We are IntechOpen,
the world's leading publisher of
Open Access books
Built by scientists, for scientists

6,900
Open access books available

186,000
International authors and editors

200M
Downloads

154
Countries delivered to

Our authors are among the

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS
BOOK CITATION INDEX
INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Issues in Screening and Surveillance Colonoscopy

Anjali Mone, Robert Mocharla, Allison Avery and
Fritz Francois

Additional information is available at the end of the chapter

1. Introduction

Colorectal cancer (CRC) is a major cause of morbidity and mortality throughout the world. However timely screening and treatment can dramatically impact outcomes. The association with well-defined precancerous lesions and long asymptomatic period provides the opportunity for effective screening and early treatment of CRC. The current options for CRC screening are strongly anchored in evidence demonstrating utility in reducing morbidity and mortality. This chapter will review the epidemiology of CRC, risk stratification, strategies for screening, as well as factors that threaten achieving health equity through appropriate screening programs.

2. Epidemiologic trends in colorectal cancer

Worldwide CRC is the third most common cancer and fourth most common cause of death. Interestingly this disease affects men and women almost equally (Haggar and Boushey, 2009). In the United States CRC is the third most commonly diagnosed cancer and constitutes 10% of new cancers in men and women (Society, 2011). In 2011, there were approximately 141,120 new cases and it is estimated that 143,460 Americans will be diagnosed with colorectal cancer in 2012 (NIH, 2009). Furthermore it is estimated up to 30% of new cases are found in the general population without known risk factors for this disease (Imperiale et al., 2000). Although there are still approximately one million new cases of CRC diagnosed each year, incidence has been steadily declining over the past 15 years (Bresalier, 2009; Ferlay et al., 2010; Kohler et al., 2011). In the United States mortality from CRC has also declined with a 7% decrease in men and 12% decrease in women between 1980 and 1990 (Jemal et al., 2008). Since 1990 decreases in CRC incidence and mortality have been even more substan-

tial, and is largely attributable to improvements in screening rates (Lieberman, 2010), especially the growing use of colonoscopy procedures (Edwards et al., 2010). Nevertheless, important trends remain in the worldwide epidemiology of CRC.

2.1. Geographic variations in CRC epidemiology

There is significant diversity in colorectal cancer incidence worldwide. Surprisingly industrialized nations have a remarkably greater occurrence of CRC accounting for 63% of all cases. In fact CRC incidence rates range from more than 40 per 100,000 people in the United States, Australia, New Zealand, and Western Europe to less than 5 per 100,000 in Africa and parts of Asia. It is notable that the US is the only country with significantly declining CRC incidence rates for both genders, and this is most likely a reflection of better screening practices and early prevention (Jemal et al., 2011).

While there is substantial disparity in CRC occurrence globally, CRC incidence has been increasing in places previously reporting low rates. For example the number of new CRC diagnoses has been rising in a number of Asian countries that recently transitioned from low-income to high-income economies. Individuals residing in China, Japan, India, Singapore, and Eastern European countries were previously reported to have the lowest rates of CRC. Countries with the highest incidence rates include Australia, New Zealand, Canada, the United States, and parts of Europe, however incidence has started stabilizing and even declining in these regions (Haggar and Boushey, 2009; Jemal et al., 2010).

Interestingly CRC incidence seems to have a close association with location. In fact studies show that migrants rapidly acquire the risk patterns for CRC associated with their new surroundings. For example the incidence rates in Japanese immigrants have been found to significantly increase after moving to the United States. Geographic influence is also evident in a study done in Israel where male Jews of Western descent were found to have a higher likelihood of developing CRC than those born in Africa or Asia. Furthermore environment may be responsible for variations within ethnic groups. This is demonstrated by higher rates of CRC among American Indians living in Alaska than those residing in the Southwest. Incidence rates among black males were found to range from 46.4 cases per 100,000 individuals in Arizona to 82.4 per 100,000 in Kentucky. In white men rates range from 44.4 per 100,000 in Utah to 68.7 per 100,000 in North Dakota (The Centers for Disease Control and Prevention [CDC], 2011).

The importance of location can also be seen by differences in CRC incidence within specific genders. CRC mortality rates for men are lower in Western states excluding Nevada, and higher in Southern and Midwestern states. These differences in CRC rates may be attributable to regional variations in risk factors including diet and lifestyle as well as access to screening and treatment. In fact one study found that up to 43% of colorectal cancers are preventable through diet and lifestyle modifications (Perera P.S., 2012).

2.2. Racial and ethnic variations

There is substantial evidence demonstrating racial disparities in CRC risk particularly for black men. In the USA this group has been found to have 20% higher incidence rate and 45% higher mortality rate from colorectal cancer compared to whites (Jemal et al., 2008; Wallace and Suzuki, 2012). There are also significant differences in life expectancy among blacks compared to whites. While there was a 39% reduction in mortality rate for white men between 1960-2005, during the same period there was a dramatic 28% increase in mortality for black men (Soneji et al., 2010). Of note incidence rates among other racial groups including Hispanics, Asian Americans, and American Indians are lower than those among whites. The factors that underlie these differences have not been fully elucidated but most likely encompass both modifiable factors (e.g. smoking, socioeconomic status, body mass index, and cultural beliefs) as well as non-modifiable factors (e.g. race/ethnicity, gender, and genetic predisposition). These findings do suggest there is a need for appropriate risk stratification for CRC and for more aggressive screening in high-risk populations, particularly among blacks in the United States. Such an approach has been recommended by both the American College of Gastroenterology as well as the American Society for Gastrointestinal Endoscopy with the suggestion to start screening blacks at the age of 45 (Cash et al., 2010; Rex et al., 2009).

2.3. The gender gap

According to SEER 2012 statistics, the overall prevalence of colorectal cancer does not vary substantially between the genders. The lifetime risk of being diagnosed with CRC is similar for men 5.7% and women 5.2%. The lifetime risk of dying from CRC is also similar; 2.3% and 2.1% for men and women respectively (NIH, 2009). Even though annually the new diagnoses of CRC have roughly been equal in men (187,973) and women (185,983), men have higher age-adjusted CRC incidence rates (Abotchie et al., 2012). Women seem have a delay of approximately 7-8 years in the development of advanced polyps (Jaroslaw Regula, 2012; Lieberman et al., 2005). Additionally age adjusted mortality rates can be up to 35-40% higher in men compared to women (CDC, 2011). Gender related disparities are not completely understood but may be attributable to variations in hormonal exposure (Chlebowski et al., 2004). These biological differences related to sex raise the issue of whether men and women should be screened differently for CRC. However current screening guidelines have not been modified based on gender (Levin et al., 2008).

2.4. Modifiers of the epidemiologic trends

Despite some overall gains, several factors remain that impact the epidemiology of CRC. Advancements in elucidating CRC pathogenesis allow for explanations of the above epidemiologic trends and have the potential for more efficient screening and treatment. It is estimated that up to 70% of CRC cases occur sporadically in individuals with no identifiable risks (Hardy et al., 2000). Factors that predispose individuals to a higher risk for developing CRC include any personal or family history of CRC or adenomatous polyps, inflammatory bowel disease (IBD), and inherited genetic syndromes such as familial adenomatous polypo-

sis (FAP), hereditary nonpolyposis colorectal cancer (HNPCC). Guidelines recommend earlier and more aggressive screening for this high-risk population.

As evidenced by the presence of both modifiable and non-modifiable risk factors, the pathogenesis of CRC seems to be influenced by a combination of genetics and the environment. Indeed the disease results from the progressive accumulation of both genetic as well as epigenetic changes in the colonic epithelium. Currently genetic tests are available that identify patients with inherited mutations associated with FAP and HNPCC. While this technology is promising, only 2-6% of CRC cases are attributable to common inherited mutations, suggesting other variables are playing a role in the development of this disease (Winawer et al., 2003).

Some of the environmental influences that have been investigated include the role of Streptococcus Bovis. Although infections are recognized as a major preventable cause in cancer, an infectious etiology has not been identified in cases of sporadic CRC, strongly suggesting that more factors are involved in the development of this disease (Boleij and Tjalsma, 2012). Similar to many other cancers, an important common thread in the pathogenesis of CRC is the presence of chronic inflammation that is thought to increase the probability of mutagenic events that lead to the production of oxidative species and damage DNA causing genomic instability (Zauber et al., 2008). This is demonstrated by patients with inherited genetic mutations who are found on colonoscopic examination to have chronic inflammatory changes that precede tumor development (Terzic et al., 2010). This can also be seen in patients colonized with S. Bovis who are found to have inflammatory changes in the bowel wall (Terzic et al., 2010). Further support for an inflammatory basis is found in recent studies showing aspirin and non-steroidal, anti-inflammatory drugs greatly reduce the risk of CRC (Rothwell et al., 2012).

2.5. Impact of screening on the epidemiology of CRC

Numerous studies show favorable CRC outcomes if the cancer is identified and treated at an early stage. In fact the 5-year survival rate is greater than 90% if CRC is identified at an early stage. However if the cancer extends beyond the colon, 5-year survival is less than 10% (Collett et al., 1999). Continuing advances in CRC therapies hold the promise of adequate treatment for advanced stages of the disease. A recent study in Nature suggests the possibility of helping patients with advanced stage CRC with targeted drugs. This study suggests that there are a finite number of genetic pathways in CRC that can be therapeutically targeted. Although these findings are promising much work is still needed before there will be a cure for CRC (Muzny et al., 2012).

Given the limited effective treatment for advanced CRC, prevention through early detection is paramount. CRC is a model disease for routine population screening since it is prevalent, has a long asymptomatic period, and precancerous lesions can be identified and treated (Pezzoli et al., 2007). Compared to other cancers where the primary goal is early detection of neoplasia, CRC can actually be prevented with detection and removal of cancer precursor lesions (Inadomi et al., 2012). It is estimated that 30% of people over the age of 50 with no history of CRC risk factors harbor adenomatous polyps (Alberti et al., 2012; Pezzoli et al., 2007), and the incidence of these polyps increases with age. Early adenoma resection is asso-

ciated with considerable reductions in CRC (Rex et al., 2009; Winawer et al., 1993b), and has now been demonstrated to have mortality benefit (Zauber et al., 2012).

Although it is difficult to identify precisely which adenomas will undergo neoplastic trans‐formation, there are certain pathologic features that can help predict their level of risk: in‐creased size ≥10 mm, increased number of 3 or more adenomas, villous histology, and high-grade dysplasia (Alberti et al., 2012; Lieberman et al., 2012). Most adenomas undergo a similar progression to invasive cancer termed the adenoma-carcinoma sequence (Levin et al., 2008; Sano et al., 2009). Given that these cancer precursors are often asymptomatic, there is compelling evidence to support early screening for healthy individuals. In fact the aver‐age-risk individuals compose 70-75% of the CRC population (Lieberman, 2010). In response to mounting evidence suggesting that screening of average-risk individuals allows for early cancer detection and prevention, CRC guidelines from several organizations were updated in 2008 (USPSTF, 2008).

2.6. CRC prevention tests

Colonoscopy allows for the direct visualization of the entire colon and for the potential to remove lesions that are identified. Results from the National Polyp Study confirm that colo‐noscopy and adenoma removal is associated with decreased rates of developing colon can‐cer in the future (Winawer S.J., 2006) and reduces mortality (Zauber et al., 2012). The finding that mortality is reduced by polypectomy is of major significance because it suggests that colonoscopy can identify a subset of adenomas which can potentially become aggressive cancers and provides further evidence that colonoscopy is in fact the best screening option because of its added benefit of decreased mortality, particularly in individuals at increased risk. In patients with no lesions detected during a screening colonoscopic examination, the interval for follow-up surveillance can be extended to 10 years compared to 5 years for sig‐moidoscopy (which visualizes only the left side of the colon) along with FOBT every 3 years. The known draw backs to colonoscopy include the need for bowel prep, sedation that may be associated with cardiopulmonary risks, higher cost compared to other methods, associa‐tion with greater risk of bleeding and perforation, and a miss rate of up to 5% for malignant colon lesions.

While colonoscopy remains the gold standard for CRC prevention, economic constraints and patient attitudes may prevent screening with this technique. In an effort to improve participation alternative tests have been endorsed. There are a range of screening meth‐ods that are categorized into two major groups, prevention and detection. Prevention tests detect cancer as well as pre-cancerous polyps, and are generally structural exams such as the colonoscopy, flexible sigmoidoscopy, CT colonography, and double-contrast barium enema. Detection tests are only able to identify CRC lesions and consist of fecal tests in‐cluding the fecal immunochemical test (FIT), fecal occult blood testing (FOBT), and Fecal DNA testing (Rex et al., 2009).

Flexible Sigmoidoscopy remains an acceptable alternative to colonoscopy for colorectal can‐cer screening (Levin et al., 2008; USPSTF, 2008; Winawer et al., 2003; Winawer et al., 1997). Although both screening techniques are similar, sigmoidoscopy requires more frequent

screenings at 5–year intervals and the benefits are confined to the distal colon only. In addition the USPSTF recommends screening with FOBT every 3 years (USPSTF, 2008). Prior studies have demonstrated a significant mortality benefit for the section of the colon examined (Wilkins and Reynolds, 2008). A recent study in the NEJM confirmed this data showing that flexible sigmoidoscopy decreases CRC incidence and mortality (Schoen et al., 2012). The advantages of sigmoidoscopy include lower cost, lower risk profile, and need for less bowel preparation compared to colonoscopy. However a major setback for this alternative is that polyp visualization is limited to the distal colon. Studies have shown that up to 30% of patients with distal colon cancer also have synchronous proximal lesions that will be missed by sigmoidoscopy (Francois et al., 2006; Imperiale et al., 2000; Lieberman et al., 2000). As such individuals with polyps in the distal colon should undergo follow up with colonoscopy given the increased prevalence of synchronous right-sided lesions. Screening only 50% of colon will preclude detection of the lesions in the portion of the colon not within reach of the sigmoidoscope. This test would also not be an appropriate screening tool for women, patients over the age of 60, patients with HIV, and African Americans who have a higher likelihood of harboring proximal polyps (Bini et al., 2006; Lieberman et al., 2000; Lieberman et al., 2005; Schoenfeld et al., 2005).

Double contrast Barium enema allows for visualization of the entire colon and must be completed every 5 years. Its high polyp miss rate (as high as 23%), lack of therapeutic intervention (another procedure is needed to remove detected polyps), and concerns regarding radiation exposure, have limited its use (Toma et al., 2008; Wilkins and Reynolds, 2008).

CT colonography is able to provide information about the entire colon and has been proposed as a possible screening option for patients who decline conventional colonoscopy. This test is less invasive compared to conventional colonoscopy, is associated with decreased risk of perforation and does not require sedation (Lieberman, 2010). Not only are detection rates far superior to the barium enema, but CT colonography (CTC) has comparable sensitivity to colonoscopy for polyps 10mm or greater in size (Johnson et al., 2008). However relative to other options, this modality is costly, and has poor sensitivity for polyps less than 7mm (Lieberman, 2010). Due to insufficient evidence for performance metrics this test is currently not supported by established guidelines. The United States Preventive Services Task Force expresses additional concern about the impact and extra costs related to following-up extra-colonic findings (USPSTF, 2008). In fact an estimated 27% to 69% of tests performed uncover abnormal extra-colonic findings (Lieberman, 2010). More studies are needed to assess this procedure's benefits and risks, particularly to determine whether this method may be missing significant lesions.

