

Clinical Gastroenterology
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Joseph C. Anderson · Charles J. Kahi *Editors*

Colorectal Cancer Screening

 Humana Press

CLINICAL GASTROENTEROLOGY

Series Editor

George Y. Wu


University of Connecticut Health Center, Farmington, CT, USA

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Editors

Colorectal Cancer Screening

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Preface

Colorectal cancer (CRC) is a major clinical and public health challenge; it is the third most common cancer and second leading cause of cancer deaths in the United States. Yet, CRC is a largely preventable disease. It has a long latency period, and it may be several years before a precursor polyp transforms into a malignant growth. These characteristics render CRC an attractive target for screening, both by detection of cancer at early, treatable stages, and more importantly, prevention by the timely detection and removal of precursor precancerous neoplasms. Recent multisociety guidelines have emphasized the central role of prevention in CRC screening strategies.

The CRC screening landscape has undergone revolutionary changes over the past two decades, and remains a dynamic area at the interface of epidemiology, clinical research, outcomes research, public health, medical technology, and molecular and genetic science. The clinician who is considering CRC screening for a patient faces an array of options, considerations, and controversies which may be complex to navigate even for an expert in the field.

In this book, we present the state of the art in CRC screening, including established and new modalities, risk factors and preventive approaches, strategies to promote participation in screening programs, and considerations in special populations. The book should not be viewed as an end statement to CRC screening debates and controversy; rather, it is intended to present an overview of current knowledge and an introduction to areas of active research and unanswered questions. The contributing authors are highly accomplished experts who are well established in their respective fields. We hope that the reader will enjoy reading this book as much as we did putting it together.

Farmington, CT
Indianapolis, IN

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Chapter 1

Colorectal Cancer Pathways

Petr Protiva

Keywords Genomic instability • Chromosomal instability • Microsatellite instability • CpG island methylator pathway

Genomic instability is a hallmark of colorectal cancer. Progressive accumulation of mutations leads to deregulation of cellular events, acquired growth advantage, and clonal expansion of abnormal cells. Subsequently, these cells become more susceptible to mutations increasing the likelihood of critical mutations and giving rise to histopathologically identifiable neoplastic growth and metastatic behavior.

About 20 years ago, a number of key molecular events associated with neoplastic lesions in the colon emerged. The traditional model of genetic alterations in the adenoma-carcinoma sequence was both simple and correlated relatively well with the observed rate of progression of many adenomatous lesions of the colorectum [1]. However, a subset of colorectal neoplastic lesions exhibited a variable natural history suggesting that polyps and resulting cancers do not all fit the traditional model. Subsequently, the discovery of the DNA mismatch repair system and its role in the development of cancer in Lynch syndrome [2] and later, the discovery of epigenetic changes in cancer suggested more than one pathway is involved in this process [3]. The location of lesions, unique histopathological features, and differential prognosis and response to chemotherapy for a given stage of the disease led to efforts to characterize the disease by its molecular features [4]. These features were thought to correlate with the natural history of the disease and allowed for development of new therapeutic strategies. Recent advances in genetics and molecular biology, combined with the relatively low cost of high-throughput molecular methods, allowed for a major understanding of the molecular events in colorectal cancer. At least three major pathways were identified. Majority of cancers (70–85%) fall into chromosomal

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instability pathway (CIN) also known as suppressor pathways. The other two pathways include the microsatellite instability or mutator pathway (MSI) and the CpG island methylator pathway (CIMP). This chapter will describe the major molecular and clinical features of lesions associated with each pathway.

Chromosomal Instability or Suppressor Pathways

The chromosomal instability (CIN) or suppressor pathway is exemplified by the “traditional adenoma-carcinoma sequence” and tumors frequently exhibit aneuploidy [5, 6]. Frequently, genes such as APC, ras, p53, DCC, SMAD2, and SMAD4 are mutated or lost by chromosomal deletion [7]. These genes play a key role in important signaling pathways governing cell proliferation, apoptosis, and mitosis. APC is a large gene with 15 exons, and the APC protein is a part of Wnt signaling pathways where it plays a critical role in down-regulating activity by binding to beta catenin. The Wnt signaling pathway regulates proliferation and mitosis. A germline mutation in one copy of the APC gene followed by somatic inactivation of the second copy leads to development of familial adenomatous polyposis. APC mutations are found in about 70% of colorectal cancers (rectal > colon) suggesting it plays an important but not universal role in carcinogenesis. Activating mutations in K-ras GTPase result in constitutive signaling in the RAS-RAF-MEK-ERK proliferation pathway and are found in 35–40% of colorectal cancers. Loss of p53 function is found in over a half of CRCs. The major function of the p53 protein is to respond to DNA damage by slowing down the cell cycle to allow DNA repair and to induce apoptosis. DCC is a membrane receptor that also promotes apoptosis, and both SMAD2 and SMAD4 are part of the TGF-beta signaling pathway known to be involved in cell growth, migration, and apoptosis. Additionally, a mutation in SMAD4 is causally linked to juvenile polyposis syndrome, which carries increased risk of CRC. Many more alterations in the important regulators of the cell cycle and cell separation during division were identified as contributing to this phenotype [7]. Overall, about 75–80% of CRCs are associated with this pathway (Fig. 1.1 and Table 1.1) and these tumors tend to occur in distal colon.

Microsatellite Instability or Mutator Pathway

During DNA replication, the polymerases occasionally introduce a mismatched nucleotide, an error that is repaired by DNA mismatch repair enzymes (MMR) composed of at least seven proteins, hMLH1, hMLH3, hMSH2, hMSH3, hMSH6, hPMS1, and hPMS2. The hMLH1 and MSH2 are essential parts of heterodimers of these proteins that form a functional enzyme. The most frequent sites of these errors are the nucleotide tandem repeats called the microsatellites, and loss of the functional repair system causes microsatellite instability (MSI) [8]. The diploid genome is maintained during this type of genomic instability, and microsatellite

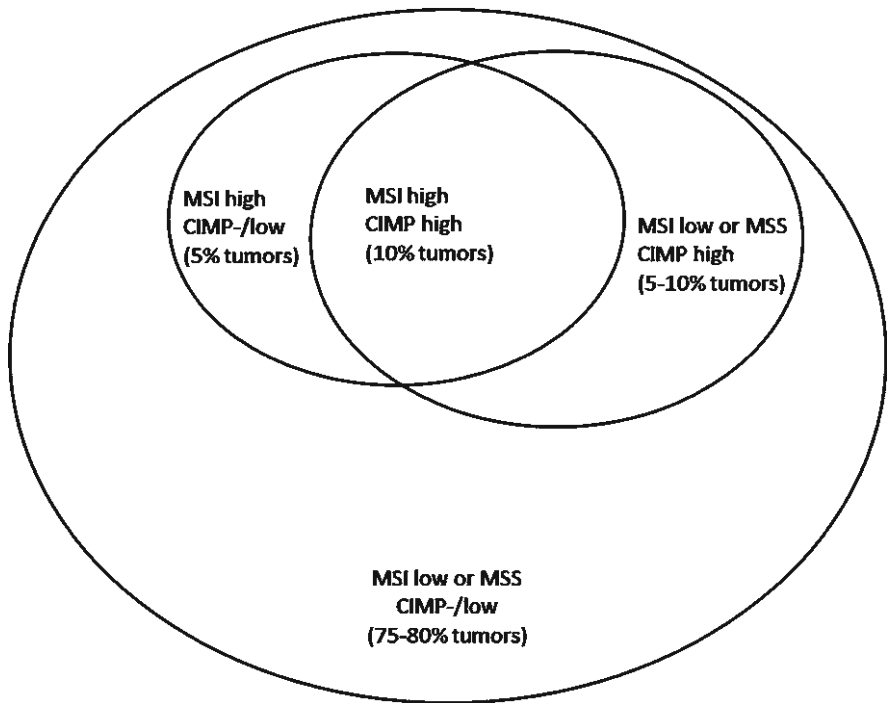


Fig. 1.1 Figure shows the distribution of CRCs according to their MSI and CIMP status. Note that the majority of tumors fall within CIN or suppressor pathway and only about 5% of tumors could be characterized as belonging to a “pure” mutator or MSI pathway. Fifteen to twenty percent of tumors are characterized by abnormal promoter methylation

instability in the gene coding or regulatory region leads to deregulation of key signaling pathways. Genes implicated in CRC containing microsatellites include TGF-beta2, beta-catenin, IGF-2, APC, MSH3, MSH6, Bax, Caspase 5, and E2F4. A standard panel of five microsatellites (BAT25, BAT26, D5S346, D2S123, and D17S250) is used to categorize tissue as microsatellite stable (MSS), when no instability is detected, MSI-L (low) when one marker is unstable or MSI-H (high) when more than two markers are unstable [9]. A germline mutation in one of the MMR genes causes MSI-H tumors in hereditary nonpolyposis colon cancer or Lynch syndrome. About 20% of CRCs show MSI-H but only about 5% have a genetic mutation in one of the MRR genes associated with Lynch syndrome, most frequently in hMLH1, hMSH2. In the remainder of the MSI-H tumors, the MMR (most frequently hMLH1) is epigenetically silenced [10] (Fig.1.1 and Table 1.1). A germline mutation in hMSH6 is associated with MSI-L [11]. Clinically and pathologically, MSI-L tumors are similar to MSS cancers but have higher frequency of K-ras mutations than either MSS or MSI-H. Compared to CRCs falling within the CIN or suppressor pathway, the tumors that belong to the mutator pathway tend to be proximal and carry a better prognosis [4].

Table 1.1 Colorectal cancer pathways and their characteristics

Pathway	MSI	CIMP	CIN	BRAF S mut	MMR G mut	MLH1 methyl	MGMT methyl	SITE colon	Precursor lesion
Mutator	High	-	-	-	+	-	-	Proximal	Advanced adenoma
Methylator	Nonhigh	+	-	+	-	+	-	Proximal	Serrated polyp
Methylator/ mutator	High	+	-	+	-	+	-	Proximal	Serrated polyp
Suppressor	Nonhigh	-	+	-	-	-	-	Distal	Advanced adenoma
Alternate methylator	Low	+	-	-	-	-	+	Distal	Serrated polyp

MSI microsatellite instability; *CIMP* CpG island methylator phenotype; *S mut* somatic mutation; *G mut* germline mutation; *MGMT methyl* promoter methylation status

CpG Island Methylator Pathway

DNA methylation at CpG islands occurs throughout the genome, and methylation of the gene promoter region is associated with epigenetic silencing of gene expression. The CpG islands of the promoter region are typically unmethylated except for X chromosome linked genes that are physiologically inactivated. CRC is associated with both global DNA hypomethylation and simultaneous hypermethylation in the promoter of genes that regulate key cellular events [12]. This epigenetic silencing results in inactivation of the gene without need for somatic mutation. CpG promoter methylation of many genes controlling cell cycle and proliferation such as p16 or hMLH1 is associated with CRC [13, 14]. It is not clear what causes the promoter hypermethylation but environmental factors, age, luminal gut contents, and dietary factors such as methyl donor micronutrients including folic acid were suggested [13]. To categorize tumors into defined subsets based on their methylation pattern as CpG island methylator phenotype positive or negative (CIMP+ or -), a revised set of methylation markers is used (CACNA1G, IGF2, NEUROG1, RUNX3, SOCS1) with up to 50% of all CRCs being CIMP+ [15]. Clinically, CIMP+ tumors tend to be proximal, and occur in elderly women. Non-MSI-H/CIMP+ cancers have a poorer prognosis compared to MSI-H tumors or tumors belonging to the CIN or suppressor pathway [4, 16]. In addition, most CIMP+ tumors have a mutation in components of the RAS-RAF-MEK-ERK pathway, either in BRAF or K-ras but not both. This pathway is involved in proliferation and additional processes such as anoikis – an apoptosis following loss of epithelial connection to basement membrane [17]. Failure of anoikis was linked to formation of hyperplastic polyps and serrated adenomas, possibly important precursors of CIMP+ CRCs [18].

As mentioned above CIMP+/MSI-H CRCs are frequently associated with epigenetically silenced hMLH1 [10] with clear overlap between sporadic mutator and methylator pathways in about 15% of CRCs (Fig. 1.1). However, an additional 5–10% of CRCs exhibiting CIMP+ are non-MSI-H. In these lesions, hMLH1 silencing is absent but there is a frequent association with the BRAF mutation and poor prognosis [16, 19]. In addition, epigenetic silencing of the DNA repair gene MGMT via promoter methylation is also significantly associated with MSI-L. This gene is involved in removal of mutagenic adducts from guanine, and its inactivation is linked to G to A transversion in K-ras, providing a mechanistic explanation for the high frequency of the K-ras mutation in a subset of MSI-L cancers without the BRAF mutation. This subset of CIMP+/MSI-L/K-ras cancers without the BRAF mutation may define the alternate methylator pathway with serrated precursor lesions (serrated pathway) [20].

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Chapter 2

Risk Factors and Screening for Colorectal Cancer

Joseph C. Anderson

Keywords Risk factors • Tobacco use • Body mass index

Screening for colorectal cancer (CRC) involves consideration of only a patient's age and their family history of CRC [1, 2], but there are other risk factors which can potentially affect screening. This section will examine known risk factors and how some of these can affect one's risk and subsequent screening for CRC. Other factors such as personal and family history of colorectal neoplasia as well as aspirin and other chemo-preventative agents will be discussed elsewhere. This section will serve as an overview of the various factors and the respective studies that examine their association with CRC as well as advanced adenomas. Age has been shown to be one of the strongest predictors of CRC [3] and will not be discussed as there is little debate as to the importance of this factor. In addition, this chapter will examine the modifiable risk factors since this is where clinicians can help patients to reduce their risk of CRC. A study by Platz et al. demonstrated that over two thirds of CRC may be preventable in men [4].

