline findings on polyp, patient, and colonoscopy procedure characteristics. It uses secondary data from a endoscopy center which has a documented higher CRC prevention rate than any community-based series documented (Xirasagar et al., 2015).

1.2 Objectives

The aims of the study are to: (a) assess the influence of a change in colorectal cancer surveillance guidelines and to characterize surveillance colonoscopy recommendations after initial screening among patients with a near-complete polyp clearance on colonoscopy at a community-based facility, and, (b) identify the predictors of guideline-concordant surveillance colonoscopy recommendations, as well as those associated with overuse or underuse relative to guidelines.

Using surveillance recommendations and risk stratification to examine the factors in surveillance timing may enable identification of measures to optimize surveillance colonoscopy use at endoscopy centers in the United States. We tested our objectives, using adenoma features (number, size, location, and histology) at initial colonoscopy,

patient characteristics (patient age, gender, race, and insurance status), and guideline date (pre-2006 period, and 2006 and later).

The main study objectives are as follows:

1. To study the timing of surveillance colonoscopy relative to the recommended intervals for patients with an initial colonoscopy in the pre-2006 period vs. 2006 and later.
2. To identify the factors driving the likelihood of guideline-concordant surveillance in a total cohort of patients with an initial colonoscopy.

1.3 Significance of the study

The quality of baseline colonoscopy plays a major role in determining the appropriate postpolypectomy surveillance interval (S. J. Winawer et al., 2006). Therefore, without a good clearing of the colon at initial screening, patients are at increased risk for subsequently advanced neoplasms(Barclay, Vicari, Doughty, Johanson, & Greenlaw, 2006). Following the surveillance guidelines can prevent the disease, and reduce the burdens on medical resources. A large number of patients with adenomas have been diagnosed as a result of the increased use of CRC screening, but adherence to surveillance guidelines remains low. Therefore, the management of surveillance colonoscopy appropriateness is very important.

This study aims to contribute the literature by:

1. Using over 10 years of clinical data on colonoscopy with the near-complete polyp clearance and with nearly completed polyp information for analysis
2. Profiling surveillance in a community-based setting, stratifying risk groups based on baseline adenoma features

3. Determining the influence of a change in the 2006 guidelines for surveillance colonoscopy on actual practice
4. Identifying the predictors at initial colonoscopy that predict guideline-concordance: adenoma features (number, size, location, or histology), patient characteristics (gender, age, race, and insurance status), and guideline date.

1.4Limitations

There are some study limitations associated with the data characteristics and study design compared to other studies in the literature.

1. The clinical dataset comes from a single endoscopy center in South Carolina. Therefore, the findings may not generalize to the US or other endoscopy centers.
2. The retrospective study design entails some loss to follow-up because some patients may have chosen to undergo surveillance colonoscopy at other facilities. It also precludes understanding the extent to which selection bias affects the composition of the study cohort.
3. In the case of multiple polyps within one clinical segment sent for pathology examination in a single jar, the pathology report may not have clearly identified the number of polyps with different histology features.
4. The clinical dataset does not document information about a family history of CRC or comorbidities. Those factors are also important because they may contribute to potential overuse or underuse of surveillance colonoscopy.

CHAPTER 2

LITERATURE REVIEW

This chapter includes 6 sections on colorectal cancer (CRC), including disease background, strategies for CRC prevention, surveillance guidelines, and management, colonoscopy quality indicators, patient characteristics affecting colonoscopy performance, and prediction of adenoma recurrence. Finally, the current research and gaps in research will be identified based on literature findings.

2.1 Colorectal cancer (CRC)

This section summarizes the background on CRC, including symptoms and risk factors, incidence and mortality, prevention methods, recommended prevention guidelines, utilization of CRC screenings, and barriers to CRC screenings.

2.1.1. Definition of colorectal cancer (CRC)

Colorectal cancer is cancer affecting the colon or rectum, and can be referred to separately as colon or rectal cancer, depending on where it is located. Most colorectal cancers develop very slowly over several years. Before cancer develops, the growth of the tissue or tumor usually begins as a non-cancerous polyp in the inner surface of the colon and rectum that may change into cancer. Certain kinds of polyps, called adenomatous polyps or adenomas, occur in 30 to 50 % of adults and can be completely and safely removed to prevent cancer. Fewer than 10% of adenomas will develop to

cancer (Levine & Ahnen, 2006). At least 25% of men and 15% of women who undergo a colonoscopic screening by experienced endoscopists are found to have one or more adenomas (ACS, 2014; Winawer et al., 2006).

A polyp can be of two types: (1) non-adenomatous lesions (hyperplastic polyps) and (2) adenomatous lesions (lesions composed of tubular and/or villous structures showing intraepithelial neoplasia). Adenomas are classified as (1) non-advanced adenomas (small, tubular adenomas) and (2) advanced adenomas (10mm in diameter or larger, presence of high-grade dysplasia (including carcinoma-in-situ), or greater than 25% villous or tubulovillous features). CRC is diagnosed when the invasion of malignant cells through the muscularis mucosa has taken place. Advanced colorectal neoplasia is defined as lesions that are either benign advanced adenomas or invasive cancer (ACS, 2014; Martinez et al., 2009; Tholoor, Tsagkournis, Basford, & Bhandari, 2013; Winawer & Zauber, 2002).

2.1.2. Incidence and mortality

CRC is the third leading cancer in both men and women in the United States, an estimated 132,700 new cases and 49,700 deaths are expected in 2015(ACS, 2015) . In South Carolina during 2015, an average of 2,130 adults is diagnosed and 840 adults die from CRC(Siegel, Miller, & Jemal, 2015). Incidence and mortality rates vary by gender, age, and race/ethnicity. From 2007 to 2011, there has been an annual 4.3% decline in CRC incidence among adults aged over 50. However, there has been a concurrent 1.8% annual increase in the below 50-age group, which is expected to amount to a 28-46% increase in this age group by 2030(ACS, 2015; Bailey et al., 2015). Younger CRC patients aged < 40 years typically present with more advanced disease, and younger CRC

patients account for more than one-tenth of CRC cases (11% of colon cancers and 18% of rectal cancers)(Ahnen et al., 2014; Bailey et al., 2015). However, patients in this age group account for 6.5% of CRC-related deaths. By gender and race, CRC incidence and mortality rates among men are 30% and 40% higher than in women, and 25% and 50% higher among blacks than in whites(Siegel et al., 2014).

2.1.3. Signs and symptoms

Screening is important to prevent the disease and detect CRC early because adenomas and early stage CRC have no symptoms. There are few than 10% of CRCs begin as polyps (Levine & Ahnen, 2006). Symptoms may include bleeding from the rectum, blood in the stool or in the toilet after having a bowel movement, having dark or black stools, a change in the shape of the stool, cramping pain in the lower stomach, a feeling of discomfort or urge for bowel movement when there is no need to have one, recent onset of constipation or diarrhea that lasts for more than a few days, and unexplained weight loss (ACS, 2015).

2.1.4. Risk factors

A risk factor is defined as anything that affects the chances of developing CRC that may increase or decrease the likelihood of colorectal polyps or cancer. The risk of CRC increases with age: about 90% of cases are diagnosed in adults aged 50 or older (Siegel et al., 2014). Hereditary factors also play a role, including family history of CRC or adenomatous polyps. About 5% of CRCs are associated with well-defined inherited syndromes, such as Lynch syndrome and familial adenomatous polyposis (FAP) (Jasperson, Tuohy, Neklason, & Burt, 2010). These conditions cause cancer typically at a younger age. About 25% of adults who develop CRC have family members who have

been affected by the disease without a defined inherited syndrome (Jasperson et al., 2010). Personal medical factors associated with increased cancer risk include a personal history of colorectal polyps or CRC, inflammatory bowel disease, or history of other cancers. Lifestyle-related factors also play an important role such as obesity, physical inactivity, smoking, dietary factors, and alcohol use(ACS, 2014).

2.2 Colorectal cancer (CRC) prevention and screening recommendations

This section describes common CRC screening types and recommended guidelines for different risk groups, the rationale for screening guidelines, screening examinations that can find colorectal polyps and cancer, screening recommendations, and utilization and barriers of CRC screening.

2.2.1. Background of CRC screening

Over several decades, CRC screening methods have improved significantly and can prevent cancer effectively. In the early years, the screening guidelines were reviewed and approved by the Practice Parameters Committee of the American College of Gastroenterology (ACG) and by the ACG Board of Trustees. It was also the first organization to recommend colonoscopy as the preferred screening tool to prevent CRC. In 2006, the guidelines were revised by a joint committee of the USMSTF and the ACS, and then again revised in 2008 in partnership with the American College of Radiology (Rex et al., 2009; Winawer et al., 2006).

The guidelines draw a distinction between screening tests that primarily detect cancer after it has developed (e.g., stool tests), and those that are more likely to detect both cancer and precancerous growths. The latter are called structural examinations that

visualize the growths. These include the flexible sigmoidoscopy, colonoscopy, CT colonography, and double-contrast barium enema (Levin et al., 2008). The screening recommendations emphasize that cancer prevention should be a main goal of screening. Thus, regular colorectal cancer screening is one of the most powerful weapons for preventing CRC because it is a process of looking for pre-cancer in adults who have no symptoms, as well as in adults with symptoms of CRC and other digestive diseases.

Despite many options for CRC screening, the screening rates remained low. There are 65% of US adults had CRC screening, which are lower than the target of 80% by 2018 (CDC, 2013; Meester et al., 2015). Thus, the preferred strategy emphasizing the use of colonoscopy in CRC screening recommendation has been replaced by the "menu of options" approach (Rex et al., 2009). The U.S. Preventive Services Task Force (USPSTF) recommends routine screening from this "menu" including colonoscopy, flexible sigmoidoscopy, and fecal blood test (FOBT or FIT). It recommends 10-year for colonoscopy, 5-year for flexible sigmoidoscopy, and 1-year for FOBT or FIT (CDC, 2013; USPSTF, 2008).

2.2.2. Tests that can detect both colorectal polyps and cancer

There colorectal cancer screening can visualize the colon physically to find abnormal areas. It can be done with an endoscope inserted through the rectum or by special imaging (x-ray) tests. Polyps found can be removed by endoscopy before they become cancerous. Therefore, these tests are the preferred tools for polyps and cancer detection. Table 2.2.1 shows the comparative features and advantages/ disadvantages of the widely used screening methods.

(1) Colonoscopy

A colonoscope is similar but more complex than a sigmoidoscope; it is, longer and can be used to examine the entire length of the colon and rectum than a sigmoidoscope. A high-quality of bowel preparation by thorough cleaning is required for the physician to view the colon clearly. It involves taking medication that causes diarrhea, and then to empty the colon. The medication is taken by mouth, and comes in liquid or tablet form (ASGE, 2016). Moreover, sedation is usually provided during the examination to minimize discomfort (Levin et al., 2008). If a polyp is found, it may be removed by passing a wire loop through the colonoscope either to cut the polyp from the wall of the colon (via hot or cold biopsy) or destroy it in place using an electric current (ACS, 2011). This may be done in a hospital outpatient department, clinic, or physician's office (ACS, 2014).

Since colonoscopy has the advantage of detecting polyps throughout the entire colon and rectum, it has become the most commonly recommended strategy to prevent the disease (Rex et al., 2009). Screening colonoscopy can reduce the incidence of CRC by 67-83% and CRC mortality by 65-89% (Kahi, Imperiale, Juliar, & Rex, 2009; S. J. Winawer et al., 1993; Xirasagar et al., 2015; Zauber et al., 2012) . A reduction in the incidence of CRC is documented at 76-90%, with 53% reduction in mortality by colonoscopic polypectomy (Winawer et al., 1993; Zauber et al., 2012).

(2) Flexible sigmoidoscopy

Flexible sigmoidoscopy is used to visualize part of the colon and rectum with a flexible sigmoidoscope. Using the sigmoidoscope, the doctor can view the inside of the rectum and the left part of the colon to detect any abnormality and remove polyps.

Because this scope is only 60 cm long, the doctor can see the entire rectum but less than half of the colon. Simple bowel preparation is needed before the test and the procedure is typically performed without sedation. However, this test may be uncomfortable because of the air injected into the colon. If a pre-cancerous adenoma or colorectal cancer is found, the patient needs to be referred for a colonoscopy so that the entire colon can be examined (ACS, 2011, 2014).

This test can detect 17.3% of adenomas, achieves 33-45% CRC prevention and reduces CRC mortality by 43% (Atkin et al., 2010; Brenner, Chang-Claude, Seiler, Sturmer, & Hoffmeister, 2007; Holme et al., 2014). Cancer prevention is increased to 50-55% when a sigmoidoscopy with abnormal findings is followed by a colonoscopy (Brenner et al., 2007).

2.2.3. Tests that mainly find colorectal cancer

These types of test examine the stool for secondary signs of cancer such as bleeding or shedding of cells and are less invasive and easier to conduct. However, positive results on one of these screening tests will require an invasive test such as a colonoscopy to find the lesions (Table 2.2.1).

The fecal occult blood test (FOBT) is a widely-used test because it is approximately equally effective in life-years gained when done regularly annually, comparable to colonoscopy and sigmoidoscopy. Use of annual high-sensitivity FOBT (sensitivity for cancer 70%) has a false-positive rate less than 10% (specificity >90%) (USPSTF, 2008; Zauber et al., 2008). The idea behind this test is that blood vessels at the surface of larger colorectal polyps or cancers are often fragile and easily damaged by the passage of feces. The damaged vessels usually release a small amount of blood into the feces, however,

rarely enough to be visible in the stool. In addition, the FOBT kit can be obtained from a health care provider for use at home. It is used to find occult blood which cannot be seen with the naked eye in feces, but which can be detected in the stool through a chemical reaction. Some foods or drugs may affect the test, so patients require a physician's advice on diet and medication before the examination. If the test is positive, a colonoscopy will be needed to find the reason for the bleeding (ACS, 2014).

An annual FOBT can reduce CRC by 20% by detecting cancer or a polyp early, resulting in their subsequent removal by colonoscopy(Mandel et al., 2000). In terms of mortality, it reduces approximately 15% of CRC deaths (Hardcastle et al., 1996; Scholefield, Moss, Sufi, Mangham, & Hardcastle, 2002). See Table 2.1.

2.2.4. Screening recommendations

The USPSTF and ACG have recommended CRC screening guidelines for different risk groups. For average-risk individuals, CRC screening should begin at age 50. Average-risk persons are those without a family history of colorectal neoplasia, except average risk African Americans (AAs) who should begin screening at age 45 (Rex et al., 2009; USPSTF, 2008) . However, adults after 75 years of age do not need to take routine screening because the potential benefits of screening may be outweighed by the harms and other competing causes of mortality (USPSTF, 2008). Regarding test characteristics, the different CRC tests have different time intervals for follow-up screenings: colonoscopy every 10 years, sigmoidoscopy every 5 years, and FOBT (or FIT) every year.

Conversely, high-risk groups should have intensive screening. High-risk groups are those with a family history of multiple relatives affected by CRC, FAP, and Hereditary Non-Polyposis Colorectal Cancer (HNPCC). A person with a first-degree relative with

CRC or advanced adenoma (adenoma ≥1cm in size, or with high-grade dysplasia or villous elements) diagnosed after 60 years of age should have a colonoscopy every 10 years beginning at age 50 years. For those with relatives diagnosed before 60 years of age or having multiple first-degree relatives with CRC or advanced adenomas should have a colonoscopy every 5 years beginning at age 40, or 10 years younger than the age at which the youngest affected relative was diagnosed (Rex et al., 2009).

2.2.5. Utilization and barriers of CRC screening

The prevalence of CRC screening in the general population has been steadily increasing since 2000. In the United States, the CRC screening rate increased 15.5% between 2005 and 2013 (Smith et al., 2015). The percent of the population that is up-to-date with CRC screening has also increased from 42.5% in 2000 to 58% in 2010(T. F. Imperiale et al., 2014; Seeff et al., 2004; J.A. Shapiro et al., 2012; J.A. Shapiro et al., 2008). Another population-based survey identified 65% of US adults had CRC screening within the recommended time in 2012 (CDC, 2013).

Despite rising CRC screening rates, screening completion rates are still significantly lower than the target of 80% by 2018 set by the National Colorectal Cancer Screening Roundtable (Meester et al., 2015). Well-established barriers to colorectal cancer screening include lack of health insurance, low education levels, low income, without routine doctor's visits, and inadequate communication between physicians and patients (CDC, 2013; Doubeni, Laiyemo, Klabunde, et al., 2010; Doubeni, Laiyemo, Young, et al., 2010; Ioannou, Chapko, & Dominitz, 2003; Klabunde et al., 2011; Seeff et al., 2004; Shapiro et al., 2012; Shapiro et al., 2008).

Table 2.1 Advantages and disadvantages of the widely used screening methods: flexible sigmoidoscopy, colonoscopy, and FOBT

Screening	Advantages	Disadvantages	Screening interval*	Prevention rate
Flexible sigmoidoscopy	• Fairly quick • Few complications • Minimal bowel preparation • Minimal discomfort • Sedation or a specialist needed	• Views only 1/3 colon • Cannot remove large polyps • Small risk of infection or bowel tear • Colonoscopy necessary if positive findings	5 years	33-45%
Colonoscopy	• Examine entire colon • Can biopsy and remove polyps • Can diagnose another disease • Required for positive findings by all other tests • Highly sensitive • Less frequent interval	• May miss some polyps or cancer • Full bowel preparation needed • Expensive • Bowel tears or bleeding • Patient may miss a day of work	10 years	67%
FOBT	• No bowel preparation • Sampling is done at home • Low cost • Noninvasive	• Multiple stool samples needed • Miss most polyps and some cancers • Have false-positives results • Colonoscopy necessary if positive findings	1 year	20%

Abbreviations: FOBT, fecal occult blood test.
*Time intervals for these CRC screenings are for the average-risk population.

2.3 Surveillance management and rationale for the recommendations

This section describes the purpose of surveillance screening, the role of adenomatous polyps in surveillance management, and some evidence related to the rationale of the guidelines and predictors for surveillance behaviors.

2.3.1. Purpose of surveillance management

Patients who've had a CRC removed are at risk for recurrent cancer and metachronous neoplasms in the colon, which are the main reasons that surveillance is needed. However, many patients with low-risk adenomas found at initial colonoscopy are more likely to have early surveillance colonoscopy (Schoen et al., 2010; Sint Nicolaas et al., 2013). This places a huge burden on medical resources applied to surveillance. The efficiency of surveillance colonoscopy can decrease the cost and risk of resources for unnecessary examinations. Thus, USMSTF and ACS updated joint guidelines on postpolypectomy and postcolorectal cancer resection surveillance in 2006, trying to shift some available resources from surveillance purposes to screening (Rex et al., 2006; Winawer et al., 2006).

There are two fundamental goals of surveillance of patients with cancer or a history of polyps. One goal is the detection of early recurrences of the initial primary cancer at an early stage, and another is the detection of metachronous colorectal neoplasms. The most important purpose is to resect synchronous adenomas missed during the initial colonoscopy (Bond, 2000; Rex et al., 2006). However, it is not always beneficial to those patients when they have a colonoscopy annually because of the huge burden on medical resources (Rex et al., 2006). The cumulative burden of subsequent surveillance

colonoscopies on the health care system becomes substantial and should be well established.

2.3.2. Roles of adenomas and serrated lesions

There are two major classes of lesions: polyps and serrated classes of colorectal adenomas. The best-known class is adenomatous polyps (adenomas). It may be characterized pathologically as high or low-grade dysplasia, tubular, or villous. Adenomas with those features are widely understood to be premalignant lesions, particularly at risk for increasing in size, acquiring high-grade dysplasia features, or villous elements (Vogelstein et al., 1988). Another class of colorectal lesions is distinct from adenomas, called serrated lesions. It includes 3 major subtypes termed as (1) hyperplastic polyp (HP), (2) sessile serrated adenoma/polyp (SSA/SSP), and (3) traditional serrated adenoma (TSA) (Snover, Ahnen, & Burt, 2010). Only HPs of serrated classes have the potential for malignancy.

Because all adenomas are dysplastic in contrast to serrated lesions, which are generally non-dysplastic, adenoma detection rates (ADRs) have become the most important quality indicators in colonoscopy performance (Hewett, Kahi, & DK., 2010; Hewett & Rex, 2010; Rex et al., 2015). Adenomatous polyps are the most common neoplastic findings in adults who have a colorectal screening or diagnosed symptoms, the characteristics of which can be a marker to determine risk level (Lieberman et al., 2012; Rex et al., 2006; Winawer et al., 2006). These adults still have a lifelong risk of subsequent adenomas and colorectal cancers despite adequate polypectomy (Blumberg, Opelka, Hicks, Timmcke, & Beck, 2000; Marae & Williams, 1982; Waye & Braunfeld, 1982). Surveillance colonoscopy to detect subsequent neoplasms has therefore become

the standard of care for those patients, particularly for these with advanced adenomas (Blumberg et al., 2000; Levine & Ahnen, 2006; Lieberman et al., 2007).

The presence of low- or high- risk adenomas determines the recommended surveillance interval. The presence of an advanced adenoma is adopted as an outcome measure requiring early surveillance tests because there are more associations with cancer development. Advanced adenomas can be a surrogate biological indicator of cancer risk (Winawer et al., 2006; Winawer et al., 1993; Zauber et al., 2012). However, the true rate of polyp recurrence is unknown since polyps detected during follow-up examinations may be cumulative (missed at the previous examination), or could be new polyp growth. The estimated miss rate for HPs is 31% versus 20% for adenomas, while miss rates for serrated lesions may be higher than for adenomas (Heresbach et al., 2008). Missed lesions may also have occurred among patients with interval CRCs (86%) (le Clercq et al., 2014). Despite missed adenomas leading to cancer, adults with serrated lesions or an advanced adenoma are shown to have a higher risk of neoplasia at follow-up (Schreiner, Weiss, & Lieberman, 2010). Appropriate follow-up screening thus becomes imperative.

2.3.3 .Surveillance methods and recommendation

A colonoscopy is a common tool for surveillance of previously developed polyps or cancers: about 24% of all colonoscopy patients and 22% of patients aged ≥ 50 years had a colonoscopy for surveillance purpose (Lieberman, De Garmo, Fleischer, Eisen, & Helfand, 2000; Lieberman, Holub, Eisen, Kraemer, & Morris, 2005). In the 1970s to early 1990s, physicians commonly recommended annual follow-up colonoscopies following all polypectomies despite there were no guidelines providing guidance on this issue (Rex et al., 2006). In order to reduce resource utilization and improve the efficiency of examination, the guidelines are continuously updated by new evidence. The results of the National Polyp Study in 1993 led to the recommendation that the first postpolypectomy examination should be done 3 years after polypectomy for most patients with large (>10mm) or multiple adenoma, published by a gastrointestinal consortium in 1997. In 2003 and 2006 the guidelines were updated, and colonoscopy is now the only follow-up examination recommended because it is the most effective tool to prevent disease (Winawer et al., 2003; Winawer et al., 2006). The 2006 guidelines are shown in Table 2.2.

Since 2006, researchers have focused on the histology and number of polyps detected, the risk of interval CRC, CRC found in the proximal colon, and the role of serrated polyps (Lieberman et al., 2012; Winawer et al., 2006). In 2012, the 2006 guidelines were reaffirmed based on stronger evidence and refined features based on risk stratification principles. Specifically, the researchers updated their recommendations for follow-up exams following a finding of no polyp, 1-2 small tubular adenomas, 3-10 tubular adenomas, one or more tubular adenomas (≥ 10 mm), or one or more villous

adenomas at baseline examination (Lieberman et al., 2012). An update of the 2012 USPSTF and ACS surveillance guidelines is currently under progress.

Individuals are recommended a 10-year follow-up colonoscopy if they have small rectal hyperplastic polyps or hyperplastic polyps without advanced features, considered normal. A 5 to 10-year follow-up is recommended when they have only 1 or 2 small (< 1cm) tubular adenomas with only low-grade dysplasia. A 3-year follow-up is recommended when they have 3 to 10 adenomas, any adenoma ≥ 1 cm, any adenoma with villous features or high-grade dysplasia, any sessile serrated polyp ≥ 1 cm, any size of the sessile serrated polyp with high-grade dysplasia, or a traditional serrated adenoma (TSA). The TSA are a type of colorectal polyp with neoplastic potential. It is a rare lesion located primarily in the left colon and rectum, and the only member of the serrated class that is uniformly dysplastic (Chetty, Hafezi-Bakhtiari, Serra, Colling, & Wang, 2015). If the follow-up colonoscopy is normal or shows only 1-2 small tubular adenomas with low-grade dysplasia, then the interval should be 5 years. The shorter (<3 years) interval is recommended when they have > 10 adenomas at the screening examination. A 2 to 6-month follow-up is recommended if they had sessile adenomas removed piecemeal. People with serrated polyposis syndrome should have surveillance colonoscopy at a 1-year interval. The intensive surveillance is indicated when the family history may indicate HNPCC, which is recommended every 2 years follow-up beginning at age 20-25 years until age 40 years, and then annually (Lieberman et al., 2012; Winawer et al., 2003; Winawer et al., 2006). The time intervals of surveillance colonoscopy by index polyp characteristics are summarized in Table 2.3 and Figure 2.1.

2.3.4 .Adherence to surveillance screening

The importance of optimal surveillance colonoscopy consistent with recommendations is to achieve higher ADRs in contrast to over-utilization of procedures (Sint Nicolaas et al., 2013). Although recent evidence supports that colonoscopic polypectomy reduces subsequent colorectal cancer incidence, adherence to surveillance guidelines is variable with reports of overutilization in the low-risk groups and underutilization in high-risk groups. Over 50% of early surveillance colonoscopies were conducted for low-risk populations (Mysliwiec, Brown, Klabunde, & Ransohoff, 2004). Another clinical trial followed participants for 5 years and demonstrated overuse of surveillance among low-risk adults and underuse among high-risk adults. For example, approximately 70-80% of low-risk adults underwent surveillance screening at 3-4 years (Schoen et al., 2010). Medicare beneficiaries who underwent colonoscopy with polypectomy (<50% received surveillance) also reported underuse of follow-up colonoscopy at 5 years, but >30% of the follow-up colonoscopies were overused in adults without any polyp (Cooper, Kou, Barnholtz Sloan, Koroukian, & Schluchter, 2013).

Other studies from other countries reported consistent findings: around 20-30% of surveillance colonoscopies were consistent with the guidelines (Schreuders et al., 2013; van Heijningen et al., 2015). However, Menees et al and Kahn et al reported ≥ 75 % higher adherence to surveillance recommendations (Kahn et al., 2015; Menees, Elliott, Govani, Anastassiades, & Schoenfeld, 2014).

These findings can provide directions for closer surveillance colonoscopies after initial examination among high-risk individuals, and longer periods between follow-ups among low-risk individuals (Ahnen et al., 2014; Morelli et al., 2013). For adults with

potential missed adenomas found in the proximal colon, more frequent follow-up examinations may helpful (Nakao, Fassler, Sucandy, Kim, & Zebley, 2013).

2.3.5. Factors are associated with surveillance behaviors

Several demographic characteristics such as race, age, and smoking behavior, are associated with behaviors using surveillance colonoscopy. Black or other race, older age groups (65-plus years), and past or current smokers were less likely to have repeat examinations (Rolnick et al., 2005; Weissfeld et al., 2002). Of patients with screening colonoscopy who had Medicare coverage, about 42.5% had early repeat examinations. Black adults who had their procedures performed by surgeons or experienced colonoscopists also underwent early examinations (Goodwin, Singh, Reddy, Riall, & Kuo, 2011). However, Kahn et al reported different findings: patients aged >65 years or with incomplete polyp resection had higher guideline-concordant surveillance(Kahn et al., 2015). A possible explanation for this behavior is a lack of knowledge of guidelines by providers: around 76% of physicians are documented to disagree or ignore guidelines (Kruse, Khan, Zaslavsky, Ayanian, & Sequist, 2015; S. D. Saini, Nayak, Kuhn, & Schoenfeld, 2009).