Capsule Endoscopy provides direct visualization of the colonic mucosa via an ingestible capsule with video cameras at both ends that wireless transmits images to a receiver. Given that bowel motility significantly affects results, this test is not performed regularly and is not supported by current guidelines.

2.7. CRC detection tests

Fecal occult blood testing (FOBT) is an annual stool test that detects cancer at an early stage. The USPSTF now specifically recommends the high-sensitivity guaiac-based testing (Hemoccult Sensa) over the standard guaiac-based testing (Hemoccult II) (USPSTF, 2008). Based on the premise that colon cancer intermittently bleeds, the FOBT tests for blood by detecting the peroxidase activity of heme (Lieberman, 2010). Not only is the test economical and convenient, patients with a positive test result have an almost 4 fold increased likelihood having cancer (Winawer et al., 2003). In fact studies have found FOBT reduces mortality by approximately 33% over a 10-year period (Lieberman, 2010). Another study reported approximately 20% reduction in mortality when FOBT was compared to controls over an 18-year period (Lieberman, 2010). Supporters of the FOBT question whether invasive measures such as the colonoscopy are harmful given that computer simulated modeling shows similar life-years gained in both tests (Zauber et al., 2008). Furthermore advocates assert that FOBT has the greatest potential for impact at the population level because it is directed at healthy people (Harvard Medical School, 2012). Additionally asymptomatic people may be more willing to participate in a less invasive and generally less inconvenient test.

While a case can be made that FOBT has some quantifiable mortality benefits, evidence suggests that colonoscopy is still the superior screening option. FOBT has many disadvantages. One major drawback of this modality is the high false positive rate because the test is not specific for human blood. In fact the test will not be accurate if patients consume red meat or any other peroxidase containing substances. Additionally three-stool sample are required on separate days (Lieberman, 2010). Single sample FOBT is estimated to miss 95% of CRC (Wilkins and Reynolds, 2008). Furthermore the test must be repeated annually to be effective. In addition to these drawbacks, this test only detects potentially high-risk individuals which means that abnormal test results require subsequent follow up with colonoscopy. Compliance with all of the aforementioned recommendations is unknown making the effectiveness of the test uncertain. In fact one survey found that up to 30% of doctors recommended inappropriate forms of follow up rendering the FOBT not useful (Nadel et al., 2005). Despite these drawbacks the FOBT sampling test is still preferable to the no screening option.

Fecal immunochemical testing (FIT) is a newer test that is easier to use and specific for humans. This means that the FIT is less susceptible to interference by diet or drugs. This modality uses antibodies to detect human blood components such as hemoglobin and albumin in stool samples (School, 2012). This alternative is appealing because it is less invasive than colonoscopy but potentially more accurate than the FOBT. Studies show over 50% sensitivity for cancer after using as small an amount as one stool sample (Lieberman, 2010). FIT may be superior to the FOBT given that one study showed higher participation in the FIT group. Participation is key for fecal tests making the previously mentioned study clinically relevant. However no randomized trials have shown that FIT decreases mortality (Wilkins and Reynolds, 2008).

Given that participation may be negatively impacted by hesitation to undergo colonoscopy screening, a recent study investigated whether FIT can serve as a valid screening alternative and no significant differences were found between FIT and colonoscopy in terms of partici-

pation (Quintero et al., 2012). Furthermore colonoscopy still detected substantially higher numbers of cancerous polyps. It is difficult from this study to declare that FIT testing is non-inferior because of colonoscopy's mortality benefit.

Fecal DNA testing detects a finite number of gene mutations in stool samples associated with colon neoplasia (Alberti et al., 2012). One large prospective trial found stool DNA testing to have greater sensitivity for cancer than standard FOBT (Imperiale et al., 2004). Furthermore patients were found to prefer fecal DNA testing to both FOBT and colonoscopy (Wilkins and Reynolds, 2008). However this option is not recommended by current guidelines because of insufficient evidence. Also there have been other studies comparing stool DNA testing to FOBT that suggest this fecal DNA testing does not measure up in terms of cost or efficacy (Lansdorp-Vogelaar et al., 2010).

2.8. Which screening test should be done?

Each of the aforementioned screening options has strengths and setbacks, however patient adherence to CRC screening remains more critical than the specific method chosen (Vijan et al., 2001). Simply put, the best test is the one that the patient accepts and complies with. Despite mounting evidence that screening is life saving, screening rates remain surprisingly low for this preventable cancer. In fact awareness of the importance of CRC screening has only recently started to approach that of other cancers. Statistics indicate only 24% of Americans have completed the FOBT within the past few years and only 57.1% have ever had a sigmoidoscopy or colonoscopy (Wilkins and Reynolds, 2008). Data from the NHIS, a national survey of the general population, shows that only 58.3% of the US population met recommendations for CRC screening in 2010 (Shapiro et al., 2012). This is increased from 54.5% in 2008. Although there has been progress in the use of CRC testing, 40-50% of individuals over the age of 50 still are not receiving routine screening for colorectal cancer.

It is apparent from these suboptimal screening rates that there is a demand for novel screening strategies that are not only effective but also economical and non-invasive. Continued research in this field is ongoing and in a fascinating study published in *Gut*, Citarda et al (Citarda et al., 2001) took steps towards attempting to find this desired formula. Their study is evidence of the increasing knowledge about the molecular properties of cancer. Based on the theory that a specific cancer smell exists, they found that a trained labrador retriever could detect the presence of colorectal cancer with 91% sensitivity and 99% specificity in breath samples and 97% sensitivity and 99% specificity in watery stool samples. Surprisingly the study dog's ability to detect cancer was not confounded by benign colorectal disease, inflammatory bowel disease, or smoking. Even though the routine use of canines for cancer screening is not practical, this study suggests there is potential for future screening tests based on cancer-specific chemical compounds.

2.9. Cost effectiveness of CRC screening

CRC screening has been found to reduce mortality and to be cost-effective. The challenge remains to make screening affordable and available to individuals who will experience the

greatest benefit. Several models have been proposed to estimate the costs of various screening programs. The 2005 Institute of Medicine comprehensive summary of CRC screening effectiveness concluded that all of the screening options are relatively comparable in terms of life-years gained as well as cost when compared with a no-screening option. FOBT was the least costly option, however most modalities are estimated to cost <$40,000 per life-year saved (Lieberman, 2010; Pignone et al., 2002). However it is difficult to rely on these models alone as they may not be entirely accurate and are not able to account for other factors such as patient compliance. In general cost benefit analysis studies suggest that CRC screening is overall a cost-effective measure and it is estimated that routine screening can save more than 18,800 lives per year (Maciosek et al., 2006; Wilkins and Reynolds, 2008).

2.10. Surveillance guidelines

Currently the United States Multi-Society Task Force (MSTF) on CRC supports a 10-year interval between subsequent screening colonoscopies for average risk patients. Case-control and observational studies indicate that the mortality benefit from colonoscopy lasts at least 10 years. However patients who are found to have adenomas on baseline colonoscopy are at increased risk of developing future adenomas and cancerous lesions (Martinez et al., 2009). Certain higher-risk patients can develop cancer as soon as 3-5 years after a colonoscopy. These are termed interval cancers. These patients require a shorter interval between subsequent follow up because this has been shown to reduce colorectal cancer incidence by as much as 66% (Citarda et al., 2001; Winawer et al., 1993a). Guidelines from the GI consortium panel advocate repeat colonoscopy 5 years after removal of a low-risk polyp and after 3 years if the polyp has higher risk features. The selection of a 3-year screening interval for subsequent follow-up is based on evidence that shows detection of advanced lesions is not improved at 1 year versus 3 years (Winawer et al., 1993b). Further research is still needed to determine whether a single negative follow up colonoscopy is sufficient (Lieberman et al., 2012).

The use of risk stratification to determine the optimal screening interval is important because physicians that refer patients for surveillance at intervals shorter than recommended may be exposing patients to unnecessary risks and costs (Lieberman, 2010). In fact a recent study revealed underuse of colonoscopies in high-risk patients and overuse in low risk patients. By ineffective allocation of resources high-risk patients are placed at increased risk for developing cancer. Furthermore optimization of screening is important in light of low screening rates for a preventable cancer. Customized screening recommendations based on risk allows for more streamlined and effective screening leaving resources that can be devoted to colon cancer education targeting the challenging subset of the population at high risk with poor adherence. Ultimately screening program success depends not only on quality but patient participation (Lieberman et al., 2012). In addition to risk stratification, the MSTF on CRC believes that high-quality baseline examination is key for effective surveillance. Interval cancers have been found to occur more frequently in patients with negative baseline exams. There is evidence to suggest that important lesions are often missed at baseline colonoscopy and it is estimated that up to 17% of 10 mm lesions are missed. This variability in

adenoma detection rates may be attributable to biologic differences in missed adenomas or disparities in endoscopist proficiency.

3. When to start screening?

As with any effective screening technique, the most important issue is always *when* to start offering the test. Although the lifetime risk of CRC is estimated to be 6%, we now understand that the chance of developing the disease increases with age. In the United States the annual incidence of CRC in people of ages 50 to 54 was found to be approximately double that found in individuals ages 45 to 49 (Imperiale et al., 2000). A successful screening test, if used on 100% of the population has the potential to save many more lives than if the test is used on only a portion of the population. However given limited medical resources, strategic optimization is necessary for maximum impact. Current recommendations support initiation of screening at age 50 for average risk men and women with earlier screening recommended for high-risk populations (Levin et al., 2008; Rex et al., 2009; USPSTF, 2008; Winawer et al., 2003). In addition to identifying optimal timing for initiation, the goals of screening have shifted to focus on cancer prevention rather than simply cancer detection (Winawer et al., 2003). As a result recent guidelines from the American College of Gastroenterology (ACG) and USPSTF now endorse colonoscopy as the preferred modality for screening (Rex et al., 2009; USPSTF, 2008).

Screening guidelines must be tailored to maximize benefit while minimizing cost to both the individual and society as a whole (Rembold, 1998). The term "number needed to screen" is defined as the amount of people needed to be screened over a timed duration to prevent one death or adverse event. Many studies have looked at the cost-effectiveness of colon cancer screening with the three most common methods (i.e. fecal occult blood annually, sigmoidoscopy every 5 years, colonoscopy every 10 years - all beginning at age 50 and stopping at age 85). Current estimates range from $6,000 – $11,900 spent for every year of life gained (Maciosek et al., 2006; Telford et al., 2010). In contrast, studies on the cost effectiveness of screening mammography estimate roughly $58,000 spent for every one year of life gained (Stout et al.). Many experts suggest that a screening policy should result in expenditure of $50,000 or less per year of life gained. Thus, it is clear that colon cancer screening makes sense medically and financially. The question of when colon cancer screening should begin and end remains, and is a complex one. While colon cancer is typically a disease of the middle age to elderly, there are many groups of high-risk patients that need screening much earlier than current guidelines. The remainder of this section will attempt to elucidate screening strategies in low-risk, average-risk, and high-risk groups.

It is important to emphasize that colon cancer is a diverse entity with many paths leading to a common endpoint, carcinoma. The adenoma-carcinoma sequence can encompass a multitude of genetic mutations that lead to the eventual progression to cancer (i.e. mismatch repair genes, tumor suppressor genes, base excision repair genes, micro-satellite genes). No single mutation results in adenocarcinoma, but as mutations compile, a carcinoma eventual-

ly develops. For the majority of colon cancers, there is a significant amount of time between development of an adenoma and its progression to a malignant lesion. The time interval for progression is often determined by type of adenoma found. Current studies estimate that the dwelling time for a tubular adenoma is roughly 26 years, 9 years for tubulovillous adenoma, and 4 years for a villous adenoma (with an overall annual transition rate of 2.2%) (Chen et al.). It is this significant window period of detection time that allows screening for colon cancer to be so incredibly effective, and thus important to optimize timing and frequency of screening. While these concepts hold true for the majority of colon cancers, not all cancers are created equal. Certain high-risk groups progress to cancer much more rapidly than the above data suggests, and these groups will be detailed ahead.

3.1. Distribution of colorectal cancer types

The vast majority (70-75%) of colorectal cancers develop in sporadic (nonhereditary) fashion and no risk factors are identified in the individuals. The next most common form (15-20%) occurs in those with a family history of colon cancer (excluding known cancer syndromes). Hereditary Non-polyposis colorectal cancer (i.e. Lynch Syndrome) makes up roughly 3-8%. Familial Adenomatous Polyposis 1%, and Colitis Associated Cancer (i.e. Inflammatory Bowel Disease) also 1% (Winawer et al.). Keeping these figures in mind, colon cancer screening has the largest absolute impact on average-risk individuals. As such, the next section will focus on screening recommendations for the average-risk group.

3.2. Approach to average-risk individuals

As mentioned before, colon cancer is a disease of the middle age to elderly. According to a review by the National Cancer Institute conducted from 2005-2009, the median age at time of diagnosis of a colorectal cancer is 69. Thus, if we extrapolate from the data provided previously (~2% annual transformation from adenoma to carcinoma), we can see that it makes sense to exclude the younger population from screening tests. In fact, the most recent USPSTF recommendations support the initiation of colon cancer screening in average-risk individuals at age 50 (Grade A Recommendation) (USPSTF). These recommendations were made based in part on the results of two microsimulation models (MISCAN and SimCRC models) that incorporated current data on colon cancer incidence and adenoma progression, and simulated the natural history of colon cancer in a large population. The models then estimated the life-years gained if screening colonoscopy was performed vs. no screening at all. Further data analysis detailed age to begin screening, age to stop screening, and time intervals between screening. The models concluded that the optimal age to initiate screening is 50 (when compared to ages 40 and 60). Of note, one simulation showed better outcomes when screening was initiated at age 40, however the alternate simulation did not corroborate the data. The Task Force concluded, "Because the evidence for both adenoma prevalence at age 40 and the duration of the adenoma-carcinoma sequence is weak, we restricted further analysis to start ages of 50 and 60." This led to the recommendation of initiating screening at age 50. Regarding interval time period between colonoscopy, the authors reviewed data on 5-year, 10-year, and 20-year intervals. They concluded, as could be expected,

shorter intervals resulted in more life-years gained (their primary endpoint). However, when comparing 5-year to 10-year, there was only a modest increase in life years gained when compared to the corresponding increase in colonoscopies performed. 20-year intervals resulted in significantly less life-years gained, so was not considered optimal. While these authors agree with the recommendations by the USPSTF for average-risk individuals, it is important that practitioners further tailor their screening strategies based on several additional factors. As mentioned, 75% of colon cancers occur in average-risk individuals, thus representing a large absolute number of persons. As such, there is much variability and associated risks among the average-risk population.

Factors that increase the risk for colorectal cancer or are protective have been identified. While these factors have not been incorporated into the USPSTF Guidelines, knowledge about their existence and influence on overall risk may be helpful in directing clinicians toward screening colonoscopy practices. Additionally, and some may argue more importantly, clinicians must take into account a patient's expected adherence to their colonoscopy recommendations. Will the patient have regular and predictable access to a skilled gastroenterologist? Will they be willing to comply with frequent colonoscopy should their risk factors or findings require it? A new concept known as once in a lifetime screening with colonoscopy is being proposed as an effective technique in some groups. Knowledge of risk factors can be especially helpful in these cases, in which a clinician can strongly encourage adherence to recommendations based on each individual's risk factors. Additionally, it is important to note that the following discussion applies only to individuals classified as average-risk, and excludes those with a family history, diagnosed genetic condition, and Inflammatory Bowel Disease. These groups will be discussed separately.