Prospective Studies

We will also review the four large prospective studies that examined risk factors and CRC. Table 2.1 shows the salient results of these large trials, and the details will be discussed in the subsequent sections. These include the Cancer Prevention Study II (CPS-II), which is a prospective cohort study funded and conducted by the American Cancer Society (ACS). The goal of the study is to examine the impact of environmental and lifestyle factors on cancer etiology in a large group of American men and

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Table 2.1 Results of selected prospective longitudinal studies

	Smoking	Red meat	Alcohol	Obesity	Physical activity	Fiber	Diabetes mellitus
Cancer prevention Study II	↑ CRC mortality	↑ Distal cancer	–	↑ Risk for WHR and BMI	↓ Colon but not rectal cancer	↑ CRC Intake fruit/veg ↑ CRC	↑ Men and ↔ women
Nurse's Health Study	↑ CRC after 35 years	↑ Colon but not rectal cancer	↑ Colon but not rectal	↑ CRC 1.5 X women w/ BMI < 21	↓ > 21 MET's/week	↔	↑ But ↔ for HbA1c
HPFS	↑ CRC after 35 years	↑ For 5 servings/week	↑ CRC > 15g/day	↑ BMI > 22.5, 29.5% of CRC attributed to this increase	↓ > 27 METS/week	↔	–
EPIC	↑ In proximal CRC in ever smokers	↑ Red meat but ↓ fish	↑ Highest risk in rectum	↑ With WHR	↓ for right sided cancer	↓ Especially distal CRC	↑ Risk for ↑ HbA1c

↑ Arrows refer to risk for CRC except where indicated

women [5]. Study participants (known as the CPS-II Baseline Cohort) completed an initial study questionnaire in 1982 that obtained information on a range of lifestyle factors such as diet, use of alcohol and tobacco, occupation, medical history, and family cancer history. Cause of death has been documented for 99% of all deaths that have occurred. The CPS-II Nutrition Cohort is a subgroup of 184,194 men and women who were mailed additional questionnaires in 1997, 1999, 2001, 2003, 2005, and 2007, to update exposure information and to obtain self-reported cancer diagnoses. The European Prospective Investigation into Cancer (EPIC) was set up to examine the association between diet, nutritional status, lifestyle and environmental factors, and the incidence of cancer. EPIC has recruited over half a million people in ten European countries: Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, and the United Kingdom [6]. The Health Professionals Follow-Up Study (HPFS) was started in 1986 by Walter Willett and Meir Stampfer [7] and has enrolled 51,529 men. The HPFS is sponsored by the Harvard School of Public Health and is funded by the National Heart, Lung, and Blood Institute and National Cancer Institute. The Nurses' Health Study (NHS) is designed to complement the HPFS and consists of a similar number of women [8].

Risk Factors

Red Meat

Red meat, in the form of beef or lamb, has been examined as a risk factor in many case control and longitudinal population studies. In most of these studies, consumption of red meat is associated with an increased risk for CRC. A recent longitudinal study from Europe, the EPIC, demonstrated an increased risk for people who consumed more than 160 g of red or processed meat per day [9]. In another prospective study from the United States, the HPFS, there was an increased risk of approximately threefold for those who consumed more than five servings per week of red meat. The comparison group ate less than one serving per month. In a study that combined the NHS and the HPFS, red meat was a risk for colon but not rectal cancer [3]. In the CPS II Nutrition Cohort, Chao et al. observed an increased risk of red meat for distal and rectal CRC [10].

There are many hypotheses regarding the increased risk from red meat, which include an increased fat consumption, increased heme absorption, and stimulation of insulin secretion. Furthermore, there are data to indicate that increased cooking time may be associated with an increased risk [11, 12] due to the increased production of heterocyclic amines [13]. In addition, how these meats are processed in the patients may also be important. A recent study NHS demonstrated that those women with a faster acetylation of the carcinogens from red meat had an increased risk of CRC [14]. With regard to the risk from fat in red meat, many studies have disputed this risk [15–17]. Regardless of the mechanism, it appears that regular consumption of meat, especially if it is cooked well, increases the risk for CRC.

Fiber Intake

Fiber, especially in the form of fruits and vegetables, has been considered beneficial in helping to lower one's risk for CRC [18–20]. Proposed mechanisms regarding the benefit from fiber include increased folic acid consumption, increased binding of carcinogens, lower colonic pH, decreased colonic transit time, an increased production of short chain fatty acids as well as micronutrients found in vegetables including anti-oxidants [21, 22]. However, results of randomized controlled studies using fiber in the form of fruits and vegetables [23] or cereal did not lower the risk of colorectal adenomas [24]. These studies contradict previous data demonstrating a decreased risk of colorectal neoplasia associated with fiber consumption. The majority of case control studies have demonstrated a benefit with a meta-analysis of 16 case control trials showing an approximately 50% reduction in CRC from fiber consumption [25]. With regard to prospective studies, the results have been mixed. While the EPIC trial demonstrated a reduction of 40% in CRC incidence in patients who consumed the most fiber [26], the NHS showed no difference in colorectal neoplasia risk in those who consumed fiber [27]. One study combining the NHS and HPFS showed no effect of fruit and vegetable consumption on CRC [28]. A more recent analysis of the EPIC trial showed similar results, but there was a positive association between fruit and vegetable intake and current smokers [29]. However in the CPS-II, risk of fatal colon cancer decreased with more frequent consumption of vegetables and high-fiber grains [30]. A more recent analysis of the CPS-II showed that men and women with low intake of fruit and vegetable increased the risk for CRC, but a higher intake did not offer protection [31]. In summary, the benefit from fruits and vegetables with respect to lowering the risk for CRC is still in question.

Physical Exertion

It has been hypothesized that increased physical activity may decrease the risk for CRC by reducing body mass, decreasing colonic transit time, better glucose tolerance, and lower insulin levels [32, 33]. One case control study from Kaiser Permanente in Northern California, Utah, and Minnesota observed that those patients with a high Body Mass Index and low physical activity had the highest risk for CRC [34]. Results from the CPS-II, a prospective mortality study of over 700,000 patients, showed an association between physical activity and lower risk for death from CRC [30]. Data from the HPFS showed a significant reduction in risk for CRC in men who had the most physical activity vs. those who had the least [35]. This dose-related effect was evident in the results of a meta-analysis of 52 patients, which demonstrated an inverse relationship between level of physical activity and risk for CRC in men and women [36]. A more recent analysis of the HPFS showed that men who engaged in more than 27 MET hours per week of physical activity had a lower adjusted hazard ratio for CRC-related death than men

who had 3 MET hours or less (HR=0.47, 95% confidence interval, 0.24–0.92) [37]. An analysis from the NHS showed a similar protective effect of exercise and CRC reduction in women [38]. Data from the EPIC study reduced the risk for right-sided cancers in lean participants but had no effect on rectal cancer [39]. Chao et al. observed in the CPS-II Nutrition Cohort that recreational physical activity reduced the risk for colon cancer as well as rectal cancer in older men and women [40]. Thus, there appears good evidence to suggest that physical exercise can lower the risk for CRC as well as the mortality associated with the disease.

Gender

Although most studies have observed an increased risk for men with regard to advanced colorectal neoplasia as well as CRC, the overall lifetime risk for CRC for men and women is numerically similar [41, 42]. In addition, women have a 5-year lag with respect to incidence of CRC. For example, a woman at 55 has a similar risk to a man at 50 years of age [43]. With regard to the risk for CRC, Nguyen et al. in a meta-analysis observed a twofold increase risk for CRC and advanced adenomas in men as compared to women [44]. Furthermore, in the CONCeRN trial, Schoenfeld et al. observed a lower risk for advanced adenomas in women compared to men [45]. A study by Bressler et al. showed that women were more likely than men to have subsequent CRC after having a colonoscopy [46]. Thus it appears that changes with respect to how we screen women as compared to men may be reasonable. More data, however, is needed to explain the paradox of different advanced adenoma rates but similar CRC rates for the genders.

Alcohol

Ethanol-based beverages have been thought to increase the risk of rectal and colon cancer through a variety of mechanisms including abnormal DNA methylation and repair, induce cytochrome p450 enzymes to increase carcinogen production and alter bile acid composition [47, 48]. An analysis from the HPFS showed that there was a positive correlation between risk of CRC and alcohol in men [49]. This risk increased after 15 g per day which is about one drink per day. In a study that combined the NHS and HPFS, alcohol increased the risk of colon but not rectal cancer [3]. Data from the EPIC trial demonstrated that after controlling for smoking and other known risk factors, alcohol increased the risk of CRC [50]. However in a sub population of the EPIC study, Park et al. observed no risk association between alcohol and CRC [51]. They did find a decrease in risk associated with wine. A study, which combined eight studies for a total of a half a million patients, observed an increased risk for patients who had more than two alcohol beverages per day [52]. In that study, all forms of alcohol increased risk including wine. However, overall it appears that regular alcohol consumption may be associated with an increased risk for CRC and that moderation of alcohol beverage intake may be the best strategy.

Tobacco

Tobacco exposure, most commonly in the form of cigarette smoking, has only been recognized recently as an important risk for CRC in both men and women. The lag in association may be due to two factors [53]. The first is that it may take up to 35 years of exposure to tobacco to increase the risk of CRC [54, 55]. Second, the increase in smoking among men and women may coincide with the two world wars respectively. Since the earliest reports which included analyses of adenoma risk [56], there have been numerous case control [57, 58] and population studies [59–62] that demonstrate the increased risk associated with smoking. Smoking is now considered to be a risk, which is responsible for 20% of all CRC in the United States [63]. Several studies report a 30% increase risk for colon and rectal cancer for male and female smokers [54, 55, 57, 62, 64] as well as an increase of up to 50% in deaths from CRC [60, 65].

An important observation that underscores the importance for screening smokers earlier is the younger age at which smokers are diagnosed with CRC. Although there may be other factors that explain this observation, an age difference of at least 5 years between smokers and nonsmokers has been noted in four separate populations over 2 decades [42, 66, 67]. Smokers may also be more likely to present with an advanced stage of CRC than nonsmokers [68]. Furthermore, smokers have perceptions which may decrease their likelihood to be screened [69, 70]. Thus focusing on smokers as a high risk group may aid in increasing screening in a population that is at risk but may be reluctant to receive appropriate testing.

Obesity

Several studies have demonstrated that obesity increases the risk of CRC in men [35, 71–75] and women [71–73, 75], although this association appears to be stronger in males. In a study examining the HPFS, the men with the highest BMI had a twofold increase risk for CRC as compared to the thinnest men [35]. For women in NHS, the risk for obese women was 1.5 times that of their thinner counterparts [38]. In the CPS-II Nutrition Cohort, there was a correlation between increased waist circumference and CRC [76]. In the EPIC trial, waist to hip ratio and waist circumference, indicators of abdominal obesity, were positively correlated with the risk for CRC [77]. Obesity is a strong risk factor for type 2 diabetes mellitus; a probable independent risk factor for CRC [78]. This association also appears to be stronger for men [79]. Hyperglycemia [80–82], hyperinsulinemia [83], and elevated levels of free insulin-like growth factor (IGF-1) [84] have tumor-promoting properties [85–87]. Carcinogenesis may result from insulin resistance leading to increased cellular proliferation and reduced apoptosis [85, 88, 89].

The identification of BMI as a risk factor for CRC is important for many reasons, especially in light of the increasing prevalence of obesity in the United States [90]. While there are many reasons for health care providers to promote good health, the

possibility of reducing the risk of colorectal neoplasia with weight loss [91] and the implication of an increased risk of cancer represent one further reason to counsel patients regarding weight reduction. Current guidelines recommend colonoscopic screening every 10 years beginning at age 50 for healthy, low risk individuals. However obese women have been shown to be less likely to have colon cancer screening [92]. Obesity may represent a risk that justifies beginning screening at an earlier age in order to reduce the progression of colorectal polyps to cancer [2].

Diabetes Mellitus

The risk of CRC associated with type II diabetes mellitus is important given the anticipated prevalence of type II diabetes by 2030, which will be over one third of a billion [93, 94]. In the Breast Cancer Detection Demonstration Project (BCDDP), women with diabetes had an over 1.5-fold increase risk for CRC than non-diabetics [95]. The risk for CRC associated with diabetes has been shown in large case control studies [96, 97] as well as a prospective study of women [98]. There are many hypotheses regarding the pathogenesis of CRC in diabetics, which include endogenous insulin, exogenous insulin [99], insulin growth factors, and glucagon-like peptide-1 [100]. The hyperinsulinemia theory is based on the premise that elevated levels of insulin and free IGF-1 promote growth of the number of colon cells and lead to a survival benefit of transformed cells, ultimately resulting in CRC [101]. An analysis of the CPS-II Nutrition Cohort showed an association between CRC and diabetes in men but not women [102]. Data from the NHS showed a direct correlation between CRC and a diagnosis of diabetes mellitus [103]. Data from the EPIC study demonstrated that increasing glycated hemoglobin was a risk for women but not men [104]. However, in the Norfolk sample of the EPIC study, patients with Diabetes Mellitus had a threefold increased risk of CRC [105]. In this study, there was direct correlation between risk and glycated hemoglobin. In an analysis of the NHS, there was no association between glycated hemoglobin and CRC [106].

Race

CRC rates are the highest for African Americans for both incidence [107] as well as overall mortality [108] when compared to white patients of both genders. The authors of a recent study hypothesized that the reasons for these differences may be related to etiologic factors such as smoking or diabetes mellitus or the decreased use of screening and diagnostic examinations among African Americans [107]. Alexander et al. conducted an exhaustive review of studies from SEER and population-based cancer registries, Veterans Affairs (VA) databases, healthcare coverage databases, and university and other medical center data sources [109]. In this review,

they observed an increase in stage-specific risks of CRC mortality as well as a shorter survival for African Americans compared with Caucasians. The biggest disparities were observed in university and non-VA hospital-based medical center studies, while a smaller discrepancy was evident in VA-based studies. They concluded that an advanced stage is responsible for the increased mortality. Laiyemo et al. concluded that the difference in mortality may be related more in access to screening rather than biology. In their analysis of data from the PLCO trial, they observed that when compared with whites, blacks were less likely to have a diagnostic test (adjusted risk ratio=0.88, 95% confidence interval=0.83–0.93). There was no statistically significant difference between blacks and whites with regard to the prevalence of adenomas, advanced adenomas, or CRC [110]. Agrawal et al. presented a rationale for screening African Americans at the age of 45 years [111]. They cited the increased incidence and mortality, a younger age of CRC diagnosis, a more proximal colonic distribution of cancers and adenomas in, and a decreased utilization of diagnostic testing and screening for CRC in African Americans compared to whites.