Table 2.2 2006 U.S. Multi-Society Task Force guidelines for surveillance colonoscopy[*]

Colorectal neoplasm characteristics and surveillance recommendations
Patients with small rectal hyperplastic polyps should be considered to have normal colonoscopies, and therefore the interval before the subsequent colonoscopy should be 10 years; an exception is patients with a hyperplastic polyposis syndrome[**]; they are at increased risk for adenomas and colorectal cancer and need to be identified for more intensive follow-up evaluation
Patients with only 1 or 2 small (<1 cm) tubular adenomas with only low-grade dysplasia should have their next follow-up colonoscopy in 5–10 years; the precise timing within this interval should be based on other clinical factors (such as prior colonoscopy findings, family history, and the preferences of the patient and judgment of the physician)
Patients with 3 to 10 adenomas, or any adenoma <1 cm, or any adenoma with villous features, or high-grade dysplasia should have their next follow-up colonoscopy in 3 years providing that piecemeal removal has not been performed and the adenoma(s) are removed completely; if the follow-up colonoscopy is normal or shows only 1 or 2 small tubular adenomas with low-grade dysplasia, then the interval for the subsequent examination should be 5 years
Patients who have more than 10 adenomas at 1 examination should be examined at a shorter (<3 y) interval, established by clinical judgment, and the clinician should consider the possibility of an underlying familial syndrome
Patients with sessile adenomas that are removed piecemeal should be considered for follow-up evaluation at short intervals (2–6 mo) to verify complete removal; once complete removal has been established, subsequent surveillance needs to be individualized based on the endoscopist's judgment; completeness of removal should be based on both endoscopic and pathologic assessments
More intensive surveillance is indicated when the family history may indicate HNPCC

[*]Reference: Winawer et al (2006). Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the U.S. Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. CA Cancer J Clin. 2006;56(3):143-59.

[**]Hyperplastic polyposis was defined by Burt and Jass for the World Health Organization International Classification of Tumors as: (1) at least 5 histologically diagnosed hyperplastic polyps proximal to the sigmoid colon, of which 2 are greater than 1cm in diameter, or (2) any number of hyperplastic polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with hyperplastic polyposis, or (3) more than 30 hyperplastic polyps of any size distributed throughout the colon. Studies have found an increased risk for colorectal cancer in these patients (Burt & Jass, 2000).

Table 2.3 Up-to-date guidelines for surveillance colonoscopy, 2012 guidelines

Colorectal neoplasm characteristics	**Time interval (years)**
Hyperplastic polyps (no adenomas) Small (< 10 mm) rectal or sigmoid hyperplastic polyps	10
1 or 2 tubular adenomas (< 1 cm)	5-10
Small SSP (<10 mm) without dysplasia	5
≥3 adenomas Any adenoma ≥10 mm Any adenoma with villous features High-grade dysplasia SSP≥10 mm SSP with dysplasia TSA	3
>10 adenomas	<3
Serrated polyposis syndrome*	1

Abbreviations: SSP, Sessile serrated polyp; TSA, Traditional serrated adenoma.

*Based on the World Health Organization definition of serrated polyposis syndrome, with one of criteria: (1) at least 5 serrated polyps proximal to sigmoid, with 2 or more ≥ 10 mm; (2) any serrated polyp proximal to sigmoid with family history of serrated polyposis syndrome; and (3) >20 serrated polyps of any size throughout the colon.

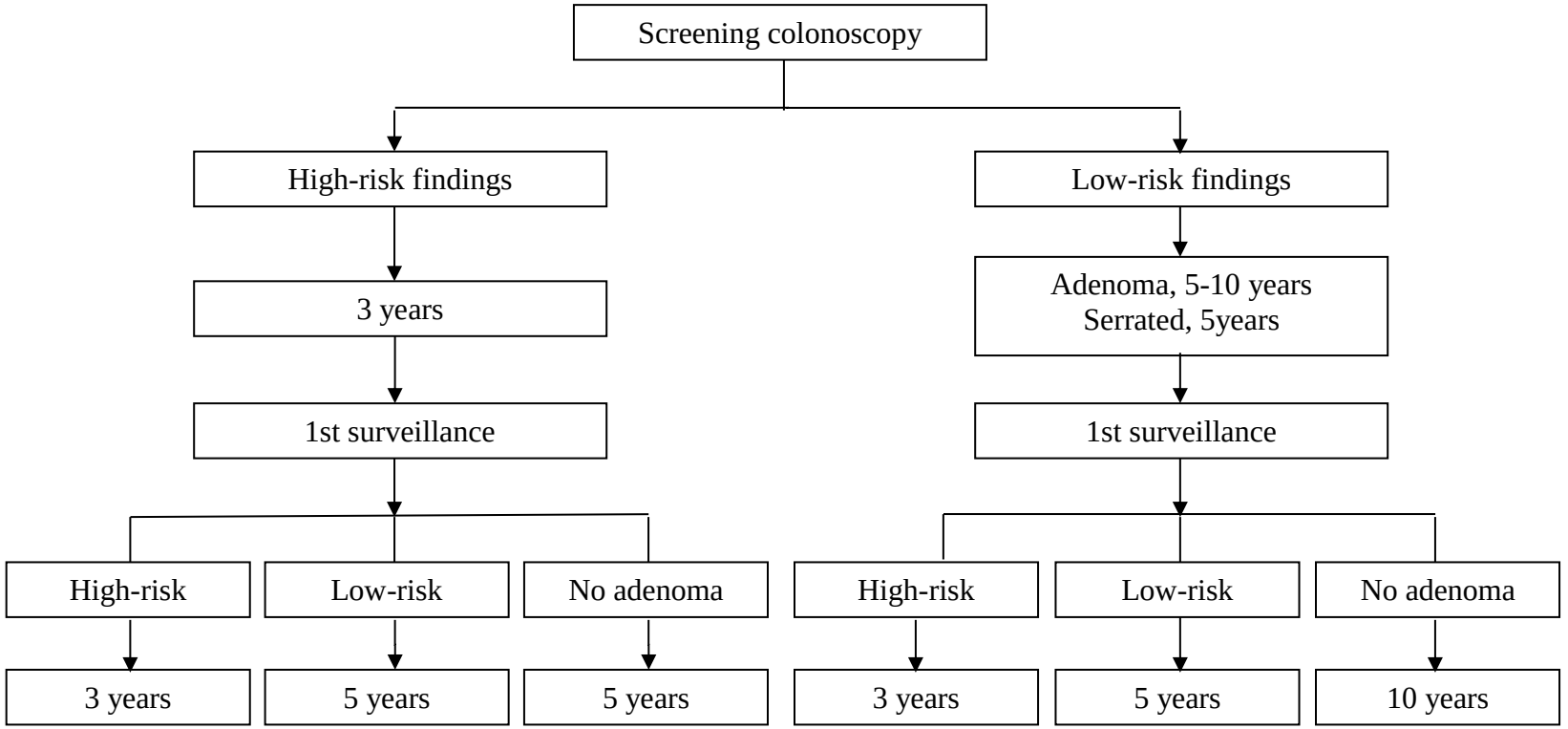

Figure 2.1 Time intervals to surveillance colonoscopy by polyp status at index colonoscopy. *High-risk findings are defined as ≥3 adenomas, any adenoma ≥10 mm, any adenoma with villous features, high-grade dysplasia, SSP≥10 mm, SSP with dysplasia, or TSA. Low-risk findings are defined as hyperplastic polyps, small (< 10 mm) rectal or sigmoid hyperplastic polyps, and small SSP (<10 mm) without dysplasia. Abbreviations: SSP, Sessile serrated polyp; TSA, Traditional serrated adenoma.

2.4 Quality indicators of colonoscopy and patient characteristics associated with colonoscopy findings

This section describes evaluation methods for improving the quality of colonoscopies. Many indicators are documented to measure the CRC screening performance, including interval CRC rates, serrated polyp detection rates, adenomatous polyps (adenoma detection rates), procedure indicators, endoscopist factors, and patient characteristics.

2.4.1. Quality of colonoscopy

Colonoscopy is the most effective screening tool to prevent CRC because it allows colonoscopic removal of polyps (Rex et al., 2009). However, the effectiveness of surveillance colonoscopy intervals assumes that high-quality examination was performed at screening and later colonoscopy. Failure of colonoscopy to consistently detect existing adenomas or other precursors of CRC is threatening the effectiveness of colonoscopy for the prevention of CRC. Good quality of colonoscopy with near-complete can prevent > 80% of early and advanced CRCs for detection of early CRCs (Xirasagar et al., 2015).

The American Society for Gastrointestinal Endoscopy (ASGE) and American College of Gastroenterology (ACG) published measures for reporting endoscopic performance in 2006 (Rex et al., 2009), including pre-procedure, intra-procedure, and post-procedure measures. Pre-procedure represents nontechnical aspects of colonoscopy, such as the use of recommended surveillance intervals. Intra-procedure focuses on technical aspects of colonoscopy, such as bowel preparation, cecal intubation rate, adenoma detection and histology, and the provider's experience (Lee, Levin, & Corley, 2013). Colonoscopic complications post-procedure are also measured for quality purposes (Hewett et al., 2010; Hewett & Rex, 2010).

Overall, the adenoma detection rate (ADR) is always the priority indicator to measure colonoscopy performance. Consideration of other indicators together is needed for detecting subsequent adenomas because each indicator may be associated with others. Although patient characteristics do not directly affect the quality of performance, it may be necessary to adjust for them to account for patient mix complexity.

2.4.2. Interval CRC

Interval CRC is defined as CRC diagnosed in the time interval between an initial and surveillance colonoscopy (Fayad & Kahi, 2014). After the first colonoscopy, patients with adenomas receive follow-ups with surveillance guidelines to identify and remove subsequent adenomas before they develop into cancer. However, colonoscopy is not always perfect, and thus interval cancers might be diagnosed between surveillance colonoscopies (Leung et al., 2010). Approximately 54- 79% of CRC patients had potential CRC at the screening or surveillance colonoscopy. The reason might relate to incomplete removal or missed cancer at prior examinations (Pabby et al., 2005; Robertson et al., 2005). About 78% of person with a history of an advanced adenoma also had a higher risk of developing cancer (Leung et al., 2010). Therefore, interval check-ups may potentially prevent cancer by improving the baseline quality of colonoscopy and can be considered a "silver standard" for performance measurement (Fayad & Kahi, 2014).

2.4.3. Serrated polyps

Non-neoplastic polyps have no malignant potential, including hyperplastic polyps (HPs) and inflammatory polyps. However, recent studies identified serrated polyps which are characterized by a saw-toothed (serrated) appearance of the crypt epithelium and may

have malignant potential. By histologic features, it can be classified as HPs, traditional serrated adenomas (TSAs), or sessile serrated adenomas (SSAs). These polyps are difficult to detect at endoscopy because they show the same color as the surrounding colonic mucosa may not be elevated and also may have a layer of adherent mucus which obscures the vascular pattern. It may need to be resected by colonoscopy several times (Bond, 2000; Kahi, 2015; Rex et al., 2012). Patients with serrated polyps had a 30% higher risk of developing CRC (Boparai et al., 2011; Chow et al., 2006). Particularly, the large serrated polyps (≥ 10 mm) are associated with advanced neoplasia with an estimated a 3-fold risk to be diagnosed with cancer (relative to patients without large serrated polyps) (Hiraoka et al., 2010; Holme et al., 2014).

2.4.4. Adenomatous polyps (adenomas)

Those polyps are classified as neoplastic with malignant potential. Most colorectal cancers arise from neoplastic adenomatous polyps (adenomas). The adenoma detection rate (ADR) is the main indicator to measure the effectiveness of screening and surveillance colonoscopies as mentioned previously. ADR is defined as the proportion of screening colonoscopies with at least one adenoma found, and is the prime metric for quality measurement (Fayad & Kahi, 2014). Patient status at initial examination predicts adenoma recurrence, particularly advanced adenomas influence. Adenoma features are also used to stratify the risk. Risk features are multiple adenomas, large adenoma (≥ 1cm), adenoma in the proximal colon, high-grade dysplasia, tubulovillous adenomas, and villous adenomas. The literature on advanced adenoma and any adenoma findings at surveillance examinations as related to baseline findings are summarized in Table 2.4 and Table 2.5, respectively.

(1) Number of adenomas

Adults with multiple adenomas had a higher risk of developing advanced adenomas, accounting for 2-4 fold higher risk among adults with at least 2 adenomas (compared to no adenoma). The risk of advanced adenomas found increased with increasing adenoma numbers (Bertario et al., 2003; Fairley et al., 2014; Martinez et al., 2009; van Heijningen et al., 2013). A meta-analysis identified adults with ≥ 3 adenomas as more likely to have advanced adenomas at follow-up examinations (RR: 2.52; 95% CI: 1.07-5.97) (Saini, Kim, & Schoenfeld, 2006). Chinese and Korean studies reported an adjusted hazard ratio (HR) of 2-3 with statistical significance among such adults (Chung et al., 2011; Huang et al., 2010).

Adenoma (any type) recurrence was reported among adults with ≥ 3 adenomas at baseline, an adjusted OR of 1.4 -2.4 showing statistical significance (Miller, Mukherjee, Tian, & Nagar, 2010; van Stolk, Beck, Baron, Haile, & Summers, 1998; S. J. Winawer et al., 1993), as also reported by Korea and Japan studies (Ji et al., 2009; Taniguchi et al., 2014).

(2) Size of adenoma

Adults with large adenoma (≥1 cm) were more likely to develop advanced adenomas at their next examination, with 2-4 fold higher risk of advanced adenoma recurrence (Bertario et al., 2003; Fairley et al., 2014; Laiyemo et al., 2008; Laiyemo et al., 2009; Martínez et al., 2001; Noshirwani, van Stolk, Rybicki, & Beck, 2000; Taniguchi et al., 2014). A meta-analysis identified a pooled relative risk (RR) of 1.39 with statistical significance (Saini et al., 2006). A study from Korea reported similar findings, a 3-fold risk of advanced adenoma outcomes among this population (Chung et al., 2011).

Having a large adenoma at initial examination was also associated with any adenoma recurrence. About 60% of adults with any adenoma >1 cm had developed an adenoma at follow-up (Winawer et al., 1993).

(3) Location of adenoma

Advanced adenoma at follow-up was more likely to happen with adenomas in the proximal colon at initial examination. About 58-65% of adults with proximal adenomas had a higher risk of having an advanced adenoma at follow-up examination (Laiyemo et al., 2008; Martinez et al., 2009; Martínez et al., 2001; van Heijningen et al., 2013). Overall, those with adenomas in the proximal colon had higher risks of developing any adenoma at surveillance, with 12.4-fold higher risk than those with adenomas in the distal colon (Miller et al., 2010). These findings were echoed by a Japanese study (Taniguchi et al., 2014).

(4) Histology of adenoma

Histology is a particularly difficult predictor to evaluate because of different growth patterns of cancer cells and should be identified by the pathologist. Adenomas are classified as tubular (TA), tubulovillous (TVA), and villous adenomas, with about 4.8%, 19%, and 38.4, respectively, showing malignant transformation (Bond, 2000; O'Brien et al., 1990). Patients with TVA or villous adenomas were more likely to develop advanced adenomas at surveillance examination, an adjusted RR of 1.26 - 2.43 (Laiyemo et al., 2008; Saini et al., 2006). Lieberman et al reported much higher risks among adults with villous adenomas (RR=6.05), compared to no adenomas neoplasia (Lieberman et al., 2007), and others reported 1.3-1.8 higher risk with TVA or villous adenomas at baseline (Bertario et al., 2003; Martinez et al., 2009). Similarly, a Chinese study reported an

adjusted HR of 2.57 (Huang et al., 2010). The risk of any adenoma recurrence was 2-fold among those with TVA compared to TA in another study (OR: 2.12; 95% CI: 1.12-4.02) (van Stolk et al., 1998).

Another pre-cancerous status is dysplasia in the colon or rectum mucosa with cells showing abnormal features. By definition, all adenomas have some levels of dysplasia (ACS, 2014; S. Winawer et al., 2003). Patients with high-grade dysplasia (HGD) were significantly more likely to develop advanced adenomas at surveillance, with an adjusted RR of 2-fold (Laiyemo et al., 2008; Saini et al., 2006). Martinez et al pooled data from 8 prospective studies and reported 5% developing advanced lesions (Martinez et al., 2009), similar to Huang et al 2010. Another study reported much higher risk among those adults with HGD in a randomized controlled trial, with 6.89 relative risks of advanced adenomas, compared to adults without any neoplasia at baseline. The key difference is that this study used "no neoplasia" as the reference group, in contrast to other studies (Lieberman et al., 2007).

Overall, advanced adenoma at baseline examination is associated with a standardized incidence rate (SIR) of 2.23 (95%CI: 1.67-2.92) for subsequent advanced lesions and higher hazard ratio (HR: 5.95; 95%CI: 3.66-9.68) (Chung et al., 2011; Cottet et al., 2012).

2.4.4. Procedure factors

Recently, the role of quality of initial colonoscopy in procedure-related factors has been studied. These features include bowel preparation status at initial colonoscopy and cecal intubation status.

(1) Bowel preparation status

Bowel preparation is a process before colonoscopy to obtain a clean bowel, allowing for examination of the whole mucosal surface. Inadequate cleansing can result in missed lesions and increased risk for subsequent adenomas. Thus, there is a strong relationship between detection of any significant lesions and bowel preparation quality (Froehlich, Wietlisbach, Gonvers, Burnand, & Vader, 2005; Harewood, Sharma, & de Garmo, 2003; Parra-Blanco et al., 2006).

Preparation adequacy can increase the detection of the colonic lesion by 21% (OR: 1.21; 95%CI: 1.16-1.25) (Harewood et al., 2003). Froehlich et al reported lesion detection rates by the quality of preparation. About 47% and 81% were patients with high-quality preparation and intermediate-quality cleansing had detectable lesions than those with poor cleansing (Froehlich et al., 2005). A recent community-based study also reported that good bowel preparation was associated with adenoma detection (30%), compared to insufficient cleaning (OR: 3.4; 95%CI: 1.6-7.4) (van Heijningen et al., 2013).

(2) Cecal intubation status

Cecal intubation is defined to be achieved if the tip of the colonoscope is advanced to a point proximal to the ileocecal valve so that the entire cecum is visualized. Incomplete cecal intubation status may result in missed adenomas or cancer. It is an important quality metric and relatively easy to measure, and can be a marker of a complete colonoscopy (Fayad & Kahi, 2014; Rex et al., 2015). Skilled colonoscopists should be able to apply techniques to overcome the difficulties in most instances and reach the cecum in ≥ 90% of all cases, and ≥ 95% of screening colonoscopies in healthy adults (Rex et al., 2015).

Reaching the cecum is lower for providers with low procedure volumes. Volumes of less than 500 in the previous year were associated with suboptimal rates of cecal intubation (OR range, 0.68-0.82) (Radaelli, Meucci, Sgroi, Minoli, & Italian Association of Hospital, 2008). It is also reported for procedures performed by non-gastroenterologists, about 60-70% of patients whose procedures performed by surgeons and internists did not achieve intubation (OR, 0.3 and 0.4, respectively) (de Jonge et al., 2012). Although cecal intubation is an important indicator of a complete colonoscopy, it is a process indicator of quality performance but not suggest determining high-quality colonoscopy.

2.4.5. Endoscopist factors

Recently, there is increased awareness that the success of colonoscopy in preventing CRC is dependent on the skill and competence of the endoscopists to detect adenoma, currently a surrogate marker for quality (Lee et al., 2013). Studies from the US reported their endoscopists' procedure volumes are associated with polyp detection and removal. About 10% of providers with the middle 50% of annual procedure volume were more likely to detect and remove polyps (Ko, Dominitz, Green, Kreuter, & Baldwin, 2010). Physicians performing > 100 colonoscopies per year also had a higher polyp detection rate (OR: 1.22; 95%CI: 1.04-1.43) in the UK (Bhangu et al., 2012).

Another driver of polyp detection and removal is the involvement of non-specialist endoscopists. The approximate rate of polyp detection and removal ranged from 7-25% when procedures are performed by non-gastroenterologists (Ko et al., 2010), rates that are validated by studies from other countries. A Canadian study reported that only 27-52% of polypectomies were complete when performed by surgeons in Canada (OR: 0.48,

0.73) (Jiang, Sewitch, Barkun, Joseph, & Hilsden, 2013). Higher polyp detection rates were reported for procedures by surgeons (OR: 1.15; 95%CI: 1.05-1.27) in the UK compared to non-gastroenterologists (Bhangu et al., 2012). Procedure performance by different specialty endoscopists is also associated with CRC detection. This is a 2-3-fold risk of missing polyps when procedures are performed by internists, general practitioners, or family physicians (Singh, Nugent, Mahmud, Demers, & Bernstein, 2010), and approximately 30-90% of missed CRC cases when performed by non-gastroenterologists (Baxter et al., 2011; Rabeneck, Paszat, & Saskin, 2010).

These studies confirm differences between specialists in polyp detection rates and removal, and therefore, the effectiveness to prevent early CRC. This may be due to differences in training because gastroenterologists generally receive the most intensive training in colonoscopy of all specialists. However, training in colonoscopy for primary care specialties is not required (American Association for the Study of Liver, American College of, American Gastroenterological Association, & American Society for Gastrointestinal, 2007)(Table 2.6).

Although colonoscopy screening performed by gastroenterologists shows higher adenoma detection rates, questions arise about whether crescent workloads are too high and may cause long waiting times for patients, particularly due to increasing caseloads for surveillance colonoscopy. Recent literature suggests shifting the workload to practitioners others than gastroenterologists, or involving assistants in procedures to increase the effectiveness of colonoscopy. Involving assistants may increase ADRs, accounting for 25-63% higher detection rates than without an assistant (23-59%), especially for small polyps (Table 2.7) (Aslanian et al., 2013; Chalifoux et al., 2014;

Dellon, Lippmann, Sandler, & Shaheen, 2008; Peters, Hasan, Jacobson, & Austin, 2010; Rogart, Siddiqui, Jamidar, & Aslanian, 2008; Xirasagar, Hurley, Sros, & Hebert, 2010). Other innovative approaches are also documented such as involving primary care physicians (PCPs), polyps search and removal during both scope insertion and withdrawal, and ensuring rescue assistance by experts if there is a difficulty during the procedure (Xirasagar et al., 2010).

In order to improve access to CRC prevention, shifting workloads to PCPs may be helpful because they are shown to perform consistent quality of CRC screening when they have the same training, about ≥25% ADR (46% among males and 30% among females) (Kolber, Wong, Fedorak, Rowe, & on behalf of the, 2013; Wilkins et al., 2009). Those findings are consistent with the USMSTF benchmark target average-risk individuals, an ADR of ≥25%, ≥30% among average-risk males and ≥20% among females (Rex et al., 2015).

2.4.6. Patient characteristics

Patient characteristics are required control variables for predicting subsequent adenomas at surveillance examinations, especially gender and age. However, most studies do not take into account patient characteristics. A few studies have reported race and education to be associated with adenoma detection and features at CRC screenings. The related studies and findings are presented in Table 2.8.

(1) Gender

Studies have reported a relationship between gender and adenoma detection. Males have a higher risk of advanced and non-advanced adenomas. The risk was nearly 2-fold with adenomas (HR, 1.6-1.9) (Bertario et al., 2003; Imperiale et al., 2008; Leffler et al.,

2012). Males were 6.5 times more likely to develop advanced metachronous adenomas at surveillance colonoscopy (Bertario et al., 2003). A Japanese study also identified an association of neoplasias with male gender (HR, 1.8; 95% CI: 1.6-2.0) (Yamaji et al., 2004). Males were more likely to have adenomas (OR, 1.44-1.59) (Thornton, Morris, Thornton, Flowers, & McCashland, 2007). However, males were less likely to have adenomas in the proximal colon (OR, 0.88; 95%CI: 0.79-0.98) (Lieberman et al., 2008).

(2) Age

Some studies reported a relationship between age and adenoma detection, particularly older age. Advanced and non-advanced adenoma detection rates increase with age (Leffler et al., 2012; D. A. Lieberman et al., 2008; Thornton et al., 2007; Yamaji et al., 2004). Adults aged > 60 years were evaluated as a risk factor of finding an adenoma on surveillance examination (Jorgensen, Kronborg, & Fenger, 1995; Taniguchi et al., 2014; S. J. Winawer et al., 1993). Much older adults (aged >70) were about 4.1 times more likely to have advanced metachronous adenomas at surveillance colonoscopy (Bertario et al., 2003) even if patients had begun screenings at the age of 40 years.

(3) Other patient factors

Few studies here examined the impact of race, education, and insurance in adenoma findings. Thornton et al reported that blacks were less likely to have any polyp at screening colonoscopy (OR, 0.77; 95% CI: 0.70-0.84). However, they were more likely to have tumors (OR, 1.78; 95%CI: 1.14-2.77) compared to whites (Thornton et al., 2007). Combining of those factors, about 62% and 16% of black females and males had a higher risk of large polyps than white females and males (Lieberman et al., 2008). Education is also associated with adenoma findings in that there was an increased risk for blacks with

a postgraduate education compared to whites with the same degree (RR, 1.29; 95%CI: 1.09-1.54) (Laiyemo et al., 2010). Although blacks had a higher prevalence of advanced adenoma at initial examination, the risk of any adenoma recurrence was not different from whites (Laiyemo et al., 2013).

2.4.7. Summary of literature findings

The totality of evidence suggests that adenomas with HGD, TVA/ villous adenomas, multiple adenomas, large adenoma, adenomas in the proximal colon, or serrated polyps are predictors of future advanced adenomas, non-advanced adenomas, or interval cancers. Particularly adenomas combining different features, such as having multiple adenomas with at least one of a large size, were more likely to develop advanced neoplasia (Vemulapalli & Rex, 2014). Although initial adenoma features can predict subsequent adenomas by multivariate analysis, there was a paucity of studies accounting for endoscopist-related or patient- related factors which might help to target patients before regarding the timing of surveillance colonoscopy.

Each indicator of colonoscopy quality has different roles: (1) quality of colon preparation and cecal intubation status are basic quality indicators for colonoscopy, and (2) adenoma detection rate (ADR) is a key index. The ADR may be associated with endoscopist skill and patient demographic characteristics (e.g., genetic factors, environmental factors, diet, cultures, etc.) (Hewett et al., 2010; Hewett & Rex, 2010; Lee et al., 2013; Vemulapalli & Rex, 2014).

Table 2.4 Risk of advanced neoplasia at surveillance among adults by adenoma characteristics at initial screening

Primary author (year)	Location	Study design	N	Time interval (years)	Adenoma characteristics
Noshirwani (2000)	US	Retrospective cohort study	697	< 3	Per 1 adenoma increased*: OR ,1.25/1.45 ≥ 1cm adenoma* (vs. < 1 cm): OR, 3.68/4.08
Martinez (2001)	US	Randomized controlled test (RCT)	1,287	3	>1cm adenoma (vs. <0.5cm): OR, 2.27 Proximal (vs. distal): OR, 1.65
Bertario (2003)	Milan	Prospective study	1,086	5(Mean)	≥ 2 adenomas (vs. 1 adenoma): OR, 1.6 >2cm adenoma (vs. ≤ 1cm): OR,1.5 TVA/ villous (vs. TA) : OR,1.3/1.8
Saini (2006)	US	Meta-analysis	5 studies	3	≥3 adenomas (vs. 1-2 adenomas) : RR, 2.52 HGD (vs. LGD) : RR, 1.84 ≥ 1cm adenoma(vs. < 1cm) : RR, 1.39 Villous (vs. no villous): RR, 1.26
Lieberman (2007)	US	RCT	3,121	5.5	TA < 10mm (vs. no neoplasia) : RR, 2.56 Villous (vs. no neoplasia) :RR, 6.05 HGD (vs. no neoplasia) : RR, 6.87
Laiyemo (2008)	US	RCT	1,905	5	HRA (vs. LRA)** : RR, 1.68 Advanced adenoma (vs. non-advanced) : RR,1.94 Villous (vs. non-villous): RR, 2.43 ≥ 1cm adenoma (vs. < 1cm): RR,1.57 HGD (vs. LGD) : RR, 1.73 Proximal (vs. distal): RR,1.58
Martinez (2009)	US	Prospective study	8 studies	4(Median)	HGD (vs. LGD) : OR, 1.05 ≥2 adenomas (vs. 1 adenoma)# : OR, 1.39-3.87 Proximal (vs. distal) : OR, 1.68 TVA/villous (vs. TA) : OR, 1.28

Table 2.4 Risk of advanced neoplasia at surveillance among adults by adenoma characteristics at initial screening (continued)

Primary author (year)	Location	Study design	N	Time interval (years)	Adenoma characteristics
Huang (2010)	China	Retrospective study	1,356	20	TVA /villous (vs. TA) : HR, 2.57 HGD (vs. LGD) : HR, 1.61 ≥3 adenomas (vs. 1 adenoma) : HR, 1.87
Cottet (2011)	France	Retrospective cohort study	5,779	7.7	Advanced adenoma: SIR, 2.23
Chung (2011)	Korea	Prospective study	2,452	5	HRA (vs. LRA)** : HR, 5.95 ≥3 adenomas (vs. 1-2 adenomas) : HR, 3.06 ≥ 10mm adenoma (vs. < 10mm): HR, 3.02
Fairley (2014)	US	Retrospective study	25,635	10	≥3 adenomas (vs. 1-2 adenomas) : OR, 2.4 ≥ 10mm adenoma (vs. < 10mm): OR, 3.6 HGD (vs. no HGD) : OR, 4.3 Villous (vs. no villous): OR, 3.7
Vemulapalli (2014)	UK	Retrospective study	1,414	Over 10	≥3 adenomas with 1 ≥ 10mm(vs. 1-2 adenomas <10 mm) : OR, 5.6-10.8 ≥5 adenomas with all < 10mm(vs. 1-2 adenomas <10 mm) : OR, 3.1
Van Heijning (2013)	Dutch	Retrospective study	2,990	6	≥2 adenomas (vs. 1 adenoma) : OR, 1.6-3.3 ≥ 10mm adenoma (vs. < 10mm): OR, 1.7 Villous (vs. no villous): OR, 2.0 Proximal (vs. not proximal): OR,1.6

Abbreviations: HGD, high-grade dysplasia; LGD, low-grade dysplasia; TA, tubular adenoma; TVA, tubulovillous adenoma.
*Outcome variable, advanced neoplasia includes tubulovillous adenoma, villous adenoma, high-grade dysplasia, carcinoma in situ, invasive cancer or size of 1cm or greater / 4 or more adenomas.**HRA, 3 or more adenomas or any advanced adenoma; LRA, 1 or 2 non-advanced adenomas.#Risk increased by per 1 adenoma increased.