3.3. Modifiable CRC risk factors

To date, several modifiable risk factors have been clearly linked with the development of colorectal carcinoma. Starting from the 10,000-foot view, many of the risk factors can be collectively grouped under the heading of total energy balance (i.e. caloric intake vs. caloric expenditure). Numerous studies have shown a clear link between Body Mass Index and resultant risk of colon cancer. For example, investigators looked at the lifetime incidence of colon cancer among the Framingham Cohort in Massachusetts, and divided the group by age group to a 30-54 year old group and a 55-79 year old group. They then looked at the overall incidence of colon cancer among the groups, and related the information to average Body Mass Index. In the 55-79 year old group, they separated the cohort into BMI >30 and BMI <30 groups. They noticed a significant 2.4 fold increased risk for the development of colon cancer for those with a BMI >30 (95% CI: 1.5-3.9) (Moore et al., 2004). Interestingly, the same study also analyzed the results with relation to waist size measurement. As BMI can be notoriously misleading, especially among males, the authors pursued this alternate measure for further support. They concluded that central adiposity (defined as a waist size >39 inches), was associated with a two-fold increase in risk for colon cancer. They further noted that the risk increased linearly with increases in waist size. This data has been replicated among many other studies, in both men and women. A large study by the Nurses' Health

Study Research Group concluded similarly that increasing BMI is associated with increased risk of colon cancer, and particularly noted a higher risk among women with an increased waist-to-hip ratio (Martinez et al., 1997). It is now widely accepted that obesity, and particularly central obesity, is an independent risk factor for the development of colon cancer. Several theories have been proposed as to why exactly this clear association exists. For now, the most supported theory proposes that insulin resistance (along with hyperinsulinemia and increased Insulin-like Growth Factor-1) plays a large role in this relationship. In fact, a recent meta-analysis has concluded that Diabetes Mellitus is itself an independent risk factor for colon cancer. Even after controlling for physical activity, smoking, and obesity, the authors found an increase in relative risk among those with Diabetes Mellitus of 1.43 and 1.35 in men and women, respectively (both statistically significant) (Yuhara et al., 2011). Pathophysiologically, both insulin and IGF-1 are involved in cell proliferation and regulation of apoptosis and it is enough to recognize that states with elevated levels of both hormones have been clearly linked to increased risk for colon cancer. Additionally, multiple studies have looked at the effect of physical activity and its influence on colon cancer. These studies and their respective meta-analyses have shown clearly an inverse relationship between physical activity and colon cancer. Among data taken from the group exhibiting the highest level of exercise, one study showed a 50% reduction in lifetime colon cancer risk (Colditz et al., 1997). Thus, an important conclusion can be reached based on the data reviewed as well as others: obese, sedentary individuals are at higher risk for colon cancer. While the USPSTF guidelines do not currently reflect this information for screening recommendations, clinicians most certainly can make use of it to provide patient-centered care. Patients should be counseled regarding overall health and the potential for primary prevention of colon cancer via improved dieting and exercise habits.

The next most common modifiable risk factors a clinician is likely to encounter is tobacco and/or alcohol use, both clearly linked with colon cancer. Multitudes of studies have been undertaken in the last two decades examining the potential link between cigarette smoking and colorectal cancer. A meta-analysis from 2009 conducted by Liang et al examined 36 such studies (Liang et al., 2009). The results of the analysis showed a clear association between age of initiation of tobacco use, amount smoked per day, and total duration of tobacco use. Data showed a relative-risk of 1.38 for an increase in 40-cigarrets per day, 1.20 for an increase of 40 years total duration, and 1.51 for an increase of 60-pack years. Interestingly, they also noted a predilection for rectal cancer over colon cancer when analyzing incidence of site-specific carcinoma. Next, studies emerging over the last decade have begun to note increases in risk for colorectal cancer even in light to moderate alcohol use. A pooled analysis of 8 cohort studies involving nearly 490,000 men and women was published in the Annals of Internal Medicine in 2004. Data showed, when compared with non-drinkers, a relative-risk of 1.41 (CI 1.16-1.72) in individuals who consumed 45g of daily alcohol (roughly three drinks) (Cho et al., 2004). There was no statistically significant correlation among daily consumption of 30-44g/daily. More recently, a meta-analysis from 2011 from the Annals of Oncology examined 27 cohort studies and 34 case-control studies (Fedirko et al., 2011). They also concluded a strong association between alcohol consumption and colorectal cancer risk. The association was strongest among heavy drinkers, relative-risk 1.82 if >100g/day. Surpris-

ingly, they even found a statistically significant increase in relative-risk to 1.07 for individuals drinking one alcoholic beverage per day (10g/day), which throws into question the current recommendations of the USDA (two drinks or less daily for men, one drink or less daily for women). Interestingly, even stronger associations were noted in studies examined the Asian population (specifically Japanese men). Clearly, there is a link between both tobacco and alcohol use and risk of colorectal cancer. Over the next few years, additional studies and meta-analyses will likely emerge further elucidating just which populations are at risk and what usage levels are most harmful. For now, clinicians should clearly state that tobacco use and even light daily alcohol ingestion increases their likelihood of developing colorectal cancer. As the current data suggests only a modest increase in relative-risk, this information may be more pertinent among individuals with additional risk factors. Clinicians should certainly take a patient's tobacco and alcohol use into account when determining how frequent they will advise screening colonoscopies.

3.4. Protective measures against CRC

Just as risk factors have been identified, there are also several clear factors that are protective against colon cancer. Physical activity was discussed earlier, thus will not be repeated here, but suffice it to mention again that it is highly protective against colon cancer. Moreover, the medical community already advocates daily exercise for a multitude of other health benefits, and the fact that it also protects against colon cancer would not alter a clinician's management of colonoscopy screening. However, several studies have clearly shown a protective relationship between common pharmaceuticals and colon cancer. Both Aspirin and Non-steroidal anti-inflammatory drugs have been shown to decrease the incidence of colon cancer. Studies from as early as the 1980s began to show a relationship between anti-inflammatory medications and colon cancer. Initial studies performed on patients with Rheumatoid Arthritis, as they were often on chronic NSAID therapy, were the first to show this relationship in the 1980s. Further studies conducted in patients on long-term aspirin therapy showed similar results. The exact mechanism by which anti-inflammatory medications provide this protective benefit currently remains unknown. Several hypotheses exist which primarily center on COX-1 and COX-2 inhibition, as they are known to promote inflammation, tumorigenesis, and angiogenesis. In a study published in the Lancet in 2007 by Flossman et al, British researchers pooled data from two large Aspirin trials in the UK (British Doctors Aspirin Trial, UK-TIA Aspirin Trial) (Flossmann and Rothwell, 2007). Among patients with complete compliance for 5 years or more of aspirin therapy, they found a statistically significant relative-risk of 0.26 (CI 0.12-0.56). The effect was less substantial among non-compliant patients, but nevertheless protective (RR 0.37). It is important to note in this study, as in many other studies, the protective benefit was most clearly seen after a latency period of at least 10 years. Moreover, study data pooled from trials related to cardiovascular protection often have used differing doses of aspirin (or NSAIDs). At this time, no clear dose, duration of therapy or type of NSAID has shown to be of greatest benefit in primary colorectal cancer chemoprevention. As such, the USPSTF has not recommended NSAIDS as a primary preventive measure for colorectal cancer. As more and more studies specifically geared and powered toward colorectal carcinoma prevention (as opposed to data analysis of

trials geared toward cardiovascular effects), it can likely be expected that clearer relationships between NSAID type, dosing, and duration will be elucidated. As it is not officially recommended by the USPSTF, clinicians are not currently advocating for NSAID use as primary prevention. However, a large portion of those at greatest risk for developing colorectal cancer (i.e. middle-age to elderly) are already on Aspirin for its cardiovascular benefits. Thus, clinicians can take this fact into account when assessing an individual's colorectal cancer risk. Again, there is no current recommendation to decrease screening intervals in patients on Aspirin therapy, however, when taken collectively with other risk factors, clinicians may further tailor how aggressive they wish to be with screening.

Another common protective measure a clinician may encounter regards the use of postmenopausal hormonal therapy. Again, as early as the 1980s, studies emerged showing an unexpected link between hormonal therapy and colorectal cancers. As in many other associations, the exact mechanism by which estrogen/progestin can inhibit cancer development is unknown. However, speculations on its pathophysiology are under active investigation. Researchers hypothesize that hormonal therapy can alter levels of bile acids, Insulin-Like Growth Factor-1, and IGF Binding Protein-3. Moreover, estrogen receptors have been found on colonic epithelial cells, and it is unclear if this may also provide a route of protection. Nevertheless, numerous studies (one of which will be described below) have shown the inverse relationship between hormonal therapy and colon cancer risk. In a prospective study of nearly 57,000 women (taken from the Breast Cancer Detection Demonstration Project) published in 2009, Johnson et al looked at hormonal therapy (including estrogen alone, combination with progestin, and duration of therapy) and its relation to colon cancer incidence (Johnson et al., 2009). Results are astoundingly clear that hormonal therapy is protective against colon cancer. The results were as follows: ever users of unopposed estrogen RR 0.83 (95% CI, 0.70-0.99), current users unopposed estrogen >10 years RR 0.74 (95% CI, 0.56-0.96). The results among estrogen + progestin users showed an even stronger relationship: estrogen + progestin RR 0.78 (95% CI, 0.6-1.02), estrogen + sequential progestin RR 0.64 (95% CI, 0.43-0.95), and strongest effect with 2-5yr use of estrogen + sequential progestin RR 0.52 (95% CI, 0.32-0.87). Similar studies conducted by the WHI (Women's Health Initiative) have shown similar results for estrogen + progestin therapy, but not estrogen therapy alone. Interestingly, they also noted that although the frequency of cancer was less in the hormonal group, the cancers were detected at later stages (increased lymph node involvement and metastatic disease) (Chlebowski et al., 2004). So, as before, we have clear evidence of a protective measure against colon cancer. Unfortunately, the same WHI trial showed an increase in myocardial infarction, stroke, dementia, pulmonary emboli, and breast cancer among hormonal therapy users. As such, there have been no widespread recommendations for primary prevention of colorectal cancer by means of hormonal therapy. However, clinicians may encounter women who are on hormonal therapy. While estrogen therapy alone may not have clear benefits, estrogen + progestin therapy has repeatedly shown to be of benefit in prevention of colorectal cancer. In fact, based on the results of the first-mentioned study, risk was decreased by a staggering 25-46%. Taking this information into account, assuming no additional risk factors exist, and clinician may be able to tailor their screening colonoscopy frequency toward a less aggressive and frequent approach.

A clinician may also encounter questions from a patient regarding diet recommendations. While a healthy, balanced diet high in non-processed, low animal fat calories is always recommended, there has been non conclusive data regarding diet and its relation to colorectal cancer. As such, the decision on when to initiate and how often to perform screening colonoscopies should not be influenced by a patient's diet. It is possible that more clear relationships will be clarified in the future, but for now, data displaying strong associations does not exist.

The next question that must be answered is what role should gender and race/ethnicity of a patient play in a clinician's screening colonoscopy recommendations? According to the most recent data from the Center for Disease Control (CDC) males have a higher incidence of colorectal cancer vs females (52.7 vs. 39.7/100,000) (Prevention). The highest incidence is found in African American males (62/100,000), followed by Caucasian males (51.5/100,000). Hispanics, Asians, and Native American/Alaskan Native groups all had a lower incidence than the comparative African-American and Caucasian groups in both the male and female categories. When comparing death rates from colorectal cancer by race, again males have an overall higher rate vs. females (20.2 vs 14.1/100,000).(NIH, 2009) African-American males displayed the highest rate at 29.8/100,000, and African-American Females the next highest rate at 19.8/100,000. The remainder of the groups showed death rates below the average of respective male and female groups analyzed. Compiling the above data, it is evident that African-Americans are most affected by colorectal cancer in comparison to other race/ethnicities. In fact, a study examining 5-year survival rates among Caucasians vs. African-Americans (among all stages of colorectal cancer) revealed a staggering difference of 64% vs. 52% (Ries). Initially, arguments were made postulating that perhaps the African-American community rate of screening colonoscopy was much lower, thus accounting for the higher incidence and mortality rate. According to the CDC data on screening rates, Caucasians are most screened at 66.2% and African-Americans are next most screened at 62.9% (Rim S.H., 2011). The lowest screening rate is found in the Hispanic population at 51.2%. While African-Americans have a higher mortality rate from colorectal cancer, it is clear that it is not solely due to inadequate screening, as African-Americans have much higher screening rates than Hispanics, yet also a much higher mortality rate. A study examining this finding concluded that African-Americans are more likely to be diagnosed at an earlier age and present at later stages of disease, as compared to Caucasians, however this data has not been consistently replicated (Chien et al., 2005). Another study postulated that socioeconomic status and access to medical care may be partially involved in this mortality discrepancy (Wudel et al., 2002). This study found that African-Americans are more likely to be treated at city hospital vs university hospitals (which are associated with better outcomes). However, when comparing survival data even among Caucasians and African-Americans at each type of hospital, African-Americans fared worse. Another study has pointed to type of care offered (i.e. adjuvant chemotherapy and radiation) as a potential factor (Govindarajan et al., 2003). This study found that African-Americans are treated less with both chemotherapy and radiation therapy vs. Caucasian patients. It is still unclear why exactly African-Americans are more often diagnosed and more often killed by colorectal cancer. Regardless of the reason, it is clear that there is a difference that needs to be addressed. It seems that while the reasons are being elucidated, more aggressive screening among African-Americans needs to be es-

tablished. Data may eventually and conclusively show that colorectal cancer appears earlier and is more aggressive in African-Americans. In the meantime, these authors would argue for earlier age at initiation of screening and more frequent screening intervals.

Finally, in the average-risk population, the issue of access to colonoscopy need always remain in the back of a clinician's mind. Many patients may not have access due to socioeconomic or geographic barriers, or simply they may choose not to undergo screening based on underlying psychological barriers or misconceptions regarding colon cancer and/or colonoscopy. As mentioned previously, many organizations are working toward colon cancer and screening awareness, however clinicians must keep public unawareness as part of their screening practice. If a patient presents at age 45 and there is concern for eventual adherence to the screening guidelines at age 50, he/she should be screened at age 45.

3.5. Risk associated with family history of CRC

As mentioned previously, the next largest group of the population diagnosed with colon cancer involves those with a family history (excluding individuals with a known colorectal cancer syndrome). This group makes up ~15-20% of all diagnoses. Currently, there are multiple efforts and studies looking into what exactly confers this higher risk among individuals with a positive family history of colon cancer. At this time, it remains unclear what genetic and/or environmental factors are involved in the pathogenesis, however, it is abundantly clear that patients with 1st degree relatives diagnosed with colon cancer, are at a significantly higher risk of developing colon cancer themselves. In fact, in one of the seminal studies published on the topic from the New England Journal Of Medicine, individuals with one 1st-degree relative with colon cancer were found to have a 1.7 fold increase in their own risk for colon cancer (Rex et al., 2009). This risk increased further as the number of diseased 1st-degree relatives increased as well. Further, they found that the increased risk was irrespective of location of diagnosed tumor in the relative (i.e. proximal vs. distal site of malignancy). As such, the American College of Gastroenterology revised its guidelines regarding individuals with a positive family history. If an individual has a 1st degree relative that was diagnosed with colon cancer before the age of 60 (or 2 or more relatives with colon cancer or advanced adenomas irrespective of age at diagnosis), they are considered to have a positive family history. If a patient is identified as having a positive family history, they should then begin colonoscopy screening at age 40 (or 10 years before the youngest age of diagnosis), and they should have an interval follow-up colonoscopy every 5 years. According to these recommendations, 2nd-degree relatives or relatives diagnosed >60 years of age are not considered as a conferring a positive family history.