Asymptomatic Screening Populations

Cross-sectional studies of asymptomatic screening populations can yield important data regarding the relative strengths of various CRC risk factors [112–114]. Large studies, which often involve symptomatic patients, cannot provide data on prevalence. Unlike studies relying on second hand data or self-report, cross-sectional studies performed in gastrointestinal suites offer the added advantage of accurate and complete endoscopic evaluation of all patients. This ensures that controls have no polyps. An example of this may be found in the risk of smoking and colorectal neoplasia. The risk of tobacco exposure in two screening population was twofold with respect to the risk for advanced neoplasia [112, 114, 115]. The magnitude of this increased risk for adenomas was confirmed in a meta-analysis published recently, which observed an Odds Ratio of 1.82 for people who had ever smoked and 2.14 for current smokers [116]. However, the risk associated with CRC was significantly less in a meta-analysis of 106 observational studies (OR = 1.25) [117]. The authors hypothesized that the difference may be due to the fact that many of the studies examining CRC are based on large population studies, which may have a limitation with respect to the evaluation of controls. Specifically, since the controls may not be endoscoped, there is no way of ensuring that they are neoplasia free with regard to adenocarcinoma or advanced neoplasia. This limitation may blunt the observed risk associated with smoking. In addition, in large population studies, there is often no distinction between those who were diagnosed and those who were screened for CRC. When the authors examined the trials in which controls were endoscoped, the risk for CRC was higher for smokers.

Another advantage of cross-sectional studies is that they can examine risk factors that may be associated with a recent trend. A good example of this is smoking, which

was identified as a risk for colorectal neoplasia in patients with adenomas prior to those with adenocarcinoma [53]. Another example may be obesity, which has been increasing in prevalence. Although a gender difference has been observed in advanced adenomas, there has been consensus in the positive association between obesity and CRC in men and women. With regard to advanced neoplasia, there has been an increased risk for women and no association in men [114, 118, 119].

In addition, since the cross-sectional studies in asymptomatic populations allow for a complete endoscopic evaluation of the enrolled patients. This allows for examination of anatomic location of polyps as well as the morphology. These aspects allowed for the identification, for example, of smoking as a risk for patients with isolated advanced neoplasia [120] as well as patients with flat neoplasia [121]. Finally, since the goal of screening for CRC with colonoscopy is prevention through identification and removal of advanced adenomas [2], identifying risk factors for these lesions may be as important as identifying risks for CRC.

Translation into Screening

Models

One of the concepts behind the strategy for individualizing CRC screening is to utilize the resources for patients that will benefit the most from these tests. Furthermore, guidelines for CRC screening recommend that patients without a family history of CRC be screened at the age of 50 with a colonoscopy. There has been a concern regarding the possibility of insufficient resources to screen all eligible patients with colonoscopy [122]. One author has suggested that perhaps there may be alternative strategies such as a sigmoidoscopy as a first step and a colonoscopy at a later age [123]. Another author has suggested that perhaps CRC screening commence for different risk groups at different ages [43]. He identified gender as a potential variable since women may lag men by 5 years with respect to their risk for colorectal neoplasia. Thus the development of models may be useful in triaging patients.

Most models have used CRC risk factors in developing the risk assessments. Betes et al. used age, gender, and BMI in their model for advanced neoplasia [124]. Kim et al. validated a model based on data from the NHS and HPFS [125, 126]. In that model, they used BMI, vegetable intake, red meat consumption, physical activity, and alcohol intake in addition to other known risk factors such as multivitamin and aspirin use. Driver et al. developed a model predicting the risk for CRC in men based on the 21,581 United States male physicians in the Physician's Health Study [127]. In that model, points were assigned based on strength of risk for each variable. The model included 2 points for every decade over 50, 1 point for history of smoking, 1 point for BMI 25–29.9, 2 points for BMI ≥ 30 , and 1 point for drinking alcohol once or more per week.

Freedman et al. developed a model which examined the risk for CRC by anatomical subsite, proximal vs. distal, for white men and women [128]. For men, personal history of colorectal neoplasia, family history of CRC, not using aspirin, smoking, consuming <5 servings of vegetables per day, and higher BMI were associated with an increased risk for proximal CRC. For distal CRC in men, the same variables except smoking and lower vegetables were associated with an increased risk. For women proximally having personal history of colorectal neoplasia, family history of CRC, not using aspirin, no regular physical activity, consuming <5 servings of vegetables per day, and negative estrogen status were associated with an increased risk. For distal CRC in women, a personal history of colorectal neoplasia, family history of CRC, not using aspirin, higher BMI, older age, and estrogen negative status increase the risk.

On the National Cancer Institute web site (<http://cisnet.cancer.gov/projections/colorectal/>), there is an interactive model with risk factors based on Health People 2010. Included in the model are smoking status (yes/no), obesity (based on body mass index (BMI)), physical activity (met-hours per week), fruit and vegetable intake (servings per day), multivitamin use (yes/no), red meat intake (servings per day as a main dish), and aspirin and HRT use. The model uses data from the Nurses Health Study (NHS) and the HPFS to estimate the effect of risk factors on CRC [129].

Screening Guidelines

The American College of Gastroenterology recently published guidelines on which they recommend that African Americans begin screening at the age of 45 years [2]. In addition, they identified people who smoke and those who are obese as populations who require special attention from practitioners. They tempered their recommendation that these patients be screened earlier by adding that these patients may have comorbidities that may reduce the benefit from screening. These are the first guidelines regarding CRC screening to consider factors other than age and family history of CRC when forming a screening paradigm.

New Problems in Screening

One of the biggest problems facing endoscopists is the proximal colon and the lack of effectiveness of colonoscopy in reducing the risk for advanced colorectal neoplasia [130, 131]. There have been many hypotheses regarding an explanation for this observation. One plausible answer may lie in the serrated pathway that is associated with BRAF and methylation abnormalities, which may account for a large percentage of interval cancers [132, 133], or those lesions that are diagnosed between scheduled colonoscopy surveillance. Serrated polyps are often proximal and associated with synchronous advanced colorectal lesions [134]. Since smokers often have cancers that

are located in the rectum and proximal colon where serrated lesions are often found, one expert has suggested that smoking may be associated with serrated histology. Recently, a trial examining aberrant crypt foci observed an association between serrated histology and smoking [135]. In addition, there was a study demonstrating a higher rate of flat adenomas in smokers [121]. In addition, Anderson et al. identified smoking as a risk for sessile serrated adenomas [136]. Thus, smokers may be at higher risk for lesions that may be difficult to detect and may require special techniques for screening. This is a good example of incorporating risk factors into a screening algorithm.

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Chapter 3

Hereditary Adenomatous Colorectal Cancer Syndromes

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Keywords Hereditary non polyposis colorectal cancer • Familial adenomatous polyposis • Genetics

Background

Colorectal cancer (CRC) is one of the most common cancer diagnoses that a digestive disease specialist or primary care physician will encounter in a patient in their practice [1]. While fewer than 10% of the cases occur within the setting of a hereditary colorectal cancer syndrome (HCCS), the burden of the disease to the patient, family, and provider is greater than when it occurs sporadically [2]. The hereditary nature of autosomal dominant CRC was first reported nearly 150 years ago in a patient with familial adenomatous polyposis (FAP) [3, 4]. It took nearly 100 years to discover that the genetic cause of FAP was due to dysfunction of the APC gene on chromosome 5 [5]. In a similar but historically more recent discovery, the clinical pedigree of hereditary nonpolyposis colorectal cancer (HNPCC) was recognized in a family with numerous cases of colorectal, uterine, and gastric cancers, well before the genetic basis of Lynch Syndrome (LS) due to defective DNA mismatch repair (MMR) gene function was discovered in the early 1990s [6].

Within the last 10 years, the genetic cause of the first known autosomal recessive CRC syndrome was discovered [7]. The syndrome, characterized by early age-of-onset CRC occurring in the setting of oligopolyposis, is due to bi-allelic mutations of the Mut Y homolog (MYH) genes which result in defective base excision repair function.

The last 2 decades have brought important advances in the identification of the genes and molecular pathways that underlie the HCCS. The use of genetic testing permits a more accurate diagnosis of the patient, based upon genetic, rather than

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clinical, criteria and allows more appropriate risk stratification and tailored management based upon test results. It is crucial for physicians to recognize the phenotype of an individual who is affected with or at risk of an HCCS because of the substantial risk of intestinal and extraintestinal, benign and malignant tumors, the need for a heightened intensity of surveillance, and potential benefit of prophylactic risk reducing surgery.

Recognizing the Patient with a HCCS

The phenotype of the HCCS may be easily recognizable when dealing with an individual within a family affected by an obvious autosomal dominant HCCS or when an individual is affected with early onset and excessive polyp formation such as in FAP, or when they harbor numerous polyps of unusual histology such as in Peutz-Jeghers syndrome (PJS) or juvenile polyposis syndrome (JPS). It may be more difficult to diagnosis a HCCS when an individual presents with a more subtle phenotype such as a later age of onset of CRC or oligopolyposis without a dominant family history of disease.

Some general clues to the presence of an HCCS include:

1. Early age of onset of colorectal neoplasia (<50 years).
2. Excessive number of colorectal polyps (in the polyposis syndromes).
3. Synchronous or metachronous primary cancers.
4. Extracolonic benign or malignant tumors.
5. Multiple relatives, successive generations affected.

Cancer control based on family history, i.e., “targeted cancer surveillance,” is not a novel concept and was proposed 25 years ago [8]. The cornerstone is based upon an accurate and comprehensive family history which should include a three-generational pedigree indicating ages and causes of death of relatives, any diagnosis of cancer including age of onset, race, and ethnic background of family members, and physical findings. The family history should be confirmed with medical records whenever possible and updated periodically to ensure proper surveillance recommendations. A web-based family history tool developed by the US Surgeon General is available online for patients to collect a complete family history [9]. Guttmacher et al. [10] reported that a clinician’s lack of knowledge of a patient’s family history of CRC can result in a failure to offer potentially lifesaving colonoscopy. Failure in obtaining sufficient family history and making appropriate referrals is a known area of medical-legal liability [11, 12].

Until recently, all of the known HCCS were thought to be acquired in an autosomal dominant fashion (Table 3.1). With the discovery in the last decade that nearly 10% of the cases of FAP in APC negative individuals were due to bi-allelic mutations in the MYH gene, the first autosomal recessive HCCS was identified [13]. Germline mutation testing for the HCCS is commercially available. National organizations are focusing educational efforts on increasing the preparedness of healthcare providers

Table 3.1 Hereditary colorectal cancer syndromes

Syndrome	Inheritance	Incidence	Polyp type	Gene mutation
Lynch syndrome	AD	1/660–1/2,000	Adenoma	MLH1, MSH2, MSH6, PMS2
FAP/AFAP	AD	1/10,000	Adenoma	APC
MAP	AR	1/5,000	Adenoma	MYH
Peutz-Jeghers syndrome	AD	1/30,000–1/100,000	Hamartoma	STK11/LKB 1
Juvenile polyposis syndrome	AD	1/100,000	Hamartoma	SMAD4 or BMPR1A
PTEN Hamartoma tumor syndrome	AD	1/200,000	Hamartoma	PTEN

AD autosomal dominant; *AR* autosomal recessive

to administer genetic tests and to recommend appropriate follow-up care [14]. It is recommended that genetic testing be offered when an individual has a personal or family history suggestive of genetic cancer susceptibility; the genetic test can be adequately interpreted; and the test results have accepted clinical utility [15].

Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

The term HNPCC was coined in 1991 by a group of experts who met in Amsterdam and developed minimum criteria also known as the Amsterdam Criteria (AC-I) for collaborative studies of families with hereditary colon cancer [16]. (Table 3.2). The criteria were criticized for being too specific and not including extracolonic cancers as a component of the criteria. Therefore, the AC-I were broadened to include the most common extracolonic cancers in the syndrome including endometrial, small bowel, ureteral, and renal pelvis and became known as the Amsterdam Criteria II (AC-II) [17]. One study of known MLH1 and MSH2 mutation carriers showed the sensitivity of AC-I and AC-II to be 39% and 22%, respectively, with the authors citing the criteria neither sensitive nor specific enough to identify individuals or families who should undergo genetic testing for HNPCC [18].