Table 2.5 Recurrence of any adenoma at surveillance among adults by adenoma characteristics at initial screening

Primary author (year)	Location	Study design	N	Time interval (years)	Adenoma characteristics
Winawer (1993)	US	RCT	1,418	3	≥3 adenomas (vs. 1 adenoma):OR,2.4 >1cm adenoma(vs. ≤ 0.5 cm) : OR, 1.6
Van Stolk (1998)	US	RCT	479	4	≥3 adenomas (vs. 1, 2 adenomas): OR, 2.25 TVA (vs. TA) : OR, 2.12
Ji (2009)	Korea	Prospective study	667	3(Mean)	≥3 adenomas (vs. 1 adenoma): HR, 3.19
Miller (2010)	US	Retrospective study	399	5 /6-10	≥3 adenomas (vs. 1 adenoma) : OR, 1.4 Proximal (vs. distal) : OR, 12.4
Taniguchi (2014) *	Japan	Retrospective study	1,111	1/2	HGD :OR, 2.40 Right-side colon :OR, 1.43 ≥ 10mm adenoma :OR, 2.89 ≥3 adenomas: OR,6.12

Abbreviations: HGD, high-grade dysplasia; LGD, low-grade dysplasia; TA, tubular adenoma; TVA, tubulovillous adenoma.
*Used scoring system to calculate the recurrence rate of colorectal adenoma and followed by 1 and 2 years.

Table 2.6 Physician characteristics associated with quality of screening and surveillance examination

Primary author (year)	Location	N	Measures of quality	Procedure volume of physician	Specialty of endoscopist
Radaelli (2008) *	Italy	12,835	Cecum intubation rate	300-500 (vs. >500): OR, 0.82 < 300 (vs. >500): OR, 0.68	-
Singh (2010) *	Canada	45,985	CRC rate	-	Rural surgeons (HR,3.38), Urban surgeons (HR,1.78), Internists (HR,2.25), Family practices (HR,3.01)
Rabeneck (2010) *	Canada	110,402	CRC rate	-	General surgery (HR, 1.4), Other[2] (HR,1.3)
Ko (2010)[1]	US	328,167	PDR/ removal	Middle annual colonoscopy volumes (vs. low volumes) #:RR,1.1	General surgery (RR,0.8), Colorectal surgery(RR,0.91), Family medicine(RR,0.86), Internal medicine (RR,0.93)
Baxter (2011) *	Canada	14,064	CRC rate	-	Others** (HR, 1.7-1.9)
Bhangu (2012)	UK	10,026	1.ADR 2. PDR	>100 colonoscopy per year (vs. no): OR, 1.22	Surgeons (vs. physicians) : OR, 1.15
de Jonge (2012) *	Netherlands	4,738	1.Cecum intubation rate 2.ADR	-	1.Surgeons (OR,0.3), Internists (OR,0.4) 2.Surgeons (OR,0.2), Internists (OR,0.71)
Jiang(2013) *	Canada	2,651	Polypectomy	-	Surgeons (OR,0.48, 0.73)

Abbreviations: PDR, polyp detection rate; ADR, adenoma detection rate.

*Reference group for comparing types of endoscopy is gastroenterologists.

**Others include internists, general practitioners, and family physicians.

#Annual colonoscopy volumes by quartile; middle volumes are 50 % of claims and low volumes are 25 % of claims.

Table 2.7 Gastroenterology fellow/assistant involvement in colonoscopy vs. adenoma detection rates (ADRs)

Primary author (year)	**Type of assistant**	**N (ADRs, %)**	
		Without assistant	*With assistant*
Dellon (2008)	GI endoscopy nurses	-	3,631 (24.8%)
Rogart (2008)	GI fellows	126 (23%)	183 (37%)
Peter (2010)	GI fellows	2,895 (27.7%)	699 (34.3%)
Xirasagar (2010)	PCPs	-	10,958 (29.9%)
Aslanian (2013)	Nurses	256 (58.6%)	336 (57.5%)
Chalifoux (2014)	GI trainees	339 (51%)	617 (63%)

Abbreviations: N, the number of colonoscopies; ADRs, adenoma detection rates; GI, Gastroenterology; PCPs, primary care physicians.

Table 2.8 Patient characteristics associated with adenoma findings at screening or surveillance examination

Primary author (year)	Location	N	Measures	Patient characteristics
Winawer(1993)	US	1,418	Adenoma	Aged ≥ 60(OR, 1.4)
Jorgensen(1995)	Denmark	673	Adenoma	Aged > 60(HR, 1.3)
Bertario(2003)	Milan	1,086	1.Metachronous adenoma 2.Advanced metachronous adenoma*	1. Male(HR,1.6) 2. Male(HR,6.5); Aged >70 (vs. <60):HR,4.1
Yamaji(2003)	Japan	6,225	1.All neoplasias 2.Advanced neoplasias	1. Aged ≥ 40 (HR, 1.5-2.2);Male (HR,1.8) 2. Aged ≥ 50 (HR, 3.6-5.5)
Thornton(2007)	US	46,726	1.Polyp 2.Tumor	1. AA (OR,0.77); Age(OR,1.05); Male (OR, 1.59) 2. AA (OR,1.78); Male (OR,1.44)
Lieberman(2008)	US	85,525	1.Large polyp 2.Proximal large polyp	1. Aged ≥ 50 (vs.<50): OR, 1.23-1.81; Black female (vs. White female): OR, 1.62; Black male (vs. White male): OR, 1.16 2. Male (OR,0.88); Aged ≥ 60 (vs.<50): OR, 1.23-1.81
Imperiale(2008)	US	2,983	Adenoma	Male (HR, 1.92)
Laiyemo(2010)	US	60,572	Adenoma	Black, postgraduate (vs. whites, postgraduate): RR, 1.29
Leffler(2012)	US	2,139	1.Adenoma 2.Advanced adenoma	1. Female (OR, 0.77); Increase patient age per year (OR, 1.04) 2. Increase patient age per year (OR, 1.03)
Tanignchi (2014)	Japan	43,195	Adenoma	Age≥ 65(OR, 1.38)

*Advanced metachronous adenoma is defined as CRC or severe dysplasia.

2.5 Prediction of subsequent adenomas by baseline adenoma status

This section reviews the literature on the timing of surveillance CRC screening, and adenoma findings at baseline examination that predict surveillance findings. Using previous screening information to predict the probability of high-risk findings on later examinations can help to optimize the finding of surveillance appropriately (Loberg et al., 2014). Adenoma features are classified into high-risk, low-risk, and average-risk groups. The main concerns are whether any advanced adenoma predicts advanced adenoma findings at surveillance. However, negative findings at initial colonoscopy do not guarantee that patients will not develop adenomas at surveillance.

2.5.1. Findings of serrated polyp at the surveillance colonoscopy based on present at baseline examination

Having serrated polyps is a rare colorectal condition associated with higher CRC risk, and their polyps are often sessile serrated adenomas/ polyps (SSAs/Ps). A recent study reported that recurrent sessile serrated adenomas or polyps occurred in 68% of patients at surveillance colonoscopy (Edelstein et al., 2013). Another study reported 15% of the SSA/P patients developed subsequent CRCs or adenomas with high-grade dysplasia (Fu, Qiu, & Zhang, 2014).

2.5.2. Adenomatous polyp at surveillance colonoscopy associated with adenomas at baseline examination

The findings at initial colonoscopy are associated with the findings at surveillance. Risk stratification of adenomas has been reported. Four studies in the US and two studies from Korea and the Netherlands reported on recurrence of adenomatous polyps based on adenoma status at the initial screening (Suh et al., 2014; van Heijningen et al., 2013). The

studies had differing approaches with regard to demographics, study design, and findings at surveillance colonoscopy as related to findings at the initial colonoscopy. Risks based on adenoma status are defined similarly: (1) high-risk is defined as having advanced adenomas, including high-dysplasia, villous or tubulovillous histology, size ≥ 1 cm, ≥3 non-advanced adenomas, and invasive carcinomas, (2) low-risk is defined as non-advanced adenomas, including 1 to 2 non-advanced adenomas, and (3) normal results are defined as hyperplastic polyps (not adenomas) or no polyp. The finding of studies on the percentage of adenomas found at surveillance colonoscopy by risk-level at baseline screening in the US and others are summarized in Table 2.9 and Table 2.10, respectively.

(1) Findings in the US

One of the studies examined a sample of patients in the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial with surveillance colonoscopy use based on a history of adenoma. Study criteria for eligible patients included no current treatment for cancer and no known prior cancer of the colorectum, prostate, lung, or ovaries. Those patients were classified into 4 groups based on findings at the initial colonoscopy: (1) advanced adenoma (AA), (2) non-advanced adenoma (NAA), (3) non-adenomatous polyps (NAP), and (4) no polyp. There were 2,607 patients who met the requirements and had surveillance colonoscopy within 6 months to 10 years from the baseline colonoscopy. Significant findings are that around 19% of individuals with advanced adenomas found at baseline colonoscopy had adenoma recurrent, but recurrence rates were fairly constant from 1 year through 10 years after initial screening (Pinsky et al., 2009).

A randomized trial examined the findings at surveillance colonoscopy and evaluated adenomas found after a mean follow-up of about 4 years in 1991-1994, the Polyp

Prevention Trial (PPT) and the PPT-Continued follow-up Study (PPT-CFS). Criteria for study eligible patients were: no history of surgical resection of adenomatous polyps, bowel resection, CRC, polyposis syndrome, or inflammatory bowel disease. The adenoma findings at baseline colonoscopy were grouped into low-risk and high-risk. Of 1,905 individuals who had adenomas removed or had a diagnostic colonoscopy who participated in the PPT, 1,297 completed the follow-up Study. The results showed approximately 31% of individuals with high-risk adenomas also had high-risk findings at surveillance (Laiyemo et al., 2009).

The same author used the same data sources to assess the utilization of the risk-stratification recommended by the 2006 guidelines. Ranges of 19.6% -46.2% of patients with a high-risk of adenoma status at initial colonoscopy have a recurrence of high-risk adenoma status at surveillance. However, they mentioned that adenoma-based risk stratification has limited predictability for findings at surveillance because demographic and lifestyle characteristics may affect the outcome (Laiyemo et al., 2008).

Another study used a different study design, but discussed similar issues in studying participants of an adenoma chemoprevention trial. All participants had screening and two surveillance colonoscopies at roughly 3 or 5 years as recommended. The risk of clinically significant adenoma recurrence was stratified based on the results of the first colonoscopy. The criterion for eligible patients was that they had a histologically documented large-bowel adenomas removed (n=564), and the study excluded those with an adenoma detected before their baseline colonoscopy and with cancer found at or before the second colonoscopy. The initial adenoma status was classified into high-risk,

low-risk, and no adenoma. About 18% of high-risk individuals had a recurrence of high-risk adenomas (Robertson et al., 2009).

Finally, another retrospective study renewed 965 patients from a single specialty gastroenterology practice between 1985 and 2010, and then quantified the risk of advanced adenomas/ high-risk findings on surveillance colonoscopy. Patients with a family history of CRC, personal or family history of FAP or HNPCC, and second and third colonoscopies performed for any reason other than surveillance purpose were excluded.

Adenomas at the index colonoscopy were categorized into high-risk, low-risk, and non-neoplastic categories. They reported that high-risk findings at the second surveillance colonoscopy were best predicted by high-risk findings at the first surveillance (22% of cases) (Morelli et al., 2013).

(2) Findings from other countries

A study from Korea estimated the risk of high-risk findings at the second surveillance colonoscopy based on the prior two results. Eligible subjects included those who underwent screening colonoscopy and also completed their second surveillance colonoscopy. Those with CRC, polyp, inadequate bowel preparation or incomplete colonoscopy at baseline, invasive CRC, or history of inflammatory bowel diseases (IBD) were excluded. The results showed that high-risk findings at the second surveillance colonoscopy were significantly associated with high-risk findings from the previous two examinations (Suh et al., 2014).

Another study from the Netherlands also reported that adenoma characteristics are associated with recurrent colorectal neoplasia. They included patients with the first adenoma diagnosed and with follow-up data (van Heijningen et al., 2013).

(3)Findings of the US vs. other countries

Although those studies have different study designs and sample characteristics, the common finding is that adenoma features observed at previous examinations are associated with subsequent adenomas. A range of 18-31% of patients with high-risk findings at previous examinations has high-risk findings at the last surveillance examination. Moreover, a range of 5-10% of patients with low-risk findings at surveillance colonoscopy had low-risk adenomas at previous examinations in the US. In comparison, the studies from Korea and the Netherlands reported around 46% and 4% of adults with high-risk findings at follow-ups, respectively. The variance of these recurrence rates may be explained by the differences in surveillance guidelines and cultures which impact patients CRC risk behaviors.

2.5.3. Likelihood of advanced neoplasia after negative screenings

Even for adults with negative findings at initial examination, the risk still exists to develop advanced adenomas because of missed lesions. Six studies examined the findings of advanced neoplasia after negative screenings, defined negatively as no polyp or adenoma found (Table 2.11).

Most of the studies involved surveillance screening at 5 years after negative findings at baseline examination. About 0.6-2.0% of these patients developed advanced neoplasia (Chung et al., 2011; Imperiale et al., 2008; Leung et al., 2009; Rex et al., 1996). Compared to these studies, one study had a more frequent surveillance interval of 3 years, and identified 0.8% of adults with negative findings having advanced neoplasia (Schoen et al., 2003). The studies with longer periods between follow-ups showed that risk findings occurred in 4.4-6.7% of cases per year of increased intervals (Brenner et al., 2007).

2.5.4. Summary of significant findings

These studies confirm the relationships between baseline findings and findings at surveillance colonoscopy. Information on baseline colonoscopy can predict subsequent adenomas. The risk of adenoma recurrence increases among individuals with high-risk adenomas at baseline examination, and adenoma recurrence is cumulative with a longer surveillance interval. In contrast, low-risk individuals did not predict low-risk or average-risk at later follow-ups. Sometimes high-risk findings or interval CRC occur between scheduled examinations due to missed lesions at previous examinations. Therefore, using findings from all previous colonoscopies to determine the probability of high-risk findings at the last surveillance colonoscopy could assist with developing optimum timing recommendations.

Table 2.9 Findings of advanced neoplasia at the last surveillance colonoscopy by findings at baseline colonoscopy in the US (by risk stratification)

Primary author		**Pinsky**	**Laiyemo**	**Robertson**	**Morelli**
Year		2009	2009	2009	2013
Type of study		PLCO*, randomized trial	PPT*, randomized trial	Medical center, prospective study	Specialty practice, retrospective study
Sample Size#		2,607	1,297	564	965
1st colonoscopy outcome	Outcome at surveillance	(%)	(%)	(%)	(%)
High-risk**	High-risk**	19.3	30.6	18.2	22.0
	Low-risk**	6.7	8.9	13.6	11.0
	No adenoma	5.9	4.8	12.3	-
Low-risk**	High-risk**	15.6	6.9	20.0	18.0
	Low-risk**	5.7	4.7	9.5	8.7
	No adenoma	3.9	2.8	4.9	-
No adenoma	High-risk**	11.5	-	-	-
	Low-risk**	4.7	-	-	-
	No adenoma	3.1	-	-	-

*PLCO: the Prostate, Lung, Colorectal, and Ovarian cancer screening trial; PPT: the Polyp Prevention Trial.

**High-risk is defined as 3 or more adenomas, tubular adenoma ≥ 10 mm, adenoma with villous histology, or high-grade dysplasia (HGD); Low-risk is defined as 1-2 tubular adenomas <10 mm.

#Subjects completed baseline colonoscopy and follow-up examinations.

Table 2.10 Findings of advanced neoplasia at the last surveillance colonoscopy by baseline colonoscopy findings in other countries (by risk stratification)

Primary author		**Suh**	**Van Heijningen**
Year		2014	2013
Location		Korea	Dutch
Type of study		Single medical center, retrospective study	Registry data, community-based study
Sample Size*		852	1,482
1st colonoscopy outcome	Outcome at surveillance	(%)	(%)
High-risk**	High-risk**	46.2	4.0
	Low-risk**	23.6	3.0
	No adenoma		4.0
Low-risk**	High-risk**	30.8	0
	Low-risk**	32.5	1.0
	No adenoma		1.0
No adenoma	High-risk**	23.1	-
	Low-risk**	43.8	-
	No adenoma		-

*Subjects completed baseline colonoscopy and follow-up examinations.

**High-risk is defined as 3 or more adenomas, tubular adenoma ≥ 10 mm, adenoma with villous histology, or high-grade dysplasia (HGD); Low-risk is defined as 1-2 tubular adenomas <10 mm.

Table 2.11 Findings of advanced neoplasia at the last surveillance colonoscopy after negative findings at initial screening[*]

Primary author (year)	Sample size[**]	Time interval (years)	Advanced neoplasia (%)
Rex (1996)	154	5	0.6
Schoen (2003)	9,317	3	0.8
Imperiale (2008)	1,256	5.3(Mean)	1.3
Leung (2009)	401	5	1.4
Brenner (2010)	533	11.9(Mean)	4.4-6.7[#]
Chung (2011)	1,242	5	2.0

[*]Negative screening is defined as no any polyp or adenoma detected at baseline examination.
[**]Number of adults with negative findings at initial examination and rescreen at interval time.
[#]Percentage with advanced neoplasia findings increased with each year (1-≥16 year).

2.6 Original contributions of the current study, research gaps addressed

A colonoscopy is a high risk and costly procedure. It is not always perfect for preventing cancer despite the fact that it has been a dominant CRC screening modality in the United State since the 1990s. Having a surveillance colonoscopy administered appropriately after the initial examination is necessary.

Adenoma features are widely used to predict subsequent adenomas by risk stratification. Although adults with high-risk adenomas at initial screening are more likely to develop subsequent adenomas, adults with high-risk findings after negative screenings still occur. A possible explanation is that residual neoplastic tissue was left behind at prior examinations. About 20% of polyps and more than 70% of interval CRC cases were attributed to missed lesions (Ji et al., 2009; Pohl & Robertson, 2010; van Rijn et al., 2006). Moreover, high-risk adenoma characteristics (large adenomas, multiple adenomas, proximal adenomas, the presence of HGD, and TVA /villous adenomas) are associated with recurrence and advanced adenoma risk at follow-up features.

The pattern of surveillance practice is still highly rationale despite guidelines having been updated. Using only adenoma-based risk stratification in the current surveillance guidelines is a limitation to study recurrence due to underuse among high-risk adults and overuse among low-risk adults (Laiyemo et al., 2008; Schoen et al., 2010). Underuse may harm at-risk adults, but overuse may result in reducing colonoscopy scene capacity for screening and surveillance (Johnson et al., 2015). Understanding the factors contributing to overuse or underuse of surveillance colonoscopy may help monitor patients better and improve guideline concordance.

However, few studies have examined patient-related and endoscopist-related factors, which may also influence the effectiveness of screening/surveillance colonoscopy. Patient-related factors such as gender, age, and race are difficult to overcome. Also, other patient factors such as poor bowel preparation, knowledge, or adherence to guidelines influence the examination. Endoscopist-related factors are more related to endoscopy skills because of the differences in training and credentialing processes, and conscientiousness in performing the procedure which may cause inadequate polypectomy or lower adenoma detection rates (Hewett et al., 2010; Hewett & Rex, 2010; Johnson et al., 2015). Lack of knowledge or disagreements on guidelines may also drive non-adherence to recommended practices by providers (Saini et al., 2009).

Overall, one comment explaining compliance of surveillance colonoscopies exclusively by adenoma risk-stratification at baseline colonoscopy. Other factors may contribute to non-adherence to timing recommendations despite guidelines having been widely published. Few data sources are available with information on patient and endoscopist covariates. Even if data sources have complete information, most suffer from selection bias, self-selected patients who may be more health-conscious or subjects overestimate findings. Therefore, surveillance utilization and factors to be targeted to improve guideline concordance should be aggressively identified. The contributions and research gaps in this area are organized in figure 2.2.

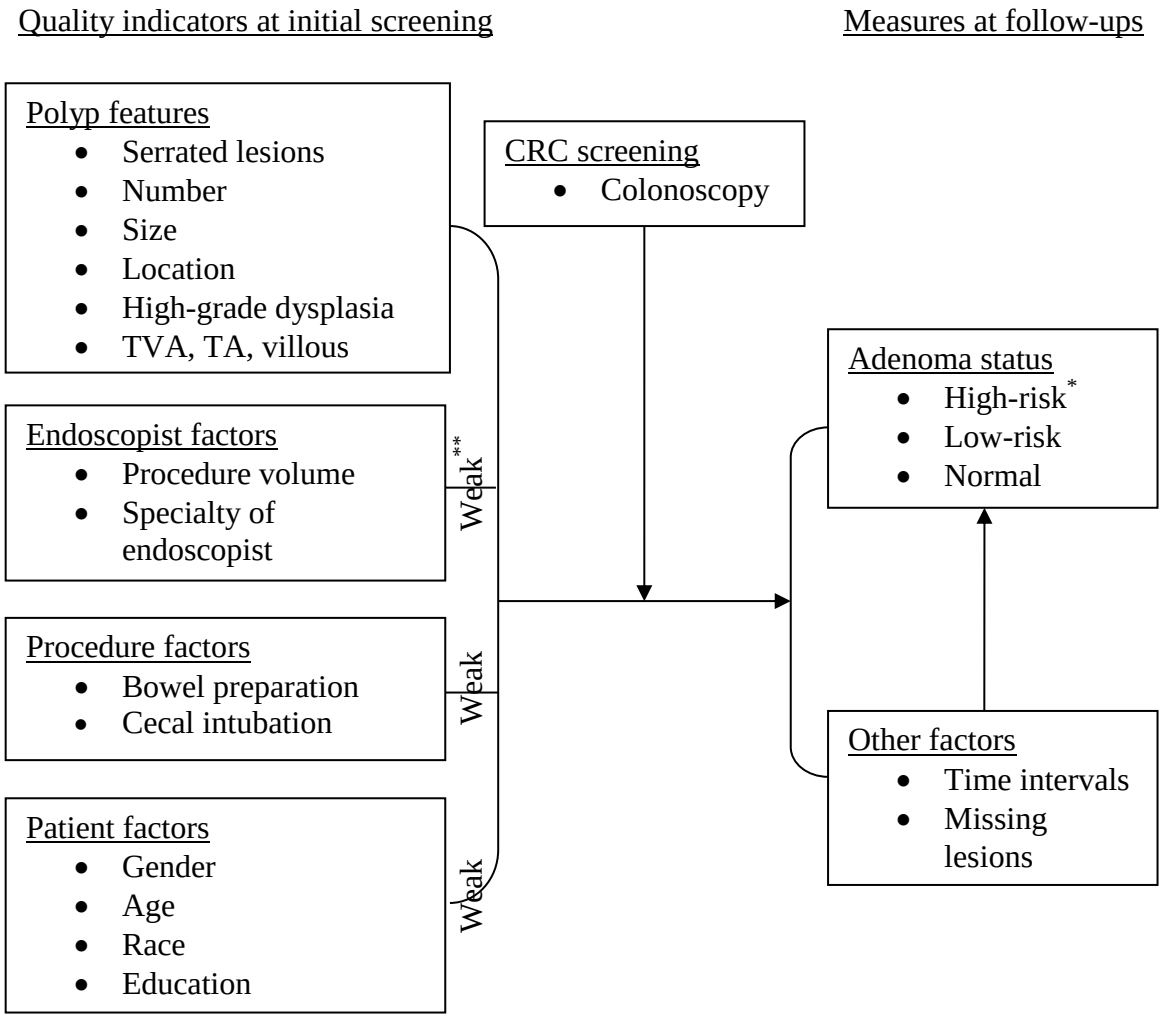

Figure 2.2 Conceptual framework: current research contributions and research gaps. *High-risk is defined as ≥ 3 adenomas, tubular adenoma ≥ 10 mm, adenoma with villous histology, or high-grade dysplasia (HGD); Low-risk is defined as 1-2 tubular adenomas <10 mm. Abbreviations: TVA, tubulovillous adenoma; TA, tubular adenoma. **Weak: Little or no research documentation exists.

2.7 Contributions and knowledge gaps remaining despite recent studies on surveillance colonoscopy

This section discusses the significant findings of two related studies, the research gaps remaining, and the potential contributions from our study. A Netherlands study examined adherence to postpolypectomy surveillance guidelines in community-based clinical practice and evaluated the influence of a change in the guidelines on adherence rates (van Heijningen et al., 2015). This country has a universal healthcare access system. Another study identified the predictors of guideline-concordant surveillance colonoscopy recommendations and factors associated with overuse or underuse of surveillance colonoscopy (Kahn et al., 2015).

2.7.1 Summary of approaches and findings of recent studies on surveillance colonoscopy use

The study from the Netherlands by Van Heijningen et al discussed adherence to recommended intervals in community-based clinical practice. Researchers studied patients with a first adenoma diagnosis from 1998 to 2002 and followed them up to 2008 (n=2,997). The significant finding was that underuse relative to the postpolypectomy surveillance guidelines was high in the Netherlands population. Less than 25% of surveillance-eligible patients underwent surveillance at the appropriate time. The study showed significant proportions of delayed surveillance among patients with high-risk adenomas and early surveillance for patients with low-risk adenomas. The study did not evaluate the prevalence of surveillance among patients without polyps or with hyperplastic polyps. Therefore, inappropriate overuse was not studied. Another research gap is that despite most of the patients in the Netherlands usually attending the same

hospital for surveillance and all other health purposes, the factors associated with low adherence rates were not explored. Finally, their outcomes do not generalize to the US population because the researchers used the Netherlands guidelines for their study. They used the 2002 guidelines which recommended that patients with one or two adenomas should have surveillance at six years, one year later than recommended by US guidelines (Snel & de Wolf, 1988).

A study from the USA by Kahn et al identified the predictors of guideline-concordant surveillance recommendations after adenoma polypectomies. Researchers studied subjects who underwent a polypectomy between 2011 and 2013 at an academic medical center's safety-net health system in Dallas in the US (n=1,822). However, the study sample consisted of only those who were eligible for surveillance as per guidelines, and excluded those who were not eligible. They reported that nearly 25% of cases were not concordant with the surveillance guidelines. Patients with ≥ 3 adenomas, aged > 65 years, or with piecemeal resection of polyps at initial colonoscopy were more likely to have guideline-inconsistent surveillance colonoscopies. Although they determined the reasons/factors for low adherence to surveillance colonoscopy, the reported rates pertain to a safety net population covered by an academic medical center. Further the authors did not evaluate the appropriateness of surveillance colonoscopy timing given the recommended time intervals, and they did not account for provider factors in the variations in surveillance colonoscopy use.