3.6. Polyposis syndromes

While the exact genetic predisposition for the majority of colon cancer remains unknown, there are several well-known (and identifiable) cancer syndromes that a clinician must take into account when making colon cancer screening advice. The most common of these is Familial Adenomatous Polyposis. It affects roughly 1 in 5,000-7,000 individuals and confers a 100% risk of eventual colorectal cancer, with the average age at diagnosis 40 (Bussey et al.,

1978). These individuals should begin screening colonoscopy in adolescence (usually started 10-12 years old), and this should be repeated annually. Ultimately these patients should receive prophylactic colectomy. Another such polyposis includes Attenuated Adenomatous Polyposis. As opposed to FAP (which involves hundreds to thousands of polyps diffusely spread throughout the colon), AAP is an oligopolyposis and typically involves <100 polyps. These polyps are more often right-sided and with a flat morphology. Patient's typically begin to have polyps appear in the 4th-5th decade of life and an average age of diagnosis of cancer at age 55 (Knudsen et al., 2003). Roughly 69% of patients with APP will eventually develop colon cancer. These patients should begin screening colonoscopy at age 25 and this should be repeated annually. Less common genetic polyposes a clinician may encounter involve: MUTYH-Associated Polyposis, Peutz-Jeghers Syndrome, and Juvenile Polyposis Syndrome. MUTYH-Associated Polyposis is an autosomal recessive cancer syndrome (heterozygotes with one affected allele are at increased risk, but homozygotes show the largest increase in risk). Variations in phenotype have been described, from hundreds to thousands of polyps distributed throughout the colon. Lifetime prevalence of colon cancer is reported at 80% (Jenkins et al., 2006). These individuals should begin annual screening at age 18-20. Clinicians may also encounter Peutz-Jeghers Syndrome, which is an autosomal dominant disorder characterized by numerous hamartomatous polyps throughout the colon. These individuals carry a 39% lifetime risk of colon cancer and should have colonoscopy screening every 2-3 years beginning in their late teen years (McGarrity and Amos, 2006). Finally, pediatric clinicians may encounter Juvenile Polyposis, which is an autosomal dominant condition characterized by numerous polyps throughout the gastrointestinal tract. These individuals are often brought to the attention of a physician following an intestinal obstruction or gastrointestinal bleed as a consequence of the numerous polyps. These patients carry a 10-38% lifetime colon cancer risk and should be screened annually beginning at age 15 (Howe et al., 1998; Jass et al., 1988).

3.7. Non-polyposis syndromes

The most common hereditary colon cancer syndrome is Lynch Syndrome, or Hereditary Non-Polyposis Colorectal Cancer. This too is an autosomal dominant condition, which is characterized by numerous, proximal adenomas. Affected individuals carry a 48-68% risk of colon cancer by age 60, with the majority being diagnosed between age 40-50 (Mecklin et al., 2007). Even more importantly, adenomas associated with HNPCC are typically more aggressive and advance to carcinoma quicker than would be otherwise expected. As such, these individuals should begin screening at age 20, and this should be repeated every 1-3 years.

3.8. CRC risk associated with Inflammatory Bowel Disease

Nearly every clinician is sure to encounter a patient afflicted with Inflammatory Bowel Disease (IBD). As such, it is important to recognize that these patients carry an increased risk for colon cancer, and they cannot be treated as average-risk individuals. The entity is referred to as Colitis-Associated Cancer, or CAC, and the resultant risk of eventual colon cancer

is related to the severity of disease (in both Ulcerative Colitis, and Crohn's Disease). The cumulative risk of colon cancer among patients with ulcerative colitis (U.C.) is thought to be roughly 2% after 10-years of disease, and up to 18% after 30-years of disease (Eaden et al., 2001). Although Crohn's Disease (C.D.) classically involves the small intestine, it can also involve the large bowel, which confers an increased risk of colon cancer as well. Crohn's patients with large intestinal involvement carry an 8.3% risk of colon cancer after 30 years of disease (Canavan et al., 2006). Currently, the recommendation is to begin screening both U.C. and C.D. patients 8-10 years post-diagnosis, and institute 1-2 year screening intervals.

4. When to stop screening?

As touched on previously, equally important to the initiation of an effective screening program involves the optimal age to finish the screening process. The question could be posed: "Why stop screening at all if it is an effective means to prevent morbidity and mortality from colon cancer?" However several factors should be considered including the fact that colonoscopy is not entirely without risk. The known complications associated with colonoscopy (e.g. bleeding, perforation, infection, diverticulitis), occur particularly in the elderly population. Furthermore, and especially true with regard to colorectal cancer screening, there exists a potentially long latency period from adenoma to carcinoma which may take years and even decades in some individuals. Elderly patients with an adenoma seen on screening may, and oftentimes do, perish as a result of other disease processes. Finally, limited resources must also be taken into account. Each and every colonoscopy takes a concerted effort from a skilled colonoscopist and their support staff, and the required financial means on the part of the patient and/or government. As such it is necessary to establish evidence-based guidelines on when patients can safely stop colon cancer screening. The following section will delve further into this topic and the current recommendations for age at which to stop screening.

4.1. Complications from screening colonoscopy

In general, colonoscopy is a relatively safe, well-tolerated procedure by patients. The majority of patients will never experience any complications, even if undergoing multiple colonoscopies throughout their lifetime. There are, however, significant and life-threatening complications that can occur. Although rare, given the enormous number of colonoscopies performed annually, it is important to be cognizant of the associated complications. In 2010, an analysis was released tracking complications rates among 18 large studies and involving over 685,000 colonoscopies (Ko and Dominitz, 2010). The most common complication seen was lower gastrointestinal bleeding, at roughly 0.1-0.6%. Fortunately, the far majority of these were not mortal bleeds. However, as most colonoscopies are undertaken in the outpatient setting, gastrointestinal hemorrhage can develop into a life-threatening event very quickly in a non-monitored setting. Next most common, bowel perforation posed a risk of less than 0.3% (Ko and Dominitz, 2010). These most often occur following barotrauma or mechanical trauma to the bowel wall. Again, although exceedingly rare, a perforated bowel

has the potential to be lethal. A perforation can be clinically evident immediately after the incident occurs, however, small perforations in the bowel can lead to an insidious course that can ultimately result in severe peritonitis and rapid clinical decompensation. Diverticulitis is also a well-established complication of colonoscopy, with a rate estimated at 0.04-0.08% (Ko and Dominitz, 2010). There also exists the known entity of post-polypectomy electrocoagulation syndrome (or post-polypectomy syndrome). Following electrocautery of the bowel wall, there is risk for a partial or transmural burn of the bowel wall. In cases of a transmural burn, patients experience symptoms of clinical peritonitis. This rarely proceeds to actual peritonitis (radiography does not visualize actual perforated bowel with free air in the peritoneum), and these patients can be managed via supportive care and antibiotics. However, resultant hospitalization and treatment is not without its own associated risks and costs, so this cannot be taken lightly either. The incidence of post-polypectomy electrocoagulation syndrome appears to be roughly 0.003%-0.01% (Ko and Dominitz, 2010). Infection as a result of colonoscopy is exceedingly rare, and can most times be attributed to poor infection control procedures involving equipment. Although the risk of transient bacteremia is postulated to be higher, the actual risk of an infection transmission purely as a result of colonoscopy is estimated at roughly 1 per 1.8 million procedures, with Pseudomonas and Salmonella species being the most commonly identified (Spach et al., 1993). Other case-reportable complications have included splenic rupture, acute appendicitis, and subcutaneous emphysema (Hirata et al., 1996; Humphreys et al., 1984; Kamath et al., 2009). Overall mortality from colonoscopy remains controversial due to complicated comorbidities among those in studies tracking colonoscopy-related mortality. Estimates range from 0%-0.09% (Ko and Dominitz, 2010). Less serious complications include nausea, vomiting, diarrhea and bloating. Fortunately, these are usually self-limited within several days following the colonoscopy. As evidenced above, colonoscopy does have rare but serious complications. However, it is important to note that complications are also related to the type of procedure performed (screening colonoscopy or polypectomy) and the age of those undergoing the procedure.

In assessing the risk of complications from colonoscopies it is important to consider the type of intervention to be employed during the procedure and the baseline characteristics of the patient. Many studies have analyzed data pertaining to complications particularly associated with different age groups. For example, a retrospective cohort study from 1994-2009 examined these risks among over 43,000 patients ages 40-85 (Rutter et al., 2012). They pooled hemorrhage, perforation, and diverticulitis as serious adverse events. They found an event rate of 4.7/1000 screening colonoscopies and 6.8/1000 for follow-up colonoscopies. Interestingly, there were significant differences between age groups. Among ages 40-49 there was a serious event rate of 4.2/1000, ages 50-64 3.7/1000, ages 65-74 7.9/1000, and for ages 75-84 13.3/1000. Thus the rate of complications clearly increases with age. They also noted an increase in events following polypectomy vs no intervention, however this proves less clinically relevant, as a clinician would certainly not forgo polypectomy based on this fact alone. With the above data, and other studies like it (Gatto et al., 2003), it becomes evident that beyond a certain age, colonoscopies may be causing more harm than good.

4.2. Timing of progression from adenoma to carcinoma

As mentioned previously, the progression from adenoma to carcinoma may take years and even decades. Some adenomas may never make the entire progression. The adenoma may never acquire all the necessary genetic mutations, or simply, an individual may not live long enough for the adenoma to significantly progress. As such, detecting an asymptomatic polyp in an elderly individual may have no significance whatsoever. In fact, while the risk of colonoscopy complications poses a real threat, the adenoma may prove to have no bearing on a patient's health. Currently, the most recent CDC data estimates that the average life expectancy in the United States is 78.7 years (76.2 for males and 81.1 for females) (Centers for disease control and prevention, 2012). This brings into question the utility of screening elderly age individuals. At what age will a screening colonoscopy likely provide no benefit to the average-risk elderly patient?

The following discussion pertains to those at average-risk as identified previously in the chapter. Individuals with predisposing factors (family history, genetic syndromes, inflammatory disease) are not included in this grouping, and should continue with regularly scheduled colonoscopies as defined previously. Many of the adenomas identified in these high-risk groups have demonstrated a more rapid rate of progression to carcinoma, and thus, they continue to need aggressive screening measures throughout their lifetime.

The incidence of colon cancer rises sharply with advancing age. Many studies have examined this relationship over the past decades, and conclusive evidence supports this claim. In fact, the rate of colon cancer among those over 65 years of age is 254.2/100,000 persons, while the risk is substantially lower among those under 65, at 18.1/100,000 persons (NIH, 2009). Clearly, the elderly are at highest risk for developing colon cancer. Likewise, the elderly are also highest at risk for complications of colonoscopy. Extrapolating from the data previously provided, the complication rate amongst individuals 75-84 is 1330/100,000 people. Therefore, there would be roughly 5 times as many serious complications from colonoscopy as there would be actual diagnoses of cancer in the age group 75-84. Further, studies have been conducted looking at the chances of actually dying from colon cancer if diagnosed late in life. Among those at age 75 (and in the middle quartile of expected life remaining), they have a 1.9% chance of actually dying from colon cancer (Walter and Covinsky, 2001). By age 85, this risk decreases to 1.6%. Among elderly patients with multiple co-morbidities, the chance of dying from colon cancer falls to 0.85%. For comparison, a 50-year old male in the middle quartile of life expectancy has a 2.3% and female a 2.2% chance of eventually dying from colon cancer. While the incidence of colon cancer increases with age, it appears the mortality from the disease actually declines (if the cancer develops at the later age). These elderly patients succumb to an illness other than colon cancer. Additionally, studies have likewise examined the actual amount of life gained due to screening colonoscopy among different age groups. Here too there is a clear association with age. Among asymptomatic individuals undergoing screening colonoscopy, younger age groups experience a much larger benefit in terms of life gained. Among 50-54 year olds undergoing asymptomatic screening, there is roughly 0.84 years of life years gained (Lin et al., 2006). However, among individuals 80 years and above, only 0.13 additional years of life are

gained. Thus, there is roughly a 6-fold difference in the actual effect of colon cancer screening between the two groups. Although younger patients have a much lower chance of developing colon cancer, they experience the lowest complication rate and benefit from the largest amount of life years gained if diagnosed and treated.

4.3. The resource allocation factor

It is also equally important to consider allocation of valuable resources when debating whether or not to forego colon cancer screening in the elderly. Colonoscopies, while cost-effective, are expensive. Those uninsured may have to pay thousands of dollars for the procedure, and those insured may have to pay copays, deductibles, etc. Moreover, the cost to society is enormous. Considering there are currently 74,008,000 Americans age 55 and above, there are millions of colonoscopies completed annually (Wagner et al., 1970). If there are no established recommendations on when it is appropriate to stop colonoscopy screening, millions of dollars will be spent for a procedure that may have minimal impact on the health of those screened. Moreover, funding that could go toward more cost-effective treatments or screening programs would be needlessly diverted. Fortunately, the Affordable Care Act (ACA) recently instated a policy in which Medicare and Medicaid "shall not impose any cost sharing requirements for evidence-based items or services that have in effect a rating of 'A' or 'B' in the current recommendations of the United States Preventive Services Task Force." Therefore, the cost of a colonoscopy to the individual may be minimized, however the cost to society will only grow. It is important to take into account the number of providers who can safely and effectively offer colonoscopy screening as well. Studies have demonstrated that colonoscopies performed by Gastroenterologists vs. non-Gastroenterologists are both more cost-effective and more beneficial to the patient (i.e. trained endoscopists are better at detection) (Hassan et al., 2012). In fact, the American Cancer Society estimates a savings of roughly $200,000,000 per year if all colonoscopies were performed by Gastroenterologists (currently both Gastroenterologists and non-Gastroenterologists are able to perform colonoscopy). Unfortunately, the number of gastroenterologists available to provide screening colonoscopies remains limited. Currently, there are roughly 10,400 practicing Gastroenterologists in the United States. As screening compliance increases (and the absolute number of individuals meeting the indication for screening increases as well), there will be a severe shortage of practicing Gastroenterologists. As mentioned previously, as of now, there is a 58.3% compliance rate to colon cancer screening. As this number increases, the limited supply of Gastroenterologists will ultimately be overwhelmed. Even those who meet indications for screening may be unable to obtain a colonoscopy in a timely manner. In effect, every colonoscopy performed on an elderly patient may mean one less colonoscopy for a young, healthy individual. Simply put, there must be established guidelines followed by all practitioners to ensure that screening colonoscopies are performed in the most cost-effective and life-preserving manner. Therefore, it is of paramount importance to take resource allocation into account when advising patients on whether to proceed with colonoscopy or not.