Genetics

The genetic basis of HNPCC is due to genetic alterations of the DNA MMR genes, MLH1, MSH2, MSH6, and PMS2. When DNA replicates, nucleotide bases on the two strands of DNA frequently become mis-paired. The mismatched nucleotide bases are normally repaired by a mechanism involving the protein products of the DNA MMR genes. Mutations in any of the DNA MMR genes result in defective enzymatic function impairing the ability of the MMR system to identify, excise, and repair nucleotide base mismatches [19]. The human genome contains widespread

Table 3.2 Criteria for hereditary nonpolyposis colorectal cancer and Lynch Syndrome**A** Amsterdam criteria-I [16]

At least three relatives with histologically verified CRC:

1. One is a FDR of the other two
2. At least two successive generations affected
3. At least one of the relatives with CRC diagnosed at <50 years of age
4. FAP has been excluded

B Amsterdam criteria-II [17]

At least three relatives with an HNPCC-associated cancer [colorectal cancer, endometrial, stomach, ovary, ureter/renal pelvis, brain, small bowel, hepatobiliary tract, and skin (sebaceous tumors)]:

1. One is a FDR of the other two
2. At least two successive generations affected
3. At least one of the syndrome-associated cancers should be diagnosed at <50 years of age
4. FAP should be excluded in any colorectal cancer cases
5. Tumors should be verified whenever possible

C Revised Bethesda Guidelines [32] for testing of CRC for microsatellite instability (MSI)

1. CRC diagnosed in a patient < age 50
2. Presence of synchronous or metachronous CRC or other HNPCC-related tumor at any age
3. CRC with MSI-related histology diagnosed in a patient < age 60
4. CRC diagnosed in ≥ 1 FDR with an HNPCC-related tumor, with one cancer diagnosed under age 50
5. CRC diagnosed in ≥ 2 first- or second-degree relatives with an HNPCC-related tumor diagnosed at any age

segments of repeated nucleotide bases, also known as microsatellites, often in key areas of genes. The microsatellites can be comprised of mononucleotides, such as a stretch of 26 adenines, or for example, dinucleotides, with the most common being cytosine and adenine, which occur in tens of thousands of locations in the germ line [20]. When microsatellite errors are not repaired, the result is referred to as microsatellite instability (MSI). MSI results in the accumulation of mutations in key genes regulating cell growth and death (i.e., BAX, TGFBR2, and their downstream targets). Somatic, MSI results in changes in nucleotide base pair length which can be detected within tumor tissue by an electropherogram [21] and by specific pathologic features within the tumor [22]. Importantly, approximately 40% of families who meet AC-I criteria do not have evidence of MSI or a mutation in one of the MMR genes. Most experts recommend these families be considered distinct from families with MSI or MMR gene mutations and referred to as “familial colorectal cancer type X” [23]. The families with evidence of MSI or an MMR gene mutation should be referred to as LS. Large studies have shown that non-LS families are only at an increased cumulative lifetime risk of CRC, not extracolonic cancers, usually with a later age of onset and lower penetrance of disease than LS patients [23, 24]. It is also reported that CRC in non-LS patients is primarily left-sided and lacks the MSI-H pathology of tumors seen in LS [25–27].

Clinical Presentation

CRC is the most common cancer in HNPCC. The median age of onset is in the mid-40s with a cumulative lifetime risk in MMR mutation carriers as high as 70% by the age of 70. The risk has been shown to vary according to gender (higher in males) and by underlying mutation (lower in MSH6) [28–30]. Recent data have shown the cumulative risk of metachronous CRC is up to 24% 20 years after the first CRC [31]. The tumors in MMR gene mutation carriers develop through a pathway of MSI and have specific pathologic features known as MSI histology [32]. These features include tumor-infiltrating lymphocytes, a Crohn's-like lymphocytic reaction, poor differentiation, mucin or signet ring cell differentiation, and a medullary growth pattern [33] (Fig. 3.1). These pathologic features are strong independent predictors of MSI. In one study, a combination of pathologic variables and specific clinical factors including proximal location in colon and age < 50 were shown to predict 93% of individuals with MSI [22].

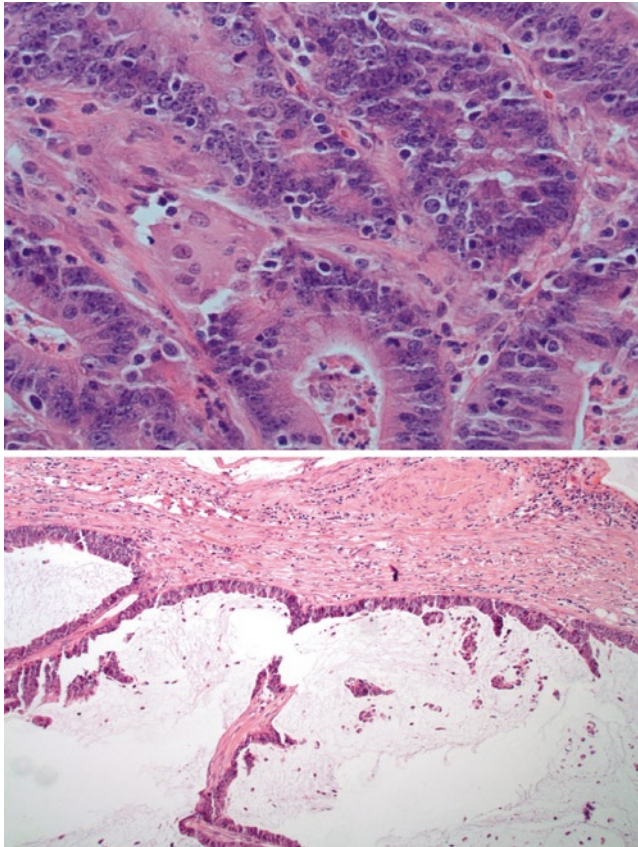


Fig. 3.1 Histology features of MSI cancers. Tumor-infiltrating lymphocytes. Mucinous histology

The extracolonic cancer spectrum in MMR carriers is broad. Females have a significantly higher cumulative lifetime risk of extracolonic cancer with the highest being due to endometrial cancer with risks of 29.2, 24.4, and 48.8% for mutation carriers of MLH1, MSH2, and MSH6, respectively [34]. The other affected organs include ovaries, stomach, small bowel, pancreas, hepatobiliary system, brain, skin (sebaceous adenomas and adenocarcinomas and keratoacanthomas) [known as Muir-Torre syndrome], and urinary tract [34, 35].

Diagnosis

It is recommended that the revised Bethesda guidelines be used to identify individuals whose tumors should be tested for molecular evidence of MSI [32] (Table 3.2). Unfortunately, even the criteria in the revised Bethesda guidelines are not optimal for the identification of MMR gene carriers. One study of 500 unselected patients with colon cancer found the prevalence of LS to be 3.6% [36]. In the study, the authors performed MSI testing and immunohistochemistry (IHC) for evidence of expression of the four MMR proteins on each CRC specimen. Mutation testing was done on the individual if either test was positive. Of those found to have LS, only 44% of patients were younger than age 50 years at the time of diagnosis, and slightly more than half (56%) had a first-degree relative with CRC or endometrial cancer. Thirty-nine percent fulfilled AC-II and 72% met the revised Bethesda guidelines, but almost one-third (27.8%) did not meet either. This study showed that wide-scale testing of tumors for evidence of LS is feasible and that both MSI and IHC perform well with a sensitivity of 100% and 94.4% and a specificity of 90.5% and 88.4%, respectively.

The molecular evaluation for LS in a CRC (or other target tissue) in an individual who meets the revised Bethesda criteria can include either MSI testing or IHC. MSI testing requires microdissection of the tumor with extraction of DNA. An additional source of patient DNA such as adjacent normal mucosa or blood lymphocytes is required. MSI analysis using a standardized panel of five DNA markers is performed comparing normal and tumor tissue. If ≥ 2 of the five microsatellite markers show instability, the target lesion is considered microsatellite unstable (MSI-H). Once the tumor is found to be MSI-H, IHC is performed to assess for expression (normal = positive nuclear staining) of the protein product of the MMR genes, MSH2, MSH6, MLH1, and PMS2. Absence of expression of the specific protein within tumor cells when compared to normal cells within the specimen suggests dysfunction of the specific gene and guides germline mutation testing. Antibodies are commercially available for MSH2, MSH6, MLH1, and PMS2 proteins. The sensitivity of IHC has been shown to be similar to or slightly less than that of MSI testing [37]. The advantage of IHC is that it is less expensive, more widely available, and potentially requires less technical expertise. Genetic counseling and testing should be recommended to individuals with MSI-H tumors or abnormal IHC expression.

Table 3.3 Surveillance recommendations in Lynch syndrome

	Interval	Age to begin	Evidence
Colonoscopy	1–2 years	20–25 years	Strong; decreased incidence and mortality
Endometrial Bx	1 year	30–35 years	Insufficient evidence
Transvaginal U/S	1 year	30–35 years	Insufficient evidence
UA/cytology	1 year	25–35 years	Insufficient evidence
Hysterectomy/BSO	After childbearing		Fair evidence

Colon Cancer Surveillance

A variety of organizations have published recommendations for the surveillance of individuals with HNPCC [38–40] (Table 3.3). Colonoscopy is recommended every 1–2 years beginning at the age of 20–25 years (or 10 years younger than the age of the youngest relative affected with CRC) until the age of 40 years, then annually thereafter. Data from observational studies have demonstrated a significant reduction in the incidence and mortality in individuals with HNPCC undergoing colonoscopic surveillance [41–44]. There is no consensus on the optimal operative approach to LS patients with CRC. One recent study showed an increase in the need for repeat abdominal surgery and decreased time to CRC recurrence in LS patients undergoing a more limited rather than extended colon resection [45].

Extracolonic Screening and Management

Gynecologic surveillance is recommended for the prevention of endometrial and ovarian cancer in females at risk of or who are carriers of germline MMR mutations. Annual gynecologic examination, transvaginal ultrasound and endometrial aspiration, beginning at age 30–35 years has been shown to detect premalignant lesions and early symptomatic cancers, but its effect on mortality is unproven. A recent study showed over 95% compliance with gynecological surveillance [46]. While evidence is insufficient to show a benefit from surveillance, there is a significant reduction in endometrial and ovarian cancer in patients with LS who undergo prophylactic TAH-BSO [47, 48]. No recommendations exist to systematic screening for the other extracolonic tumors associated with LS.

Familial Adenomatous Polyposis

FAP is an autosomal dominant, adenomatous polyposis syndrome which is caused by a genetic alteration in the APC gene located on chromosome 5. APC mutations occur in 1 in 10,000 births [49]. There is 100% penetrance and nearly 100% risk of

CRC in classic cases if colectomy is not performed. Approximately 70% of FAP have a family history of the disease and 30% of the cases are de novo [50, 51].

Genetics

Over 825 disease-causing APC mutations have been described and a genotype–phenotype correlation exists for some manifestations of FAP [52]. When a mutation occurs in exon 9 or in the 3' or 5' end of the gene, oligopolyposis usually results (<100 polyps) in a form of FAP called attenuated FAP (AFAP) [53]. Classic FAP with early onset disease and profuse polyposis (>1,000 polyps) is often seen in association with genetic alterations in exon 15 (codons 1,250–1,464). Some of the extracolonic manifestations of FAP such as desmoids tumors, thyroid cancer, and congenital hypertrophy of the retinal pigmented epithelium (CHRPE) have been associated with other mutational “hot spots” in the APC gene (Table 3.4). Patients with FAP who have associated desmoids tumors, osteomas, epidermoid/sebaceous cysts, lipomas or fibromas, congenital hypertrophy of the retinal pigment epithelium, or dental anomalies are referred to as having the Gardner syndrome variant of FAP. Genetic alterations (mutations/deletions/rearrangements) are found in the APC gene in nearly 90% of patients with FAP and in 30% of patients with AFAP [54].

Clinical Presentation

Classic or profuse FAP is characterized by the development of hundreds to thousands of adenomas diffusely in the colorectum usually with an onset by 10–12 years of age (Fig. 3.2). CRC often occurs by the mean age of 39 years if patients are not identified and undergo prophylactic colectomy. Patients with AFAP have a later age of onset of disease (4th to 5th decade), lower lifetime risk of CRC (60%), and the polyps are often right-sided [55]. Patients with a family history of disease usually present for colorectal surveillance while those who do not know they have

Table 3.4 Prevalence of extraintestinal features of FAP

Type	Lifetime risk (%)
Fundic gland polyposis	90
Duodenal adenomas	>80
Desmoid tumors	15
Thyroid carcinoma	2–17
Adrenal adenoma	7–13
Osteomas	50–90
Supernumerary teeth	11–27
Congenital hypertrophy retinal pigmented epithelium	70–80
Lipomas, fibromas, sebaceous cysts	50
Hepatoblastoma	<2

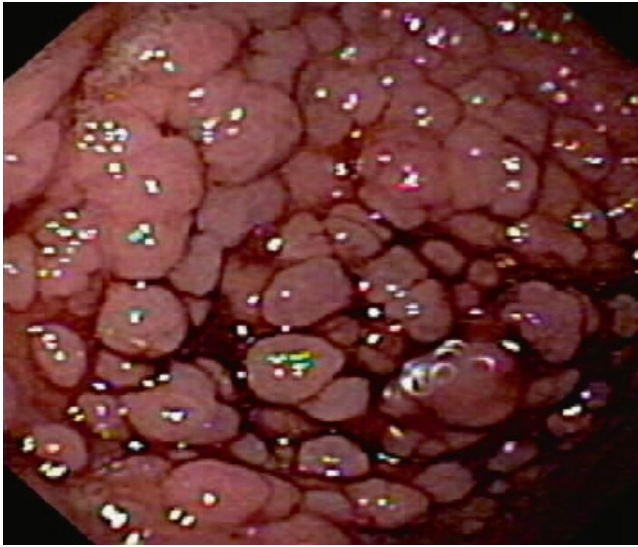


Fig. 3.2 Multiple polyps in the colon during colonoscopy in patient with FAP

or are at risk of disease may present with gastrointestinal bleeding, abdominal pain, or change in bowel habits due to the colorectal polyp burden.

Hepatoblastoma is a rare hepatic malignancy that is reported in <1% of infants and toddlers with FAP. It is highly curable if detected early [56].

Upper gastrointestinal polyps are the most frequent extracolonic manifestation of FAP. Nearly 90% of patients with FAP will develop duodenal adenomas by a mean age of 44, with cumulative lifetime risk of nearly 100% [57]. Duodenal and periampullary cancer is the leading cause of cancer in FAP patients, once colectomy is performed. The incidence ranges from 2 to 36% and is dependent on the duodenal polyposis stage. Most duodenal adenomas occur in the second portion of the duodenum around or on the papilla. The polyps may appear as subtle, individual white plaques or coalesce to carpet the mucosal surface. Duodenal polyposis is staged according to the Spigelman criteria based on the number, size, histology, and degree of dysplasia of the adenomas (Table 3.5) [58]. The staging system is important because it helps guide management and surveillance recommendations and has prognostic value [59].