2.7.2 Contribution of the current study

Based on the contributions of the reported studies some research gaps remain. This study examines the overall use of surveillance and premature repeat screenings of a total cohort of patients with an initial colonoscopy at a community-based endoscopy center in South Carolina. It uses a large sample of 26,523 consecutive colonoscopies performed from September 4, 2001, to February 12, 2011 to study the pattern of surveillance colonoscopy use. We use the 2006 U.S. Multi-society Task Force guidelines to determine appropriate or inappropriate timing of surveillance and evaluate overuse, underuse and appropriate use among all patients and stratified by risk status at baseline colonoscopy. Inappropriate overuse will also be studied among patients without polyps or with hyperplastic polyps. More in-depth exploration of the relationship between timeliness of surveillance colonoscopy and baseline findings on polyp, patient, and colonoscopy characteristics will be determined.

CHAPTER 3

METHODS

This chapter describes the research questions and methodology used in the study, including sample selection process and statistical analysis methods. There are 5 sections: (1) study questions, (2) data source and description, (3) study variables, (4) statistical methods, and (5) steps of data analysis.

3.1 Study questions

To address the knowledge gap regarding surveillance based on prior literature, the following are the research objectives, study questions, and hypotheses.

3.1.1 Research objectives

There are few data sources available to study surveillance frequency due to very few colonoscopy series reporting on surveillance colonoscopies. A few studies evaluated the status of surveillance colonoscopy use relative to the recommended guidelines, and the great variation in surveillance utilization. One reason could be differences in the populations covered by the colonoscopy series – with selection bias in some populations towards more educated or health-conscious subjects rather than randomly selected members of the general population as in a randomized clinical trial or academic systems. The consistency of surveillance frequency with the professional society recommendations remains a little-studied topic (Laiyemo et al., 2009; Pinsky et al., 2009).

Studies that examined the utilization of surveillance colonoscopy have not reported on patient-related or endoscopist-related factors that may affect the risk of colorectal polyps' recurrence, which drives surveillance timing decisions. The lack of this information limits the ability to study surveillance timeliness adjusted for polyp risk factors. Although a recent study documented an influence of a change in colonoscopy guidelines on practice, they did not examine the reasons that may affect the findings of surveillance colonoscopy (van Heijningen et al., 2015). Our study will address this gap. Another study documented that patients with ≥ 3 adenomas, aged >65 years, or with piecemeal resection of polyps at initial colonoscopy were more likely to have guideline-inconsistent follow-ups. However, this study was mainly based on guideline recommendations and not all categories of patients (Kahn et al., 2015).

Therefore, the study research objectives are as below. It will use the data on initial colonoscopies to evaluate the appropriateness of surveillance use and timeliness relative to 2006 joint guidelines of the U.S. Multisociety Taskforce Guidelines [the American College of Gastroenterology (ACG) and the American Society for Gastrointestinal Endoscopy(ASGE)] (Winawer et al., 2006).

Study objectives:

(1) To compare the appropriateness of surveillance colonoscopy timing at a major endoscopy center in SC among patients with an initial colonoscopy in the pre-2006 period (pre-guideline) vs. 2006 and later, relative to the recommended surveillance intervals. The appropriateness is determined based on concordance of timing with the 2006 guidelines.

(2) To study the demographic, insurance and polyp-related factors at initial colonoscopy associated with the likelihood of timely surveillance.

To address these objectives, the study will mainly use the adenoma status (advanced adenoma and non-advanced adenoma), adenoma features (number, size, location, and histology), and period relative to guideline date (pre-2006, and 2006 and later) of these variables at initial colonoscopy will be used to explore the relationship with timely surveillance.

3.1.2 Research questions

The original contribution of this work and how it addresses the research gaps have been explained in the previous chapter. The study purpose is to evaluate the impact of professional society guidelines on practice at a setting that is highly invested in high-quality colonoscopy services as evidenced by very high CRC prevention among its screening colonoscopy clients compared to almost any other practice-based cohort documented in the literature. It has to achieve CRC prevention rates similar to the only clinical trial documented in the literature. Given the quality focus of the center, we seek to study the impact of the 2006 guidelines on the center's surveillance or re-screening frequency. Before 2006, there were no official guidelines firmly recommending timings of surveillance based on characteristics of patients and polyps found at initial screening. The study will address the following research questions to achieve the objectives.

(1) Is the timing of surveillance colonoscopies relative to the 2006 recommended interval different for initial colonoscopies done pre-2006 vs. post-2006 and later procedures?

(2) Are the post-2006 repeat colonoscopy procedures concordant in timing with the 2006 guidelines?

(3) Is the timing of surveillance associated with initial adenoma status, adenoma features, and patient-related factors, and how does this differ in the pre-2006 period vs. post-2006 and later?

3.1.3 Research hypotheses

Those research questions are studied by testing the following hypotheses:

(1)Hypotheses on the timing of surveillance colonoscopies at guideline date

a. The surveillance colonoscopy interval is different among patients with initial colonoscopy in the pre-2006 period compared to those screened 2006 and later after adjusting for baseline adenoma features. (We include patients with an initial colonoscopy in 2006 in the post-guideline group because their earliest possible surveillance would be in 2007 when guidelines were operational.)

b. Predictive factors for the timing of surveillance colonoscopies relative to baseline colonoscopy in terms of adenoma features and demographic characteristics will be different for patients with initial colonoscopy before 2006, and those of 2006 and later.

(2) Hypothesis on the predictors of timely surveillance colonoscopy

a. The likelihood of appropriate timing of surveillance colonoscopy is associated with initial adenoma status, adenoma features, patient demographic characteristics, and guideline date.

3.2 Description of methods

The section introduces the data source and builds the study structure based on research objectives. The sample selection process is also presented.

3.2.1 Data source

Data for the study comes from a licensed ambulatory surgery center for endoscopy, South Carolina Medical Endoscopy Center (SCMEC), in Columbia, South Carolina, now known as Carolina Colonoscopy Center (CCC). Data was extracted on colonoscopies performed from September 4, 2001 to February, 2011. A notable feature is that the Center mainly uses primary care physicians (PCPs) to perform procedures. About 72.7% of procedure were done by PCPs. Involving PCPs can help expand colonoscopy capacity to meet the demand for screening colonoscopy. The center also uses a unique protocol. One feature is search and removal of polyps during both scope insertion and withdrawal. The center has documented higher CRC prevention rates than other community-based centers, and comparable to that of the only clinical trial in the literature (Xirasagar et al., 2010; Xirasagar et al., 2015). Shifting some of the screening workloads to PCPs may enhance the US populations access to cancer prevention if they have the proper training. In this study, ≥25% ADR was achieved by PCPs, 36.6% among males and 27% among females, exceeding the performance benchmark of the U.S. Multisociety Task Force (Rex et al., 2015; Xirasagar et al., 2015).

Post-training, the procedure performance protocol, and hands-on technical support provided to PCPs compensate for potential skill deficiencies of PCPs due to lack of formal gastroenterology training (They do not have pre-training). The center's training process is similar to gastroenterology fellows' fellowship training for credentialing in

colonoscopy. It ensures hands-on supervision and achieves participation by a credentialed expert by the University of South Carolina Medical School teaching hospital for the first 140 procedures of the PCP-in-training. The training procedure number is identical to the ASGE-specified number of procedures for hospital credentialing (Faigel, Baron, Lewis, Petersen, & Petrini, 2007). At the center, the supervising specialist/expert is a gastroenterologist, colorectal surgeon, or the colonoscopy-credentialed director of the center's colonoscopy training program, an internal medicine specialist with extensive experience in independently performed colonoscopies board-credentialing. The specialist/expert trains PCPs, providing hands-on endoscope management to advance the scope through the colon, tip manipulation to expose mucosal fields hidden in the colonic folds, viewing the video screen to coach the trainee on identifying tissue abnormalities and polyp recognition, and directing the performing of the patient and endoscope to enable safe and complete polypectomies. Hand on assistance is gradually reduced until the PCP is fully proficient with these operations and achieves mastery in the above skills over the 140 training procedures. Prior to completing 140 procedures, the manual assistance is gradually replaced by verbal assistance to help navigate flexures, difficult colonic segments, and/ or diverticula.

Post-training, the PCP performs procedures without specialist oversight. However, an expert is always available on-site while any PCP is performing at the center to provide rescue assistance. The specialist's rescue assistance may be navigational or therapeutic when called for by the PCP, particularly to safely remove large or vascular adenomas, polyps at difficult locations, to control bleeding, or manage spasms. Training of PCPs

was started in 2001 and 54 PCPs performed colonoscopies at the center as of February 12, 2011.

The center has implemented a polyp detection-maximizing protocol that has been updated regularly consistent with professional society guidelines and based on findings of published studies since 2001 (Sweeney & Lloyd, 2007; Xirasagar et al., 2010). The procedure protocol requires a 2-person technique for all PCPs since 2001. The center also encourages the use of the 2-person technique by colonoscopy-credentialed specialists and experts (bringing their cases to the center or hired by the center as back-up experts). The main features of the colonoscopy protocol at the CCC are: "(1) an endoscopy technician advances the colonoscope while the physician manipulates the scope tip for polyp search and removal. This can minimize the missing of polyps and ensure more persons watching the video screen for polyps; (2) at least 3 additional persons view the video screen to identify abnormal areas; (3) polyp search and removal takes place since March 2006 during both the insertion and withdrawal phases; (4) propofol sedation was implemented to replace the conventional midazolam-meperidine combination sedation. The advantages of propofol sedation are that enable vary rapid induction of deep sedation and rapid recovery. Because there is more efficient utilization of the endoscopist's time, it can reduce additional costs of the associated staff and infrastructure while patients' gradual recovery with midazolam-meperidine or others (Cohen et al., 2007). Intravenous propofol is administered by a nurse-anesthetist; (5) Gradual insertion and circumferential withdrawal which is 6 minutes or greater of the colonoscope is done to maximize mucosal surface inspection. In preoperative preparation, patients received a phone call reinforcing bowel preparation instructions 2 days before the colonoscopy." (Xirasagar et

al., 2015). In addition patient positioning assistance to enable complete targeting of abnormal tissue for safe and complete removal or destruction in place is an important function served by the additional personnel in the room, especially the assisting endoscopy technician and the nurse anesthetist.

3.2.2 Study design and structure

This is a retrospective cohort study to study the timing of surveillance colonoscopy as related to the initial examination. Data for this study comes from a total of 26,523 procedures performed by the 54 PCPs and 5 experts at the center from September 4, 2001, up to February 12, 2011. The study objectives are to evaluate the relationship between the timing of surveillance and patient, colonoscopy procedure, and adenoma characteristics at baseline colonoscopy (Figure 3.1). Hypothesized factors affecting surveillance timing are baseline adenoma status, adenoma features, patient characteristics, and professional society guideline date relative to the initial colonoscopy. Adenoma status includes advanced adenoma and non-advanced adenoma. Adenoma features that would influence surveillance timing are the presence of advanced adenoma features, which are the number, size, location, and histology (tubular, tubulovillous /villous, hyperplastic, or dysplasia features). Patient characteristics include gender, age, race, and insurance status. Because specific and detailed surveillance guidelines were established in 2006, comparison of surveillance timing between screening colonoscopies pre and post-guidelines is important. The time interval to surveillance is the key variable of interest for this study.

3.2.3 Study sample selection and preparation of data

The Patient, Polyp, and Procedure datasets were linked by the procedure identifier (ID). In addition to the procedure ID, the patient ID was used to identify multiple

procedures of the same patient. To populate missing data in several fields and resolve discrepant information between datasets, over 10,000 patient charts were reviewed manually. Updates were done in 2011, 2012, and 2014 and will be continued in 2016 to populate any other missing data. After merging the datasets and resolving discrepancies as mentioned above, duplicate entries of procedures were removed. Some variables were recoded from a text format into categorical form, and some categories were regrouped. Variables for which recording was done included: dysplasia level, pathology text, and pathology results. Pathology results were updated again in October 2012 because of missing data for polyps during a certain period due to alternate fields used by temporary CCC staff.

After updating, the final datasets for analysis were: a) Procedure dataset which had patient characteristics and procedure information, and b) Polyp dataset which included colorectal segment-wise polyp histology. Polyp ID or procedure ID was used to link to patient characteristics. Each patient has unique procedure ID in a procedure, which can be used to link procedure information between Polyp and Procedure datasets. Figure 3.2 shows the relationship of two datasets for linking procedure information in a patient.

A total of 26,523 colonoscopies were performed from September 4, 2001, to February 12, 2011. Of those 997 procedures were 3rd or higher order procedures of a single individual. The next step was to designate the second procedure is done within 6 months of the first colonoscopy as the first procedure (n=255) and assign their 3rd order procedures to become 2nd or surveillance procedures. Then, we integrate both polyp findings into one record. This is done because a second procedure within 6 months is

almost always due to the incomplete or unsatisfactory colonoscopy for whatever reason (Schoen et al., 2010; van Heijningen et al., 2015; Winawer et al., 2006).

The remaining 25,271 procedures were considered for the study. There were 20,912 adults with a first procedure. Of these, 4,359 had a second procedure more than 6 months after the first procedure (Figure 3.3). Of patients with an initial colonoscopy, we excluded 2,343 adults due to a) being aged below 40 years (not within the age group normally expected to undergo the adenoma-cancer sequence), aged more than 74 years (not recommended for routine screening and surveillance as per standard guidelines). We also excluded those with cancer at baseline procedure (n=103). This led to a potential sample of patients is 18,466. However, of these patient 1,569 had not yet completed the recommended surveillance interval as per the 2006 guidelines, as of February 11, 2011.

The surveillance recommendation recommends that adults with different risk adenomas at initial colonoscopy should undergo surveillance examination at <1-year, 1-year, 3- year, and 5-year intervals, respectively. Based on these criteria 1,569 patients were excluded. We allowed an additional 6 months over the recommended intervals to classify patients as surveillance completion eligible, as documented in the literature (van Heijningen et al., 2015). After exclusions, the study sample consisted of 16,897 eligible adults with a first procedure, of whom 4,234 eligible patients for surveillance. 1,793 of 12,571 total patients who are not eligible for surveillance have come back early (Figure 3.3).

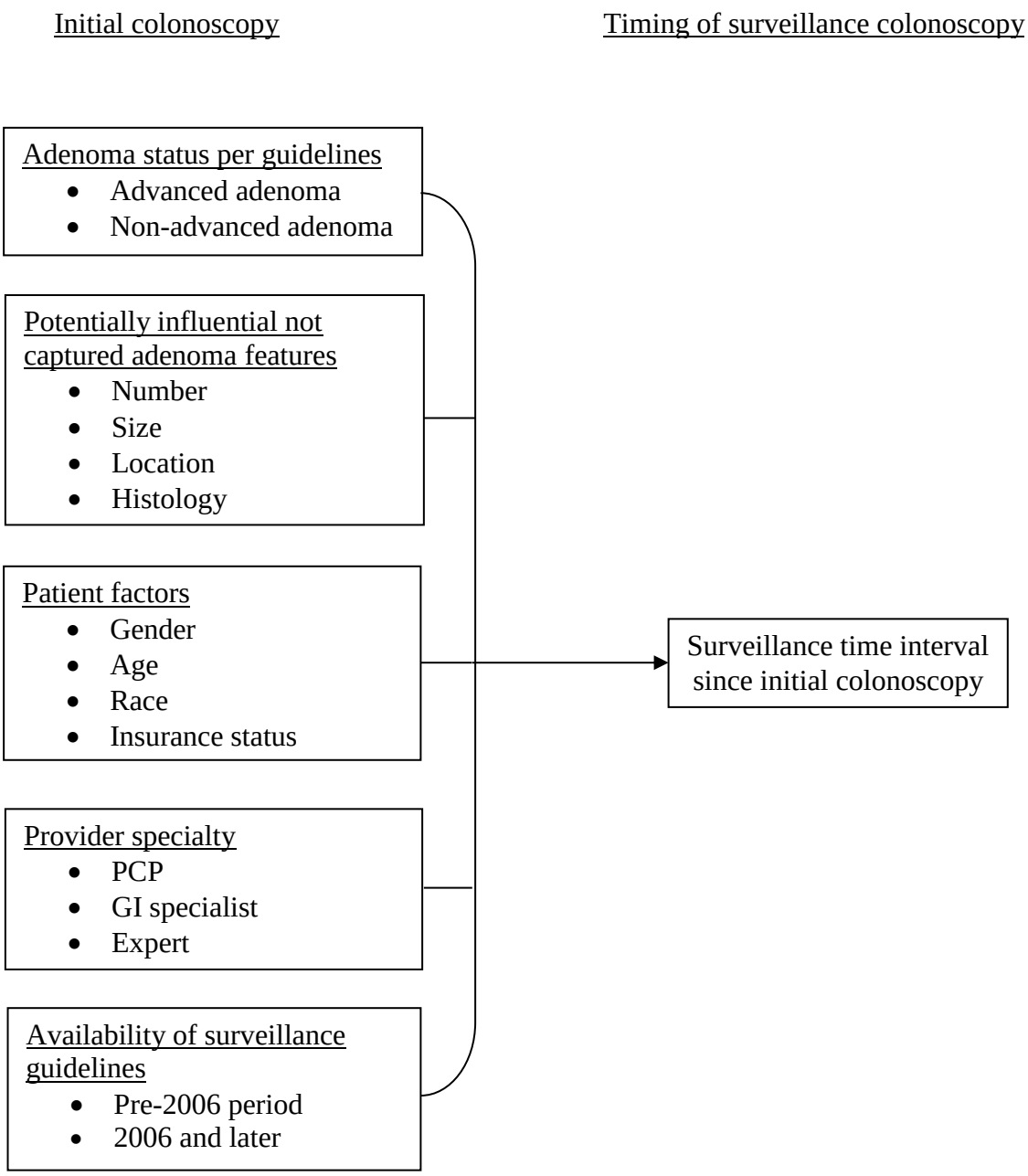

Figure 3.1 Study conceptual framework: predictors of surveillance time interval since initial colonoscopy

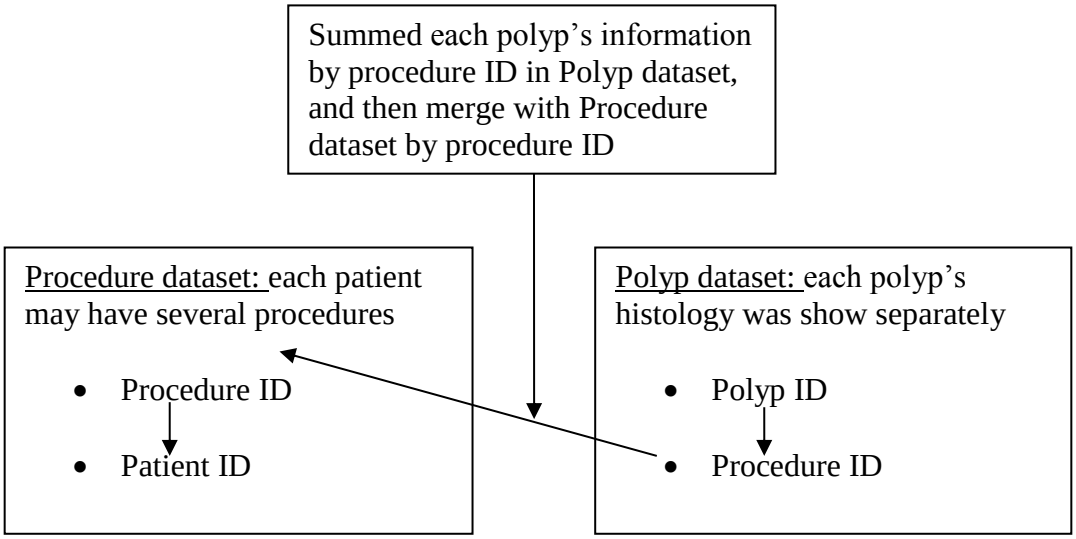

Figure 3.2 IDs used to link the two datasets to link procedure and patient information

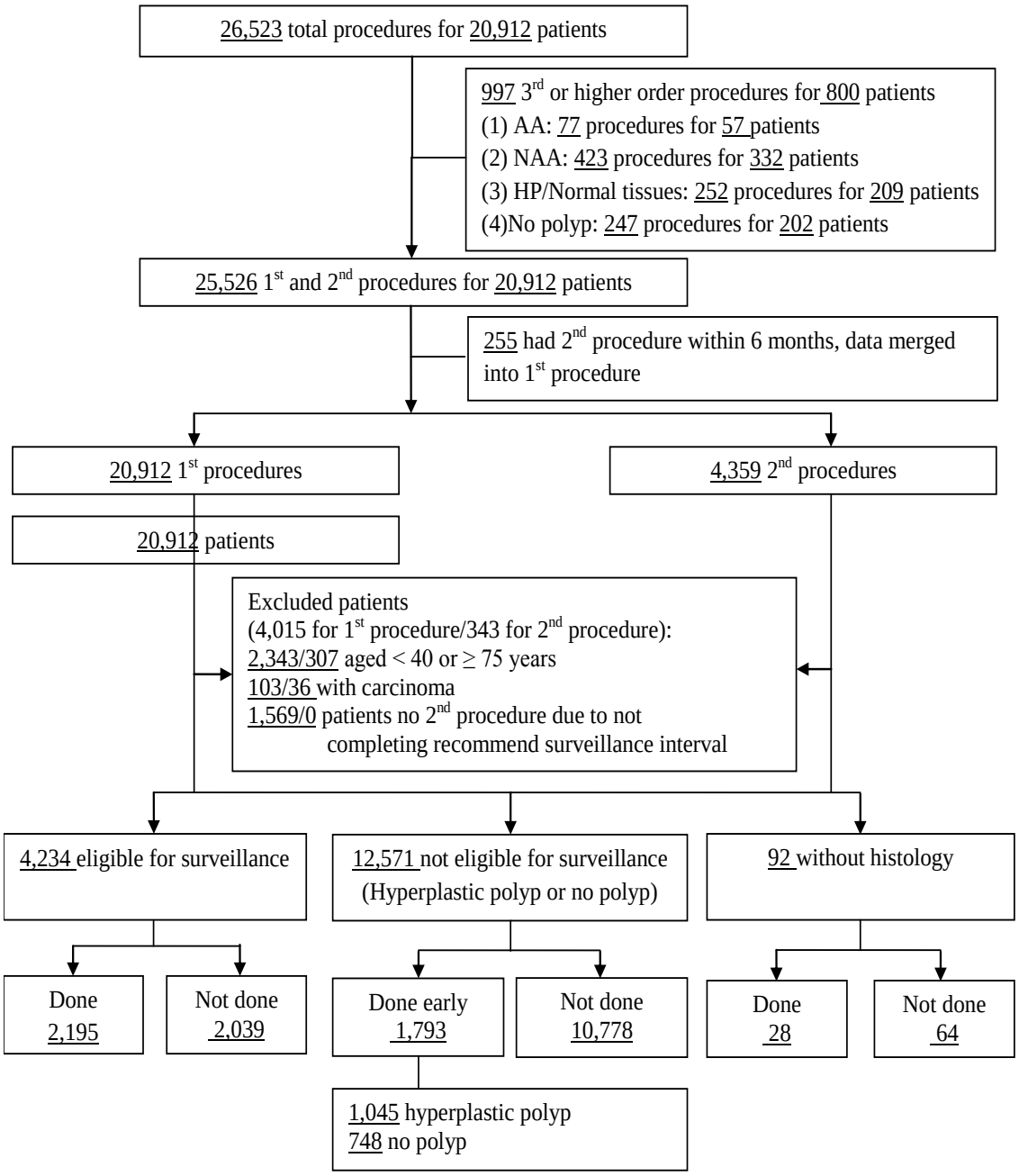

Figure 3.3 Identification of study eligible patients with baseline and first surveillance colonoscopy. Abbreviations: AA, Advanced adenoma; NAA, Non-advanced adenoma; HP, Hyperplastic polyp.

3.3 Study variables

This section describes the dependent, independent, and control variables of interest. All study variables of interest are summarized in Table 3.3 and 3.4, showing variable names, description, variable categories, and attributes.

3.3.1 Dependent variables of interest and definition

The time interval to surveillance colonoscopy is our key variable of interest. It is defined as the interval from initial colonoscopy to the second colonoscopy. It is calculated from the database variable *Procdate*, the procedure dates of baseline and second colonoscopy. The calculated interval is named *InterTime*. Patients with a *Procdate* each for baseline and surveillance colonoscopy are those who had surveillance. Otherwise, *Surveillance* = zero (no surveillance).

The third variable is appropriate surveillance, defined by the USMSTF on Colorectal Cancer (ACG and ASGE keep expand joint guidelines) of 2006. Table 2.2 of chapter 2 presents the guidelines for various risk groups based on screening colonoscopy findings. To summarize, the guidelines recommend 2-6 months for patients with sessile adenomas are removed piecemeal, 1-year surveillance for patients with hyperplastic polyposis syndrome or > 10 adenomas, 3-year surveillance for patients with 3-10 adenomas, ≥ 1 cm adenoma, or any adenoma with villous features, or high-grade dysplasia, 5-year surveillance for patients with 1 or 2 small tubular adenomas or any adenoma without advanced features, and 10-year surveillance for patients with small rectal hyperplastic polyps or normal tissues (hyperplastic or no polyp). The updated guidelines were published in 2006, which updated the criteria on histology and number of polyps detected.

We defined the timing of surveillance colonoscopies as appropriate if the surveillance was within a range of ±3 months for the ≤ 1-year surveillance group and ±6 months for ≥ 2-year surveillance time interval as per recommendations. The allowance of 3 or 6 months before or after is consistent with the documented literature on community-based series (van Heijningen et al., 2015). Those with surveillance earlier than these dates were classified as Overuse and later than these dates as Underuse. If patients had multiple polyp characteristics, the most severe one is used as the main indicator for determining time intervals. The corresponding appropriate surveillance intervals followed with the 2006 guidelines and are presented in Table 3.1 (Winawer et al., 2006). We grouped different time intervals as per guidelines into 5 levels: <1-year surveillance, 1-year surveillance, 3-year surveillance, 5-year surveillance, and 10-year rescreening. Patients were classified into these groups under the variable, *TimeGroup*. For guideline-concordance, the variable was coded into Overuse, Appropriate, Underuse, and No need for surveillance, called *TimelySur*. The overall compliance with timely surveillance colonoscopy was regrouped into guideline-inconsistent, and guideline-concordant, under the variable, *GuideConcordant*.

3.3.2 Independent variables of interest and definition

There are three key predictor variables of interest. These are adenoma features at baseline, guideline date (pre-2006 vs. 2006 and beyond), and insurance status.

(A)Adenoma related variables at baseline colonoscopy

1) Presence of adenoma/ advanced adenoma/ polyp

We identified patients who had an adenoma or polyp detected at surveillance colonoscopy. Each adenoma has a *Polypid* and a *Procedureid* to link each polyp

to the patient. All polyp information is documented in the Polyp dataset. If a patient ID exists in the Polyp dataset, it indicates this patient had a polyp. If the polyp was a histological adenoma, these patients were coded as" yes" for the variable "*Adenoma"* in the Procedure dataset. If a patient ID was not found in the Polyp dataset, or if the polyp showed normal tissue or hyperplastic tissue the patient was coded as" no" for the *Adenoma* variable.

A similar method was used to create a variable for the presence of advanced adenoma and any polyp, called *AdvAdenoma* and *Polyps*, respectively. The presence of advanced adenoma is defined as yes/no, yes=at least one advanced adenoma was found. Advanced adenoma is defined as villous features, the size of 1 cm or more, high-grade dysplasia, or early invasive cancer by Winawer et al recommendations (Winawer & Zauber, 2002). We defined another variable as *AdvAdenomaPlus* to add patients of a recently added high-risk category, these with ≥ 3 adenomas. Polyp presence is defined as yes/no. Yes= at least one polyp was found which were not normal tissues. Finally, we categorized patients by the most advanced adenoma found at baseline colonoscopy: advanced adenoma, non-advanced adenoma, and no adenoma, called *AdenoStatus*.

2) Number of polyps/adenomas (summarized at patient/ procedure level)

The number of polyps found in the patient was summarized within each patient using the patient ID in the Polyp dataset. The count of polyps was summed into the Procedure dataset, called *SumPolyp* by patient ID (using only hyperplastic or adenomatous polyps to count; polyps found to be of normal tissue of any kind were coded as no polyp in the Procedure dataset). *SumAdenoma* and

SumAdvAdenoma were created using a similar method. Another variable, polyp quantity is available, the total number of polyps found in the same colonic segment. These were summed across hyperplastic and adenomatous polyps and called *SumPolypQuantity* in the Procedure dataset. We also summed adenomatous polyps only to separate variable, called *SumAdenoPolypQty*. We created a categorical variable, in the polyp dataset *AdenoPolypQty* with 3 levels: no adenoma, 1-2 adenomas, 3-6 adenomas, and ≥ 7 adenomas.