4.4. Evidence based approach to ending screening

The USPSTF currently recommends that colon cancer screening via colonoscopy be terminated at age 75 (USPSTF, 2008). This recommendation is based upon a Decision Analysis published in 2008. Again, using two simulation models, the authors examined the average life-years gained and the number of colonoscopies that would be required based upon the age at which colonoscopy screening was stopped (and assuming a 10-year interval screening method in average-risk individuals). The authors primarily tested ceasing colonoscopy at age 75 vs 85. In essence, they found that by stopping screening at age 75, they decreased the number of life-years gained by only 2-5/1000 people. However, the number of colonoscopies needed decreased by 348-398/1000 people. The ranges given signify the results from both simulation models. While some may argue that adding 2-5 life-years per 1000 people should take paramount importance, this unfortunately cannot be the case given the limited resources as discussed above. Until resources are infinite, it is necessary to funnel finances and medical staff toward the population that will most benefit from screening. Distributing the additional 348-398 colonoscopies to a younger population will result in more life-years gained, lives saved, and far fewer complications. Therefore, for the time being, it seems that ceasing colonoscopy screening at age 75 is both responsible and in the best interest of society.

4.5. Surveillance after late stage cancer diagnosis

Lastly, it is important to recognize that not all colonoscopies will be performed for strictly screening purposes. Ultimately, the goal of colonoscopy is early diagnosis and curative treatment by either polypectomy or bowel resection. However, as colon cancer is unfortunately still such a large cause of mortality in the United States and the screening rate is not 100%, many individuals will still be diagnosed with late-stage and unresectable colon cancer. This then poses the question, what is the utility in surveillance colonoscopy in these individuals?

To date, limited data exists concerning this topic. The primary treatment for patients with diagnosed Stage IV inoperable colon cancer is palliative chemotherapy. Occasionally, chemotherapy may be able to shrink the tumor(s) to an operable state, but this is more often not the case among late-stage diagnoses due to multiple metastases. Studies have analyzed prognostic indicators among patients with inoperable disease and found that performance status, ASA-class, CEA level, metastatic load, extent of primary tumor, and chemotherapy were the only independent variables affecting prognosis in these patients (Stelzner et al., 2005). While the initial diagnostic colonoscopy can provide valuable tissue data and information regarding depth of invasion, at this time surveillance colonoscopy does not appear to play a role in the management beyond initial diagnosis. Given that there is no clear benefit to surveillance colonoscopy after diagnosis of inoperable colon cancer and there are a multitude of risks associated with the procedure, surveillance colonoscopy is not indicated in these patients.

5. Factors that impact effective screening

Colonoscopy is an accurate and effective screening technique that is endorsed by many societies including the American Cancer Society, U.S. Multi-society Task Force, American College of Radiology, and American College of Gastroenterology (ACG) (Levin et al., 2008; Rex et al., 2009; USPSTF, 2008). While it may seem that screening for CRC is a well-established and accepted standard of care, screening rates for CRC have only recently started to approach that of other cancers. Increasing interest in the issue of best practice for CRC screening is attributable to updates to screening guidelines as a result of recent studies indicating significant mortality benefits. In addition to changes in the actual screening guidelines, the goal of screening has shifted to focus on cancer prevention by removing polyps rather than simply cancer detection (USPSTF, 2008). Important factors exist that impact the effectiveness of available screening modalities for CRC, and these originate from physicians, patients, as well as from society. While current recommendations support initiation of screening at age 50 for all average risk men and women, earlier initiation is advocated for those at higher risk including African American men and women. Knowledge about these guidelines can impact screening practice. Consideration must also be given to the modality of CRC screening. The ACG recommends colonoscopy as the preferred mode of screening, and the gold standard given it diagnostic and therapeutic potential (Rex et al., 2009). Studies demonstrate that most physicians overwhelmingly prefer colonoscopy as the test of choice (Guerra et al., 2007). In fact, 70% of PCPs strongly believe colonoscopy is the best available colorectal cancer-screening test. Furthermore, a large proportion of physicians are concerned over lawsuits if they do not offer screening colonoscopies. The fear of facing a lawsuit over colonoscopy complications can be outweighed by the fear of being sued if the procedure is not offered at all (McGregor et al., 2010; Varela et al., 2010). While CRC screening saves lives, the use of colonoscopy and other available options, remains suboptimal. Pinpointing the reasons why people are not getting screened, either by choice or by circumstance, is essential in order to increase screening outcomes and compliance. There are unquestionably many barriers to effective healthcare delivery in the US, let alone being able to appropriately screen for CRC (Hoffman et al., 2011). Barriers can be sorted into a few main categories: physician, patient, societal related factors. This section will touch on some of these obstacles.

5.1. The role of the physician in CRC screening

Physician recommendations play a crucial role in the decision to get screened for CRC (Zapka et al., 2011). A mere discussion of CRC screening at the time of an office visit may be sufficient and motivate patients to complete CRC screening. Given the prominence of the physician factor it is important to consider elements that impact physician recommendation of colonoscopy to their patients. Collegial norms, patient preferences, and published evidence including guidelines from the ACS and USPSF have been identified as important elements. Physicians in the US favor endoscopy and often fail to adequately present alternatives such as stool testing. One study found that 50% of the patients surveyed did not receive the test they requested, and most underwent a colonoscopy instead (Hawley et al., 2012). However, since all screening tests have some benefit, even if they are not on par with

colonoscopy, physicians need to be sensitive and attuned to patient preferences. Techniques other than colonoscopy may be more suitable for specific patients, given their individual circumstances. For example, a recent study published in *Cancer* found that wealthy patients frequently opt for colonoscopy while lower socioeconomic groups tended to choose at home stool testing over endoscopy (Bandi et al., 2012). Patient preference varies by ethnicity as well, with African Americans less likely to choose endoscopy than Caucasians (Dimou et al., 2009). From their trial data, Inadomi and colleagues (Inadomi et al., 2012) predict that if colonoscopy were the only option offered, fewer patients would be screened. It is evident that the choice of screening test should take into consideration not only the physician's, but also the patient's perspective because some form of screening still remains superior to no screening at all. Considering the evidence above, physicians should recommend one best option to their patients using evidence-based medicine and taking into account patient specific factors. CRC screening guidelines are complicated and offering multiple options still requires shared decision making in practice (Zapka et al., 2011).

Although Medicare coverage has lessened these concerns, many physicians reported that health insurance remains very influential for screening recommendations (White et al., 2012). Of note, individuals of lower socioeconomic classes have expressed concerns that they experience a lack of screening offers from doctors. This is supported by physicians who admit they do not recommend colonoscopy, if patients do not have insurance or ready access. Another interesting difference in physician screening recommendation was the age of the physician, with younger physicians recommending the test more. Although this is merely speculation, younger physicians may be more comfortable ordering this newer test (Zapka et al., 2011).

In practice, physicians often fail to mention CRC screening because of limited time, competing issues, and forgetfulness. At times the many pressing issues that need to be addressed, preclude the lengthy discussion about available cancer screening tests. Additionally, many patients only go to a clinic to address urgent issues. These clinics are often overbooked and the main focus is to stabilize the acute problem. Some patients lack health insurance or are unwilling to wait for appointments (Guerra et al., 2007). At best, some physicians may recommend a follow up health maintenance visit. In addition, one national survey suggested that the primary care physicians may not adequately discuss all test options available with average risk patients because they are under the assumption that this will be addressed in more depth by specialists. Screening rates suffer from lack of coordination between specialists and PCPs (Doubeni et al., 2010). Physician forgetfulness and unfamiliarity with guidelines is a preventable obstacle to screening (White et al., 2012). The screening and surveillance recommendations differ significantly for a subset of CRC patients with hereditary syndromes. There is a marked lack of knowledge about screening guidelines for high-risk populations based on family history and also ethnicity. Primary care physician recommendations are often inconsistent with published guidelines. Among those most intimate with guidelines, the gastroenterologists, only a fraction recommended genetic counseling, which is also a part of appropriate screening (White et al., 2012).

Studies have suggested that physicians may not be fully aware of patient's attitudes and values towards screening. Physicians underestimated test discomfort and did not recognize the importance of helping patients make informed decisions for screening. In addition, several studies have shown that PCPs recommendations are affected by their demography including age, sex and ethnicity. For example, non-Caucasian physicians are less likely to recommend cancer screening compared to Caucasian doctors. Hispanic physicians in the US were found to be less likely to recommend CRC screening. In a study in Australia, general practitioners of Middle Eastern ethnicity estimated CRC incidence to be lower in immigrants compared to patients born in Australia, which may have resulted in lower recommendations of CRC screening for immigrants (Koo et al., 2012). Thus in general, primary care physicians need greater awareness about CRC rates and screening.

While patients cite physician recommendation as the number one motivator for screening, other factors might impact compliance. Research demonstrates that providing excessive choices can be overwhelming subsequently leading to confusion and indecision. Selection of one preferred alternative may help simplify the discussion about screening (Inadomi et al., 2012). Studies that target physician recommendations have been shown to be more effective than those that focus only on the patient (Guerra et al., 2007). In contrast, others argue that options are needed because every CRC screening modality has its own strengths and limitations. Additionally, there does not seem to be a clear consensus among patients about preferred methods. Thus, an important question arises: would patients be more willing to participate in screening, if they are given the opportunity to choose? Engaging patients in the decision-making process can improve satisfaction by taking into account each patient's unique needs. A patient-centered approach improves screening compliance (Inadomi et al., 2012).

5.2. Patient-based factors in CRC screening

At the center of the discussion related to screening is the patient's participation in completing the process. While low participation rates in screening related to infrequent or lack of follow-up is a difficult barrier to overcome, other factors are also important. It is notable that most of the data about reasons for screening non-compliance comes from direct physician report (Hoffman et al., 2011). Physicians reported offering screening to all of their high risk and most of their average risk patients, and most were surprised at the low adherence rates. Through their interactions with patients, physicians believed barriers to screening were fear of the test, embarrassment, lack of insurance, and lack of knowledge about cancer and screening. Interestingly, when patients were asked the same questions, they did not feel that discomfort or embarrassment kept them from undergoing the procedure. Patients reported lack of physician recommendation as one of the main factors for not getting tested, along with lack of symptoms that might suggest a colon neoplasm (Jones et al., 2010). Of course these studies are limited in terms of the particular patient population sampled and may not be applicable to all patients; however, it is important to note that patients place great importance on the conversation with primary care providers about CRC screening (Fenton et al., 2011). Furthermore, this is directly linked to patient's knowledge about CRC and screening. Misconceptions continue to prevail as barriers to CRC screening, indicating a continued

need for brief, direct encouragement from providers to educate patients about screening, particularly in the absence of symptoms or family history of CRC. Physicians can have great impact on CRC screening, particularly with lifesaving colonoscopy, which is greatly underutilized in the US.

In a questionnaire investigating the patient barriers to CRC screening, hesitation about screening was highest among never-screened respondents, intermediate among ever-screened respondents who were overdue for testing, and lowest among the people adherent with guidelines suggesting that different obstacles exist within each target group. The only difference between those groups of patients is *prior screening status*. These results also demonstrate that people who have undergone screening are less fearful of the test itself, this could be attributed to the fact that they have first hand experience instead of false information or misconceptions. Patients who are more educated are likely to be aware of the risks and benefits of CRC screening (Winterich et al., 2011).

5.2.1. Patient attitudes, beliefs, and knowledge of CRC

Low compliance for CRC screening by patients can be attributed to several factors including lack of insurance, cost, lack of knowledge of cancer and screening, not seeing a need for testing, embarrassment, lack of symptoms or health problems, fear of perceived pain, and anxiety of testing. This is in addition to failure by recommendation from a physician (Jones et al., 2010). Studies have suggested that many patients dread getting ready for and having the test and also worry about the test results. Additional research has found that the participants did not understand the purpose of screening for cancer, were not able to distinguish between screening tests from any other tests and did not realize that screening is performed when a person feels well (Shokar et al., 2005).

Lack of knowledge is a major barrier to screening, particularly for immigrants, ethnic minorities, and underserved populations because of challenges in effective communication, as will be discussed later. Studies looking into lack of knowledge about colon cancer screening identified many other knowledge gaps including low health literacy. Some individuals did not have a basic understanding of human anatomy and were not able to identify the location of the colon nor its purpose. A subset of these individuals did not believe colon cancer existed. Furthermore, a surprising amount of educated individuals could not accurately describe the colon's function, confusing it with the rectum and anus (Francois et al., 2009; Winterich et al., 2011).

Those that had some fundamental knowledge of colon anatomy lacked an adequate understanding about the causes and risk factors of colon cancer. Many individuals without symptoms or family history do not feel concerned about this disease. Some are under the impression that causes of colon cancer center around food and thought that bowel cleansing was a good way to maintain or re-establish health. Others cited that they did not get screened because they did not smoke, drink, eat unhealthy foods, or participate in anal sex, all of which they perceived to be high-risk behaviors (Francois et al., 2009).

In addition to poor understanding about colon cancer, many misperceptions about colonoscopy itself were identified. One study captured the reasons some people did not like colonoscopy including that the preparation was "inconvenient", "uncomfortable", and involved a "compromising position". Men of all races and levels of educational attainment shared the male specific gender barrier that they were turned off by the invasive nature of the colonoscopy. While males and females have similar screening rates, men expressed more initial hesitation about screening because of the fear that it threatens their masculinity. Men who associated their masculinity with these exams experienced them more negatively (Winterich et al., 2011). Interestingly, Winterich et al. (Winterich et al., 2011) found that as education increased, men's negative views of colonoscopy also seemed to increase. Most individuals of a low-educational attainment generally described the colonoscopy as a "good" test because of the culturally dominant view that medical care is important (Winterich et al., 2011).

5.2.2. Racial and ethnic disparities in CRC screening

As mentioned earlier, screening rates differ based on race and ethnic groups. The National Health Interview Survey reported that racial disparities seen with CRC screening are related to socioeconomic status, however, racial disparities persist despite coverage for CRC screening in a Medicare population (Wilkins et al., 2012). Compared to whites, blacks and Hispanics are less likely to be screened. Overall rates of CRC screening are estimated to be 50% and it is even lower for minorities. Screening rates vary even within a racial or ethnic group, e.g among Asians, Koreans and Vietnamese have lower rates of screening; among whites, those living in Appalachia have lower screening rates. Minority populations and low socioeconomic status are considered to be factors resulting in low CRC screening rates (Linsky et al., 2011). Research studies also suggest that immigrants may experience unique barriers such as language and cultural differences with their health care providers which can lead to poorer communication about the importance of screening (Goel et al., 2003).

5.2.3. The language divide

Patients who do not speak English are less likely to be screened (Linsky et al., 2011). According to the 2005-2007 American Community Survey, minorities comprise 26% of the population, and nearly 20% of Americans speak a language other than English at home. By 2050, minorities could make up about half of the US population, with a similar increase in individuals speaking a language other than English at home. Spanish speaking Hispanics are 43% less likely to receive CRC screening. Communication problems when discussing cancer screening are also documented with Vietnamese Americans (Linsky et al., 2011). Additionally, for Creole speaking Haitian Americans the language barrier may also be a factor in communicating with physicians (Francois et al., 2009). While patient-physician language discordance presents a barrier, it is possible to address it through initiatives such as translation services so that disparities in screening rates can be reduced.

5.2.4. Cultural chasms

Cultural beliefs can result in lower screening rates, for example, Italian- Australians, Macedonian-Australians and Greek- Australians were found to believe that nothing can be done to treat 'malignant' cancers and that in fact, treatment of cancers may hasten death (Severino et al., 2009). They also believe that consumption of 'unnaturally' grown foods, eating foods sprayed with pesticides or experiencing strong emotions may cause cancer. Studies with African Americans have indicated that the lack of CRC knowledge, lack of physician recommendation, and a distrust of the health care system and providers impede screening; as well as a fatalistic belief (beliefs that screening and treatments are 'futile' since it is in "God's hands") which has also been reported as a barrier for CRC screening (James et al., 2002). A subset of individuals connected colon cancer with "someone putting a curse on you" (Francois et al., 2009). Studies in Latino population suggest that fatalistic attitudes and fear of cancer are barriers to cancer screening and misconceptions about the causes of cancer as well as perceived discomfort and embarrassment (Walsh et al., 2004).