Fundic gland polyposis occurs in nearly 90% of patients with FAP [57]. While fundic gland polyps have been thought to be nonneoplastic, studies have demonstrated that up to 43% of patients will harbor foveolar epithelial dysplasia in their fundic gland polyps which is sometimes misinterpreted as adenomatous change [57, 60]. Gastric cancer occurs rarely in FAP, but has been reported to arise from fundic gland polyposis. Gastric adenomas occur in less than 15% of patients, are usually limited to the antrum, and most often are solitary. The incidence of jejunal and ileal adenomas and cancer in FAP is < 10% and <1%, respectively [61].

Table 3.5 Staging of duodenal polyposis [58]

	1 Point	2 Points	3 Points
Number of polyps	1–4	5–20	>20
Polyp size (mm)	1–4	5–10	>10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Stage I: 1–4 points, Stage II: 5–6 points, Stage III: 7–8 points, Stage IV: 9–12 points

Referenece: [58]

Desmoid tumors are fibrous tumors which are reported to occur in up to 15% of patients with FAP [62, 63]. They are usually intra-abdominal and occur in the root of the small bowel mesentery. When identified preoperatively or intraoperatively, they can require alteration of the surgical approach. Their local complications result in obstruction of the small bowel or ureters, vascular thrombosis, or compression of peripheral nerves.

There is an increased lifetime risk for endocrine tumors in individuals with FAP. This includes adrenal gland adenomas and papillary carcinoma of the thyroid, which has been reported in up to 12% in some series with nearly 80% of those affected being female [64, 65].

Diagnosis

The diagnosis of FAP is based on the identification of numerous colorectal adenomatous polyps in the appropriate clinical setting. The diagnosis of AFAP may be more difficult because of the subtle phenotype. Often times, the EGD findings will help confirm the diagnosis if gastric or duodenal polyposis is observed. It is recommended that individuals who have ≥ 10 adenomas detected on a single colonoscopy or who are first-degree relatives with patients with FAP (or MYH) undergo a genetic evaluation and testing for mutations in the APC gene (or MYH if APC testing is negative). It has been shown that up to 29% of FAP patients who are APC negative will have bi-allelic mutations in the MYH gene [13].

Colon Cancer Screening and Surveillance

All patients with FAP should be offered genetic counseling and mutation analysis. If a mutation is identified, the FDRs of the patient should also be offered genetic testing. Many practice guidelines suggest individuals who have an APC mutation and families with the clinical diagnosis of FAP, but who have not been tested for or whose families are without a detectable APC mutation should undergo flexible sigmoidoscopy every 1–2 years starting at approximately 10–12 years of age [39, 66–68]. If colorectal adenomas are identified, surgical options should be discussed and annual colonoscopic surveillance should commence. In a family with

a known APC mutation, individuals who test negative for the family mutation may undergo CRC screening as per general population guidelines. For individuals with AFAP, due to the later age of disease onset, colonoscopy every 1–2 years should commence at approximately age of 18 years. If polyps are identified on the initial exam, annual colonoscopy should be performed. The aim of colonoscopic surveillance in FAP is to resect large or suspicious-appearing polyps, not clearance of the total polyp burden, and colectomy should be performed based upon polyp burden or other psycho-social factors. Surgical options include total colectomy and ileo-rectal anastomosis or total proctocolectomy and ileal pouch anal anastomosis. The type of operation is dependent on colonic and extracolonic phenotype, genotype, and other factors. Once colectomy is performed, annual sigmoidoscopy is recommended for surveillance of recurrent rectal or ileal pouch polyposis and cancer. The frequency of exams is based upon the polyp burden. Chemoprevention with sulindac 150 mg or celecoxib 400 mg twice per day has been shown to regress colorectal adenomas in FAP and may be useful as an adjunct to endoscopy in the management of the colorectal polyp burden in individuals with FAP [69, 70].

Extracolonic Screening and Surveillance

Screening for duodenal carcinoma is recommended beginning at the age of 20 years with forward and side-viewing upper endoscopy including visualization and biopsy of the papilla and periampullary region [66, 68]. Patients with stage I–III duodenal polyposis have a 2.5% risk of duodenal cancer, while those with stage IV are reported to have up to a 36% risk [71]. The frequency of endoscopic surveillance should increase as the stage of duodenal polyposis progresses (Table 3.6). Patients with stage IV duodenal polyposis are recommended to have a consultation with an experienced surgeon for consideration of a prophylactic, pylorus-preserving, pancreas sparing duodenectomy (PPPSD) to minimize the risk of cancer [68]. Neither endoscopic nor local surgical resection has been shown to be as effective for polyp eradication, prevention of recurrence, or avoidance of duodenal carcinoma as

Table 3.6 UGI surveillance for FAP/AFAP/MAP [57]

Stage	Interval	Method	Intervention
0	5 years	EGD	None
I–II	3 years	EGD	None
III	1 year	EGD	Celecoxib 400 twice daily/ eradication of large polyps
	3 years	Small bowel capsule endoscopy	
IV	3–6 months	EGD	Pylorus preserving pancreas sparing duodenectomy ^a
	3 years	Small bowel capsule endoscopy	

^aPreferred strategy is pylorus-preserving prophylactic duodenectomy, but recommend aggressive surveillance if surgical resection is not performed

PPPSD [72]. Regression of duodenal polyposis by blinded endoscopic video review was demonstrated in a 6-month placebo-controlled trial with celecoxib, 400 mg orally twice daily [73]. Some experts recommend removal of only large duodenal adenomas, especially when adjunctive celecoxib therapy can be used to control disease recurrence [57, 68].

MYH-Associated Polyposis (MAP)

Bi-allelic mutations in the MYH gene may result in an autosomal recessive, adenomatous polyposis syndrome phenotypically indistinguishable from AFAP or in early onset microsatellite stable CRC [55, 74].

Genetics

MYH is a base excision repair (BER) gene on chromosome 1. DNA damage is caused by reactive oxygen species (ROS) produced from exposure to ionizing radiation or chemicals, or through cellular metabolism. MYH, OGG1, and MTH1 are the BER genes which prevent ROS-induced cellular damage [75, 76]. Tumors in patients with defective MYH BER gene function are typified by acquired mutations in the APC gene caused by G: C to T: A transversions [77, 78]. More than 80 germline MYH mutations have been reported [79]. In Caucasian populations, the most commonly reported are Y165C and G382D which account for 80% of MYH mutations.

Clinical Presentation

MAP typically presents with the development of multiple adenomatous polyps at a mean age of diagnosis of 47 years. Eleven to forty-two percent of affected individuals are reported to have an oligopolyposis (10–100 adenomas) and 7.5–29% of patients present with classic polyposis (>100 adenomas) [13, 74, 80–83]. Synchronous CRC is seen in greater than 60% of patients with bi-allelic MYH mutations, and in one study, 60% of individuals with CRC due to bi-allelic MYH mutations had fewer than three polyps [84].

Diagnosis: Genetic testing for bi-allelic MYH mutations should be performed in patients who test negative for an APC mutation, but have clinical features of FAP, a personal history of >10 synchronous or >15 cumulative colorectal adenomas, or a recessive family history of polyposis. Emerging data show that bi-allelic MYH mutations result in early onset microsatellite stable CRC (diagnosed at <60 years) with or without associated adenomas and therefore warrant MYH testing.

Screening and Surveillance

The management of patients with MAP is similar to that recommended for individuals with AFAP/FAP. Genetic counseling and testing, as well as colonic and extracolonic surveillance, is warranted. There is no data studying the use of chemoprevention in MAP. This author (CAB) has used sulindac in one patient with excellent results in regression of colorectal adenomas. Surgical intervention should be considered early due to the high risk of CRC even in individuals with very few adenomas.

Conclusions

The adenomatous HCCS comprises a group of genetically disparate but occasionally phenotypically indistinguishable disorders. It is important for clinicians to recognize the syndromes due to the burden of disease to the affected individual as well as the potential risk to the at-risk family members. When the genetic basis of the syndrome can be determined, it has predictive as well as prognostic value. Risk reducing management should be offered to affected and at-risk relatives.

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Chapter 4

Screening and Surveillance Guidelines

Robert J. Chehade and Douglas J. Robertson

Keywords High risk • Advanced adenomas • Surveillance

Background

Over the past decade, efforts to guide practice have increasingly relied upon best medical evidence. To facilitate such “evidenced based practice” organizations have increasingly developed guidelines to assist clinicians in their decision making. In fact, guideline clearinghouses now exist to provide clinicians with direct access to these reviews. The Agency for Health Care Research and Quality (AHRQ) maintains a website (www.guideline.gov) that serves as a comprehensive database of guidelines across the medical spectrum that includes structured summaries and search capability.

While the development and publication of guidelines likely improves overall clinical practice, there are a number of potential problems with such widespread promulgation of these documents. First, the guidelines themselves vary in their quality particularly as it relates to the requirement that they are evidence based. Second, the sheer number of guidelines from diverse organizations leads to a situation where, inevitably, inconsistencies arise leaving the clinician to choose between competing recommendations.

In this chapter, we will review the current highest profile guidelines as they pertain to colorectal cancer screening and surveillance. While differences between guidelines will be reviewed, efforts will be made to synthesize current recommendations and highlight common themes to assist the clinician faced with decision making in this area. With regards to colorectal cancer screening we will also review best evidence as it relates to “tailored” approaches that may offer the best hope to optimize screening in the future.

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Colorectal Cancer Screening

Best Evidence for CRC Screening

Cancer prevention is typically categorized as primary or secondary. Primary prevention involves the identification and modification of important genetic, biologic, or environmental factors to prevent disease. Chemoprevention is considered a primary prevention strategy and there is evidence that some agents (e.g., calcium) may favorably alter colorectal carcinogenesis [1]. This topic is the subject of Chap. 13 and will not be reviewed further here.

Secondary prevention (screening) refers to efforts to detect disease before it is symptomatic. Screening for a given disease is feasible when the condition is common, lethal, and there is an identifiable and actionable preclinical phase. Colorectal cancer fulfills these criteria. Colorectal cancer is the second leading cause of cancer death in the United States [2]. Further, as outlined in Chap. 1, most cancers are thought to transition through an identifiable precursor – the colorectal adenoma. Therefore, colorectal cancer screening affords the opportunity to detect early (more treatable) colorectal cancers. Screening can also lead to the identification and removal of the adenoma and thus reduce the subsequent burden of CRC in the population.

Indirect evidence regarding the effectiveness of colorectal cancer screening primarily derives from encouraging trends in colorectal cancer incidence and mortality. Analysis based on pooled data from Surveillance Epidemiology and End Results (SEER) program and the CDC's National Program of Cancer Registries found that over the past 20 years, CRC incidence declined 22% while CRC mortality declined 26%. When further applying modeling techniques, it was estimated that about one third of the reduction was accounted for by modification in risk factors and one half of the reduction by screening (with the remainder of the reduction explained by improvement in treatment of CRC). Of course these models are based upon assumptions that are not all verifiable, but the trends observed are encouraging [3].

The best direct evidence for the effectiveness of colorectal cancer screening derives from large randomized controlled trials. Until recently, the only randomized controlled trials of CRC screening employed fecal occult blood testing (FOBT) [4]. There were three large FOBT trials which all found a benefit to annual or biennial screening [5–7]. In the US based study, individuals who were screened annually experienced a 33% decrease in mortality from colorectal cancer as compared to unscreened controls [7]. These results were supported by trials in England [5] and Denmark [6] using biennial FOBT which observed a 15–18% reduction in mortality relative to controls.

There is now also evidence that endoscopic screening can reduce colorectal mortality. A recent UK based randomized control trial comparing once-only flexible sigmoidoscopy found a 23% decrease in CRC incidence and a 31% decrease in mortality during a median follow-up of 11.2 years [8]. These reductions in incidence and mortality were determined relative to controls who indicated a willingness to

participate in a flexible sigmoidoscopy screening program, but were not invited to participate. This study along with another encouraging interim result from a flexible sigmoidoscopy trial conducted in Norway [9] are the first pieces of definitive evidence that endoscopic screening can be effective in reducing the burden of CRC. While it is likely that up front screening colonoscopy affords protection from CRC mortality as well, at this time, trials are just getting underway (ClinicalTrials.gov NCT00906997, NCT00883792, and NCT01239082).

History of Screening Guidelines

Given that colorectal cancer as a disease lends itself to screening and that there is randomized controlled trial evidence that such screening is effective, it is not surprising that a number of organizations have developed guidelines recommending the practice. The United States Preventive Services Task Force [10], American Cancer Society [11], and the Gastroenterology subspecialty societies both jointly [11] and independently [12, 13] all provide recommendations in this area. Generally recommendations for colorectal cancer screening have endorsed panels of testing options along with time frames for repeating the exam if negative. These documents, in some cases, have evolved over decades reflecting changing opinions about the merits of the available testing modalities. For example, in 1980 the American Cancer Society recommended that persons over age 40 should undergo a digital rectal exam, proctoscopic exam, and occult blood testing at their regular check up [14]. Twenty years later, these guidelines had changed both in terms of the age at which to start screening (50 and older) as well as the modalities recommended for screening (e.g., adding barium enema and colonoscopy) [15]. The most recent guidelines for average risk screening broaden the recommendations even further including tests such as computed tomographic colonoscopy (CTC) and fecal DNA to the panel of options [11].