3) Largest adenoma size (coded at the level of each adenoma)

The size of the adenoma was extracted from the Polyp dataset, polyp size in millimeters, called *Polypsizemm*. It was merged into Procedure dataset based on procedure ID, and the size taken in was based on hierarchically ordering all polyp size of the patient and selecting the largest adenoma. The largest adenoma size was categorized into ≥ 10 mm, 5.1-9.9mm, and ≤ 5mm, under the variable, *AdenoSize*.

4) Polyp anatomic location

The anatomic location of the polyp was extracted from Polyp dataset, which is *PolypLocation.* It is the original variable from primary data from the center, used to create the intermediate variables. The definition of the left colon is a location in the splenic flexure or descending colon. The location was defined as right if located in the cecum, ascending colon, hepatic flexure, or transverse colon. The remaining locations were defined as rectum and sigmoid if located in the rectum and sigmoid, respectively.

Two variables were created in the Polyp dataset for identifying: (1) The location of the largest adenoma, and (2) Number of colonic locations with an

adenoma. We created a variable for the location of largest adenoma, using three intermediate variables, *PolypLocation, Adenoma,* and *LargestPolyp. LargestPolyp* was created to identify the size of the polyp by hierarchical order in a procedure. Another intermediate variable was created to produce the number of locations with adenomas, *PolypLocation.* Those new variables were summarized at the procedure level based on procedure ID, called *LargAdenoLoc* and *SumNumLocAdeno*, respectively. *LargAdenoLoc* had four categories: "Largest adenoma located in the right colon", "Largest adenoma located in the left colon", "Largest adenoma located in the rectum colon", and "Largest adenoma located in the sigmoid colon". *SumNumLocAdeno* was categorized into 2 levels: adenomas at 1-3 locations, and adenomas at 4 locations.

5) Variables on histology of the polyp (tubular, tubulovillous/villous adenomas, polyps with dysplasia features, and hyperplastic polyps)

The polyp characteristics were extracted from the Polyp dataset, from the fields of *Pathologytext* and *Path_result* (These two variables fields were used by the center to record histology during different time periods or a study period). Data from both fields were drawn into a new intermediate *Polyp_result* variable with three values, tubulovillous/villous, hyperplastic, and tubular. For tubulovillous/villous and tubular adenoma, we also used the *adenoma* variable to capture, called *TubVillous* and *Tubular*. A new variable *HyperPolyp* (yes/no) was recoded directly from *Polyp_result* to designate whether it was a hyperplastic polyp.

A *dysplasia* variable was coded from *Pathologytext* and *Path_result*, which was initially coded based on raw date into 8 levels: Not mentioned (a level of

dysplasia not mentioned but stated to have dysplasia), Mild or no dysplasia, Moderate, Severe, Carcinoma in situ, Invasive carcinomas, Carcinoid tumor, and Probably invasive. We also coded patients with 2 or more advanced adenoma characteristics, which include ≥ 1cm adenoma, tubulovillous/villous adenomas, or any adenoma with high-grade dysplasia. The variable *AdcAdenoFea* (yes/ no) was created.

(6) Variable in polyp type (based on U.S. MSTF surveillance guidelines, Winawer et al 2006)

Variables on polyp type were created to align with the 2006 guidelines of surveillance colonoscopy timing. (1) small (< 1cm) rectal hyperplastic polyp, *SmallRtHP,* (2) 1 or 2 small (<1 cm) tubular adenoma with low-grade dysplasia, *TwoSmallTA*, (3) 3-10 adenomas, *ThreeToTenAdenoma,* (4) ≥1 cm adenoma, *BigAdenoma,* (5) tubulovillous/villous adenomas, *TubVillous,* (6) high-grade dysplasia, *HGD,* (7) hyperplastic polyposis syndrome, *HPPS,* (8) > 10 adenomas, *TenPlusAdenoma,* and (9) sessile adenomas removed piecemeal, *SessileAdenPiecemeal,* respectively (Table 3.2).

All those combinations were created from different source variables (*TubVillous* was mentioned earlier). *SmallRtHP* was coded based on *HyperPolyp*, *Polypsizemm,* and *PolypLocation* from the Polyp dataset. *TwoSmallTA* was coded from *Tubular* and *Polypsizemm. ThreeToTenAdenoma* and *TenPlusAdenoma* were coded from *SumAdenoPolypQty. BigAdenoma* was coded from *Polypsizemm.* Patients had high-grade dysplasia feature was coded from *Dysplasia. HPPS* was coded from *HyperPolyp, Polypsizemm,* and *PolypLocation*. Finally, patients with sessile adenomas removed piecemeal were coded from *PeduncSessile* and *Destroyed*. *PeduncSessile* was itself created from the text in the field, *Morphology* which has polyp morphological characteristics recorded by the performing physician, supplemented by additional notes from *Pathologytext*. The definition of *FullDestroyed* is: was the polyp completely removed in the procedure. All were extracted into the Procedure dataset based on the procedure ID where these new 9 variables were created. These patients were coded as" yes" for each variable of they had those features.

(B) Variable to designate initial colonoscopy, pre- or post- 2006 guideline

Prevalence of surveillance guideline at the time of baseline colonoscopy was coded based on *Procdate* (procedure date at baseline colonoscopy) into a variable, *PreGuideDate*. If the initial procedure date was before 2006, *PreGuideDate* was coded "Pre-2006 period"; if the initial colonoscopy took place in 2006 and later, it was coded "2006 and later".

(C)Insurance status at baseline colonoscopy

Patient's insurance information was collected at the time of initial colonoscopy from the original variable in the Procedure dataset, called *Inscarrier.* Insurance carriers were grouped into 4 groups: Medicare, Medicaid, private, and uninsured, called *Insurance2*.

3.3.3 Control variables

Patient demographic characteristics were adjusted in the models to examine their associations with the timeliness of surveillance.

(A) Patient demographic variables

Patient gender (female and male) was titled *PatGender.* Patient age was calculated from the patient's date of birth extracted from the CCC's administrative billing system, called *PatAge. PatAge* was recorded as a categorical variable, *AgeGro* into 3 age groups: 40-49, 50-59, and 60-74 years. Patient race was coded as Whites, Blacks, Other or unknown, called *PatRace*.

(B) Number of observation years available

It is defined as the interval from initial colonoscopy to the end of the study period. It is calculated from the database variable *Procdate,* the procedure dates of baseline and February 11, 2011. The variable is called *NumOfYrAvailable.*

Table 3.1 Operational criteria definitions used for classifying surveillance colonoscopy timing since initial colonoscopy to define Appropriate timing, Underuse, and Overuse category*

	Interval recommendation (in years)	No surveillance needed (time interval in years)		
Polyp types		Overuse	Appropriate	Underuse
Normal tissues (include few hyperplastic polyps or no polyp) –Not eligible for surveillance	10	<9.5	9.5-10.49	NA
Small rectal hyperplastic polyps	10	<9.5	9.5-10.49	NA
		Surveillance timelines category (time interval in years)		
1 or 2 small (<1 cm) tubular adenomas with low-grade dysplasia	5	<4.5	4.5-5.49	>5.5
Any adenoma without advanced features	5	<4.5	4.5-5.49	>5.5
3-10 adenomas, adenoma ≥1 cm, any adenoma with villous features, or high-grade dysplasia	3	<2.5	2.5-3.49	>3.5
Hyperplastic polyposis Syndrome**	1	<0.75	0.75-1.25	>1.25
>10 adenomas	1	<0.75	0.75-1.25	>1.25
Sessile adenomas that are removed piecemeal	<1	-	0-0.75	>0.75

*Winawer et al 2006; Levin et al 2008.

**Hyperplastic polyposis was defined by Burt and Jass for the World Health Organization International Classification of Tumors as: (1) at least 5 histologically diagnosed hyperplastic polyps proximal to the sigmoid colon, of which 2 are greater than 1cm in diameter, or (2) any number of hyperplastic polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with hyperplastic polyposis, or (3) more than 30 hyperplastic polyps of any size distributed throughout the colon. Since our study did not have information on first-degree relatives, we included first and third definitions in hyperplastic polyposis (Burt & Jass, 2000).

Table 3.2 Study variable definitions used to create polyp types as the 2006 guidelines[*]: baseline colonoscopy

Variable name	Description	Categories	Attribute
Adenoma characteristics			
Polyps	Does this patient have any polyp?	No, Yes	Dichotomous
Adenoma	Does this patient have any adenoma?	No, Yes	Dichotomous
AdvAdenomaPlus	Does this patient have advanced adenoma?[**]	No, Yes	Dichotomous
SmallRtHP	Any polyp is small (< 1cm) rectal hyperplastic polyp?	No, Yes	Dichotomous
TwoSmallTA	Is any 1 or 2 small (<1 cm) tubular adenoma with low-grade dysplasia?	No, Yes	Dichotomous
ThreeToTenAdeoma	Are any 3-10 adenomas?	No, Yes	Dichotomous
BigAdenoma	Is any ≥1 cm adenoma?	No, Yes	Dichotomous
TubVillous	Any polyp is tubulovillous/ villous adenoma?[#]	No, Yes	Dichotomous
HGD	Is any adenoma with high-grade dysplasia?	No, Yes	Dichotomous
HPPS	Is any hyperplastic polyposis syndrome?	No, Yes	Dichotomous
TenPlusAdenoma	Are any >10 adenomas?	No, Yes	Dichotomous
SessileAdenPiecemeal	Any polyp is sessile adenomas that are removed piecemeal?	No, Yes	Dichotomous

[*]The polyp types were created as follow the guidelines by Winawer et al 2006.

[**]Advanced adenoma is defined as villous features, the size of 1 cm or more, high-grade dysplasia, 3 or more adenomas, or early invasive cancer.

[#]According to the 2006 guidelines, we mainly considered patients who had sessile adenoma that are removed piecemeal. Therefore, we did not consider other morphology.

Table 3.3 Study variable definitions used in analysis: baseline colonoscopy (all variables at the patient level)

Variable name	Description	Categories	Attribute
Patient characteristics			
PatGender	Patient gender	Female, Male	Dichotomous
AgeGro	Patient age	40-49, 50-59, 60-74	Categorical
PatRace	Patient race	Whites, Blacks, Other or unknown	Categorical
Insurance2	Insurance status	Medicare, Medicaid, Private, Uninsured	Categorical
Colonoscopy characteristics			
PreGuideDate	When does this patient take first procedure?	Pre-2006 period, 2006 and later	Dichotomous
NumOfYrAvailable	The number of years from initial colonoscopy to the end of the study period		Continuous (Numeric)
Adenoma characteristics			
AdenoStatus	The most advanced of adenoma found	Advanced adenoma, Non- advanced adenoma, No adenoma	Categorical
LargAdenoLoc	The location of largest adenoma found	Right colon, left colon, rectum, sigmoid colon	Categorical
SumNumLocAdeno	The number of locations with adenomas found	1-3 locations, 4 locations	Categorical
AdenoSize	The largest size of adenoma found	$\geq$ 10 mm, 5.1-9.9mm, $\leq$ 5 mm	Categorical
AdenoPolypQty	The number of adenomas found in the same colonic segment	1-2 adenomas,3-6 adenomas, $\geq$ 7 adenomas	Categorical
AdcAdenoFea	Any 2 or more advanced adenoma characteristics found?	No, Yes	Dichotomous

Table 3.4 Study variable definitions used in analysis: surveillance colonoscopy

Variable name	Description	Categories	Attribute
SurveillanceStatus*	The status of surveillance colonoscopy by the end of study period	Event = Yes or No	Categorical
InterTime	Time interval (years) to surveillance colonoscopy		Continuous (Numeric)
TimeGroup	Time interval (years) to surveillance/ rescreening colonoscopy by 2006 guidelines	<1-year, 1-year, 3-year, 5-year, 10-year rescreening for overuse,10-year rescreening	Categorical
TimelySur	Timing of surveillance colonoscopies with 2006 guidelines	Overuse, appropriate, underuse, no surveillance needed	Categorical
GuideConcordant	Does this patient have surveillance colonoscopy concordant with the guideline?	No (Guideline-inconsistent), Yes(Guideline-concordant)	Dichotomous

**SurveillanceStatus* variable is used in Kaplan-Meier (KM) curves estimation and the definition is described under section 3.4 Statistical Methods.

3.4 Statistical methods

This section describes the process of data management and analysis including statistical methods. The study used descriptive and inferential analysis. Finally, the preliminary findings on sample distribution are presented to assist further recoding of variables in answering the research questions.

3.4.1 Data management and analysis

The study uses data on all colonoscopies conducted from September 4, 2001, to February 12, 2011, imported from the CCC's Microsoft Excel databases. The primary datasets were Physician (no names imported), Procedure, Polyp, and Patient datasets (without patient identifiers except a numeric patient ID corresponding to the number on their medical record at CCC). The Procedure dataset consisted of data entered by CCC staff into Excel based on clinical procedure notes. Procedure data fields used for the study were based on raw variables: total procedure time (time of scope insertion, time out of anus, time of starting withdrawal), sequential number of the physician's procedure if it was < 140^{th} for that physician, and cecum reached status; The Polyp data used are histology of the polyp, whether this polyp an adenoma, size, dysplasia level, whether the polyp was removed, how was the polyp removed, and location of the polyp. The Patient fields used were the patient age at the initial procedure date, gender, and race.

Data preparation on to satisfy the study objectives, for all patients with a first procedure up to February 12, 2011, first surveillance procedures if done is described in section 3.2. We excluded those who are not eligible for surveillance colonoscopy and those who did not have any second procedure due to not completing the surveillance interval as of the end of the study period. The following statistical analyzes were used to

examine associations between the dependent and independent variables of interest as defined earlier. SAS v9.4 was used.

3.4.2 Descriptive statistics

Descriptive statistics are used to describe the patients, procedures, and polyps and to examine bivariate associations between the dependent and independent variables of interest. Chi-square and analysis of variance (ANOVA) are used. In the descriptive tables, distribution of patients, procedures, and polyps are shown using percentages for categorical variables and means with standard deviation (mean±SD) for continuous variables.

(1)Chi-square test

A chi-square test (X^2) is used to determine whether there is a significant difference between the expected and observed frequencies in one or more categories.

(2)Fisher's exact test

The Fisher's exact test is a statistical significance test used in the analysis of contingency tables. It is applied when we plan to conduct a chi-square test, but one or more cells have an expected frequency of 5 or less (Fisher, 1922).

(3)ANOVA test

The ANOVA test is used to analyze differences between group means and their associated procedure. It provides a statistical test of whether or not the means of several groups are equal, of generalizes the t-test to more than two comparison groups, using 0.05 levels of significance.

3.4.3 Inferential statistics

Inferential statistics is used to judge the probability that an observed difference between groups is not merely a matter of chance. Kaplan-Meier (KM) curves with log-rank test, logistic regression model, and multinomial logistic regression model are used.

(1) Kaplan-Meier (KM) curves

The original definition of the Kaplan-Meier curves was published for dealing with those incomplete observations with an incomplete event by the end of study period by Edward L. Kaplan and Paul Meier in 1958. Kaplan-Meier (KM) curves have become a familiar way of dealing with differing survival times (time-to-event), especially when not all the subjects continue in the study. In the use of KM curves, survival time does not need to relate to death as the event. The event may be any event of interest (Kaplan & Meier, 1958). It has also been applied to estimate the surveillance probability (getting a colonoscopy) or any adenoma recurrence by time to surveillance, using adenoma features at index screening (Huang et al., 2010; Schoen et al., 2010; van Heijningen et al., 2015).

In preparing the data for KM survival analysis, each subject is characterized by three elements: (1) their period in the study, (2) the status at the end of their time, and (3) the study group they are in. Time-to-event is defined as time duration for each subject having a beginning and an end anywhere along the timeline of the complete study. It can begin when the subject is enrolled into a study or when treatment begins (in this case initial colonoscopy date), and ends when the end-point is reached (surveillance) or is censored from the study for other reasons. Censoring occurs when the subject's total time duration at risk for the event cannot be accurately determined, such as in the case of dropouts, lost to follow-up, or required data is not available. KM curves illustrate the change in the

cumulative probability of the event in a given length of time while breaking up time into many small intervals, which was used to calculate a step-wise estimate (Rich et al., 2010).

Based on these features, KM estimates can be applied to surveillance colonoscopy use, which is the simplest way to compute surveillance use over time, despite the challenge of subjects lost to follow-up in the study period. It is a nonparametric statistic used to estimate the surveillance function from lifetime data. The main purpose is to measure the fraction of patients who have surveillance colonoscopy over a certain amount of time after the initial colonoscopy in clinical practice. Our study estimated probability curves to compare the pattern of timing of surveillance colonoscopies relative to recommended intervals for patients with an initial colonoscopy in the pre-2006 period vs. post-2006(includes those with the first procedure in 2006). *InterTime* variable is our main dependent variable for comparison of surveillance colonoscopy use pre- and post-guideline. The comparisons are also adjusted for the differences in patient gender, age, and race by time interval groups to surveillance colonoscopy.

The survival time is defines as the time lapsed from a defined starting point (initial colonoscopy in this study) to the occurrence of a given event (surveillance). Subjects who did not undergo surveillance are counted as right censoring since they may have surveillance in the future. Variable *SurveillanceStatus* was created to identify censoring status on surveillance colonoscopy use. It defined as an event (*SurveillanceStatus* variable=1) when patients had the second procedure by the end of the study period. *SurveillanceStatus* =0 if they had no second procedure until February 11, 2011.

The conditional probability of surveillance colonoscopy at any particular time (t) is calculated by the formula as follow as:

$$S(t) \quad = 1 - \frac{Number\ of\ patients\ completed\ surveillance\ at\ time\ t}{Number\ of\ patients\ eligible\ for\ \ surveillance\ at\ time\ t}$$

Surveillance probability at time t is calculated as the product of the conditional probability till time t.

(2) Comparison of Kaplan-Meier (KM) estimates: log-rank test

The log-rank test is the most common method to compare the difference between survival curves. Our study applied this test for comparing surveillance colonoscopy use by patients with the first colonoscopy in two different periods, pre-2006 period vs. 2006 and later. Log-rank test is used to examine whether two periods are statistically different on probability of surveillance colonoscopy use. This test is to calculate the expected number of surveillance colonoscopy in the two periods (E1 and E2) against the actual total number of observed surveillance colonoscopy events (O1 and O2) in the two periods, respectively. The test statistic is as follow as:

$$Log - rank\ test\ statistic = \frac{(O_1 - E_1)}{E_1} + \frac{(O_2 - E_2)}{E_2}$$

Where O_1 represents the sum of the observed number of surveillance colonoscopy for the pre-2006 cohort and E_1 represents the sum of the expected number of surveillance colonoscopy this cohort. Similarly, we can define O_2 and E_2 with the post cohort.

The test statistic and significance can be drawn by comparing the calculated value with the critical value, using chi-square tables, at one degree of freedom (Goel et al 2010; Rich et al 2010) (Goel, Khanna, & Kishore, 2010; Rich et al., 2010).

(3)Logistic regression model (Wang, Xie, & Fisher, 2009)

The logistic regression model is for binary outcome measures in non-hierarchically structured data. It has been used in many surveillance colonoscopy studies predicting adenoma recurrence, as mentioned in the prior chapter. Multinomial logistic regression is used to predict categorical placement in, or the probability of category membership of a multi-level dependent variable predicted by multiple independent variables. This model is also a simple extension of binary logistic regression to accommodate more than two categories of the dependent variable. Since multinomial logistic regression does necessitate consideration of the sample size, we should follow sample size guidelines which indicate a minimum of 10 cases per independent variable (Hosmer & Lemeshow, 1989).

Statistically in logistic regression, the probability of "event" is usually converted to an odds ratio [*p/ (1-p)*], resulting in the following logistic regression or logit model:

$$logit(p) = \log\left[\frac{p}{1-p}\right] = \beta_0 + \sum_{n=1}^{n} \beta_n X_n$$

Where β_n is the regression slope coefficient of the explanatory variable X_n

The logit model can be expressed in terms of the probability of an event occurring:

$$p = \Pr(y_i = 1 | X) = \frac{\exp(z)}{1+\exp(z)} \quad \text{or} \quad p = \frac{1}{1+\exp(-z)}$$

Where z=$\beta_0 + \sum_{n=1}^{n} \beta_n X_n$. Those equations called the logistic function have an S-shaped distribution, which signifies a non-linear relationship between the outcome probability and covariates.

This study will use bivariate and multivariate logistic regression models to determine the factors that drive the likelihood of having timely surveillance. The main dependent variable is *GuideConcordant*, which is whether the surveillance colonoscopy is guideline-concordant.

Therefore, we mainly test the association between surveillance concordance and the variables of initial adenoma status, adenoma features (includes the location of largest adenoma, number of locations with adenoma, the largest size of adenoma, number of adenomas found in the same colonic segment, and with 2 or more advanced adenoma characteristics) and insurance status, adjusting for the remaining variables. The model is as follows:

$Y_{\text{Guideline-concordant (Yes vs. No)}} = \beta_0 + \beta_1 \times$patient gender$+ \beta_2 \times$patient age$+ \beta_3 \times$patient race$+ \beta_4 \times$insurance status$+ \beta_5 \times$period relative to guideline $+ \beta_6 \times$adenoma status$+ \beta_7 \times$ location of largest adenoma$+ \beta_8 \times$ number of location with adenoma$+ \beta_9 \times$ the largest size of adenoma$+ \beta_{10} \times$ number of adenomas found in the same colonic segment$+ \beta_{11} \times$ 2 or more advanced adenoma characteristics$+ \varepsilon_{error}$

Then, we use bivariate and multivariate multinomial logistic regression to determine the factors that drive the likelihood of timely surveillance. The main outcome is *TimelySur*, which is surveillance colonoscopy prevalence relative with the guidelines being overuse, appropriate, or underuse. It mainly tests the association between initial adenoma status, adenoma features (includes the location of largest adenoma, number of locations with adenoma, the largest size of adenoma, number of adenomas found in the same colonic segment, and with 2 or more advanced adenoma characteristics) and insurance status in relation with timely surveillance, adjusting for the remaining variables.

Since the outcome variables with 3 categories, we assign appropriate to be reference group. There are two models are used to discuss. The first model is to compare overuse to appropriate of surveillance colonoscopy, as follows:

$Y_{\text{Timely Surveillance(Overuse vs. Appropriate)}} = \beta_{10} + \beta_{11} \times$patient gender$+ \beta_{12} \times$patient age$+ \beta_{13} \times$patient race$+ \beta_{14} \times$insurance status $+ \beta_{15} \times$ period relative to guideline $+ \beta_{16} \times$adenoma status$+ \beta_{17} \times$ location of largest adenoma$+ \beta_{18} \times$ number of location with adenoma$+ \beta_{19} \times$ the largest size of adenoma$+ \beta_{110} \times$ number of adenomas found in the same colonic segment$+ \beta_{111} \times$ 2 or more advanced adenoma characteristics$+ \varepsilon_{error}$

The second model will compare underuse to appropriate surveillance colonoscopy, as follows:

$Y_{\text{Timely Surveillance(Underuse vs. Appropriate)}} = \beta_{20} + \beta_{21} \times$patient gender$+ \beta_{22} \times$patient age$+ \beta_{23} \times$patient race$+ \beta_{24} \times$insurance status $+ \beta_{25} \times$ period relative to guideline $+ \beta_{26} \times$adenoma status$+ \beta_{27} \times$ location of largest adenoma$+ \beta_{28} \times$ number of location with adenoma$+ \beta_{29} \times$ the largest size of adenoma$+ \beta_{210} \times$ number of adenomas found in the same colonic segment$+ \beta_{211} \times$ 2 or more advanced adenoma characteristics$+ \varepsilon_{error}$

3.5 Steps of data analysis

This section describes the plan for applying the above statistical methods in our study to answer the research questions. Statistical models are used to examine associations between the timing of surveillance colonoscopies (dependent variable) and independent variables of interest. For our two objectives, the following steps will be used for reporting outcomes in Figures and Tables.

3.5.1 Dependent and independent variables of interest

Time to surveillance colonoscopy is the dependent variable. Adenoma status, adenoma features (includes the location of largest adenoma, the number of locations with adenoma, the largest size of adenoma, number of adenomas found in the same colonic segment, and with 2 or more advanced adenoma characteristics) and insurance status are our key independent factors of interest. The control variables include patient demographics (gender, age, and race), and number of observation years available. P values of < 0.05 will be considered as statistically significant.

3.5.2 Analysis steps for objective 1

Our first objective is to compare the observed timing of surveillance colonoscopies relative to the 2006 recommended intervals for patients with an initial colonoscopy in the pre-2006 period vs. 2006 and later. This section presents the preliminary frequency distributions to assess the feasibility of answering the research questions.

Identification of study eligible patients with a baseline colonoscopy showing exclusions from the full patient sample is presented in Figure 4.1. It presents the number with a second procedure by date of initial colonoscopy of the eligible initial colonoscopies. The criteria of define appropriate surveillance interval as per guidelines are shown in Table 4.1. Table 4.2 presents characteristics of the study population at baseline colonoscopy, including patient gender, age, race, insurance status, and other variables. The chi-square test will be used to examine the relationship of surveillance appropriateness with the guideline date (pre-2006 period, vs. 2006 and later).

Then, Kaplan-Meier (KM) curves will be used to estimate the surveillance probability over time since the initial colonoscopy. The analysis is stratified by the two cohort

periods relative to guideline date, and by recommended time interval groups based on findings baseline colonoscopy: ≤ 1-year surveillance, 3-year surveillance, and 5-year surveillance (Figure 4.2-4.4). Patients who do not qualify for surveillance had a premature second procedure will also be shown (Figure 4.5). Comparisons of characteristics between groups will be presented by the log-rank test.

The study will further examine the timing of surveillance colonoscopies relative to guideline-concordance among the pre-2006 period patients vs. 2006 and later patients, and by time interval groups at initial colonoscopy. Timing of surveillance colonoscopy will be stratified into 3 categories: overuse, appropriate, and underuse. A Pearson's chi-square or Fisher's exact test will be used to compare the percentages with timely surveillance, overuse and underuse between pre-guideline and post-guideline cohorts (Table 4. 3).

3.5.3 Analysis steps for objective 2

Our second objective is to study the factors that determine the likelihood of timely surveillance. We test our independent variables of interest associated with timely surveillance, adjusting for the remaining variables.

Characteristics of study subjects with a screening colonoscopy between September 4, 2001 and February 11, 2010 are presented in Table 5.1. Table 5.2 shows the percentage of surveillance-eligible patients with guideline-concordant surveillance relative to recommended guidelines (overuse, appropriate, late, and not done). We use the Pearson chi-square test to profile the study population by features at initial colonoscopy that are associated with surveillance use (Table 5.2). Then, we identify variables of interest that drive the likelihood of having a 2nd procedure among total study sample and surveillance-

eligible patients after controlling for the remaining variables presented in Table 5.3 and 5.4. Logistic regression results will be used.

Association of surveillance timing intervals with polyp, patients, and procedure-related characteristics among surveillance-eligible who completed surveillance by recommended surveillance intervals are shown in Table 5.5-5.8. Linear regression results will be applied. The variables of interest associated with the likelihood of the timing of surveillance colonoscopy relative to recommended intervals after controlling for the remaining variables will be presented in Table 5.9. Since our primary outcome of interest has 4 levels, multinomial logistic regression will be performed.

3.6 Preliminary reviews of sample distribution by key dependent and independent variables

The study presents the preliminary sample distribution by patient demographics, utilization of surveillance colonoscopy, time intervals to surveillance colonoscopy, and adenoma features at baseline colonoscopy (location of largest adenoma, number of anatomic locations with an adenoma, the largest size of adenoma, number of adenomas within the same colonic segment, and patients with 2 or more advanced adenoma characteristics). The distributions and the changes made to variable categories for final analyses, keeping in view cell sizes are shown below.

3.6.1 Characteristics of study population and utilization of surveillance colonoscopy

Of 16,897 eligible patients with an initial colonoscopy, about 56.4% of patients had an initial colonoscopy in the pre-2006 period. All patients 4,016 (23.8%) had a second colonoscopy after a mean of 3.5 years (SD 1.7). Majority of patients were female (54.1%), aged ≥ 50 years (49.5% and 34.2% at age 50-59 years and 60-74 years, respectively), and

were Black (51.9%). Having insurance coverage may affect the surveillance colonoscopy use. About 70.7% of patients had private insurance and 17.8% had Medicare coverage. The majority of the procedures were performed by PCPs (74.0%) (Table 3.5). Regarding surveillance colonoscopy use, patients with adenoma and advanced adenoma found at baseline colonoscopy had higher rates of repeat examinations (Table 3.6).