Among other factors, family recommendations and cultural norms weighed heavily on perceptions about cancer and colonoscopy. For example, studies with Mexican and Hispanic communities have cited the need for strategies to distribute the information without causing any stigma or embarrassment. Privacy is highly valued in Mexican culture and thus individualized educational sessions are a good approach. On the other hand, Hispanic communities prefer group educational workshops. Emphasis on family and being healthy to provide for the family was effective, as well as convincing women within families of the importance of screening. Latinos also tend to see doctors only when sick and combine traditional and home healing with physician prescribed medications. Religion and spirituality seem to impact the willingness to accept CRC screening, as does low income and less education (Getrich et al., 2012).

In a study of Haitian immigrants, preventive care was not emphasized by the community. Haitians make one of the largest immigrant groups in US and have the lowest percentage of insurance coverage. Instead of having a primary physician they seem to rely on emergency rooms and do not see a doctor unless there is something wrong, there is not an operating concept valuing 'check ups'. Undocumented persons, seek help only in an emergency situation and instead rely on home remedies. These individuals expressed that they simply did not want to know if there was something wrong with them, because finding one problem might lead to other ones (Francois et al., 2009).

5.2.5. Health literacy and educational outreach in CRC screening

Efforts to empower patients to become involved in their own care have proven to be effective. Health literacy campaigns in New York City have improved CRC screening rates. Community education is required to promote screening and public education campaigns are shown to be effective. For example Mr. Polyp ads, a public service announcement from the American Cancer Society, led many to ask their doctors about colonoscopies (Guerra et al., 2007). Population based interventions aimed at increasing the demand for screening include, reminders and incentives, mass and small media, group and one-on-one education. Bilin-

gual verbal communication and 'word of mouth' are also potentially very effective modalities. Blumenthal et al. (Blumenthal et al., 2010) tested three interventions intended to increase the rate of CRC screening among African Americans. They concluded that group education doubled screening rates and reduced out of pocket expenses. Furthermore, differences in attitudes and perceived barriers among ethnic and minority population may need culturally tailored interventions. Focus groups with Hispanics identified fear of finding cancer and fear of embarrassment from the examination, as screening obstacles. With this information, Varela et al. (Varela et al., 2010) developed targeted educational materials to promote colonoscopies among Hispanics. Similar educational materials could tap into faith-based programs like the successful Witness Project for breast cancer.

5.2.6. Patient navigators and customized CRC screening

As previously mentioned, ethnic and cultural differences can pose a great barrier to effective cancer screening. Patient advocates who help coordinate care provide an option for tackling screening disparities. Termed patient navigators, these individuals are laypersons from the community who help patients navigate the intricacies of the health care system (Lasser et al., 2011). They can better address the unique needs of a patient and are responsible for almost anything such as helping patients get insurance, finding transportation to doctors' appointments, healthcare education, and emotional support. For example, patients that require interpreters are found to be less compliant with screening recommendations. Providing patients with a healthcare ambassador who speaks their preferred language has proven to be a simple yet extremely powerful intervention. In a randomized controlled trial, recently published in the Archives of Internal Medicine, researchers found quantifiable benefits from assigning black and non-English speaking patients with a healthcare navigator. These patients had a greater likelihood of being screened by FOBT than control subjects (33.6% vs 20.0%; P<.001) and were also more likely to undergo colonoscopy (26.4% vs 13.0%; P,.001). Moreover, these patients had more adenomas detected (8.1% vs 3.9%; P<.06) and more cases of CRC prevented (Lasser et al., 2011). This study highlights the importance of a multidisciplinary approach to medicine. The impact of patient navigators, especially on urban and racial minorities, is demonstrated by numerous studies (Chen et al., 2008; Lasser et al., 2011; Lasser et al., 2009; Ma et al., 2009; Myers et al., 2008; Nash et al., 2006). A recent study found patient navigators to be effective for Creole or Portuguese speaking patients. This model can be observed in practice in Boston where Partners in Health routinely trains paramedical personnel to assist in providing customized care for patients with HIV and TB in Haiti and Rwanda.

The benefit of a team approach to healthcare is further evidenced by studies demonstrating that the use of nurse practitioners and physicians assistants further streamlines healthcare delivery and improves screening compliance. Moreover, telephone counseling and printed materials can help improve follow up and overall quality of life in colorectal cancer survivors. Clouston et al. (Clouston et al., 2012) performed a study to evaluate use of a website and telephones on CRC screening rates and concluded that both increased compliance significantly. However, a strong and trusting family physician-patient relationship must be

maintained; otherwise, patients will experience a fundamental disconnect in the patient-physician relationship that may discourage screening. The team-based approach does not look to replace the physician, but can enhance patient-physician discourse.

Customized programs targeted to specific individuals may help improve patient participation rates. Tailored screening guidelines have been advocated for certain groups based on noted prevalence and anatomic location of colonic lesions in these populations. For example, women are known to have an increased risk of right-sided polyps and cancer (Chu et al., 2011), while African Americans tend to develop colorectal cancer at an earlier age (Agrawal et al., 2005). The recommendation for tailored screening guidelines as suggested by the ACG have the potential to help address existing disparities in CRC but must be balanced by ease of implementation as well as healthcare financing concerns.

5.3. Public policies, outreach, and CRC screening

Although screening rates for CRC remain suboptimal, there has been an overall upward trend. Endorsement from various recommending organizations helped promote awareness of CRC screening in the medical community. Supported by population-based studies, gastroenterology organizations have promoted screening with colonoscopy as the best screening test. The healthcare policy to support CRC screening through Medicare reimbursement was impactful in developing further acceptance. Medicare's decision to support screening colonoscopy had a significant impact on the popularity of this modality as other payers followed suit. With insurance companies willing to pay, doctors were more inclined to recommend screening and free to choose their preferred modality, colonoscopy. In fact, gastroenterologists report they are now performing many more colonoscopies than before. Some spend 50% to 80% of their time performing this one procedure, a dramatic increase from before (Ransohoff, 2005).

Public perception and support has greatly impacted the implementation of screening, especially colonoscopy. All of the aforementioned factors are geared at gaining strong popular support, a necessary ingredient for any widespread screening practice. For example, prostate cancer screening became widely practiced on the basis of popular support, even without evidence of mortality reduction. Arguably the most influential aspect of colon cancer and screening awareness was the increasing presence of colonoscopy in the media. Famous people affected by colon cancer include Ronald Reagan, Audrey Hepburn, and Daryl Strawberry to name a few. Public interest in colonoscopy reached a turning point in March of 2000, the first colon cancer awareness month. This initiative was spearheaded by news icon Katie Couric, who advocated for CRC screening on the national stage by televising her own colonoscopy after her husband's death (Cram et al., 2003). Similar appearances of colonoscopy in the media impacted CRC screening practices in the United States. Most recently, Dr. Oz underwent a colonoscopy on his eponymous television show. An editorial featured in the New York Times entitled "Going the distance-the case for true colorectal-cancer screening" garnered further support for colonoscopies stating that sigmoidoscopy, that only screens part of the colon, is comparable to mammography for only one breast. Numerous editorials and front page articles have featured colonoscopies (Ransohoff, 2005). For example a news-

paper ad made the assertion, "your golden years deserve the gold standard of colon cancer screening" (American College of Gastroenterology [ACG], 2012). Additional marketing on the web has helped improve awareness among the public who increasingly use the web for health information (Cohen and Adams, 2011).

5.3.1. Healthcare access

For patients to consider screening, it is important that to have insurance coverage, access to healthcare or both. Only 24% of uninsured Americans, who do not have a usual source of health care and are eligible, participate in CRC screening (Shapiro et al., 2012). Patients with higher incomes are likely to have health insurance and tend to have a consistent source of care. A recent systemic review reported that lower socioeconomic status was correlated with a higher incidence and mortality rate (Wilkins et al., 2012). Subramanian et al. (Subramanian et al., 2010) argue that when budgets are tight, options other than colonoscopies are better for screening, basing this on the premise that some form of screening is better than no screening at all. This study asserts that state and federal agencies have screening programs for the uninsured and underinsured that may not be able to support colonoscopy in their limited budget. However efficacy of the guaiac based fecal blood test depends on 100% compliance. This is often not practical and the study's authors admit that colonoscopy is still a better screening test if annual testing is not feasible.

In addition to financial access, geographic access can pose a problem for individuals in rural areas. In New York City and other urban centers, most hospitals and many private practices will offer colonoscopy; however, this is not the case in every part of the country. Several studies have found lower screening rates in rural versus nonrural areas (Wilkins et al., 2012). Geographic distance is a factor and individuals are less likely to be screened if the nearest colonoscopy-offering center is over an hour away. The rural countries in the study by Wilkins et al. (Wilkins et al., 2012) had higher poverty rates, lower educational level, limited access to doctors, and less insurance coverage.

5.3.2. National programs

The benefits of a team approach to healthcare is further evidenced by national programs that help promote patient awareness and education about CRC screening. Health policy initiatives need to underscore the importance of screening programs to improve quality of cancer screening. Cancer registries may be of use to identify and monitor the incidence, stage of cancer and screening rate across regions. A CRC screening registry similar to Breast Cancer Surveillance Consortium could be established to monitor rates of screening, overuse, quality and complications. An ideal monitoring system should be able to estimate rates of screening regardless of patient's insurance status and demographic characteristics, assess use, appropriateness and outcomes. Efforts should be made to support expansion, analysis and collaboration of existing data sources and databases such as Clinical Outcome Research Initiative (CORI) endoscopy data base, the Cancer Research Network (CRN) and the Computed Tomography Colonography Registry.

5.3.3. Communication via current technologies

The use of systems strategies can improve physician delivery of healthcare. Systems strategies employ patient and physician screening reminders, performance reports of screening rates, and electronic medical records (Yabroff et al., 2011). Given time constraints, remembering to perform all routine screenings for every patient is difficult. The increasing use of electronic medical records (EMR) has helped physicians overcome this obstacle. Pop-up reminders can help minimize forgetfulness, as well as the added pressure of remembering individualized guidelines. These electronic prompts have the additional advantage of flexibility, which allows for screening to account for the patient's personal and family history. In one retrospective survey, the physicians that utilized this technology, which automatically provided appointments for CRC screening at a certain age, had the highest screening rates (Fenton et al., 2011).

In addition to physician prompts, organized screening programs make use of patient reminders to improve screening compliance. These programs reach out to all members of the population due for CRC screening via mailed reminders (Levin et al., 2011). In addition to outreach mailings, the Task Force on Community Preventive Services of the Centers for Disease Control and Prevention recommend performance reports for doctors. Monetary incentive from insurance companies for completing age-appropriate screening is effective. Additionally, better reimbursements are needed to encourage spending time on preventive medicine (Guerra et al., 2007). Brouwers (Brouwers et al., 2011) conducted a systemic review that included 66 randomized controlled studies and a cluster of randomized controlled trials. They concluded that client reminders, small media and provider audit and feedback appear to increase screening rates significantly. Despite evidence that systems strategies are effective, relatively few physicians report using a comprehensive plan to promote cancer screening (Yabroff et al., 2011).

5.3.4. Health insurance coverage for colonoscopy

Ensuring health insurance coverage and usual source of care will most likely increase use among those who have never been screened. Following Medicare's example, private insurance coverage of CRC screening will be a step towards resolving the cost issue for physicians and patients. Asking patients to pay thousands of out of pocket expenses to undergo a colonoscopy, will not help increase the rates of this life saving procedure. In a step to increase testing accessibility and affordability, the Affordable Care Act will ask insurers to cover screening colonoscopies. This will include not only colonoscopy, but the use of anesthesia (e.g. propofol) as opposed to conscious sedation (e.g., midazolam, fentanyl). Providing increased options for sedation is likely to remove the patient barrier related to discomfort and make it more likely that individuals will comply with colonoscopy as a life-saving screening modality (Liu et al., 2012).

6. Conclusion

This chapter has summarized the current body of knowledge related to colorectal cancer screening and surveillance recommendations in the context of addressing risk stratification, when to start and stop screening, as well as factors that impact screening rates. Overall, screening, detection, and removal of precancerous lesions allow for the prevention of CRC. It is notable that although strong evidence now exists for the mortality benefits of CRC screening, significant disparities remain in the disease thus giving rise to opportunities to address physician, patient, as well as societal factors that can improve screening rates.

Acknowledgements

Author details

Anjali Mone, Robert Mocharla, Allison Avery and Fritz Francois

New York University Langone Medical Center, USA

References

[1] Abotchie, P.N., Vernon, S.W., and Du, X.L. (2012). Gender differences in colorectal cancer incidence in the United States, 1975-2006. J Womens Health (Larchmt) 21, 393-400.

[2] American College of Gastroenterology. 2012. Your golden years deserve the gold standard of colon cancer screening. Retrieved from s3.gi.org/patients/ccrk/crcad2.pdf.

[3] Agrawal, S., Bhupinderjit, A., Bhutani, M.S., Boardman, L., Nguyen, C., Romero, Y., Srinivasan, R., and Figueroa-Moseley, C. (2005). Colorectal cancer in African Americans. Am J Gastroenterol 100, 515-523; discussion 514.

[4] Alberti, L.R., De Lima, D.C., De Lacerda Rodrigues, K.C., Taranto, M.P., Goncalves, S.H., and Petroianu, A. (2012). The impact of colonoscopy for colorectal cancer screening. Surg Endosc.

[5] Bandi, P., Cokkinides, V., Smith, R.A., and Jemal, A. (2012). Trends in colorectal cancer screening with home-based fecal occult blood tests in adults ages 50 to 64 years, 2000 to 2008. Cancer.

[6] Bini, E.J., Park, J., and Francois, F. (2006). Use of flexible sigmoidoscopy to screen for colorectal cancer in HIV-infected patients 50 years of age and older. Arch Intern Med 166, 1626-1631.

[7] Blumenthal, D.S., Smith, S.A., Majett, C.D., and Alema-Mensah, E. (2010). A trial of 3 interventions to promote colorectal cancer screening in African Americans. Cancer 116, 922-929.

[8] Boleij, A., and Tjalsma, H. (2012). Gut bacteria in health and disease: a survey on the interface between intestinal microbiology and colorectal cancer. Biological reviews of the Cambridge Philosophical Society 87, 701-730.

[9] Bresalier, R.S. (2009). Early detection of and screening for colorectal neoplasia. Gut and liver 3, 69-80.

[10] Brouwers, M.C., De Vito, C., Bahirathan, L., Carol, A., Carroll, J.C., Cotterchio, M., Dobbins, M., Lent, B., Levitt, C., Lewis, N., et al. (2011). What implementation interventions increase cancer screening rates? a systematic review. Implementation science : IS 6, 111.

[11] Bussey, H.J., Veale, A.M., and Morson, B.C. (1978). Genetics of gastrointestinal polyposis. Gastroenterology 74, 1325-1330.

[12] Canavan, C., Abrams, K.R., and Mayberry, J. (2006). Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. Aliment Pharmacol Ther 23, 1097-1104.