In the United States, colonoscopy has become the dominant mode of screening for colorectal cancer although as outlined above direct evidence supporting its use is lacking. Specifically, the best evidence for colonoscopy derives primarily from observational data [16–18] relative to randomized trial evidence that supports FOBT [4] and sigmoidoscopy [8]. In 1996, the United States Preventive Services Task Force which relies most heavily on high quality evidence did not endorse colonoscopy as a stand alone screening test [19]. However, the following year, colonoscopy was recommended as a screening tool by a multisociety group (that included the American Cancer Society) suggesting a frequency of 10 years [15]. By 2002, the USPSTF did include colonoscopy on the list of available options equally alongside other less invasive approaches such as FOBT and flexible sigmoidoscopy [20]. Since that time, two gastroenterology subspecialty guidelines have endorsed colonoscopy as the “preferred” modality relative to other options [12, 13]. Such strong recommendations regarding screening colonoscopy combined with legislation that authorized payment for it (e.g., by Medicare) has led to increasing use for CRC

screening. The most recent Behavioral Risk Factor Surveillance System survey clearly indicates more screening being performed by endoscopy and less with stool testing [21].

Current Recommendations for Average Risk Screening

The current US CRC screening recommendations for average risk patients can be seen in Table 4.1. The broadest recommendations for screening are those from the American Cancer Society, the US Multisociety Task Force on CRC, and The American College of Radiology [11] (USMSTF). They recommend as possible screening modalities flexible sigmoidoscopy, colonoscopy, double-contrast barium enema, computed tomography colonography, and stool testing including both conventional FOBT and DNA testing. The recommended screening modalities are grouped according to tests that detect adenomatous polyps or cancer (i.e., structural tests like endoscopy and CT colonography) and tests that primarily detect cancer (i.e., non invasive stool tests). In so doing, the authors favor those modalities that offer the opportunity at “cancer prevention” – the structural tests that detect adenomatous polyps and cancer.

Table 4.1 Screening options for average risk patients by society

US preventative services task force [10]	American Cancer Society, the US multisociety task force on CRC, and The American College of Radiology [11]	American College of Gastroenterology [13]	American Society for Gastrointestinal Endoscopy [12]
FOBT annually	Tests that detect	Colonoscopy	Colonoscopy
Flexible sigmoidoscopy every 5 years	adenomatous polyps and cancer	every 10 years (preferred)	every 10 years (preferred)
with FOBT every 3 years	Flexible sigmoidoscopy every 5 years	Alternatives include Flexible sigmoidoscopy every 5–10 years	Alternatives include FOBT annually Flexible sigmoidoscopy every 5 years
Colonoscopy every 10 years	Colonoscopy every 10 years	CT colonography every 5 years	FOBT annually and flexible sigmoidoscopy every 5 years
	Double-contrast barium enema every 5 years	FOBT annually	
	CT colonography every 5 years	Stool DNA testing every 3 years	
	Test that primarily detect cancer		
	FOBT annually		
	Stool DNA testing, interval uncertain		

While the USPSTF gives colorectal cancer screening a “grade A” recommendation; they endorse a much smaller panel of tests; only including FOBT, flexible sigmoidoscopy, and colonoscopy [10]. They do not recommend newer modalities (such as CTC or fecal DNA) nor do they distinguish between tests that detect adenomas and those that do not.

Interestingly while the American College of Gastroenterology (ACG) endorses the USMSTF guidelines discussed above, they also issue independent recommendations that take a stronger approach with respect to recommending colonoscopy. Specifically, the ACG guideline highlights colonoscopy every 10 years as the *preferred* screening strategy but includes CTC, flexible sigmoidoscopy, hemocult test, and fecal DNA as alternatives [13]. Like the ACG, the American Society of Gastrointestinal Endoscopy also recommends colonoscopy as the preferred test [12].

Given the variation among these guidelines, what should practitioners recommend for their patients? The most consistently recommended modalities are colonoscopy, flexible sigmoidoscopy, and conventional stool testing (e.g., FOBT) and these would all appear to be reasonable approaches. While both CTC and fecal DNA are included in the USMSTF guidelines some practical questions regarding their application in screening remain. For example, the type and timing of follow-up examination for those identified with a small or even medium sized polyp on CT colonography is not clear. Similarly, what work up to consider in those who are fecal DNA positive and colonoscopy negative remains to be determined. While some guidelines emphasize colonoscopy as the best (i.e., “preferred”) screening modality, at present, there is no randomized controlled trial evidence to support that claim. Moreover, quantitative fecal immunochemical testing (FIT) for detection of human hemoglobin in stool is now widely available and may offer advantages over conventional FOBT [22, 23]. In summary, it is likely that there is no “one best screening test” for all individuals. Well done cost effectiveness analysis [24] suggest that patient compliance is critically important to the success of any colorectal cancer screening program. Therefore, the choice of colorectal cancer screening test is best made after careful discussion of the available modalities and utilizes patient preference in determining the right choice for a given individual.

High Risk Screening

Family History

One common clinical scenario is providing screening recommendations to those individuals with one or more family members with colorectal cancer. There is evidence to suggest that family history significantly modifies lifetime risk of CRC. Studies suggest that first degree relatives of individuals with colorectal cancer have a two to threefold increase for CRC. Even the presence of cancer in a second or third degree family member portends a more modest 50% increase in

Table 4.2 Screening guidelines for increased or high risk patients

Society	Category	Recommendation	Comment
American Cancer Society, the US Multisociety Task Force on CRC, and The American College of Radiology [11]	CRC or adenomatous polyps in a first degree relative before age 60	Colonoscopy starting at age 40 or 10 years before the youngest case	Continue screening with colonoscopy every 5 years
	CRC or adenomatous polyps in two or more first degree relatives at any age		
	Colorectal cancer or adenomatous polyps in a first degree relative age 60 or older CRC in two second degree relatives	Screening starting at age 40	After initial screening can continue at intervals recommended for average risk patients
American College of Gastroenterology [13]	Single first degree relative with CRC or advanced adenoma diagnosed at age <60	Colonoscopy starting at age 40 or 10 years before the youngest case	Continue screening with colonoscopy every 5 years
	Two first degree relatives with CRC or advanced adenomas at any age		
	Single first degree relative with CRC or advanced adenoma diagnosed at age >60	Colonoscopy every 10 years starting at age 50	Same as average risk
American Society for Gastrointestinal Endoscopy [12]	First degree relative(s) with CRC diagnosed at age <60	Colonoscopy starting at age 40 or 10 years before the youngest case	If normal, repeat every 3–5 years
	First degree relative(s) with CRC diagnosed at age >60	Colonoscopy starting at age 40	If normal, repeat every 10 years
	First degree relative(s) with adenomatous polyps at age <60	Colonoscopy starting at age 40 or 10 years before the youngest case	If normal, repeat every 5 years
	First degree relative(s) with adenomatous polyps at age >60	Colonoscopy for screening, age individualized	If normal, same as average risk
	Second or third degree relative with cancer or polyps	Colonoscopy as average risk individuals	If normal, same as average risk

risk above average risk [25]. Likewise, studies also indicate that first degree relatives of individuals with adenomatous polyps have about a twofold increase for CRC [26].

Screening recommendations for individuals at an increased or high risk for colorectal cancer can be seen in Table 4.2. Patients are considered to have an increased

risk for colorectal cancer if they have a family history of colorectal cancer or adenomatous polyps. Again, guidelines vary between organizations, but generally colonoscopy is recommended in these populations and often at an earlier age as compared to average risk individuals. For examples, the USMSTF guidelines [11] recommend that individuals with one first degree relative with a history of colon cancer or adenomatous polyps *before the age of 60* or in two or more first degree relatives at any age, screening with colonoscopy is recommended starting at age 40 or 10 years before the presentation of the family member(s). Screening should be repeated every 5 years thereafter. While the ACG guidelines for this population are quite similar, they only include those with a first degree relative with cancer or *advanced* adenomas [13]. Advanced adenomas are those that are large (≥ 1 cm) or have advanced histologic (“villous”) features and compose only a small percentage of adenomas.

The guideline recommendations are more varied when the first degree relative with cancer or adenomas is first detected *after the age of 60*. The USMSTF guidelines [11] endorse starting screening earlier (age 40) in such cases, but any acceptable screening modality (e.g., including FOBT or flexible sigmoidoscopy) is an option. The ACG [13] (which has a “colonoscopy first” approach to average risk screening) recommends colonoscopy starting at age 50 (identical to average risk recommendations). The most recent guidelines from the ASGE [12] are similar to the multisociety guidelines except that surveillance is recommended every 3–5 years in individuals with a first degree relative with CRC diagnosed before the age of 60.

To summarize, family history is a relatively important risk factor and most guidelines recommend a more aggressive approach in these patients. The guidelines are most uniform when the affected relative developed neoplasia at younger age (e.g., <60). Starting earlier and using colonoscopy as the modality for screening seems prudent. There is more latitude if the affected relative was greater than 60 (or only had adenomas and not cancer). Guidelines generally recommend starting earlier (e.g., age 40), but other screening modalities (e.g., FOBT) might be considered.

The discussion to this point has focused on those individuals with a family member with sporadic colorectal cancer or adenomas. Of course, individuals in families affected by familial polyp and cancer syndromes (e.g., FAP, HNPCC), are at even higher risk for colorectal cancer. A full discussion of these syndromes is included in Chap. 3.

Tailored Screening

The epidemiology and risk factors for colorectal cancer have been fairly well described (see Chap. 2). Given that risk for developing CRC varies across demographics and relative to certain environmental exposures, some have suggested that this information be utilized in refining screening recommendations. The future of screening for CRC may lie with a tailored approach where individuals with risk factors for colorectal cancer are targeted for screening. Specifically, higher risk subgroups may be targeted for screening at an earlier age or up front with a more invasive modality (e.g., colonoscopy) given their increased risk for colorectal cancer mortality. While this approach intuitively makes sense it is possible that further complicating screening

recommendations could negatively impact adherence rates. As noted, compliance with screening is critically important to the success of any screening program. Below we consider some of the factors that have been suggested to tailor general screening recommendations.

Race

Racial variation with regards to colorectal cancer incidence and mortality has been well described. For example, colorectal mortality rates for Black men and women are 38–43% higher than for White men and women, respectively. Incidence rates comparing Blacks and Whites track similarly [27]. While some of this variation in risk likely reflects socioeconomic factors (e.g., access to health care), biology and genetics also likely play a role. Data regarding adenoma risk tracks similarly to cancer risk. A study by Lieberman using information available on colonoscopy exams in over 85,000 asymptomatic individuals found that the absolute prevalence of larger polyps (>9 mm) was significantly higher in Blacks (7.7%) than Whites (6.2%) and these differences remained in fully adjusted models [28].

Based upon some of the evidence reviewed above, the ACG does recommend screening in average risk African-Americans starting at age 45 instead of 50 [13]; however, none of the other guidelines specifically tailor recommendations on this factor.

Gender

Male sex has also been reported as a significant risk factor for polyps and colorectal cancer mortality. Analysis of Surveillance and Epidemiology and End Results data found that women ages 50–59 have a 2.9% absolute of CRC compared with 4.7% for men [29]. A large study from Poland analyzing 43,042 participants who underwent screening colonoscopy also determined that male gender was significantly associated with risk of advanced neoplasia (OR of 1.73) [30]. However, it is important to note that the lifetime risk of colorectal cancer is comparable between men and women (5.1% for women vs. 5.5% for men) [31]. While tailoring the guidelines on gender was considered in both the USMSTF guidelines [11] and ACG guidelines [13], neither specifically tailored guidance in this area although both acknowledged the recommendations would be reevaluated as additional evidence appears.

Tobacco

Cigarette smoking has been more difficult to correlate with colorectal cancer with some positive and other negative studies over the past two decades; however more recent studies suggest an effect. A 2009 meta-analysis of 28 prospective cohorts from the US, Europe, and Asia by Tsoi et al., did find a significantly increased risk of CRC in smokers. Current smokers had a modest 20% increase in risk compared

to individuals who had never smoked [32]. A 2008 meta-analysis of 42 observational studies by Botteri et al. found even more striking results when examining the association between cigarette smoking and adenomatous polyps [33]. The increase in relative risk for current, former, and ever smokers in comparison to never smokers was 2.14, 1.47, and 1.82, respectively. While the ACG guidelines [13] do not specifically endorse earlier screening in smokers, they do suggest that those with an “extreme smoking history” begin screening at an earlier age (perhaps at age 45).

Diabetes Melitus

There have also been numerous studies linking diabetes and colorectal cancer. Hyperinsulinemia, which develops during the early stages of type 2 diabetes, has been associated with decreased apoptosis, and increased proliferation and tumorigenesis within the colorectum [34]. Clinical studies that suggest the potential importance of this factor include a cohort study based in Rochester Minnesota that compared colorectal cancer incidence in approximately 2000 diabetic patients. Those with type 2 diabetes were approximately 40% more likely to develop CRC than population based controls (SIR of 1.39) [34]. The effect of diabetes also seems to translate to adenoma risk. A case-control study examining women with type 2 diabetes found a greater rate of adenomas (37 vs. 24%) compared to controls [35]. While the data does suggest some increased risk, to date, no organization recommends tailored screening on this factor.