3.6.2 Bivariate distributions relevant to objective 1

Study objective is to compare the timing of surveillance colonoscopies relative to the recommended surveillance intervals among the pre- and post-guideline cohorts. The time interval to surveillance is our main dependent variable. Table 3.7 presents timeliness of surveillance colonoscopy by recommended time interval groups. Among 4,234 eligible patients for surveillance, most of the patients did not have follow-up screening at <1-year (51.7%), 1-year (46.3%), and 3-year (48.9%) recommended time interval groups. The frequency of overuse and underuse which is not done surveillance colonoscopy are similar in 5-year groups. 1,793 of 12,571 total patients who are not eligible for surveillance have come back early.

3.6.3 Bivariate distributions relevant to objective 2

Study objective 2 is to examine the factors associated with the likelihood of timely surveillance. Timeliness of surveillance is our key dependent variable, which is categorized into overuse, appropriate, and underuse. We pool the various polyp/adenoma patient groups into the 3 categories based on each patient recommended time and observed the timing of surveillance. This pooling was done as a Table 3.1. The frequencies of independent variables of interest show that the majority of the patients had 1-2 adenomas (13.3%) and 3-6 adenomas (9.8%) in the same colonic segment (Table 3.8).

Regarding the largest size of adenomas found, about 15.6% and 4.6 % of patients had ≤ 5 mm and ≥ 10 mm adenoma found (Table 3.9). Moreover, there were most of the patients with the largest adenoma had it in the right colon (12.5%). The distribution is similar for adenomas found in the left colon, rectum, and sigmoid colon (3.5%, 3.9%, and 4.7%, respectively) (Table 3.10). Several polyp features were also identified at the initial colonoscopy. There were 454 of patients had any adenoma with tubulovillous/villous (2.7%), 3,826 tubular (22.7%), and 149 high-grade dysplasia (0.9%) features at initial colonoscopy (Table 3.11).

Overall, these preliminary reviews of the sample distributions guided our scheme for recoding variables and the models used to address our research questions.

3.6.4 Potential limitations

Overall, our study has some potential limitations relative to our data characteristics. Our findings may not generalize to the US because we use data comes from a single endoscopy center in SC. Moreover, the retrospective study design may result in some loss to follow-up because some patients will have surveillance colonoscopies at other facilities. Another potential limitation is that the pathology report may not have clearly identified the number of polyps with different histology because multiple polyps were recorded within one colonic segment. Finally, our dataset does not document information on a family history of CRC or comorbiditites, which may drive surveillance colonoscopy appropriateness.

Table 3.5 Characteristics of the study population at baseline colonoscopy (n=16,897)

	All patients, N (%) (n=16,897)
Gender	
Male	7,673(45.41%)
Female	9,144(54.12%)
Missing	80(0.47%)
Age	
40-49	2,755(16.30%)
50-59	8,367(49.52%)
60-74	5,775(34.18%)
Race	
White	7,470(44.21%)
Black	8,771(51.91%)
Other/ Unknown	656(3.88%)
Insurance status	
Medicare	3,008(17.80%)
Medicaid	525(3.11%)
Private	11,939(70.66%)
Uninsured	1,425(8.43%)
Initial procedure timing	
Pre-2006 period	9,526(56.38%)
2006 and later	7,371(43.62%)

Table 3.6 Utilization of second colonoscopy by polyp status at initial colonoscopy (n=16,897)

		Surveillance colonoscopy	
	Total, N (%)	Yes, N (%) (N=4,016)	No, N (%) (N=12,881)
Advanced adenoma	1,683(9.96%)	900(53.48%)	783(46.52%)
Non-advanced adenoma	2,551(15.10%)	1,295(50.76%)	1,256(49.24%)
Hyperplastic polyp or normal tissue	5,654(33.46%)	1,045(18.48%)	4,609(81.52%)
No polyp	6,917(40.94%)	748(10.81%)	6,169(89.19%)
Missing*	92(0.54%)	28(30.43%)	64(69.57%)

*The definition of missing is without histology information for that polyp.

Table 3.7 Timeliness of surveillance colonoscopy by time interval groups at initial colonoscopy*

Recommended time interval groups	Overuse	Appropriate	Underuse-late	Underuse-not done	No surveillance needed
< 1-year (n=757)	0	9 (1.19%)	357 (47.16%)	391 (51.65%)	-
1-year (n=54)	2 (3.70%)	11 (20.37%)	16 (29.63%)	25 (46.30%)	-
3-year (n=1,891)	589 (31.15%)	281 (14.86%)	97 (5.13%)	924 (48.86%)	-
5-year (n=1,532)	763 (49.80%)	43 (2.81%)	27 (1.76%)	699 (45.63%)	-
10-year rescreening for overuse	1,793	-	-	-	-
10-year rescreening	-	-	-	-	10,778

*92 missing are without histology information for that polyp. We excluded 1,569 patients no 2nd procedure due to not completing recommended surveillance interval, including 0 for ≤ 1-year, 3 for 1-year, 556 for 3-year, and 1,010 for 5-year follow-ups.

Table 3.8 Number of adenomas found in the same colonic segment at initial colonoscopy

	N (%)
No polyp	6,917 (40.94%)
Hyperplastic polyp or normal tissue	5,654 (33.46%)
1-2 adenomas	2,249 (13.31%)
3-6 adenomas	1,656 (9.80%)
≥ 7 adenomas	283 (1.67%)
Missing	138 (0.82%)

Table 3.9 The largest size of adenoma found at baseline colonoscopy

	N (%)
No polyp	6,917 (40.94%)
Hyperplastic polyp or normal tissue	5,654 (33.46%)
≤5mm	2,635 (15.60%)
5.1-9.9mm	774 (4.58%)
≥10mm	768 (4.55%)
Missing	149 (0.88%)

Table 3.10 The location where the largest adenoma found at baseline colonoscopy

	N (%)
No polyp	6,917 (40.94%)
Hyperplastic polyp or normal tissue	5,654 (33.46%)
Right	2,107 (12.47%)
Left	589 (3.49%)
Rectum	651 (3.85%)
Sigmoid	793 (4.69%)
Missing	186 (1.10%)

Table 3.11 Frequency of patients with any adenoma showing the features of (1)Tubulovillous/villous adenomas, (2)tubular adenomas, and (3) high-grade dysplasia features at baseline colonoscopy* (Total patients= 16,897; No polyp=6,917; Hyperplastic polyp=5,654; Adenomatous polyp=4,234)

	Tubulovillous/villous adenomas, N (%)	Tubular adenomas, N (%)	High-grade dysplasia, N (%)
No	3,780(22.37%)	408(2.41%)	4,085(24.18%)
Yes	454 (2.69%)	3,826 (22.65%)	149 (0.88%)
Missing	92 (0.54%)	92 (0.54%)	92 0.54%)

*Features are not mutually exclusive.

CHAPTER 4

AN ASSESSMENT OF COMPLIANCE WITH SURVEILLANCE GUIDELINES ISSUED BY PROFESSIONAL SOCIETIES, AND IMPLICATIONS FOR RESOURCE UTILIZATION

Abstract

Background

Colorectal cancer (CRC) can be prevented by population-wide colonoscopy screening and polyp removal, followed by periodic surveillance of those with adenomatous polyps. Both overuse (premature) and underuse of colonoscopy (delayed/not done) are documented. Underuse may undermine CRC prevention while overuse causes inefficient use of provider workforce and reduced system screening capacity. We examined the impact of the 2006 U.S. Multi-Society Task Force guidelines on surveillance timing.

Methods

We studied the timing of surveillance colonoscopies in a community-based cohort of patients with a screening colonoscopy between September 2001 and February 2010 at a large endoscopy center in South Carolina, followed through February 2011. We compared patients with screening colonoscopy done in the pre- and post-2006 periods for appropriate surveillance use, overuse (delayed surveillance), and underuse (premature or

not done), classified by recommended surveillance interval category, using chi-square tests and Kaplan-Meier (KM) estimation with the log-rank test.

Results

Of 16,897 study patients, 4,234 were found to have adenomatous polyps (surveillance-eligible), of whom 2,195 (51.8%) had a surveillance colonoscopy. Surveillance timing was inappropriate for 91.8% of patients, being similar in the pre-and post-guideline periods. Underuse was more likely among ≤1- and 3-year recommended surveillance groups ($p<0.001$), and overuse among 5-year recommended surveillance ($p<0.001$). Among those without adenomas at screening colonoscopy, 14.3% (1,793 of 12,571 pre-period patients) had a premature second colonoscopy after a mean of 4.65 years, vs. the recommended 10-yearly repeat colonoscopy.

Conclusions

Premature repeat colonoscopies among low-risk patients who do not qualify for surveillance per guidelines, and premature surveillance colonoscopies in patients with low-risk polyps consume significant provider resources. Minimizing overuse will spare scarce provider time for surveillance of high-risk patients at appropriate time intervals which may improve population outcomes at no extra cost. Underuse among all risk categories of surveillance-eligible patients should be addressed.

Keywords: Surveillance colonoscopy, time intervals, adenoma features, guideline date.

Introduction

Colorectal cancer (CRC) is the third most common cancer in the United States, and the second leading cause of cancer death in men and women combined. In South Carolina during 2015, an average of 2,220 adults are diagnosed and 830 adults die from CRC

(Siegel, Miller, & Jemal, 2016). Individuals with adenomatous polyps are at risk of recurrence (metachronous lesions), which may increase the likelihood of cancer. Screening colonoscopies followed by periodic surveillance is recommended by the joint guidelines issued by the US Multi-Society Task Force on Colorectal Cancer (USMSTF) and the American Cancer Society (Winawer et al., 2006).

Surveillance guidelines have changed significantly since 1997, a summary of which is provided in Table 4.1. In 1997, 3-year surveillance was recommended for patients with large (>10mm) or multiple adenomas, and no specific guidelines were given for those with lower-risk adenomas (Winawer et al., 2006). There was no mention of person without adenomas or those with only hyperplastic polyps. The guidelines became more specific for the lower risk group (persons with 1-2 small, tubular adenomas) in 2003, recommending surveillance colonoscopy at 5 years rather than 3 years for this group (Winawer et al., 2003). In addition, the guidelines cautioned that evidence was still evolving, and that the interval could be changed with new evidence. The surveillance recommendations keep updated in the joint guidelines issued in 2006, which remains valid to date. The increased and lower risk groups were definitively recommended for 3-year and 5-year surveillance with an expectation that such definitive risk stratification would reduce the intensity of surveillance procedures in a substantial proportion of patients (Winawer et al., 2006). In the US, an estimated 25% of all colonoscopies were performed for surveillance purposes (Lieberman et al., 2000; Lieberman et al., 2005).

Both overuse (or premature) and underuse (or delayed/not done) of surveillance are reported, underuse among high-risk adults and overuse among low-risk adults (Cooper et al., 2013; Schoen et al., 2010). In the Netherlands, which has a universal access, single-

payer health system, less than 25% of patients with adenomas received appropriately timed surveillance as per the Netherlands guidelines (van Heijningen et al., 2015). They also assessed the influence of a change in the Netherland's guidelines issued in 2002. They found that was consistent with the recommendation in 24% of before the guideline date, vs. 11% of after the guideline date. The practice changed in favor of overuse after the guideline, while the percentage with underuse remained similar. Underuse threatens CRC prevention, while overuse causes inefficient use of colonoscopy resources and reduced screening capacity.

Few studies have evaluated actual adherence to the surveillance guidelines in the US on a large enough scale to identify patterns stratified by risk group, based on community-based patient cohorts. The documented studies are based on self-reported patient surveys (Schoen et al., 2010), small sample sizes (Schreuders et al., 2013), academic medical center data (Kahn et al., 2015), and nation-wide histopathology registry data from other countries (the Netherlands) (van Heijningen et al., 2015). One study on surveillance compliance with guidelines was based on physicians' self-reported practices in a survey (Mysliwiec et al., 2004). All studies have excluded persons without adenomas (low risk population not recommended for surveillance), except for two studies (Menees et al., 2014; Schoen et al., 2010).

This study evaluated adherence to the 2006 USMSTF-ACS joint guidelines in a community-based screening cohort stratified by risk, and including surveillance-ineligible patients. We used data from a community endoscopy center in South Carolina, with a documented high CRC prevention rate (Xirasagar et al., 2015). The purpose was to

document the surveillance practice before the 2006 guidelines and evaluate whether the guidelines resulted in surveillance practice changes to confirm to guideline.

Methods

We used data from a licensed ambulatory surgery center for endoscopy in Columbia, South Carolina. The center is largely focused on providing screening and surveillance colonoscopies to average risk persons. Specifically, patients with inflammatory bowel disease, prior cancer history, or syndromic, inherited colorectal cancers are not served at the center. We obtained patient, procedure, and polyp data from the center's databases populated by the center staff from patient charts. The center trains primary care physicians' (PCPs) in colonoscopy using the gastroenterology fellowship training protocol used in academic medical centers for credentialing in colonoscopy. Training includes simulation on a mannequin followed by hands-on training by an endoscopy-credentialed expert for the first 140 procedures. Post-training, performance quality and patient safety are ensured through a clinical performance protocol and technical support mechanisms that are designed to compensate for PCPs' lack of formal gastroenterology training. The center's polyp detection-maximizing clinical protocol involves a two-person engagement in the procedure, required to be used by all trained PCPs. PCPs are credentialed to perform procedures at the center with an expert available on-site for back-up or rescue assistance (Xirasagar et al., 2015).

Study design

This is a retrospective cohort study to evaluate the timing of surveillance colonoscopy based on findings at initial examination. The study period was September 4, 2001 to February 11, 2011. A total of 26,523 screening and second procedure

colonoscopies were provided to 20,912 patients during the study period. We excluded 997 procedures that were the third or higher colonoscopy for the index patient. We combined data on second procedures performed within 6 months of the first into the first procedure data, as those are make-up colonoscopies for sub-optimal completion of the first procedure, e.g. poor bowel preparation. The exception to this rule was a surveillance colonoscopy within 6 months recommended for specific risk individuals described below.

The 2006 surveillance guidelines recommend surveillance 2-6 months following the initial examination for patients with sessile adenomas that were removed piecemeal. We identified piecemeal removal by a variable "Destroyed=no" in the polyp dataset. The guidelines recommend 1-year surveillance for patients with hyperplastic polyposis syndrome or > 10 adenomas; 3-year surveillance for patients with 3-10 adenomas, ≥ 1 cm adenoma, or any adenoma with villous or tubulovillous features, or high-grade dysplasia; and, 5-year surveillance for patients with 1 or 2 small (<1cm) tubular adenomas or any adenoma without advanced features. No surveillance is recommended for patients without adenomatous polyps or less than 3 small hyperplastic polyps, only rescreening after 10 years. Based on these timing criteria, we excluded patients without a second procedure who had not completed the recommended surveillance interval during the study period (n=1,569). The final study sample consisted of 16,897 eligible study patients with a screening colonoscopy.

Measures

Time interval to surveillance colonoscopy was the main outcome measure. Patients without adenomatous polyps or less than 3 small hyperplastic polyps were defined as not eligible for surveillance. Appropriate surveillance was defined based on the 2006

guidelines (S. J. Winawer et al., 2006). Timing was classified as appropriate if the surveillance was within 3 months before or after the recommended due date for the ≤ 1-year surveillance group, and within 6 months before or after the due date for the ≥ 2-year surveillance group (van Heijningen et al., 2015). Early surveillance before the 3- or 6-month window was overuse (premature, before due), and delayed beyond the window was underuse (delayed, or not done). Table 4.2 summarizes the 2006 guidelines recommending surveillance at five different intervals: <1-year, 1-year, 3-year, and 5-year surveillance, and 10-year rescreening. The table also shows the operational definitions used in the study. For patients with multiple polyps, the most severe polyp characteristic was used to determine the surveillance interval category. Pre-guideline screening colonoscopies were those done in 2005 or earlier, and the remaining was classified as post-guideline patients.

All patients, pre- and post-guideline patients were evaluated for surveillance finding against the 2006 recommendations. Because the purpose was to evaluate provider practice changes once clear guidelines was issued, the 2006 recommended surveillance timings was used to assign a patient to overuse, underuse, and appropriate use category.

Statistical analysis

Kaplan-Meier (KM) curves were used to estimate the cumulative probability of surveillance procedures over time following the screening colonoscopy. Patients were stratified into pre- and post- 2006 periods, and observed for the second procedure timing since the initial colonoscopy. The event of interest was having the second procedure during the study period. Subjects without surveillance are considered censored.

Study group differences were assessed using chi-square, Fisher's exact test, and ANOVA test with a p-value of 0.05 for statistical significance. The log-rank test was used to compare KM curves of the pre- and post-2006 cohorts on the time-related probability of surveillance colonoscopy. SAS Version 9.4 statistical software was used for all analyses. The study was approved by the University of South Carolina Institutional Review Board.

Results

Study sample characteristics

Of study-eligible procedures, 20,912 were first (screening) procedures and 4,359 were second procedures. Of 20,912 patients, we excluded patients aged below 40 years and more than 74 years (n=2,343), and cancer detected at first procedure (n=103). There were 9,526 patients with initial colonoscopy in the pre-guideline period (2005 or earlier) and 7,371 in the post-guideline period, 2006 and later (Figure 4.1). We classified patients screened in 2006 into the post guideline group because the earliest possible surveillance would have been due in the post guideline period (2007 or later) and could have complied with the guideline.

A total of 16,897 patients were included in the study. The mean follow-up period was 7.25 (SD, 1.22) years for the pre-guideline cohort and 2.85 (SD, 1.43) years for the post-guideline cohort. The majority were: female (54.1%), aged ≥ 50 years (83.7%), and Black (51.9%). Of total screened patients, 4,234 were surveillance-eligible (i.e., had adenomatous polyps). Of them 2,195 (51.8%) completed a surveillance colonoscopy, 1,635 pre-guideline patients and 560 post-guideline patients. Among those without adenomas at screening colonoscopy, 14.3% (1,793 of 12,571 patients) had a premature

second colonoscopy after a mean of 4.65 years. Of the total cohort, 4.8%, 11.2% and 9.1%, were eligible for surveillance at ≤ 1 year, 3 years and 5 years, respectively, and 74.4% were not eligible for surveillance (Table 4.3).

Timeliness of surveillance in the pre- and post-guideline periods

The mean surveillance interval was 2.52 years among surveillance-eligible patients who completed the procedure, 2.71 years (SD, 1.22) and 1.95 years (SD, 0.99) for the pre- and post- guideline cohorts, respectively ($p<0.001$). Among patients who did not qualify for surveillance and had a premature second colonoscopy, their mean interval was 4.82 years (SD, 1.27) and 2.35 years (SD, 1.22) in the pre- and post- periods, respectively ($p<0.001$).

Kaplan-Meier analysis showed that post-guideline patients had, on average, earlier surveillance compared to the pre-2006 cohorts among the 5-year recommended surveillance group ($p<0.001$). Among the no-surveillance recommended group, pre-guideline patients had a higher probability of premature second colonoscopy than post-guideline patients ($p<0.001$). There was no difference in surveillance timing of the pre- and post-guideline cohort among the ≤1-year and 3-year surveillance groups. The Kaplan-Meier surveillance probability curves are shown in Figures 4.2a, b, c, d.

Overall, surveillance timing was inappropriate for 91.8% of patients, similar in the pre-and post-guideline periods, with 2.8%, 14.9%, and 2.8% of patients recommended for ≤ 1-year, 3-year, and 5-year follow-ups, receiving appropriately timed surveillance. Delayed or no surveillance occurred for 96.8% and 54.0% of ≤ 1-year and 3-year recommended surveillance groups. By contrast, among the 5-year recommended group, 49.8% of total group showed overuse, higher among post-guideline patients (61.4%).

Among patients without adenomas at screening, 1,793 of 12,571(14.3%) patients had a premature second colonoscopy, 25.7% of pre-guideline patients, and 2.0% of post-guideline patients ($p<0.001$) (Table 4.4).

Discussion

The study found a high rate of deviation (91%) from the 2006 guidelines in a community-based cohort in South Carolina. About 50% of the cohort did not complete surveillance within the study period, which is concerning because of the risk of adenoma recurrence and cancer over their lifetime (Laiyemo et al., 2009; Morelli et al., 2013; Pinsky et al., 2009; Robertson et al., 2009). However, one study limitation is the possibility that some of these patients may have undergone surveillance with a different provider and therefore were not captured by the study.

Among ≤ 1-year and 3-year surveillance recommended groups, delay was the most common finding (96.8% and 54.0%, respectively). However, 48.7% and 51.1% had completed surveillance by the end of study period. Overuse (premature) surveillance was high among the 5-year surveillance groups (49.8% of patients). Overuse was higher in the post-2006 period (61.4%). Our findings are consistent with another community-based cohort study, high-risk patients with advanced adenomas (Schoen et al., 2010). The surveillance timeline adherence rate of 15.8% among the surveillance-eligible is lower than the rates reported in Canada (33%) and the Netherlands (21%) (Schreuders et al., 2013; van Heijningen et al., 2015). Both countries have single-payer health systems and nation-wide, integrated claims or registry databases. In the Netherlands, 63.5% of surveillance-eligible patients completed surveillance; of whom 21% adhered to the timeline. Both rates are higher than our study cohort rate of 51% surveillance completion,

and, among them, 15.8% timeline adherence. The Netherlands guidelines recommend 6-year surveillance for patients with one or two adenomas, one year later than the 2006 US guidelines (Snel & de Wolf, 1988). Both the Canadian and Netherlands studies did not assess second procedures among patients who do not qualify for surveillance due to lack of adenomas at screening. In the US, a Medicare claims study documented a second procedure rate of 61.3% over 5-years among patients with a polypectomy aged over 70 years (histology not known) or having a family history of gastrointestinal neoplasm (Cooper et al., 2013).

A recent study examined provider adherence to the 2012 USMSTF guidelines in the physician's follow-up notes recommending surveillance (Kahn et al., 2015). This study used data on a 2011-2013 cohort from an academic medical center and reported that providers recommended surveillance as per the guidelines for 77.4% of patients in the follow-up notes (Kahn et al., 2015).

Delayed colonoscopy is reasonable and anticipated among ≤ 1-year and 3-year surveillance groups because the recommended intervals are short. Possible reasons for delay may be procrastination due to the patient's experience of discomfort or dislike of the bowel prep process, or a busy personal schedule (Jones, Devers, Kuzel, & Woolf, 2010; Jones, Woolf, et al., 2010; Medina, McQueen, Greisinger, Bartholomew, & Vernon, 2012). Our finding of overuse (premature surveillance) among the 5-year group in the post-guideline period, may be due to providers being cautious and defaulting to the earliest 1997 guidelines (3-year surveillance for patients with large or multiple adenomas, no recommendation for patients with small adenomas or other advanced histology features that were acknowledged in the 2003 guidelines) (Winawer et al., 2003; Winawer

et al., 1997; Winawer et al., 2006). In the 2003 guidelines, high-grade dysplasia is not mentioned as a surveillance criterion, and a tentative recommendation was made for 5-yearly surveillance for patients with 1-2 small adenomas (Table 4.1). These factors, together with the fast-changing adenoma risk perceptions published during the study period may have contributed to the heightened, post-2006 overuse of colonoscopy among the 5-year surveillance group.

Studies have documented providers' lack of knowledge of guideline revisions, and a preference for a cautious interpretation of the research evidence used to support the revised recommendations (Imperiale, 2011; Kruse et al., 2015; Saini et al., 2009). A recent survey assessed gastroenterologists' opinions about the 2006 guidelines and the factors driving their own follow-up recommendations. It found that 11% of gastroenterologists felt that the guidelines were not adequate to prevent cancer (Patel, Tong, Ahn, Singal, & Gupta, 2015). Some authors have supported shorter surveillance intervals because of potentially missed adenomas at screening colonoscopy (Kim et al., 2012; Nakao et al., 2013). Increasing CRC risk with age, particularly the high risk beyond 70 years of age may heighten this concern and contribute to early surveillance (Goodwin et al., 2011; Imperiale, 2011). These factors may explain the significant overuse observed in our study. To address providers' lack of knowledge of the guidelines, it has been suggested that electronic medical record (EMR) systems may provide a solution, by triggering automated reminders to patients and providers when follow-up is due (Leffler et al., 2011). Increasing patients' awareness of the significance of their adenoma findings and about timely surveillance is also necessary (Sint Nicolaas et al., 2012).

An important finding is that 14.3% of patients without adenomas at screening colonoscopy had a premature second colonoscopy after a mean period of 4.65 years. Of those, 37.1% (665 out of 1,793) had hyperplastic polyps, mostly small, in the left colon, and less than three in number. The distribution of these patients by pathology findings at screening is shown in Table 4.5. A family history of CRC and bowel symptoms could have caused these premature second procedures. However our data lack this information that could explain part of the overuse.

There are few studies on the rate of premature second screening colonoscopies in the US. A Veterans Administration study of physicians' notes reported that about 9.2 % of patients with 1 to 2 small (<1cm) non-adenomatous polyps were recommended for a second colonoscopy before the recommended 10-year interval (Menees et al., 2014). Because bowel symptoms may prompt a colonoscopy in this age group regardless of the originally planned follow-up schedule, the actual rate of second colonoscopies may be similar to the rate observed in our study.

Our study has several strengths. It is one of the few studies to evaluate changes in surveillance practice in a community-based practice setting in the United States following the issuance of definitive guidelines. Despite 74.4% (12,571 of 16,897 patients) not qualifying for surveillance, 14.3% of them had a premature second procedure. This contributes a large volume of procedures that may occupy provider time with minimal cancer-reducing value. Another strength of our study is the availability of data on the total number of adenomatous polyps, including numbers found within a colonic segment that are typically sent for histology in a single jar. This data field resulted in re-classifying 712 patients from the 5-year surveillance group to the 3-year surveillance

group (16.8% of the surveillance-eligible sample). Most prior studies of adenoma characteristics base the number of adenomas on a count of the polyp jars, which is the data typically found in claims data or the Clinical Outcomes Research Initiative (CORI) database that is the most widely reported dataset in colonoscopy studies (D. A. Lieberman et al., 2008).

Our study has several limitations. Our findings may not generalize to the US population or other endoscopy centers because we used data from one center. The retrospective study design also entails some loss to follow-up because some patients may have undergone surveillance colonoscopy at other facilities. However, the center's surveillance completion rate of 51.8% is close to the Netherlands' population-based rate of 63.5%, and the rate of 61.3% among Medicare beneficiaries with a polypectomy in the US. Additionally, the study center has a surveillance colonoscopy proportion of 23.8% of all colonoscopies, compared to 25%, nationally, documented in the US (Lieberman et al., 2000; Lieberman et al., 2005). These similarities may suggest that the observed surveillance completion rate at the center may be close to the true surveillance completion of the cohort.

Another limitation is that because of study period constraints we have shorter follow-up for post-guideline patients, which may misclassify some of the tardy surveillance cases as not completed, if they completed it after the study period. Finally, our data lack family history data and symptomatology data which may account for part of the early surveillance or premature second screening cases (Schoen et al., 2010). Approximately 11.2% of the population aged 45-70 years has at least one first-degree relative with CRC (de Jong & Vasen, 2006).

In conclusion, less than 10% of surveillance-eligible patients received timely surveillance. Less than 50% surveillance rate (after counting tardy surveillance) among high-risk patients (recommended ≤1- or 3-year surveillance) indicates that active follow-up among these patients should be a priority. To accommodate the increased load due to needed surveillance cases, the current pattern of overuse among the 5-year surveillance group and no-surveillance recommended group should be addressed. Minimizing overuse will spare scarce provider time for surveillance of high-risk patients at appropriate time intervals, which may improve colorectal cancer prevention at no extra cost.