[13] Cash, B.D., Banerjee, S., Anderson, M.A., Ben-Menachem, T., Decker, G.A., Fanelli, R.D., Fukami, N., Ikenberry, S.O., Jain, R., Jue, T.L., et al. (2010). Ethnic issues in endoscopy. Gastrointest Endosc 71, 1108-1112.

[14] Chen, C.D., Yen, M.F., Wang, W.M., Wong, J.M., and Chen, T.H. (2003). A case-cohort study for the disease natural history of adenoma-carcinoma and de novo carcinoma and surveillance of colon and rectum after polypectomy: implication for efficacy of colonoscopy. Br J Cancer 88, 1866-1873.

[15] Chen, L.A., Santos, S., Jandorf, L., Christie, J., Castillo, A., Winkel, G., and Itzkowitz, S. (2008). A program to enhance completion of screening colonoscopy among urban minorities. Clin Gastroenterol Hepatol 6, 443-450.

[16] Chien, C., Morimoto, L.M., Tom, J., and Li, C.I. (2005). Differences in colorectal carcinoma stage and survival by race and ethnicity. Cancer 104, 629-639.

[17] Chlebowski, R.T., Wactawski-Wende, J., Ritenbaugh, C., Hubbell, F.A., Ascensao, J., Rodabough, R.J., Rosenberg, C.A., Taylor, V.M., Harris, R., Chen, C., et al. (2004). Estrogen plus progestin and colorectal cancer in postmenopausal women. N Engl J Med 350, 991-1004.

[18] Cho, E., Smith-Warner, S.A., Ritz, J., van den Brandt, P.A., Colditz, G.A., Folsom, A.R., Freudenheim, J.L., Giovannucci, E., Goldbohm, R.A., Graham, S., et al. (2004).

Alcohol intake and colorectal cancer: a pooled analysis of 8 cohort studies. Ann Intern Med 140, 603-613.

[19] Chu, L.L., Weinstein, S., and Yee, J. (2011). Colorectal cancer screening in women: an underutilized lifesaver. AJR American journal of roentgenology 196, 303-310.

[20] Citarda, F., Tomaselli, G., Capocaccia, R., Barcherini, S., and Crespi, M. (2001). Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence. Gut 48, 812-815.

[21] Clouston, K.M., Katz, A., Martens, P.J., Sisler, J., Turner, D., Lobchuk, M., and McClement, S. (2012). Does access to a colorectal cancer screening website and/or a nurse-managed telephone help line provided to patients by their family physician increase fecal occult blood test uptake?: A pragmatic cluster randomized controlled trial study protocol. BMC Cancer 12, 182.

[22] Cohen, R.A., Adams P.F. Use of the Internet for Health Information: United States, 2009. NCHS data brief, no 66. Hyattsville, MD: National Center for Health Statistics. 2011.

[23] Colditz, G.A., Cannuscio, C.C., and Frazier, A.L. (1997). Physical activity and reduced risk of colon cancer: implications for prevention. Cancer Causes Control 8, 649-667.

[24] Collett, J.A., Platell, C., Fletcher, D.R., Aquilia, S., and Olynyk, J.K. (1999). Distal colonic neoplasms predict proximal neoplasia in average-risk, asymptomatic subjects. J Gastroenterol Hepatol 14, 67-71.

[25] Cram, P., Fendrick, A.M., Inadomi, J., Cowen, M.E., Carpenter, D., and Vijan, S. (2003). The impact of a celebrity promotional campaign on the use of colon cancer screening: the Katie Couric effect. Arch Intern Med 163, 1601-1605.

[26] Dimou, A., Syrigos, K.N., and Saif, M.W. (2009). Disparities in colorectal cancer in African-Americans vs Whites: before and after diagnosis. World J Gastroenterol 15, 3734-3743.

[27] Doubeni, C.A., Laiyemo, A.O., Young, A.C., Klabunde, C.N., Reed, G., Field, T.S., and Fletcher, R.H. (2010). Primary care, economic barriers to health care, and use of colorectal cancer screening tests among Medicare enrollees over time. Annals of family medicine 8, 299-307.

[28] Eaden, J.A., Abrams, K.R., and Mayberry, J.F. (2001). The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 48, 526-535.

[29] Edwards, B.K., Ward, E., Kohler, B.A., Eheman, C., Zauber, A.G., Anderson, R.N., Jemal, A., Schymura, M.J., Lansdorp-Vogelaar, I., Seeff, L.C., et al. (2010). Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer 116, 544-573.

[30] Fedirko, V., Tramacere, I., Bagnardi, V., Rota, M., Scotti, L., Islami, F., Negri, E., Straif, K., Romieu, I., La Vecchia, C., et al. (2011). Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. Annals of oncology : official journal of the European Society for Medical Oncology / ESMO 22, 1958-1972.

[31] Fenton, J.J., Jerant, A.F., von Friederichs-Fitzwater, M.M., Tancredi, D.J., and Franks, P. (2011). Physician counseling for colorectal cancer screening: impact on patient atti‐ tudes, beliefs, and behavior. J Am Board Fam Med 24, 673-681.

[32] Ferlay, J., Shin, H.R., Bray, F., Forman, D., Mathers, C., and Parkin, D.M. (2010). Esti‐ mates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 127, 2893-2917.

[33] Flossmann, E., and Rothwell, P.M. (2007). Effect of aspirin on long-term risk of color‐ ectal cancer: consistent evidence from randomised and observational studies. Lancet 369, 1603-1613.

[34] Francois, F., Elysee, G., Shah, S., and Gany, F. (2009). Colon cancer knowledge and attitudes in an immigrant Haitian community. J Immigr Minor Health 11, 319-325.

[35] Francois, F., Park, J., and Bini, E.J. (2006). Colon pathology detected after a positive screening flexible sigmoidoscopy: a prospective study in an ethnically diverse cohort. Am J Gastroenterol 101, 823-830.

[36] Gatto, N.M., Frucht, H., Sundararajan, V., Jacobson, J.S., Grann, V.R., and Neugut, A.I. (2003). Risk of perforation after colonoscopy and sigmoidoscopy: a population-based study. J Natl Cancer Inst 95, 230-236.

[37] Getrich, C.M., Sussman, A.L., Helitzer, D.L., Hoffman, R.M., Warner, T.D., Sanchez, V., Solares, A., and Rhyne, R.L. (2012). Expressions of machismo in colorectal cancer screening among New Mexico Hispanic subpopulations. Qualitative health research 22, 546-559.

[38] Goel, M.S., Wee, C.C., McCarthy, E.P., Davis, R.B., Ngo-Metzger, Q., and Phillips, R.S. (2003). Racial and ethnic disparities in cancer screening: the importance of for‐ eign birth as a barrier to care. J Gen Intern Med 18, 1028-1035.

[39] Govindarajan, R., Shah, R.V., Erkman, L.G., and Hutchins, L.F. (2003). Racial differ‐ ences in the outcome of patients with colorectal carcinoma. Cancer 97, 493-498.

[40] Guerra, C.E., Schwartz, J.S., Armstrong, K., Brown, J.S., Halbert, C.H., and Shea, J.A. (2007). Barriers of and facilitators to physician recommendation of colorectal cancer screening. J Gen Intern Med 22, 1681-1688.

[41] Haggar, F.A., and Boushey, R.P. (2009). Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. Clinics in colon and rectal surgery 22, 191-197.

[42] Hardy, R.G., Meltzer, S.J., and Jankowski, J.A. (2000). ABC of colorectal cancer. Mo‐ lecular basis for risk factors. BMJ 321, 886-889.

[43] Hassan, C., Rex, D.K., Zullo, A., and Cooper, G.S. (2012). Loss of efficacy and cost-effectiveness when screening colonoscopy is performed by nongastroenterologists. Cancer.

[44] Hawley, S.T., McQueen, A., Bartholomew, L.K., Greisinger, A.J., Coan, S.P., Myers, R., and Vernon, S.W. (2012). Preferences for colorectal cancer screening tests and screening test use in a large multispecialty primary care practice. Cancer 118, 2726-2734.

[45] Hirata, K., Noguchi, J., Yoshikawa, I., Tabaru, A., Nagata, N., Murata, I., and Itoh, H. (1996). Acute appendicitis immediately after colonoscopy. Am J Gastroenterol 91, 2239-2240.

[46] Hoffman, R.M., Espey, D., and Rhyne, R.L. (2011). A public-health perspective on screening colonoscopy. Expert review of anticancer therapy 11, 561-569.

[47] Howe, J.R., Mitros, F.A., and Summers, R.W. (1998). The risk of gastrointestinal carcinoma in familial juvenile polyposis. Ann Surg Oncol 5, 751-756.

[48] Humphreys, F., Hewetson, K.A., and Dellipiani, A.W. (1984). Massive subcutaneous emphysema following colonoscopy. Endoscopy 16, 160-161.

[49] Imperiale, T.F., Ransohoff, D.F., Itzkowitz, S.H., Turnbull, B.A., and Ross, M.E. (2004). Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. N Engl J Med 351, 2704-2714.

[50] Imperiale, T.F., Wagner, D.R., Lin, C.Y., Larkin, G.N., Rogge, J.D., and Ransohoff, D.F. (2000). Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. N Engl J Med 343, 169-174.

[51] Inadomi, J.M., Vijan, S., Janz, N.K., Fagerlin, A., Thomas, J.P., Lin, Y.V., Munoz, R., Lau, C., Somsouk, M., El-Nachef, N., et al. (2012). Adherence to colorectal cancer screening: a randomized clinical trial of competing strategies. Arch Intern Med 172, 575-582.

[52] James, A.S., Campbell, M.K., and Hudson, M.A. (2002). Perceived barriers and benefits to colon cancer screening among African Americans in North Carolina: how does perception relate to screening behavior? Cancer Epidemiol Biomarkers Prev 11, 529-534.

[53] Jaroslaw Regula, A.C., Michal F. Kaminski (2012). Should There Be Gender Differences in the Guidelines for Colorectal Cancer Screening? Curr Colorectal Cancer Rep 8, 32-35.

[54] Jass, J.R., Williams, C.B., Bussey, H.J., and Morson, B.C. (1988). Juvenile polyposis--a precancerous condition. Histopathology 13, 619-630.

[55] Jemal, A., Bray, F., Center, M.M., Ferlay, J., Ward, E., and Forman, D. (2011). Global cancer statistics. CA: a cancer journal for clinicians 61, 69-90.

[56] Jemal, A., Center, M.M., DeSantis, C., and Ward, E.M. (2010). Global patterns of cancer incidence and mortality rates and trends. Cancer Epidemiol Biomarkers Prev 19, 1893-1907.

[57] Jemal, A., Siegel, R., Ward, E., Hao, Y., Xu, J., Murray, T., and Thun, M.J. (2008). Cancer statistics, 2008. CA Cancer J Clin 58, 71-96.

[58] Jenkins, M.A., Croitoru, M.E., Monga, N., Cleary, S.P., Cotterchio, M., Hopper, J.L., and Gallinger, S. (2006). Risk of colorectal cancer in monoallelic and biallelic carriers of MYH mutations: a population-based case-family study. Cancer Epidemiol Biomarkers Prev 15, 312-314.

[59] Johnson, C.D., Chen, M.H., Toledano, A.Y., Heiken, J.P., Dachman, A., Kuo, M.D., Menias, C.O., Siewert, B., Cheema, J.I., Obregon, R.G., et al. (2008). Accuracy of CT colonography for detection of large adenomas and cancers. N Engl J Med 359, 1207-1217.

[60] Johnson, J.R., Lacey, J.V., Jr., Lazovich, D., Geller, M.A., Schairer, C., Schatzkin, A., and Flood, A. (2009). Menopausal hormone therapy and risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev 18, 196-203.

[61] Jones, R.M., Woolf, S.H., Cunningham, T.D., Johnson, R.E., Krist, A.H., Rothemich, S.F., and Vernon, S.W. (2010). The relative importance of patient-reported barriers to colorectal cancer screening. Am J Prev Med 38, 499-507.

[62] Kamath, A.S., Iqbal, C.W., Sarr, M.G., Cullinane, D.C., Zietlow, S.P., Farley, D.R., and Sawyer, M.D. (2009). Colonoscopic splenic injuries: incidence and management. J Gastrointest Surg 13, 2136-2140.

[63] Knudsen, A.L., Bisgaard, M.L., and Bulow, S. (2003). Attenuated familial adenomatous polyposis (AFAP). A review of the literature. Familial cancer 2, 43-55.

[64] Ko, C.W., and Dominitz, J.A. (2010). Complications of colonoscopy: magnitude and management. Gastrointest Endosc Clin N Am 20, 659-671.

[65] Kohler, B.A., Ward, E., McCarthy, B.J., Schymura, M.J., Ries, L.A., Eheman, C., Jemal, A., Anderson, R.N., Ajani, U.A., and Edwards, B.K. (2011). Annual report to the nation on the status of cancer, 1975-2007, featuring tumors of the brain and other nervous system. J Natl Cancer Inst 103, 714-736.

[66] Koo, J.H., You, M.Y., Liu, K., Athureliya, M.D., Tang, C.W., Redmond, D.M., Connor, S.J., and Leong, R.W. (2012). Colorectal cancer screening practise is influenced by ethnicity of medical practitioner and patient. J Gastroenterol Hepatol 27, 390-396.

[67] Lansdorp-Vogelaar, I., Kuntz, K.M., Knudsen, A.B., Wilschut, J.A., Zauber, A.G., and van Ballegooijen, M. (2010). Stool DNA testing to screen for colorectal cancer in the Medicare population: a cost-effectiveness analysis. Ann Intern Med 153, 368-377.

[68] Lasser, K.E., Murillo, J., Lisboa, S., Casimir, A.N., Valley-Shah, L., Emmons, K.M., Fletcher, R.H., and Ayanian, J.Z. (2011). Colorectal cancer screening among ethnically

diverse, low-income patients: a randomized controlled trial. Arch Intern Med 171, 906-912.

[69] Lasser, K.E., Murillo, J., Medlin, E., Lisboa, S., Valley-Shah, L., Fletcher, R.H., Emmons, K.M., and Ayanian, J.Z. (2009). A multilevel intervention to promote colorectal cancer screening among community health center patients: results of a pilot study. BMC family practice 10, 37.

[70] Levin, B., Lieberman, D.A., McFarland, B., Andrews, K.S., Brooks, D., Bond, J., Dash, C., Giardiello, F.M., Glick, S., Johnson, D., et al. (2008). Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology 134, 1570-1595.

[71] Levin, T.R., Jamieson, L., Burley, D.A., Reyes, J., Oehrli, M., and Caldwell, C. (2011). Organized colorectal cancer screening in integrated health care systems. Epidemiologic reviews 33, 101-110.

[72] Liang, P.S., Chen, T.Y., and Giovannucci, E. (2009). Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis. Int J Cancer 124, 2406-2415.

[73] Lieberman, D. (2010). Progress and challenges in colorectal cancer screening and surveillance. Gastroenterology 138, 2115-2126.

[74] Lieberman, D.A., De Garmo, P.L., Fleischer, D.E., Eisen, G.M., and Helfand, M. (2000). Patterns of endoscopy use in the United States. Gastroenterology 118, 619-624.

[75] Lieberman, D.A., Holub, J., Eisen, G., Kraemer, D., and Morris, C.D. (2005). Prevalence of polyps greater than 9 mm in a consortium of diverse clinical practice settings in the United States. Clin Gastroenterol Hepatol 3, 798-805.

[76] Lieberman, D.A., Rex, D.K., Winawer, S.J., Giardiello, F.M., Johnson, D.A., and Levin, T.R. (2012). Guidelines for Colonoscopy Surveillance After Screening and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology.