Surveillance

Background

While colorectal cancer screening guidelines are used for asymptomatic individuals with no prior personal history of colorectal adenomas or cancer, colorectal surveillance guidelines have been developed for these higher risk individuals. Colonoscopy is always the modality recommended for surveillance and the interval for follow-up colonoscopy varies considerably based upon the prior colonoscopic findings (Table 4.3)

Given the frequency with which screening is performed and the prevalence of colorectal adenomas, it is not surprising that surveillance colonoscopy is a major source of colonoscopy utilization in the United States. Based upon review of a national endoscopic database associated with the Clinical Outcomes Research Initiative (CORI) endoscopic repository, it has been estimated that about 20% of colonoscopic exams are performed for surveillance [36]. Since there are such a large (and growing) number of individuals affected by these recommendations, it is critically important that such guidelines are followed so that resources are utilized

Table 4.3 Recommendations for patients with adenoma or cancer history based upon US multisociety task force on colorectal cancer, and the American College of Radiology Guidelines [11]

Finding at colonoscopy	Recommended follow up interval	Notes
Hyperplastic polyps	Continue screening intervals recommended for average risk patients	Hyperplastic polyposis syndrome is not covered by this recommendation
1 or 2 small tubular adenomas	5–10 years	Interval should be based on clinical factors such as prior colonoscopy findings, family history, patient preference, and endoscopist judgment
3–10 adenomas or 1 adenoma >1 cm, or any adenoma with villous features or high-grade dysplasia	3 years	If follow-up is normal or shows only 1–2 small tubular adenomas, the interval for subsequent evaluations should be in 5 years
>10 adenomas on a single examination	<3 years as determined by endoscopist	Consider an underlying familial syndrome
Sessile adenomas that are removed piecemeal	2–6 months to verify complete removal	Subsequent surveillance based on the endoscopist's judgment
Patients undergoing curative resection for colon or rectal cancer	Initial high quality clearing exam and then repeat colonoscopy 1 year after surgery. Assuming normal exams, the next exam should be in 3 years and then in 5 years	Patients with low anterior resections for rectal cancer may require more frequent (q 6 months) exams to exclude local recurrence

appropriately. Given that the supply of colonoscopy in the United States is finite, inappropriate use of surveillance colonoscopy may negatively impact efforts to increase screening that also relies on colonoscopy [37]. In fact, there is some fairly strong evidence that surveillance guidelines are generally not correctly followed in the United States. A national survey of endoscopists found that nearly one quarter of respondents recommended follow-up surveillance colonoscopy when no surveillance exams would be indicated based upon the guidelines [38].

Personal History of Adenomas

The guidelines are based on the notion that patients who make adenomatous polyps are at a higher risk for colorectal cancer and should therefore have more frequent exams. It is critically important to note that all “polyps” are not adenomas. A polyp simply implies that a raised mucosal lesion has been identified on the colonic mucosa. At present, histopathologic examination is required to definitively determine the etiology.

Broadly speaking, polyps are often identified as either hyperplastic or adenomatous. Hyperplastic polyps are generally not considered to have premalignant potential. Adenomatous polyps, on the other hand, are the result of mucosal cells that have undergone a genetic mutational event and such lesions harbor the potential for true malignant transformation. In truth, it is estimated that very few polyps (e.g., 1:20) ultimately progress to cancer and that the latency period (from adenomatous polyp to cancer) is lengthy [39]. But the history of prior adenomatous polyps does place the patient at risk for adenoma recurrence and so guidelines recommend more frequent exams in these patients. The specific interval between exams changes depending on the number, size, and histopathology of the adenomas identified.

Based upon recommendations in the most current USMSTF guidelines [11], patients with one or two small adenomas without any advanced features (e.g., villos transformation) on colonoscopy should have a follow-up colonoscopy within 5–10 years. This interval is decreased to 3 years for patients with multiplicity (3–10 adenomas) or with at least one adenoma with advanced features (>1 cm, with villos features or high-grade dysplasia). Much more rarely, adenoma surveillance patients require shorter follow-up than 3 years. These include patients found with large number of adenomas (e.g., >10 adenomas on a single examination). In such cases the exact interval should be decided by the endoscopist depending on the clinical context (i.e., number and size of polyps). Similarly, those found with large sessile adenoma(s), where there is a concern that the adenoma was not entirely removed, require repeat examination in 2–6 months to examine the resection site for evidence of residual tissue. Adequate polyp removal is typically confirmed with visual inspection or biopsies. Subsequent surveillance is again best left to the discretion of the endoscopist.

It is important to note that hyperplastic polyps *do not* require more frequent follow-up; patients can continue with screening at intervals recommended for average risk individuals. Therefore, for those found only with a few hyperplastic polyps on a screening exam, repeat surveillance colonoscopy is not required and a routine 10 year follow-up colonoscopy may be considered.

Personal History of Colorectal Cancer

Based upon USMSTF guidelines [11], patients with a new diagnosis of colorectal cancer should undergo colonoscopy before or within 3–6 months after resection to rule out a synchronous lesion. If colonoscopy is not possible prior to resection due to an obstructing lesion, CTC or DCBE can be used instead. One year after resection, a repeat colonoscopy should be performed. This examination is in addition to the exam completed at the time of cancer diagnosis. If the 1 year exam is normal the next exam should be in 3 years. If that exam is normal subsequent exams should take place every 5 years.

It is important to note that generally speaking, local recurrence of colon cancer is unlikely. While the surveillance examination can closely examine the anastomosis,

most colon cancer recurrence is metachronous. For those undergoing low anterior resection for rectal cancer, the risk of local recurrence is much higher. Therefore, in these patients, more frequent sigmoidoscopy (e.g., every 3–6 months) is recommended to exclude local recurrence of cancer.

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Chapter 5

Barriers to Colorectal Cancer Screening: Patient, Physician, and System Factors

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Keywords Colorectal cancer screening • Barriers • Facilitators

Reduced incidence and mortality from colorectal cancer (CRC) associated with early detection of CRC and precursor lesions by screening [1] is well documented in the literature. Screening for CRC is widely recommended for average-risk adults starting at age 50 [1], and numerous efforts directed at increasing awareness of CRC, CRC screening and its efficacy have been deployed. Yet currently, adherence to CRC screening recommendations in the United States, by eligible adults remains low. In 2008, 53.2% of age-eligible women and men reported having an FOBT or endoscopic exam [2]. This rate of screening falls short of the American Cancer Society goal for 2015 of a recent CRC screening exam for 75% of U.S. adults aged 50 and older [3].

To increase adherence to CRC screening guidelines and thus reduce incidence and death attributed to this disease, it is essential to understand factors which influence screening behaviors among patients and healthcare providers. Efforts to explain low rates of CRC screening have focused on identifying barriers to use of screening – an approach with theoretical support. When applied to CRC screening, the decision balance constructs of the Transtheoretical and [4, 5] Precaution Adoption Process [6] models of health behavior change postulate that greater perceptions of positive aspects (“pros”) of screening and fewer perceptions of negative aspects and barriers (“cons”) to screening, are associated with a greater likelihood of obtaining CRC screening. Thus, adults who obtain CRC screening according to recommended guidelines have been shown to report fewer barriers to CRC screening and to endorse more positive attitudes about screening as well [7, 8].

Barriers contributing to the underutilization of CRC screening are generally organized as those specific to patients, providers, and healthcare systems. Numerous

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published studies have examined associations among patient, provider and system characteristics, and utilization of screening in national and local samples. Other studies have examined actual patient and provider reports of perceived barriers to screening, through surveys of national and local samples and through focus group discussion. This literature also includes several review articles which present extensive compilations of what is currently known about barriers to CRC screening (see Vernon [9], Subramanian et al. [10], Beydoun and Beydoun [11], and Guessous et al. [12]). Thus, this chapter is not meant to be exhaustive but rather provides an overview of the barriers to CRC screening. Awareness of barriers to the use of CRC screening and understanding which barriers may be of most concern is important for identifying subgroups at greater risk for nonadherence and for informing the development and implementation of targeted efforts to increase screening through the reduction of modifiable barriers to screening.

Patient Barriers to CRC Screening

Lack of a physician recommendation for CRC screening remains a noteworthy barrier to CRC screening and is among barriers most commonly cited by patients, even those at high risk for CRC (and after controlling for education, income and insurance status) [7, 8, 12–17]. In one recent study using a diverse sample of 3,357 patients in a practice-based research network, the relative importance of a number of patient-reported barriers to CRC screening was examined. The healthcare provider “never suggested I get this test” was cited as the primary barrier to CRC screening among those who had never screened or were overdue for screening – and was cited as a potential barrier among those who were up-to-date with screening [13]. In another study, employing a national sample of adults aged 64–89, 77–87.5% of those who had heard of FOBT, sigmoidoscopy, and colonoscopy reported that their healthcare provider did not recommend CRC screening to them [16]. The results of a recent review article supports lack of a provider recommendation as a particularly significant problem for older patients (age 65 years and older) [12] despite the facilitating effect of Medicare on financial barriers to CRC screening in this age group. 28% of 1901 Medicare recipients residing in North and South Carolina in 2001 and 21–30% of 3,675 Medicare-recipient respondents to the National Adult Immunization Survey in 2004, reported no physician recommendation for CRC screening [7, 18]. The odds of receiving a physician recommendation for CRC screening decrease with decreasing age [7]. It has been suggested that this may be due to the fact that currently guidelines for age at which CRC screening should not continue are not yet clear-cut [12].

This barrier is of particular concern because provider recommendation for CRC screening, when given to a patient, is a strong predictor of whether that patient will actually have screening [10, 19–23]. For example, in a recent study of 2,416 average-risk patients from 24 Veterans Affairs medical facilities, physician recommendation was most strongly related to CRC screening adherence than other demographic, cognitive, or environmental factors. Patients who received a physician

recommendation were nearly 3 times more likely to be adherent with CRC screening guidelines. Whereas, the relative risk of CRC screening nonadherence for patients reporting no physician recommendation was 3.00 [19]. Data obtained from 2,994 respondents to the 2002 Maryland Cancer Survey show that having a physician recommendation for CRC screening improved the odds of completion by a factor of 8 [24]. These findings highlight the significance of provider recommendation on patient screening behavior.

The influence of physician recommendation on screening completion has been shown to vary with individual patient characteristics such as age and gender. The results of a study of a small ($n=104$) diverse sample of primary care patients suggest that having a physician recommendation for screening was most strongly associated with screening completion among patients less than 65 years of age while patients aged 65 and older who reported a physician recommendation were not more or less likely to complete screening than those in the same age range who did not have a screening recommendation [7]. In another study utilizing national data obtained from the 1999 Behavioral Risk Factor Surveillance System, women and men were equally as likely to receive a recommendation for CRC screening but men were nearly twice as likely as women to obtain CRC screening [21].

In addition to age, *other patient characteristics* are associated with receiving a physician recommendation for CRC screening. Men are more likely to receive a recommendation [25] (although in other studies women are more likely). Good to excellent health status [25], and having a female physician [25] have been positively associated with receiving a recommendation. Conversely, younger age has been associated with lack of physician CRC screening recommendation [26], in addition to Hispanic [26] or Asian [27] ethnicity, racial/ethnic minority status [28] and lower educational attainment [26]. However, these findings for sociodemographic characteristics and provider recommendation are not consistent across studies – perhaps because of differences in insurance and access to medical care among different participant study samples. Where access to health care is available and insurance coverage is not significantly related to CRC screening overall, disparities in CRC screening recommendations by providers may still relate to type of screening exam. In a comparison of CRC screening utilization among a sample of county health center registrants and a sample of private physician practice patients, health center registrants were more likely to report no provider recommendation for endoscopy compared to private practice patients – while private practice patients were less likely to report provider recommendations for FOBT [8].

Lack of awareness of the importance of screening/not knowing that screening is necessary is also commonly cited as a barrier to CRC screening, despite education campaigns to increase awareness of CRC and promote CRC screening [13, 14, 16, 29, 30]. In the study of 3,357 patients in a practice-based research network, noted above, this was the second most frequently barrier to CRC screening among those who never screened (relative to no physician recommendation) [13]. Lack of awareness about CRC and screening and the belief that screening is not needed also emerged as frequent and significant barriers to screening utilization among the elderly (aged 65 and older). [8, 12] In fact, in a national survey of Medicare recipients, the belief that CRC was not needed or lack of knowledge that CRC screening was

needed surpassed lack of physician recommendation as a barrier to screening [18]. Taken together with lack of a provider recommendation, these barriers underscore the significant influence of inadequate patient/physician communication about CRC and screening on patient nonadherence to screening guidelines.

Patient barriers to CRC screening also relate to the characteristics of specific screening modalities. For example, nonusers or those who attempted but did not complete CRC screening were more likely than those who completed a CRC screening exam to cite attitudinal or perceptual factors such as discomfort, concern about complications, embarrassment, or fear of results as factors which could influence their decisions to have CRC screening [31]. Among those who attempted CRC screening at least once, were barriers to test completion varied with the type of exam – a greater proportion of those who attempted FOBT reported that they “forgot” or that the test was “too unpleasant.” Those who attempted colonoscopy or sigmoidoscopy were more likely to cite “pain” or worry about exam risks as barriers [31].

Individual *patient characteristics* such as race, ethnicity, and socioeconomic status (apart from level of education and insurance coverage) are associated with CRC screening utilization [2]. Disparities in CRC screening use are associated with racial/ethnic minority status (African-American race/Hispanic and Asian ethnicity), compared to Whites, despite the fact that mortality from CRC is higher in these groups than in Whites [12, 17, 27]. These screening disparities have been attributed to differences in socioeconomic status and access to medical care among racial/ethnic subgroups [30]. When compared to Whites, racial/ethnic minority respondents were more likely to cite practical and logistical concerns such as inconvenience and not finding the time to get tested as well as cost of screening and cost of CRC treatment (if diagnosed with CRC) as barriers to screening [28]. These are barriers that likely affect all low-income populations. Cultural differences in attitudes and beliefs about CRC screening also play a role in CRC screening decisions. Distrust of the medical system and perceived bias in the delivery of health care are barriers among African-Americans [30, 32]. Data obtained from a racially diverse sample of adults eligible for CRC screening suggested that compared to Whites, African-American, Hispanic, Asian-American, and Native American respondents more frequently cited the preparation, pain, embarrassment, forgetting, and fear of cancer as significant barriers to CRC screening [28].

Lower levels of education, low income and no/inadequate insurance coverage are significant barriers to adherence of CRC screening guideline among disadvantaged populations [20, 26, 27, 33, 34]. Less education and low health literacy likely relate to patient-reported barriers of lack of awareness of CRC and screening, knowledge deficits, and the belief that screening is not needed. Lower health literacy is associated with a lower likelihood of seeking information about CRC screening and less confidence in one’s ability to participate in screening [35]. Thus, adults with low health literacy have less knowledge of CRC screening and report more barriers to screening [36] and are less likely to obtain CRC screening [37]. Nonetheless, there is evidence that provider recommendation improves completion of CRC screening, regardless of health literacy level [38].