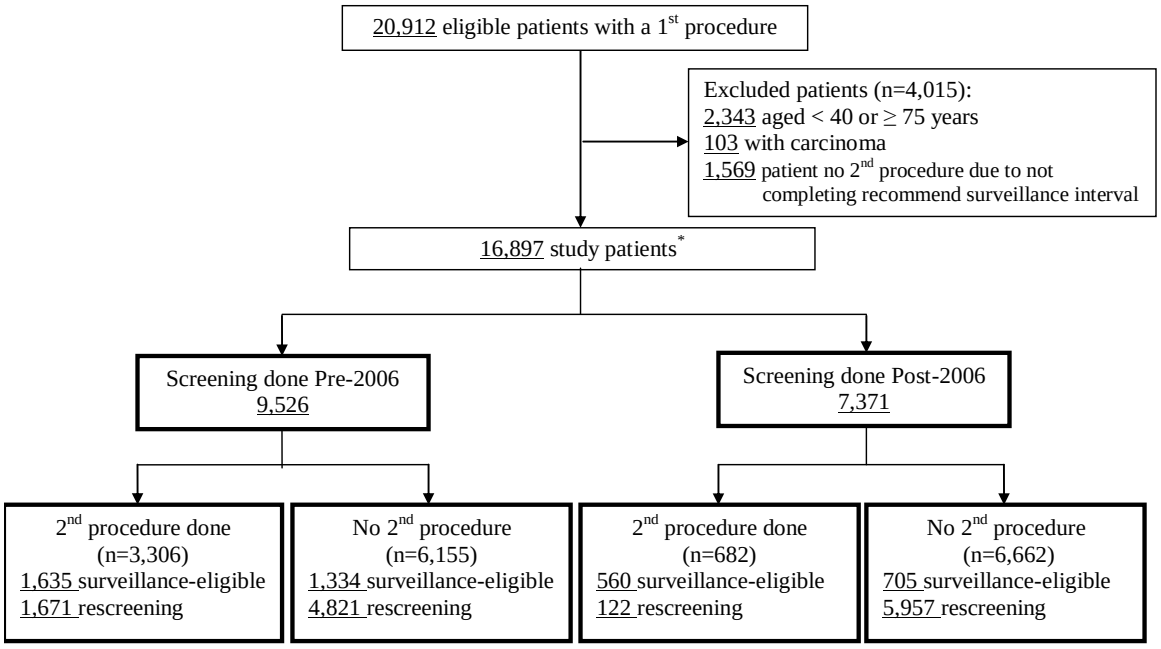

Figure 4.1 Study-eligible patients with a screening colonoscopy, and use of second procedure, pre- and post-2006 guidelines.* 92 patients without polyp histology were not shown.

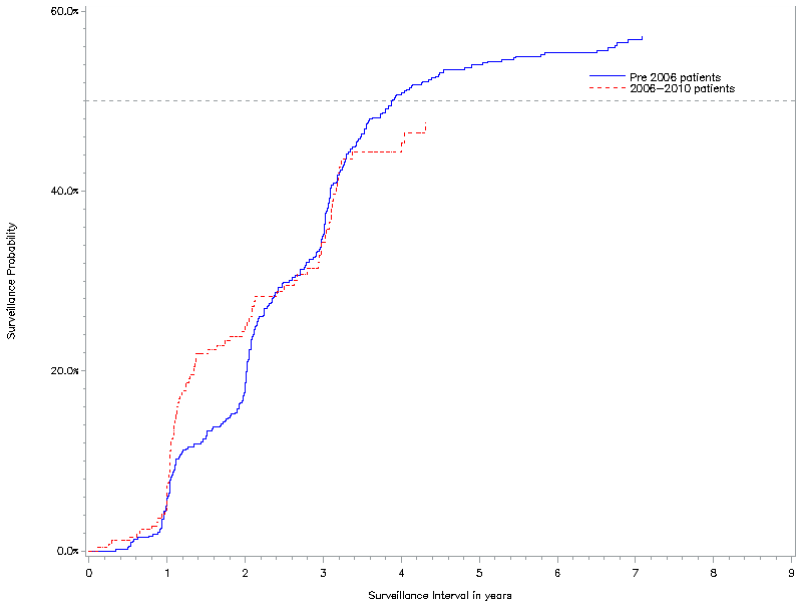

Figure 4.2a Cumulative probability of surveillance colonoscopy among the ≤1-year surveillance recommended group (pre vs. Post guideline) (P=0.778)

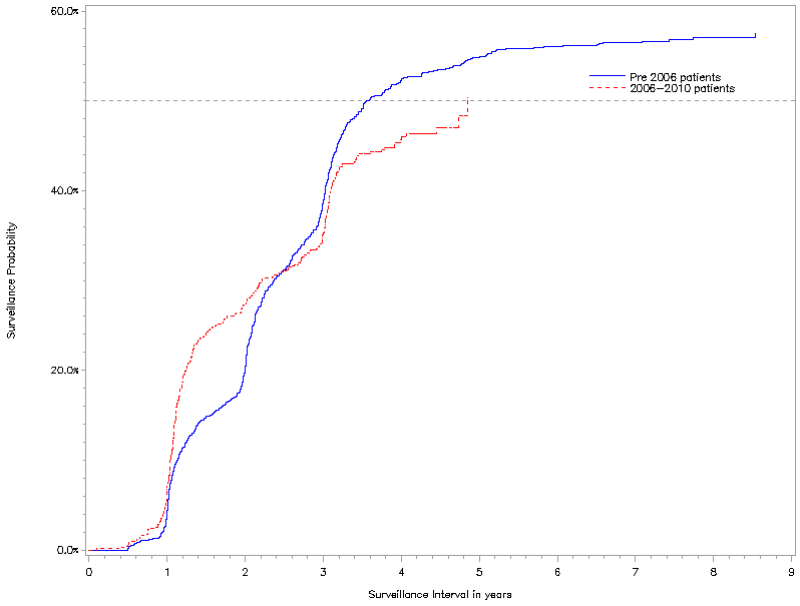

Figure 4.2b Cumulative probability of surveillance colonoscopy among the 3-year surveillance recommended group (pre vs. Post guideline) (P=0.169)

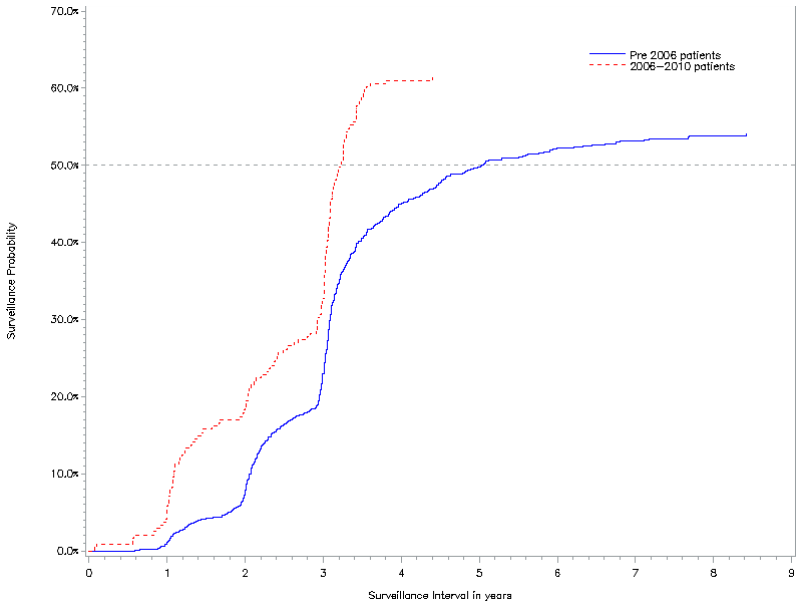

Figure 4.2c Cumulative probability of surveillance colonoscopy among the 5-year surveillance recommended group (pre vs. Post guideline) (P<0.001)

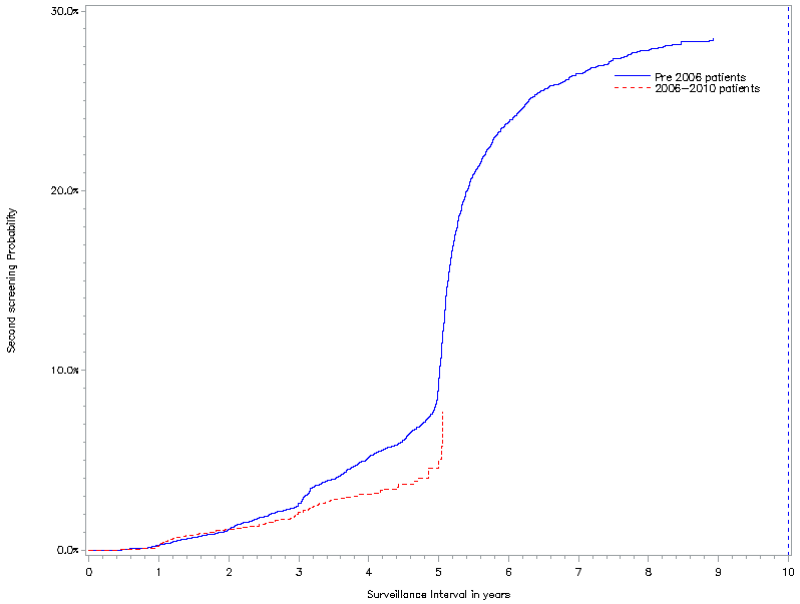

Figure 4.2d Cumulative probability of surveillance colonoscopy among the no-surveillance recommended group (pre vs. Post guideline) (P<0.001)

Table 4.1 Details of the 1997, 2003, and 2006 surveillance guidelines recommendations

	Surveillance interval recommendation
1997 recommendations	
Large (≥1cm), multiple adenomas	3 years
Lower-risk adenomas (1-2 small adenoma,<1cm)	No specific guidelines
High-grade dysplasia or villous features	No specific guidelines
2003 recommendations	
Numerous adenomas, a malignant adenoma (with invasive cancer), a large sessile adenoma	A short interval (based on clinical judgment)
Large (≥1cm), villous adenoma, ≥3 adenomas	3 years
1-2 small (<1 cm) tubular adenomas	5 years (but noted that change in light of evidence is evolving)
High-grade dysplasia	No specific guidelines
2006 recommendations	
Sessile adenomas that are removed piecemeal	2-6 months
a) Hyperplastic polyposis syndrome* b) >10 adenomas	1 years
a) 3-10 adenomas b) adenoma ≥1 cm c) any adenoma with villous features or high-grade dysplasia	3 years
a) 1 or 2 small (<1 cm) tubular adenomas with low-grade dysplasia b) Any adenoma without advanced features	5 years
a) Small (<1 cm) rectal hyperplastic polyps b) Normal tissues (include few hyperplastic polyps or no polyp)	10-year rescreening (no surveillance)

*Hyperplastic polyposis is defined as: (1) at least 5 histologically diagnosed hyperplastic polyps proximal to the sigmoid colon, of which 2 are greater than 1cm in diameter, or (2) any number of hyperplastic polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with hyperplastic polyposis, or (3) more than 30 hyperplastic polyps of any size distributed throughout the colon. Since our study does not have data on first-degree relatives, we included the first and third criteria to define hyperplastic polyposis (Burt & Jass, 2000).

Table 4.2 Operational definitions used for classifying surveillance colonoscopy as appropriate, overuse, and underuse [*]

	Surveillance interval recommendation (in years)	Operational study definitions of appropriate timing (in years)
Polyp types		
1) Small (<1 cm) rectal hyperplastic polyps 2) Normal tissues (include few hyperplastic polyps or no polyp)	No surveillance,10-years rescreening	9.5-10.49
		Surveillance timelines category (time interval in years)
1) 1 or 2 small (<1 cm) tubular adenomas with low-grade dysplasia, 2) Any adenoma without advanced features	5	4.5-5.49 (<4.5 years=overuse, >5.49 years=underuse)
1) 3-10 adenomas, 2) adenoma ≥1 cm, 3) any adenoma with villous features or high-grade dysplasia	3	2.5-3.49 (<2.5 years=overuse, >3.49 years=underuse)
1) Hyperplastic polyposis Syndrome[**] 2) >10 adenomas	1	0.75-1.25 (<0.75 years=overuse, >1.25 years=underuse)
Sessile adenomas that are removed piecemeal	2-6 months	0-0.75 (<0 years=overuse, >0.75 years=underuse)

[*]The criteria used for classifying surveillance colonoscopy timing are based on the 2006 guidelines {Winawer, 2006 #62}.

[**]Hyperplastic polyposis is defined as: (1) at least 5 histologically diagnosed hyperplastic polyps proximal to the sigmoid colon, of which 2 are greater than 1cm in diameter, or (2) any number of hyperplastic polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with hyperplastic polyposis, or (3) more than 30 hyperplastic polyps of any size distributed throughout the colon. Since our study does not have data on first-degree relatives, we included the first and third criteria to define hyperplastic polyposis {Burt, 2000 #227}.

Table 4.3 Study population at screening colonoscopy, classified by date of screening colonoscopy, pre- or post-guideline (n=16,897) **

		Date of screening colonoscopy	
	Total (n=16,897)	Pre-2006 period (n=9,526)	2006 and later (n=7,371)
Patient characteristics			
Gender*			
Male	7,673(45.4%)	4,304(45.2%)	3,369(45.7%)
Female	9,144(54.1%)	5,143(54.0%)	4,001(54.3%)
Missing	80(0.5%)	79(0.8%)	1(0.0%)
Age(years)*			
40-49	2,755(16.3%)	1,447(15.2%)	1,308(17.8%)
50-59	8,367(49.5%)	4,642(48.7%)	3,725(50.5%)
60-74	5,775(34.2%)	3,437(36.1%)	2,338(31.7%)
Race*			
White	7,470(44.2%)	4,166(43.7%)	3,304(44.8%)
Black	8,771(51.9%)	4,829(55.1%)	3,942(44.9%)
Other or unknown	656(3.9%)	531(5.6%)	125(1.7%)
Insurance status*			
Medicaid	525(3.1%)	322(3.4%)	203(2.8%)
Medicare	3,008(17.8%)	1,750(18.4%)	1,258(17.1%)
Private	11,939(70.7%)	6,238(65.5%)	5,701(77.3%)
Uninsured	1,425(8.4%)	1,216(12.8%)	209(2.8%)
Recommended surveillance interval*			
<1-year surveillance	757(4.5%)	523(5.5%)	234(3.2%)
1-year surveillance	54(0.3%)	23(0.2%)	31(0.4%)
3-year surveillance	1,891(11.2%)	1,132(11.9%)	759(10.3%)
5-year surveillance	1,532(9.1%)	1,291(13.6%)	241(3.3%)
No surveillance recommended (10-year rescreening only)	12,571(74.4%)	6,492(68.2%)	6,079(82.5%)
Missing	92(0.5%)	65(0.7%)	27(0.4%)
Mean person year of observation	5.33(2.55)	7.25(1.22)	2.85(1.43)

*P<0.05 for tests of difference between guideline date and characteristics of study population, using Chi-square tests.

**Mean screening follow-up was 7.25 years for pre-guideline group (range,5.11-9.44; SD,1.22) and 2.85 years for post-guideline group (range,0.02-5.11, SD,1.43).

Table 4.4 Timing of surveillance colonoscopy relative to the 2006 recommended surveillance intervals among the pre-guideline and post-guideline cohorts (pre- vs. post- guidelines)

Recommended surveillance interval group	Overuse (Premature before being due)	Appropriate (Timing as recommended)	Late (Delayed relative to recommendation)	Not done (by end of study period)	10-year rescreening group (Not screening)
Total all surveillance groups (n=4,234) *	1,355(32.0%)	347(8.2%)	493(11.6%)	2,039(48.2%)	
Total Pre-2006(n=1,291)	970(32.7%)	255(8.6%)	410(13.8%)	1,334(44.9%)	
Total Post-2006(n=241)	385(30.4%)	92(7.3%)	83(6.6%)	705(55.7%)	
Total ≤ 1-year surveillance (n=811) *	3(0.4%)	23(2.8%)	369(45.5%)	416(51.3%)	-
Pre-2006 (n=546)	2(0.4%)	9(1.7%)	297(54.4%)	238(43.6%)	-
Post-2006 (n=265)	1(0.4%)	14(5.3%)	72(27.2%)	178(67.2%)	-
Total 3-year surveillance (n=1,891) *	589(31.2%)	281(14.9%)	97(5.1%)	924(48.9%)	-
Pre-2006 (n=1,132)	353(31.2%)	203(17.9%)	86(7.6%)	490(43.3%)	-
Post-2006(n=759)	236(31.1%)	78(10.3%)	11(1.5%)	434(57.2%)	-
Total 5-year surveillance (n=1,532) *	763(49.8%)	43(2.8%)	27(1.8%)	699(45.6%)	-
Pre-2006(n=1,291)	615(47.6%)	43(3.3%)	27(2.1%)	606(46.9%)	-
Post-2006(n=241)	148(61.4%)	0	0	93(38.6%)	-
Total 10-year rescreening group(No need for surveillance) (n=12,571) *	1,793(14.3%)	-	-	-	10,778(85.7%)
Pre-2006 (n=6,492), Mean follow-up period=7.27 (1.25)	1,671(25.7%)	-	-	-	4,821(74.3%)
Post-2006(n=6,079) , Mean follow-up period=2.70 (1.44)	122(2.0%)	-	-	-	5,957(98.0%)

*P<0.05 for tests of difference between guideline date and appropriateness of interval time, using Chi-square test and Fisher's exact test.

CHAPTER 5

PATIENT VARIABLES AND PROFESSIONAL SOCIETY GUIDELINES DRIVING THE TIMING OF SURVEILLANCE COLONOSCOPY AMONG AVERAGE-RISK SCREENING PATIENTS

Abstract

Background

Well-performed colonoscopy can prevent colorectal cancer (CRC). Because of the higher risk of adenoma recurrence or CRC, surveillance colonoscopy is recommended in all patients with a history of high-risk polyps. The factors driving the actual patterns of surveillance use remain unclear. Understanding the extent to which individual risk factors influence surveillance compliance and the timing decision is important to improve adherence and reduce cancer incidence.

Methods

This is a retrospective, cohort study of patients with a screening colonoscopy at a community-based endoscopy center between September, 4, 2001 and February, 11, 2010, observed through February 2011. Surveillance overuse (premature) and underuse (delayed or not done) were defined based on surveillance completion earlier, or later than guideline-recommended intervals (5-year and ≤3-year recommended groups based on

risk2006 guidelines). We used logistic and linear regression modeling to identify the patient, polyp and procedure factors associated with surveillance timing, including possible risk factors not specified in the guideline in making the recommendations.

Results

Of 16,805 study-eligible patients, majority were female (54.1%), aged 50-59 years (48.5%), Black (51.9%), and had Medicare or private insurance (88.5%). Of 4,234 surveillance-eligible patients, 2,195 patients (51.8%) had a surveillance colonoscopy. Only 8.2% (347 of 4,234) surveillance-eligible patients were compliant with guideline-recommended timing. Adjusted analysis showed that overuse was more likely among the 5-year surveillance group (OR: 14.39; 95%CI: 10.03-20.64) relative to the ≤3-year surveillance group. Other significant factors predicting overuse were having a large adenoma (OR: 1.81; 95%CI: 1.25-2.63), having multiple advanced adenoma characteristics (OR: 2.26; 95%CI: 1.30-3.93), and post-guideline period (OR: 1.73; 95%CI: 1.30-2.31). Delayed surveillance was more likely among patients with the largest adenoma found in the right colon (OR: 1.49; 95%CI: 1.12-1.98) and Medicaid beneficiaries (OR: 3.22; 95%CI: 1.14-9.09). Within the ≤3-year surveillance group, patients with adenomas larger than 5 mm, or multiple advanced characteristics were more likely to have early surveillance. Among those not eligible for surveillance, premature re-screening (before 10 years) was associated with having a non-adenomatous polyp (vs. no polyp) and higher age.

Conclusions

Contrary to expectations, surveillance overuse increased following the issuance of surveillance guidelines, after adjusting for adenoma-based risk factors at screening

colonoscopy. The findings suggest that concerns about individual patients' cancer risk beyond the criteria used in surveillance guidelines may underlie many decisions of premature surveillance. Lack of family history data is a study limitation, which could account for part of the premature surveillance cases. Significant underuse among Medicaid beneficiaries exists, and should be explored to identify the barriers to surveillance in this group.

Keywords: Surveillance colonoscopy, polyp features, insurance status, initial procedure year.

Introduction

Colorectal cancer (CRC) is the third leading cancer in the United States, with nearly 50,000 deaths in 2015 (ACS, 2015). In South Carolina, an estimated 2,220 new cases and 830 deaths are expected in 2016 (Siegel et al., 2016). Well-performed screening colonoscopies help prevent cancer through visualization of the entire colonic surface and removal of precancerous polyps (adenomas) (Winawer et al., 1993; Xirasagar et al., 2015; Zauber et al., 2012). Screening colonoscopy followed by colonoscopic surveillance for patients with adenomatous polyps is recommended, because of the risk of adenoma recurrence and cancer (Leung et al., 2010; Pinsky et al., 2009). Surveillance guidelines were updated by the U.S. Multi-Society Task Force (USMSTF) and American Cancer Society in 2006, which emphasized risk stratification by polyp features at screening colonoscopy in recommending surveillance intervals following screening colonoscopies (Winawer et al., 2006).

Although evidence supports that colonoscopic polypectomy can reduce cancer incidence, the time to surveillance colonoscopy in practice varies from the guideline

recommended intervals. The literature shows overuse of surveillance (too early) among low-risk adults and underuse (delayed) among high-risk adults (Schoen et al., 2010; Sint Nicolaas et al., 2013). The purpose of efforts to increase guideline concordance is to achieve higher adenoma detection, and to emphasize that overuse of surveillance does not increase cancer prevention (Sint Nicolaas et al., 2013). Understanding the factors driving overuse or underuse may help to identify patient groups at risk for inappropriate surveillance timing, and alert providers and patients about the risks of unnecessary colonoscopies or delaying surveillance.

Previous studies of surveillance have mostly examined pre-2006 cohort data (Lieberman et al., 2008; Lieberman et al., 2007; Martinez et al., 2009). Most studies did not account for patient and screening procedure characteristics that may influence physicians' recommendations for follow-up procedures (Ko et al., 2010; Laiyemo et al., 2010; Lieberman et al., 2008). Moreover, studies of surveillance practice compared to guidelines have used patient survey data with no data on polyp features (Saini et al., 2009), small sample sizes (Kim et al., 2012), or cohorts from academic medical centers which may be more up-to-date with the latest practice guidelines (Kahn et al., 2015). There is little documentation on surveillance practices as compared to guideline recommendations at community-based endoscopy centers, and no literature on "surveillance" of patients who do not qualify for surveillance based on the professional society guidelines.

This study seeks to identify the patient-level factors associated with surveillance colonoscopy completion and timing, adjusting for the professional society guideline date. Patient-level factors may be: polyp features at screening that are not used as risk criteria

by the guideline issuing society in recommending the surveillance intervals, patient demographics, or procedure-related factors. We used data from a large cohort served at a community endoscopy center in South Carolina, which has a documented high rate of CRC prevention among its screened patients (Xirasagar et al., 2015).

Methods

Study population and sample selection

This is a retrospective cohort study of patients provided screening colonoscopy at a community-based endoscopy center between September 4, 2001, and February 11, 2010, observed through February 2011. The center mainly uses colonoscopy-trained primary care physicians (PCPs) who bring their screening-eligible, primary care patients for screening and surveillance colonoscopy at a licensed endoscopy center. As a general policy, the center mainly focuses on screening colonoscopies of average-risk patients and their surveillance (those without inflammatory bowel disease, prior cancer history, or syndromic, inherited colorectal cancers). The center's polyp detection-maximizing clinical protocol requires a 2-person technique, required to be used by all PCPs who perform procedures at the center, with an expert on site for back-up assistance (Xirasagar et al., 2015).

Polyp features at screening, patient demographics, and procedure-related characteristics were obtained from center's administrative and medical databases. We reviewed a total of 26,523 screening and second procedure colonoscopies provided to 20,912 patients during the study period. Third or higher order procedures provided to a patient were excluded (n=997). Further, we combined data from 225 second procedures performed within 6 months of the first procedure into the first procedure data because these are make-up procedures for sub-optimal first procedure. Of study-eligible

procedures, 20,912 were the screening procedure. Of those 20,912 patients, we excluded 2,343 aged < 40 or ≥ 75 years, and 103 patients with cancer found at screening colonoscopy.

We adjusted for guideline date by classifying patients into a variable, guideline concordance. The variable categories were overuse, delayed, and not done relative to the recommended surveillance interval per the 2006 joint guidelines of the U.S Muti-Society Task Force (USMSTF) on Colorectal Cancer and the American Cancer Society (Winawer et al., 2006). The guidelines recommend surveillance examinations after <1-year, 1-year, 3- years, and 5-years, depending on polyp characteristics at screening. Based on these timings, 1,569 patients who had not completed their recommended surveillance interval by the end of study period were excluded from study.

Measures

We had three primary outcomes of interest: any second colonoscopy (yes/no), the timing of the second colonoscopy relative to the screening procedure (categorized into overuse, appropriate, late or not done), and time interval since screening (continuous variable, years). Consistent with a documented study, we defined guideline concordant surveillance if the procedure took place within a range of ±3 months from due date for the ≤ 1-year surveillance-recommended group, and ±6 months for >1 year surveillance group (van Heijningen et al. 2015). Overuse was surveillance earlier than the range, (premature relative to guideline), delayed (later than the range), and not done, as of the end of study period.

Polyp findings at screening colonoscopy, patient insurance status, and screening procedure year (pre- or post-guideline) were our main independent variables of interest.

Patient adenoma status was defined by their most advanced adenoma at screening procedure (if they had more than one adenoma). Patients with advanced characteristics were those with ≥ 3 adenomas of any size, an adenoma with >25% villous features, adenoma of 1 cm or more, or high-grade dysplasia (Winawer & Zauber, 2002; Winawer et al., 2006). According to the 2006 guidelines, patients with advanced adenoma characteristics by histology and ≥3 adenomas are recommended surveillance at 3 years. We identified patients with 3 or more adenomas using two variables; we summed the polyp jars reported with adenoma histology, and identified those with 3 or more adenomas in the same colonic segment using another data field, Polyp quantity which is specified for each segment represented by a single polyp jar.

We explored the potential role of adenoma features that are not assigned as high-risk adenomas meriting a specific surveillance recommendation. These were: location of the largest adenoma (right vs. left), number of colon anatomic locations found to have adenoma,(1-2 vs. 3-4 locations), the largest size of the patient's adenomas (≤5mm, 5.1-9.9mm, and ≥10mm), number of adenomas found in the same colonic segment (1-2 adenomas and ≥ 3 adenomas), and presence of ≥ 2 advanced adenoma characteristics (yes/ no). Insurance was classified into Medicaid, Medicare or private, and uninsured. Finally, we defined patients based on their screening year, before 2006, pre-guideline, and 2006 or later, post-guideline.

Statistical analysis

Multiple logistic and multinomial logistic regressions were performed to identify the factors associated with the likelihood of any second procedure, and of timely surveillance (overuse, late, not done). We also assessed the association of surveillance interval as a

continuous variable (in years) with the patient, procedure, and polyp characteristics. SAS Version 9.4 was used for statistical analysis and a p-value < 0.05 was used.

Results

Patient characteristics

A total 16,805 patients with a screening colonoscopy were studied after excluding 92 patients with missing histology. The demographic distribution of patients, screening period (pre- or post- guideline) and polyp characteristics at screening colonoscopy are presented in Table 5.1. Of the total sample, 4,234 (23.7%) were eligible for surveillance, and 2,195 (51.8%) had completed surveillance colonoscopy. Of 12,571 patients who were not eligible for surveillance, 1,793 (14.3%) had a premature second procedure (within 10 years).

Of the total sample, majority (54.1%) were female, Black (51.9%), and the largest age group (48.5%) was 50-59 years. Most had private or Medicare insurance (88.5%). The majority of the sample (56.3%) had their screening procedure in the pre-2006 period. Of surveillance-eligible patients, 48.7%, 51.1% and 54.4% of the 1-year, 3-year and 5-year surveillance groups had completed the second procedure (Table 5.2). The mean follow-up period was 5.3 years (±2.6), 7.25 years for the pre-guideline cohort (±1.2) and 2.85 years for the post-guideline cohort (±1.4), not reported in the table.

Adherence to recommendations among surveillance-eligible patients

Table 5.2 shows that overall, 8.2% (347 of 4,234) had appropriate timing of surveillance, 32.0% had overuse, 11.6% had delayed procedures, and 48.2% of surveillance-eligible patients did not complete it by the end of the study period. Overall among the surveillance-eligible, 61.7% (1,355 of 2,195) of those who completed

surveillance had overuse (earlier than recommended surveillance). Table 5.2 also shows the demographic distribution of adherent and non-adhering patients. The mean surveillance interval was 2.37, 2.22, and 2.94 years among the ≤1-year, 3-year, and 5-year surveillance groups, respectively (not shown in the tables).