[77] Lin, O.S., Kozarek, R.A., Schembre, D.B., Ayub, K., Gluck, M., Drennan, F., Soon, M.S., and Rabeneck, L. (2006). Screening colonoscopy in very elderly patients: prevalence of neoplasia and estimated impact on life expectancy. JAMA 295, 2357-2365.

[78] Linsky, A., McIntosh, N., Cabral, H., and Kazis, L.E. (2011). Patient-provider language concordance and colorectal cancer screening. J Gen Intern Med 26, 142-147.

[79] Liu, H., Waxman, D.A., Main, R., and Mattke, S. (2012). Utilization of anesthesia services during outpatient endoscopies and colonoscopies and associated spending in 2003-2009. JAMA 307, 1178-1184.

[80] Ma, G.X., Shive, S., Tan, Y., Gao, W., Rhee, J., Park, M., Kim, J., and Toubbeh, J.I. (2009). Community-based colorectal cancer intervention in underserved Korean Americans. Cancer epidemiology 33, 381-386.

[81] Maciosek, M.V., Solberg, L.I., Coffield, A.B., Edwards, N.M., and Goodman, M.J. (2006). Colorectal cancer screening: health impact and cost effectiveness. Am J Prev Med 31, 80-89.

[82] Martinez, M.E., Baron, J.A., Lieberman, D.A., Schatzkin, A., Lanza, E., Winawer, S.J., Zauber, A.G., Jiang, R., Ahnen, D.J., Bond, J.H., et al. (2009). A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy. Gastroenterology 136, 832-841.

[83] Martinez, M.E., Giovannucci, E., Spiegelman, D., Hunter, D.J., Willett, W.C., and Colditz, G.A. (1997). Leisure-time physical activity, body size, and colon cancer in women. Nurses' Health Study Research Group. J Natl Cancer Inst 89, 948-955.

[84] McGarrity, T.J., and Amos, C. (2006). Peutz-Jeghers syndrome: clinicopathology and molecular alterations. Cellular and molecular life sciences : CMLS 63, 2135-2144.

[85] McGregor, S., Hilsden, R., and Yang, H. (2010). Physician barriers to population-based, fecal occult blood test-based colorectal cancer screening programs for average-risk patients. Canadian journal of gastroenterology = Journal canadien de gastroenterologie 24, 359-364.

[86] Mecklin, J.P., Aarnio, M., Laara, E., Kairaluoma, M.V., Pylvanainen, K., Peltomaki, P., Aaltonen, L.A., and Jarvinen, H.J. (2007). Development of colorectal tumors in colonoscopic surveillance in Lynch syndrome. Gastroenterology 133, 1093-1098.

[87] Moore, L.L., Bradlee, M.L., Singer, M.R., Splansky, G.L., Proctor, M.H., Ellison, R.C., and Kreger, B.E. (2004). BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. Int J Obes Relat Metab Disord 28, 559-567.

[88] Muzny, D. (2012). Comprehensive molecular characterization of human colon and rectal cancer. Nature 487, 330-337.

[89] Myers, R.E., Hyslop, T., Sifri, R., Bittner-Fagan, H., Katurakes, N.C., Cocroft, J., Dicarlo, M., and Wolf, T. (2008). Tailored navigation in colorectal cancer screening. Med Care 46, S123-131.

[90] Nadel, M.R., Shapiro, J.A., Klabunde, C.N., Seeff, L.C., Uhler, R., Smith, R.A., and Ransohoff, D.F. (2005). A national survey of primary care physicians' methods for screening for fecal occult blood. Ann Intern Med 142, 86-94.

[91] Nash, D., Azeez, S., Vlahov, D., and Schori, M. (2006). Evaluation of an intervention to increase screening colonoscopy in an urban public hospital setting. Journal of urban health : bulletin of the New York Academy of Medicine 83, 231-243.

[92] NIH (2009). Surveillance Epidemiology and End results. US National Institutes of Health. Cancer Facts 2006 (online). .

[93] Pezzoli, A., Matarese, V., Rubini, M., Simoni, M., Caravelli, G.C., Stockbrugger, R., Cifala, V., Boccia, S., Feo, C., Simone, L., et al. (2007). Colorectal cancer screening: results of a 5-year program in asymptomatic subjects at increased risk. Dig Liver Dis 39, 33-39.

[94] Pignone, M., Saha, S., Hoerger, T., and Mandelblatt, J. (2002). Cost-effectiveness analyses of colorectal cancer screening: a systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 137, 96-104.

[95] Prescilla S. Perera, R.L.T.a.M.J.W. (2012). Recent Evidence for Colorectal Cancer Prevention Through Healthy Food, Nutrition, and Physical Activity: Implications for Recommendations. Current Nutrition Reports 1, 44-54.

[96] Prevention, C.f.D.C.a. Colorectal (Colon) Cancer Incidence Rates. In CDC Features, Data & Statistics by Date (Atlanta, GA).

[97] Center for disease control and prevention. 2011. Data & Statistics. Retrieved from http://www.cdc.gov/features/dsColorectalCancer/

[98] Center for disease control and prevention. 2012. Life Expectancy. Retrieved from http://www.cdc.gov/nchs/fastats/lifexpec.htm

[99] Ransohoff, D.F. (2005). Colon cancer screening in 2005: status and challenges. Gastroenterology 128, 1685-1695.

[100] Rembold, C.M. (1998). Number needed to screen: development of a statistic for disease screening. BMJ 317, 307-312.

[101] Rex, D.K., Johnson, D.A., Anderson, J.C., Schoenfeld, P.S., Burke, C.A., and Inadomi, J.M. (2009). American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. The American journal of gastroenterology 104, 739-750.

[102] Ries, L.A., Kosary C.L., Hankley B.F., Miller B.A., Edwards B.K., editors SEER cancer statistics review, 1973-1995. Bethesda (MD): National Cancer Institue; 1998.

[103] Rim S.H., J.D.A., Steele C.B., Thompson T.D., Seeff L.C. (2011). Colorectal Cancer Screening-United States, 2002, 2004, 2006, and 2008. In Morbidity and Mortality Weekly Report (MMWR).

[104] Rothwell, P.M., Price, J.F., Fowkes, F.G., Zanchetti, A., Roncaglioni, M.C., Tognoni, G., Lee, R., Belch, J.F., Wilson, M., Mehta, Z., et al. (2012). Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. Lancet 379, 1602-1612.

[105] Rutter, C.M., Johnson, E., Miglioretti, D.L., Mandelson, M.T., Inadomi, J., and Buist, D.S. (2012). Adverse events after screening and follow-up colonoscopy. Cancer Causes Control 23, 289-296.

[106] Sano, Y., Ikematsu, H., Fu, K.I., Emura, F., Katagiri, A., Horimatsu, T., Kaneko, K., Soetikno, R., and Yoshida, S. (2009). Meshed capillary vessels by use of narrow-band

imaging for differential diagnosis of small colorectal polyps. Gastrointest Endosc 69, 278-283.

[107] Schoen, R.E., Pinsky, P.F., Weissfeld, J.L., Yokochi, L.A., Church, T., Laiyemo, A.O., Bresalier, R., Andriole, G.L., Buys, S.S., Crawford, E.D., et al. (2012). Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 366, 2345-2357.

[108] Schoenfeld, P., Cash, B., Flood, A., Dobhan, R., Eastone, J., Coyle, W., Kikendall, J.W., Kim, H.M., Weiss, D.G., Emory, T., et al. (2005). Colonoscopic screening of average-risk women for colorectal neoplasia. N Engl J Med 352, 2061-2068.

[109] School, H.M. (2012). Does colonoscopy save lives? A recent study suggests it might, but it isn't the last word. Harvard Health Letter.

[110] Does colonoscopy save lives? A recent study suggest it might, but it isn't the last word. Harvard health letter/from Harvard Medical School 2012; 37:3.

[111] Shapiro, J.A., Klabunde, C.N., Thompson, T.D., Nadel, M.R., Seeff, L.C., and White, A. (2012). Patterns of Colorectal Cancer Test Use, Including CT Colonography, in the 2010 National Health Interview Survey. Cancer Epidemiol Biomarkers Prev 21, 895-904.

[112] Shokar, N.K., Vernon, S.W., and Weller, S.C. (2005). Cancer and colorectal cancer: knowledge, beliefs, and screening preferences of a diverse patient population. Family medicine 37, 341-347.

[113] Society, A.C. (2011). Colorectal Cancer Facts & Figures 2011-2013. Atlanta: American Cancer Society.

[114] Soneji, S., Iyer, S.S., Armstrong, K., and Asch, D.A. (2010). Racial disparities in stage-specific colorectal cancer mortality: 1960-2005. Am J Public Health 100, 1912-1916.

[115] Spach, D.H., Silverstein, F.E., and Stamm, W.E. (1993). Transmission of infection by gastrointestinal endoscopy and bronchoscopy. Ann Intern Med 118, 117-128.

[116] Stelzner, S., Hellmich, G., Koch, R., and Ludwig, K. (2005). Factors predicting survival in stage IV colorectal carcinoma patients after palliative treatment: a multivariate analysis. Journal of surgical oncology 89, 211-217.

[117] Stout, N.K., Rosenberg, M.A., Trentham-Dietz, A., Smith, M.A., Robinson, S.M., and Fryback, D.G. (2006). Retrospective cost-effectiveness analysis of screening mammography. J Natl Cancer Inst 98, 774-782.

[118] Subramanian, S., Bobashev, G., and Morris, R.J. (2010). When budgets are tight, there are better options than colonoscopies for colorectal cancer screening. Health Aff (Millwood) 29, 1734-1740.

[119] Telford, J.J., Levy, A.R., Sambrook, J.C., Zou, D., and Enns, R.A. (2010). The cost-effectiveness of screening for colorectal cancer. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 182, 1307-1313.

[120] Terzic, J., Grivennikov, S., Karin, E., and Karin, M. (2010). Inflammation and colon cancer. Gastroenterology 138, 2101-2114 e2105.

[121] Toma, J., Paszat, L.F., Gunraj, N., and Rabeneck, L. (2008). Rates of new or missed colorectal cancer after barium enema and their risk factors: a population-based study. Am J Gastroenterol 103, 3142-3148.

[122] USPSTF (2008). Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 149, 627-637.

[123] Varela, A., Jandorf, L., and Duhamel, K. (2010). Understanding factors related to Colorectal Cancer (CRC) screening among urban Hispanics: use of focus group methodology. Journal of cancer education : the official journal of the American Association for Cancer Education 25, 70-75.

[124] Vijan, S., Hwang, E.W., Hofer, T.P., and Hayward, R.A. (2001). Which colon cancer screening test? A comparison of costs, effectiveness, and compliance. Am J Med 111, 593-601.

[125] Wagner, M., Kiselow, M.C., Keats, W.L., and Jan, M.L. (1970). Varices of the colon. Arch Surg 100, 718-720.

[126] Wallace, P.M., and Suzuki, R. (2012). Regional, Racial, and Gender Differences in Colorectal Cancer Screening in Middle-aged African-Americans and Whites. Journal of cancer education : the official journal of the American Association for Cancer Education.

[127] Walsh, J.M., Kaplan, C.P., Nguyen, B., Gildengorin, G., McPhee, S.J., and Perez-Stable, E.J. (2004). Barriers to colorectal cancer screening in Latino and Vietnamese Americans. Compared with non-Latino white Americans. J Gen Intern Med 19, 156-166.

[128] Walter, L.C., and Covinsky, K.E. (2001). Cancer screening in elderly patients: a framework for individualized decision making. JAMA 285, 2750-2756.

[129] White, P.M., Sahu, M., Poles, M.A., and Francois, F. (2012). Colorectal cancer screening of high-risk populations: A national survey of physicians. BMC research notes 5, 64.

[130] Wilkins, T., Gillies, R.A., Harbuck, S., Garren, J., Looney, S.W., and Schade, R.R. (2012). Racial disparities and barriers to colorectal cancer screening in rural areas. J Am Board Fam Med 25, 308-317.

[131] Wilkins, T., and Reynolds, P.L. (2008). Colorectal cancer: a summary of the evidence for screening and prevention. American family physician 78, 1385-1392.

[132] Winawer, S., Fletcher, R., Rex, D., Bond, J., Burt, R., Ferrucci, J., Ganiats, T., Levin, T., Woolf, S., Johnson, D., et al. (2003). Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. Gastroenterology 124, 544-560.

[133] Winawer, S.J. (2006). The achievements, impact, and future of the National Polyp Study. Gastrointest Endosc 64, 975-978.

[134] Winawer, S.J., Fletcher, R.H., Miller, L., Godlee, F., Stolar, M.H., Mulrow, C.D., Woolf, S.H., Glick, S.N., Ganiats, T.G., Bond, J.H., et al. (1997). Colorectal cancer screening: clinical guidelines and rationale. Gastroenterology 112, 594-642.

[135] Winawer, S.J., Zauber, A.G., Ho, M.N., O'Brien, M.J., Gottlieb, L.S., Sternberg, S.S., Waye, J.D., Schapiro, M., Bond, J.H., Panish, J.F., et al. (1993a). Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 329, 1977-1981.

[136] Winawer, S.J., Zauber, A.G., O'Brien, M.J., Ho, M.N., Gottlieb, L., Sternberg, S.S., Waye, J.D., Bond, J., Schapiro, M., Stewart, E.T., et al. (1993b). Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. The National Polyp Study Workgroup. N Engl J Med 328, 901-906.

[137] Winterich, J.A., Quandt, S.A., Grzywacz, J.G., Clark, P., Dignan, M., Stewart, J.H., and Arcury, T.A. (2011). Men's knowledge and beliefs about colorectal cancer and 3 screenings: education, race, and screening status. American journal of health behavior 35, 525-534.

[138] Wudel, L.J., Jr., Chapman, W.C., Shyr, Y., Davidson, M., Jeyakumar, A., Rogers, S.O., Jr., Allos, T., and Stain, S.C. (2002). Disparate outcomes in patients with colorectal cancer: effect of race on long-term survival. Arch Surg 137, 550-554; discussion 554-556.

[139] Yabroff, K.R., Zapka, J., Klabunde, C.N., Yuan, G., Buckman, D.W., Haggstrom, D., Clauser, S.B., Miller, J., and Taplin, S.H. (2011). Systems strategies to support cancer screening in U.S. primary care practice. Cancer Epidemiol Biomarkers Prev 20, 2471-2479.

[140] Yuhara, H., Steinmaus, C., Cohen, S.E., Corley, D.A., Tei, Y., and Buffler, P.A. (2011). Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? Am J Gastroenterol 106, 1911-1921; quiz 1922.

[141] Zapka, J.M., Klabunde, C.N., Arora, N.K., Yuan, G., Smith, J.L., and Kobrin, S.C. (2011). Physicians' colorectal cancer screening discussion and recommendation patterns. Cancer Epidemiol Biomarkers Prev 20, 509-521.

[142] Zauber, A.G., Lansdorp-Vogelaar, I., Knudsen, A.B., Wilschut, J., van Ballegooijen, M., and Kuntz, K.M. (2008). Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. Ann Intern Med 149, 659-669.

[143] Zauber, A.G., Winawer, S.J., O'Brien, M.J., Lansdorp-Vogelaar, I., van Ballegooijen, M., Hankey, B.F., Shi, W., Bond, J.H., Schapiro, M., Panish, J.F., et al. (2012). Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 366, 687-696.