Table 5.3 presents the adjusted likelihood of a second procedure among the sample. Older persons (aged over 50 years, ORs, 1.42,1.23), and Blacks (OR: 1.22; 95% CI: 1.07-1.39) were more likely to complete the second procedure, as was the 5-year surveillance group (compared to the ≤1-year group, OR, 1.26, 95%CI 1.06-1.51), patients with multiple advanced adenoma characteristics (OR, 1.64; 95% CI, 1.28-2.11), undergone screening in the pre-guideline period (OR: 1.61), and those with private/Medicare insurance (OR 1.29 95%CI: 1.04-1.61).

Predictors of earlier surveillance than recommended within risk categories

Analyses were done within each risk category represented by the recommended surveillance interval. Table 5.4 presents the associations of surveillance time interval (continuous variable) among those who completed surveillance. Post-guideline patients had, on average, 6-6.8 months earlier surveillance. Patients with adenomas larger than 5mm, and those with multiple advanced adenoma characteristics were associated with earlier surveillance (2.8-7.8 months earlier, represented by coefficient estimates 0.23 and 0.65 respectively).

Table 5.5 presents the results of adjusted analyses of overuse (early), delayed surveillance, and surveillance not done among the surveillance eligible. Factors driving overuse were post-guideline period, being in the 5-year surveillance group, larger adenoma size, and having multiple advanced adenoma characteristics. Factors driving

delayed surveillance were Medicaid, and adenoma located in the right colon. Factors associated with not completing surveillance were post-guideline period, and being in the 5-year surveillance group.

The odds of non-completion of surveillance (vs. completion) are shown in Table 5.6. Non-completion was less likely among those of younger age (50-59 years), Blacks, Medicare or private insurance, belonging to the 5-year surveillance group, and having multiple advanced adenoma characteristics, all consistent with the findings for overuse. Non-completion was more likely among post-guideline patients.

Premature second procedure among those not eligible for surveillance

Table 5.7 shows the adjusted likelihood of a second procedure among those who were not eligible for surveillance. Older persons (aged over 50 years, ORs, 1.33-1.58), Blacks (OR: 1.59; 95% CI: 1.41-1.78), pre-guideline period (OR: 16.7), and having a polyp (hyperplastic or normal tissue, ORs, 2.03 and 2.47, respectively) were associated with increased likelihood of a second procedure. Of 1,793 persons who had a second procedure, 93.2 % were from the pre-guideline period, and 37.1 % (665 patients) had hyperplastic polyps (table not shown).

Discussion

Our study found that 51.8% of surveillance-eligible patients had completed a surveillance procedure, although guideline-concordance of timing was very low (8.2%). The surveillance completion rate is similar to the documented rate of 53.9% among a National Cancer Institute - recruited community-based screening cohort of the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial, followed up for a median period of 8.9 years, compared to 5.3 years of mean follow-up in our study (Schoen et al.,

2010). Within the risk sub-groups, our study found that 51.1% of the 3-year surveillance group and 54.4% of the 5-year surveillance group had completed surveillance, compared to 58.2% and 46.7% respectively among the PLCO study participants. The differences in rates are consistent with the shorter follow-up period in our study; this is supported by our finding that the post-guideline cohort had a lower adjusted likelihood of surveillance completion. The post-guideline cohort had a mean follow-up period of 2.9 years compared to 7.3 years for the pre-guideline cohort.

Regarding surveillance timing concordance, a Canadian academic medical center study reported a 33% rate of guideline timing concordance among 265 patients who completed surveillance (Schreuders et al., 2013). Comparatively our rate of guideline concordant timing among those who completed surveillance is 15.8% (347 out of 2,195 patients). A Netherlands study reported 21% timing concordance among 2,997 surveillance-eligible patients in their national registry, compared to our corresponding rate of 8.2% (van Heijningen et al., 2015). The US has a shorter recommended surveillance interval for persons with 1-2 adenomas (5 years) compared to the Netherlands (6 years). The Netherlands and Canada have a universal healthcare coverage system. Among patients with advanced adenomas, the Canadian study reported 29% completing surveillance on time, and the Netherlands reported 18%, compared to 29.1% in our study (281 out of 967) (Schreuders et al., 2013; van Heijningen et al., 2015).

The PLCO study of the US did not explore timing concordance with the guidelines. Our study adds to the literature by presents the timing concordance with guidelines in the US, and further, examined the role of specific polyp and patient characteristics that may have influenced the physician's individual patient recommendation or the patient's

compliance. We found that within each surveillance risk group, polyp characteristics that are not identified as risk criteria in the surveillance guidelines may be driving at least a part of the earlier-than-recommended surveillance. Patients with larger adenoma sizes, and those with multiple advanced adenoma characteristics are receiving earlier than recommended surveillance, about 6 months earlier. These findings suggest that the practicing clinician may be considering the individual patient's risk of developing cancer based on polyp features in tailoring the surveillance recommendation.

Our finding is also consistent with a recent study of physician recommendations for surveillance following screening at an academic medical center. They showed that patients with more than three adenomas were more likely to be recommended earlier than guideline-suggested surveillance (overuse) (Kahn et al., 2015). Our findings are also consistent with another study that reported increased overuse among patients with dual advanced features (co-existing high-grade dysplasia and large size) (Zhan et al., 2015). A higher risk of adenoma recurrence or cancer among patients with advanced adenomas is documented by several authors (Laiyemo et al., 2008; Lieberman et al., 2007; Saini et al., 2006).

Our finding of overuse (early surveillance) among patients with 5-year recommended intervals (compared to 3-year) is consistent with other studies (Saini et al., 2006; Schreuders et al., 2013; van Heijningen et al., 2015). The high overuse rate among the 5-year group, post-guideline (which changed the recommendation for this group from 3 years to 5-years) may reflect a persistent effect of the 1997 guidelines. These guidelines recommended 3-year surveillance among patients with large (>10mm) or multiple adenomas and remained silent about patients with 1-2 small adenomas (Winawer et al.,

1997). While the 2003 guidelines indicated a timing of 5 years for "lower-risk" patients (1-2 small tubular adenomas), it also emphasized that the evidence was still evolving and that the recommended interval could change with new evidence. Part of the 14.3% "surveillance" among the no-surveillance recommended group may be attributable to a family history of CRC (data not available) and the lack of definitive guidelines before 2006. It should be noted that 93.2% of patients who underwent premature second procedures were screened before 2006.

Other authors have suggested that overuse may partly be driven by concerns about interval CRCs arising from lesions missed at screening colonoscopy, prompting earlier surveillance among patients with elevated risk status (Saini et al., 2009). Concurrent with overuse, underuse is also a problem, with 48.2% not completing surveillance. A new finding is that right colon adenomas are associated with delayed surveillance (compared to left-sided adenoma). This is contrary to the expected overuse for this group, they have a 2-fold risk of advanced neoplasia at surveillance (Laiyemo et al., 2008; Martinez et al., 2009). Notably, this finding appears to be confounded by race. When race was included in the model and anatomic location was excluded, Black race was associated with the same coefficient estimate as anatomic location. When both were included, the anatomic location showed significance and race lost significance. Because Blacks are more likely to have right-sided adenomas (Nouraie et al., 2010) and given the nearly 50% excess CRC mortality experienced by Blacks, our finding needs further study with a larger sample size and multi-center studies.

Medicaid was associated with delayed surveillance, which is consistent with studies showing underuse of screening for all cancers, presentation with later stage CRC, and

worse CRC survival among Medicaid beneficiaries (Parikh, Robinson, Zaydfudim, Penson, & Whiteside, 2014; Shapiro et al., 2012; Ward et al., 2008). Our finding may support why late stage diagnosis and poorer survival is taking place among Medicaid beneficiaries. Further analysis of our data showed that Medicaid beneficiaries have a higher frequency of advanced adenoma than private insurance (11.8% vs. 9.2%, respectively, $p<0.001$), which may play into late-stage CRC diagnosis and poorer survival when combined with delayed surveillance.

An important new contribution is our reporting on "surveillance" among those not eligible for surveillance, with a 14.3% rate of second procedures that represent premature re-screening. This needs further exploration in datasets with family history data. One study reported that 9.2 % of surveillance-ineligible patients were recommended by their physician for an early second procedure. No data was reported on completed second procedures (Menees et al., 2014). Another new contribution of our study is that it accounted for all adenomas including multiple adenomas within a colonic segment, and accounted for co-existing, multiple advanced adenoma characteristics. Most studies have not reported on co-existing multiple characteristics that qualify for an advanced adenoma designation. They identified one advanced characteristic among a patient's adenomas and used a single feature for analysis (Lebwohl, Capiak, Neugut, & Kastrinos, 2012). Unlike studies based on claims data or the Clinical Outcomes Research Initiative (CORI) database (Lieberman et al., 2008), our data has complete information on the number of polyps removed from each anatomic segment, enabling us to more accurately account for all adenomas found. We identified an additional 712 patients as increased risk patients based on the criterion of ≥ 3 adenomas, beyond what was possible with counting the

number of polyp jars with a reported adenoma histology. Our study also did not limit analysis to the features of the largest adenoma, typical of other studies on colonoscopy findings (Lebwohl et al., 2012).

The reason for significant overuse in the post-guideline period among the 5-year surveillance group, 61.4% vs. 47.6% in the pre-period (not shown in tables) needs further study based on regional or multi-center samples. We could not explore the possible role of a family history of CRC due to lack of this data, a major study limitation. One study showed that screened patients with a family history of CRC are twice more likely to have completed surveillance than those without a family history (Schoen et al., 2010). Comorbidity is may be another consideration among both patients and providers in the surveillance decision. We could not study its role as data are not available. We also did not study provider factors in surveillance timing adherence as this is a single-center study. Provider factors are important due to varying levels of awareness, knowledge, and attitudes about practice guidelines across providers (Imperiale, 2011; Kruse et al., 2015; Saini et al., 2009).

Another study limitation is that the pathology reporting did not specify the number of polyps with differing histology within the same jar. The center transports multiple small polyps within a colonic segment with similar morphologic appearance in one polyp jar for histology, per standard practice consistent with insurer reimbursement criteria (Zauber, 2010). We assumed that reported adenoma histology applied to all polyps in the same jar. We also had fewer observation years to track surveillance use among post-guideline patients (post-2006 period). This may have biased the observed completion rate; post-guideline patients indeed had higher odds of non-completion. Finally, we did not

distinguish patient's insurance status at surveillance colonoscopy, which may play a role in surveillance use.

In conclusion, patients with adenomas larger than 5 mm, and multiple advanced characteristics, not captured by the 2006 guideline criteria, were associated with premature surveillance. Further, surveillance overuse was most prevalent among the 5-year recommended surveillance group. These factors need more exploration in multi-center studies, and data with family history, comorbidities, and symptomatology information. Finally, our study also suggests a need to understand and reduce the barriers to surveillance colonoscopy faced by Medicaid beneficiaries.

Table 5.1 Study eligible patients with screening colonoscopy between Sep 4, 2001 and Feb 11, 2010 (n=16,805)

		Had 2nd colonoscopy	
	Total (n=16,805)	Yes (n=3,988)	No (n=12,817)
Patient characteristics			
Gender*			
Male	7,629(45.4%)	1,993(26.1%)	5,636(73.9%)
Female	9,096(54.1%)	1,993(21.9%)	7,103(78.1%)
Missing	80(0.5%)	2(2.5%)	78(97.5%)
Age at screening colonoscopy (years) *			
40-49	2,746(16.3%)	476(17.3%)	2,270(82.7%)
50-59	8,322(48.5%)	1,945(23.4%)	6,377(76.6%)
60-74	5,737(34.1%)	1,567(27.3%)	4,170(72.7%)
Race*			
White	7,433(44.2%)	1,678(22.6%)	5,755(77.4%)
Black	8,721(51.9%)	2,178(25.0%)	6,543(75.0%)
Other or unknown	651(3.9%)	132(20.3%)	519(79.7%)
Insurance status at screening colonoscopy*			
Medicaid	522(3.1%)	113(21.7%)	409(78.4%)
Medicare or Private	14,866(88.5%)	3,465(23.3%)	11,401(76.7%)
Uninsured	1,417(8.4%)	410(28.9%)	1007(71.1%)
Procedure-related characteristics			
Initial procedure year*			
Pre-2006 period (pre guideline)	9,461(56.3%)	3,306(34.9%)	6,155(65.1%)
2006 and later	7,344(43.7%)	682(9.3%)	6,662(90.7%)
No surveillance recommended (10-year rescreening only)	12,571(74.8%)	1,793(14.3%)	10,778(85.8%)
Total surveillance-eligible*	4,234	2,195	2,039
≤1-year surveillance **	811(4.8%)	395(48.7%)	416(51.3%)
3-year surveillance **	1,891(11.3%)	967(51.1%)	924(48.9%)
5-year surveillance **	1,532(9.1%)	833(54.4%)	699(45.6%)
Number of observation years per patient# (mean, SD)	5.33(2.55)	6.62(1.76)	4.93 (2.62)

*Chi-square test and ANOVA P<0.001. **Recommended surveillance interval as per 2006 guidelines; the interval is based on adenoma findings at screening colonoscopy;≤1 year for those with sessile adenomas are removed piecemeal, hyperplastic polyposis syndrome, or > 10 adenomas; 3 years for those with advanced adenoma status, 3-10 adenomas, ≥ 1 cm adenoma, villous features, or high-grade dysplasia; 5 years for those with 1 or 2 small tubular adenomas or any adenoma without advanced features. #Refers to number of years of observation, from screening colonoscopy to the end of study period, Feb 11, 2011.

Table 5.2 Surveillance-eligible study subjects classified by surveillance use relative to recommended guidelines (n=4,234)

	Overuse (Premature before due) (n=1,355)	Appropriate (Timing as recommended) (n=347)	Late (Delayed relative to due date) (n=493)	Not done (by end of study period) (n=2,039)
Patient characteristics				
Gender				
Male	728(31.8%)	198(8.6%)	267(11.7%)	1,098(47.9%)
Female	627(32.5%)	149(7.7%)	226(11.7%)	926(48.0%)
Missing	0	0	0	15(100.00%)
Age at screening colonoscopy (years)*				
40-49	131(27.2%)	41(8.5%)	49(10.2%)	260(54.1%)
50-59	651(34.1%)	157(8.2%)	232(12.1%)	871(45.6%)
60-74	573(31.1%)	149(8.1%)	212(11.5%)	908(49.3%)
Race*				
White	623(30.3%)	166(8.1%)	228(11.1%)	1,038(50.5%)
Black	691(34.2%)	170(8.4%)	248(12.3%)	910(45.1%)
Other or unknown	41(25.6%)	11(6.9%)	17(10.6%)	91(56.9%)
Insurance status at screening colonoscopy				
Medicaid	39(27.1%)	6(4.2%)	19(13.2%)	80(55.6%)
Medicare or Private	1,191(32.5%)	301(8.2%)	431(11.8%)	1,743(47.6%)
Uninsured	125(29.5%)	40(9.4%)	43(10.1%)	216(50.9%)
Procedure-related characteristics				
Initial procedure year*				
Pre-2006 period (pre guideline)	970(32.7%)	255(8.6%)	410(13.8%)	1,334(44.9%)
2006 and later	385(30.4%)	92(7.3%)	83(6.6%)	705(55.7%)
Recommended surveillance interval*				
≤1-year surveillance	3(0.4%)	23(2.8%)	369(45.5%)	416(51.3%)

*Chi-square test P<0.05 for the difference between surveillance use and the respective characteristic of the study population.

Table 5.2 Surveillance-eligible study subjects (continued)

	Overuse (Premature before due) (n=1,355)	Appropriate (Timing as recommended) (n=347)	Late (Delayed relative to due date) (n=493)	Not done (by end of study period) (n=2,039)
3-year surveillance	589(31.2%)	281(14.9%)	97(5.1%)	924(48.9%)
5-year surveillance	763(49.8%)	43(2.8%)	27(1.8%)	699(45.6%)
Number of observation years available* (Mean, SD)	6.06(2.02)	6.36(1.81)	6.65(1.55)	6.01(2.13)
Polyp characteristics				
Adenoma status*				
Advanced adenoma/ ≥ 3 adenomas	592(24.15%)	304(12.4%)	333(13.6%)	1,222(49.9%)
Non-advanced adenoma	763(42.79%)	43(2.4%)	160(9.0%)	817(45.8%)
Location of the largest adenoma*				
Right	639(30.3%)	172(8.2%)	302(14.3%)	994(47.3%)
Left	680(33.5%)	160(7.9%)	186(9.2%)	1,007(49.5%)
Missing	36(38.3%)	15(16.0%)	5(5.3%)	38(40.4%)
Number of anatomic segments with adenoma*				
1-2 locations	1167 (34.1 %)	240 (7.0 %)	376 (11.0 %)	1640 (47.9%)
3-4 locations	152 (21.2 %)	92 (12.8%)	112 (15.6 %)	361 (50.4%)
Missing	36 (38.3%)	15 (16.0%)	5(5.3%)	38(40.4%)
Size of largest adenoma*				
≤ 5mm	816(31.0%)	215(8.2%)	321(12.2%)	1,283(48.7%)
5.1-9.9 mm	271(35.0%)	55(7.1%)	83(10.7%)	365(47.2%)
≥10 mm	244(31.8%)	64(8.3%)	86(11.2%)	374(48.7%)
Missing	24(42.1%)	13(22.8%)	3(5.3%)	17(29.8%)
Number of adenomas*				
1-2 adenomas	925(41.1%)	89(4.0%)	199(8.9%)	1,036(46.1%)
3+ adenomas	408(21.0%)	245(12.6%)	293(15.1%)	993(51.2%)
Missing	22(47.8%)	13(28.3%)	1(2.2%)	10(21.7%)
Has ≥ 2 adv. adenoma characteristics*				
No	1,230(31.3%)	326(8.3%)	460(11.7%)	1,917(48.7%)
Yes	125(41.5%)	21(7.0%)	33(11.0%)	122(40.5%)

*Chi-square test P<0.05 for test of the difference between surveillance use and the respective characteristic of the study population.

Table 5.2 Surveillance-eligible study subjects (continued)

	Overuse (Premature before due) (n=1,355)	Appropriate (Timing as recommended) (n=347)	Late (Delayed relative to due date) (n=493)	Not done (by end of study period) (n=2,039)
Location of the largest adenoma*				
Right	639(30.3%)	172(8.2%)	302(14.3%)	994(47.3%)
Left	680(33.5%)	160(7.9%)	186(9.2%)	1,007(49.5%)
Missing	36(38.3%)	15(16.0%)	5(5.3%)	38(40.4%)
Number of anatomic segments with adenoma*				
1-2 locations	1167 (34.1 %)	240 (7.0 %)	376 (11.0 %)	1640 (47.9%)
3-4 locations	152 (21.2 %)	92 (12.8%)	112 (15.6 %)	361 (50.4%)
Missing	36 (38.3%)	15 (16.0%)	5(5.3%)	38(40.4%)
Size of largest adenoma*				
≤ 5mm	816(31.0%)	215(8.2%)	321(12.2%)	1,283(48.7%)
5.1-9.9 mm	271(35.0%)	55(7.1%)	83(10.7%)	365(47.2%)
≥10 mm	244(31.8%)	64(8.3%)	86(11.2%)	374(48.7%)
Missing	24(42.1%)	13(22.8%)	3(5.3%)	17(29.8%)
Number of adenomas*				
1-2 adenomas	925(41.1%)	89(4.0%)	199(8.9%)	1,036(46.1%)
3+ adenomas	408(21.0%)	245(12.6%)	293(15.1%)	993(51.2%)
Missing	22(47.8%)	13(28.3%)	1(2.2%)	10(21.7%)
Has ≥ 2 adv. adenoma characteristics*				
No	1,230(31.3%)	326(8.3%)	460(11.7%)	1,917(48.7%)
Yes	125(41.5%)	21(7.0%)	33(11.0%)	122(40.5%)

*Chi-square test P<0.05 for test of the difference between surveillance use and the respective characteristic of the study population.

Table 5.3 Logistic regression model of the likelihood of completing the surveillance procedure among surveillance-eligible patients (n=4,234)

	OR (95%CI)
Patient characteristics	
Gender: Female vs. male	0.98(0.86,1.11)
Age (years) (Ref:40-49)	
50-59**	1.42(1.16,1.74)
60-74**	1.23(1.00,1.51)
Race (Ref: White)	
Black**	1.22(1.07,1.39)
Other or unknown	0.89(0.63,1.27)
Insurance status (Ref: Uninsured)	
Medicaid	0.87(0.59,1.30)
Medicare or Private **	1.29(1.04,1.61)
Procedure-related characteristics	
Initial procedure timing	
Post guideline* (vs. pre-2006 period) **	0.62(0.54,0.72)
Recommended surveillance interval (Ref: ≤1-year surveillance)	
3-year surveillance	1.14(0.96,1.35)
5-year surveillance**	1.26(1.06,1.51)
Polyp characteristics	
Anatomic location of the largest adenoma : Right (vs. Left)	1.08(0.95,1.22)
Patient has ≥ 2 advanced adenoma characteristics**	1.64(1.28,2.11)
Hosmer and Lemeshow Goodness-of-Fit statistic	p=0.147

*Post guideline: screening colonoscopy done in 2006 or later.
** P<0.05 are statistical significance.

Table 5.4 Association of surveillance time interval (in years) with patient, procedure, and polyp characteristics among surveillance-eligibles who completed surveillance (n=2,195)*

	Total, n=2,195	≤1-year, n=395	3-year, n=967	5-year, n=833
	Estimate	Estimate	Estimate	Estimate
Patient characteristics				
Age(years) (Ref: 40-49)				
50-59	0.02	-0.27	-0.05	0.24
60-74	-0.16#	-0.48#	-0.21	0.03
Procedure-related characteristics				
Initial procedure timing: Post guideline(vs. pre-2006 period)	-0.56#	-0.57#	-0.54#	-0.51#
Recommended surveillance interval : 3-year surveillance (vs. ≤1-year)	0.11	-	-	-
Recommended surveillance interval : 5-year surveillance (vs. ≤1-year)	0.19	-	-	-
Polyp characteristics				
Anatomic location of the largest adenoma : Right (vs. Left)	0.06	-0.16	0.08	0.16#
Size of largest adenoma : ≥10 mm (vs. <10mm)	-0.30#	-0.53#	-0.23#	-
Size of largest adenoma : 5.1-9.9mm (vs. ≤ 5 mm)	-	-	-	-0.65#
Number of adenomas: ≥3 adenomas (vs. 1-2)	0.15	-0.13	0.19#	-
Patient has ≥ 2 advanced adenoma characteristics (vs. 1)	-0.50#	-0.39	-0.53#	-
R square	0.185	0.165	0.186	0.103

*Gender, race, insurance status were not statistically significant (P>0.05), and exclude from the field models (data not shown).

# P<0.05 are statistical significance.

Table 5.4a Association of surveillance time interval (in years) with patient, procedure, and polyp characteristics among the sub-group recommended to undergo surveillance at 5 years per 2006 guidelines (n=833)

	Model 1*		Model 2*	
	Estimate	SE	Estimate	SE
Patient characteristics				
Gender : Female vs. male	0.07	0.08	0.06	0.08
Age(years) (Ref: 40-49)				
50-59	0.18	0.13	0.24	0.13
60-74	-0.02	0.14	0.03	0.13
Race (Ref: White)				
Black	-0.16**	0.08	-0.14	0.08
Other or unknown	0.12	0.23	0.13	0.22
Insurance status (Ref: Uninsured)				
Medicaid	-0.14	0.25	0.10	0.24
Medicare & Private	-0.03	0.13	0.20	0.13
Procedure-related characteristics				
Initial procedure timing				
2006 and later (vs. Pre-2006 period)	-0.63**	0.10	-0.51**	0.10
Polyp characteristics				
Anatomic location of the largest adenoma : Right (vs. Left)	-	-	0.16**	0.07
Size of largest adenoma : 5.1-9.9 mm (vs. ≤5mm)	-	-	-0.65**	0.11
	R^2=0.058, Adj R^2=0.049		R^2=0.103, Adj R^2=0.092	

*Model 1 includes patient and colonoscopy characteristics, and Model 2 includes patient, colonoscopy, and adenoma characteristics.

**P<0.05, statistically significant.

Table 5.5 Likelihood of overuse, delayed and not completed surveillance among surveillance-eligible patients (n=4,234)

	Overuse (Premature before due vs. recommended timing) OR (95%CI)	Late (Delayed vs. recommended timing) OR (95%CI)	Not done (by end of study period) OR (95%CI)
Patient characteristics			
Gender: Female vs. male	1.08(0.83,1.39)	1.06(0.80,1.42)	1.10(0.86,1.40)
Age(years) (Ref: 40-49)			
50-59	1.49(0.98,2.26)	1.23(0.77,1.98)	0.95(0.65,1.39)
60-74	1.51(0.99,2.30)	1.12(0.70,1.81)	1.08(0.73,1.59)
Race (Ref: White)			
Black	1.01(0.78,1.31)	1.04(0.78,1.39)	0.83(0.66,1.06)
Other or unknown	0.85(0.41,1.75)	0.96(0.43,2.14)	0.99(0.51,1.94)
Insurance status (Ref: Uninsured)			
Medicaid	1.85(0.70,4.90)	3.22(1.14,9.09)*	2.27(0.90,5.69)
Medicare or Private	1.30(0.84,2.00)	1.52(0.93,2.50)	1.00(0.67,1.49)
Procedure-related characteristics			
Initial procedure timing			
2006 and later (vs. Pre-2006 period)	1.73(1.30,2.31)*	0.50(0.35,0.70)*	1.86(1.42,2.43)*
Recommended surveillance interval			
5-year surveillance (vs. ≤3-year surveillance)	14.39(10.03,20.64)*	0.31(0.18,0.53)*	4.41(3.11,6.25)*
Polyp characteristics			
Anatomic location of the largest adenoma : Right (vs. Left)	0.86(0.67,1.11)	1.49(1.12,1.98)*	0.94(0.74,1.19)
Size of largest adenoma : ≥10 mm (vs. <10mm)	1.81(1.25,2.63)*	0.83(0.55,1.26)	1.28(0.91,1.80)
Patient has ≥ 2 advanced adenoma characteristics (vs. 1)	2.26(1.30,3.93)*	1.15(0.60,2.20)	1.02(0.59,1.76)

* P<0.05 are statistical significance.

Table 5.6 Logistic regression model of the likelihood of non-completion surveillance (vs. any surveillance use) among surveillance-eligible patients (n=4,234)

	Non-completion patients OR (95%CI)
Patient characteristics	
Gender	
Male	(ref)
Female	1.03(0.90,1.16)
Age at screening colonoscopy (years)	
40-49	(ref)
50-59*	0.71(0.57,0.87)
60-74	0.81(0.66,1.00)
Race	
White	(ref)
Black*	0.82(0.72,0.93)
Other or unknown	1.12(0.79,1.59)
Insurance status at screening colonoscopy	
Medicaid	1.14(0.77,1.70)
Medicare or Private	0.78(0.62,0.97)
Uninsured	(ref)
Procedure-related characteristics	
Initial procedure timing	
Post guideline(vs. pre-2006 period)*	1.60(1.39,1.85)
Recommended surveillance interval (Ref: ≤1-year surveillance)	
3-year surveillance	0.88(0.74,1.04)
5-year surveillance*	0.80(0.66,0.96)
Polyp characteristics	
Anatomic location of the largest adenoma : Right (vs. Left)	0.93(0.82,1.05)
Size of largest adenoma : ≥10 mm (vs. <10mm)	1.05(0.86,1.28)
Patient has ≥ 2 advanced adenoma characteristics*	0.59(0.44,0.79)

* P<0.05 are statistical significance.

Table 5.7 Logistic regression model of the likelihood of a 2nd procedure among those who were not eligible for surveillance (n=12,571)

	Had 2nd procedure OR (95%CI)
Patient characteristics	
Gender	
Male	(ref)
Female*	0.83(0.74,0.92)
Age at screening colonoscopy (years)	
40-49	(ref)
50-59*	1.33(1.13,1.56)
60-74*	1.58(1.34,1.87)
Race	
White	(ref)
Black*	1.59(1.41,1.78)
Other or unknown	0.80(0.59,1.07)
Insurance status at screening colonoscopy	
Medicaid	0.74(0.52,1.07)
Medicare or Private	0.98(0.83,1.17)
Uninsured	(ref)
Procedure-related characteristics	
Initial procedure timing	
Pre-2006 period	(ref)
2006 and later	0.06(0.05,0.07)
Polyp characteristics	
Polyp status	
Hyperplastic polyp*	2.03(1.80,2.94)
Normal tissue*	2.47(2.13,2.87)
No polyp	(ref)

* P<0.05 are statistical significance.

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