However, as noted previously, when women and men are equally as likely to receive a recommendation, men may be more likely as women to complete CRC screening [21], suggesting that barriers to CRC screening may be different for women and men. Qualitative findings obtained with a sample of patients at a Veterans Affairs Medical Center showed that women were more likely to view CRC as a male disease, thus perceiving themselves to be less susceptible to this disease. Women also perceived the preparation for colonoscopy and sigmoidoscopy exams as a greater barrier to screening than men. Interestingly, women's fears and concerns had an affective component – e.g., concerns about the invasive nature of colonoscopy or sigmoidoscopy included being unclothed, while men were primarily concerned with how far the scope would be advanced, risk of perforation, and pain (in other studies men were also more concerned about pain than women [30]). Women viewed sedation as a means of reducing affective barriers (fear and anxiety), while men viewed sedation in terms of pain reduction [39]. Several studies suggest overweight and/or obese adults may be less likely to have CRC screening compared to those of normal weight [40], and that this may be a greater problem for women rather than men [41–43].

Lower use of CRC screening is seen in eligible adults who concurrently engage in multiple (but modifiable) health risk behaviors. Smokers in particular may further exacerbate their risk for CRC by engaging in concurrent health behaviors also associated with increased risk for CRC [44] and by not utilizing preventive services such as having CRC screening exams, compared to nonsmokers [44–46].

As noted earlier, adults who obtain CRC screening according to recommended guidelines have been shown to endorse more positive attitudes about screening as well [7, 8]. Patient attitudes toward preferences for who makes CRC screening decisions – patient alone, provider alone, or shared decision making – may also present barriers to screening. For example, in a community-living sample of 2,119 adults age-eligible for CRC screening, not having any recent CRC screening exam was associated with lower odds of preferring any physician involvement in screening decisions (that is, respondent alone prefers to make decisions rather than share decision making with physician or rely on physician alone to make decisions). This may relate to the greater likelihood of endorsing negative rather than positive attitudes about screening among respondents who preferred to make all CRC screening decisions. These findings also suggest that patients who prefer to make their own CRC screening decisions may do so to avoid physician messages to be screened [47].

Provider Barriers to CRC Screening

As noted previously, the strongest predictor of whether a patient will actually have screening is *receiving a provider recommendation* for screening [12–14, 24]. However, as also noted, patients report that their healthcare providers do not consistently recommend CRC screening according to guidelines.

Provider-identified barriers to recommending CRC screening for their eligible patients relate to their patients' characteristics and attitudes; their own characteristics and attitudes about CRC screening, as well systems-level factors (which are noted below). In a study utilizing in-depth interviews, focus group discussions, and chart-stimulated recall, 29 primary care physicians described barriers and facilitators of recommending CRC screening to their eligible patients [48]. Patient characteristics described as barriers to screening recommendation included: patient comorbidity; patient refusal or noncompliance with previous CRC screening recommendations; language barriers – non-English speaking; patient attitudes reflecting distrust, “antimedical” or “suspicious” attitudes; choosing to recommend other types of cancer screening that may be more acceptable to patients who are not compliant with CRC screening (e.g., recommending mammography rather than CRC screening for women who are overdue for mammograms). Providers, however, noted that patients who requested screening were more likely to receive a recommendation for screening. Providers also identified younger age (i.e., 50–59) as a facilitator to screening recommendation [48]. In another study utilizing responses from 1235 primary care physicians obtained from the national Survey of Colorectal Cancer Screening Practices, 80% of physicians reported patient lack of knowledge, awareness, and motivation as a barrier to screening [14]. Competing medical priorities, lack of knowledge about CRC screening and lack of patient motivation have also been cited by other provider focus groups as barriers to CRC screening for their patients [30].

Physicians have also noted their own forgetting to recommend CRC screening. In the study described above [48], this was the most frequently cited physician barrier to screening. These providers also cited their assumption that CRC screening would be addressed for those patients under the care of a gastroenterologist, as another barrier to recommending screening [48].

Sarfaty in the *How to Increase Colorectal Cancer Screening Rates in Practice: A Primary Care Clinician's Evidence-Based Toolbox and Guide, 2008* [49] notes provider-related barriers to CRC screening which include lack of knowledge about current CRC screening guidelines, overestimation of current screening rates, confusion about the goals of CRC screening (prevention), low confidence in the efficacy of CRC screening exam modalities for reducing mortality and for patient acceptability.

Wolfe et al. [50] speculate that physician–patient discussions about CRC screening may be influenced by the availability of screening resources and the providers perception of what their patients prefer. Nonetheless, if providers incorrectly perceive which factors or characteristics serve as barriers or facilitators of screening for their patients, they might recommend (or fail to recommend) screening exams which are consistent with patient preferences, with failure to complete screening as the unintended consequence. For example, Klabunde et al. [14] found that although primary care physicians and their patients agreed that provider recommendation and lack of patient awareness of CRC and screening were important barriers to screening, physicians were more likely to place emphasis on patient embarrassment and anxiety about CRC screening exams and concerns about insurance and cost,

than their patients. In another study, physicians were less likely to recognize the importance of the “experience of others” on patients decisions to have CRC screening – but were more likely than patients, to recognize the contribution of patients health beliefs, patient knowledge, and cost and access on CRC screening completion [51].

Systems Barriers to CRC Screening

As noted previously, barriers to CRC screening utilization among the underserved and disadvantaged include no or inadequate insurance coverage. Among socioeconomically disadvantaged populations, underuse of CRC screening due to healthcare system barriers such as no/inadequate insurance coverage [14] may be a greater barrier to CRC screening than individual patient characteristics [30]. Adults who have a regular source of health care and who are seen by the same healthcare provider, are more likely to adhere to CRC screening guidelines [10, 30].

Physician forgetting to recommend CRC screening to eligible patients (described above) likely relates to the lack of office reminder systems to support CRC screening [48, 52]. Limited time during clinical encounters and competing priorities during acute care visits, as well as lack of insurance coverage, and long waits for colonoscopy appointments have also been noted by physicians as reducing the likelihood that they will recommend CRC screening to a patient [30, 48, 53]. Having organized programs to help patients complete screening through the reduction of systems barriers such as lack of tracking of the return of FOBT cards or the results of endoscopy exams, difficulty finding local endoscopists or sources of low-cost screening for those with no/inadequate insurance, difficulties obtaining appropriate follow-up of positive findings, etc. – can greatly improve screening completion – yet there is evidence that these supports are not widely in place [27]. Patient navigators have been shown to facilitate CRC screening completion by helping patients to overcome these systems barriers to CRC screening, especially among non-English speaking patients [54].

Reducing Barriers to CRC Screening

A discussion of interventions and strategies to reduce barriers to CRC screening is beyond the scope of this chapter. The importance of provider recommendations and patient awareness of the importance and need for screening have been clearly highlighted in the literature, as well as the contribution of no or inadequate insurance coverage for the likelihood of screening completion. Strategies to improve CRC screening utilization that target modifiable barriers at patient and provider levels within distinct healthcare delivery systems are clearly called for.

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Chapter 6

Screening for Colorectal Cancer Using Colonoscopy

Douglas K. Rex

Keywords Colonoscopy • Proximal Colon • Mucosa

Rationale and Efficacy for Screening Colonoscopy

The first study to clearly demonstrate the efficacy of colorectal cancer screening was a case-control study published in 1992, which found a 60% reduction in distal colorectal cancer mortality associated with sigmoidoscopy [1]. Subsequently, case-control studies at the Marshfield Clinic in Wisconsin [2] and in Washington State [3] demonstrated that flexible sigmoidoscopy was associated with an 80% reduction in distal colorectal cancer incidence. In addition, evaluation of a randomized controlled trial of fecal occult blood testing demonstrated that fecal occult blood testing had resulted in not only a reduction in colorectal cancer mortality but also in a 20% reduction in incidence of colorectal cancer [4]. The latter appeared related to identification of large colorectal polyps by fecal occult blood testing and their subsequent removal by colonoscopy and polypectomy. In 1993, evaluation of an adenoma cohort participating in the National Polyp Study reported that colonoscopy and polypectomy was associated with a 76–90% reduction in the incidence of colorectal cancer by comparison of incident cancer rates in the adenoma cohort compared to expected rates in three reference populations [5].

The combined evidence regarding flexible sigmoidoscopy screening, together with the proven efficacy of fecal occult blood testing [6] (but relatively low absolute levels of cancer reduction), and the interpretation of the National Polyp Study data, became the foundation of a movement in the 1990s toward screening colonoscopy. The goal of this movement was an extension of the benefits of endoscopic screening

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(that seemed clear for the left colon based on sigmoidoscopy studies) to the entire colon. Initial studies at Indiana University in screening patients demonstrated the feasibility of high completion rates in screening examinations, safety of screening colonoscopy, and a surprisingly high yield of advanced neoplasms and cancers, including patients with proximal colon advanced neoplasia with no distal colon neoplasia [7]. A private practice group at St. Francis Hospital in Indianapolis organized a city-wide low-cost screening colonoscopy study for employees and retirees (and their spouses) of the Eli Lilly Corporation and funded by Eli Lilly [8]. A description of the yield and findings of the program was published in 2000 in *The New England Journal of Medicine* [9], alongside a similar federally funded study of the feasibility, yield, and safety of screening colonoscopy in multiple Veterans Administration hospitals in the United States [10]. An accompanying editorial [11] to these papers voiced the increasingly held opinion that sufficient evidence was available to launch widespread screening colonoscopy in the United States. In July 2001, at the legislative directive of the U.S. Congress, the Health Care Financing Administration (now the Center for Medicare and Medicaid Services) began to cover screening colonoscopy in age eligible Medicare recipients. Private insurers in the United States soon followed suit, and screening colonoscopy is now widely available in the United States. However, colonoscopy is not provided as part of a national screening program, but rather on a case-finding basis through physician/patient interaction. National screening programs have appeared in Germany, Poland, and Italy, but the level of adherence to screening colonoscopy in European countries is far below that in the United States.

Colonoscopy emerged as a dominant form of colorectal cancer screening in the United States without being evaluated in randomized controlled clinical trials. Rather, colorectal cancer screening was established as effective by randomized controlled trials of fecal occult blood testing [12–14]. A widely held belief by experts has been that any test with performance characteristics for detection of cancer and adenomas that are superior to fecal occult blood testing should have comparable or superior efficacy for colorectal cancer prevention and should be part of the pantheon of available colorectal cancer screening tests [6, 15]. However, comparing the sensitivity of single time testing of various screening methods may not provide insight into their relative program sensitivity if the tests are recommended at different intervals. For example, colonoscopy is recommended at 10-year intervals for average risk screening. This interval is based on evidence from flexible sigmoidoscopy case control studies, which found that the benefits of flexible sigmoidoscopy for protection against left-sided colorectal cancer have a duration of at least 10–16 years [2, 3]. Subsequently, cost-effectiveness analyses of colonoscopy have assumed its performance at 10-year intervals [6, 15]. However, since the recommended interval for colonoscopy is much different than that for fecal occult blood testing, the programmatic performance of colonoscopy vs. fecal occult blood testing remains uncertain.

In the past 10 years, two new but substantial concerns have arisen regarding colonoscopy as a screening test. The first is that the procedure is highly operator dependent with regard to adenoma detection [16–18]. Some individual colonoscopists miss more than half of the large adenomas in the colon [16–18], and miss up to 90% of all of the adenomas in the colon [16]. The true prevalence of adenomas

in the screening population is >40% [19, 20] and many individual endoscopists have adenoma detection rates which are below the recommended thresholds [21, 22] (at least 25% of men and 15% of women age ≥ 50 years should have at least one adenomatous polyp). Colonoscopists below these thresholds are failing to detect any adenomas in half or more individuals who have adenomas and in at least one in every five individuals in whom they perform screening colonoscopy. This operator dependence is potentially devastating to the effectiveness of colonoscopy and is a major flaw in its use as a screening strategy. It is also a flaw in colorectal cancer prevention strategies that rest on other tests, since invariably these tests result in colonoscopy when positive [6]. Colonoscopy is thus a pivotal step in the detection and prevention of colorectal cancer regardless of screening method. Thus, recent guidelines that endorse colonoscopy as the preferred colorectal cancer screening strategy emphasize that it should only be used as a screening test in the context of a quality improvement program, and that quality program must make a priority of measures of mucosal inspection quality [6, 23].

The second new and major concern regarding screening colonoscopy surrounds evidence that the efficacy of screening colonoscopy in preventing cancer was overestimated. Recent studies have found in particular that colonoscopy is more effective in the left colon than in the proximal colon [24–27]. This finding is particularly disturbing, since the original rationale for moving from flexible sigmoidoscopy to colonoscopy screening was the desire to extend the benefits of endoscopic screening from the left colon to the right colon. This approach was based on the assumption, perhaps incorrect in retrospect, that colonoscopy could and would perform similarly in the proximal and distal colons.

Indeed, evidence on the overall effectiveness of colonoscopy for reduction in cancer incidence and prevention of cancer mortality has been mixed since the original publication of the National Polyp Study. An adenoma cohort study from Italy found an 80% reduction in colorectal cancer incidence, similar to the National Polyp Study [28]. A small randomized controlled trial, comparing no screening to flexible sigmoidoscopy with colonoscopy and polypectomy performed for any polyp detected during flexible sigmoidoscopy, also identified an 80% reduction in colorectal cancer incidence in the screened arm, although there was an actual increase in overall mortality in the group undergoing screening [29]. A case control study performed in the U.S. Veterans Administration system found a 50% reduction in colorectal cancer mortality associated with colonoscopy [30]. A case control study from Germany identified a substantial reduction in incidence of colorectal cancer associated with colonoscopy [31], and population-based studies in the United States have identified stage shifts to earlier stage diagnosis associated with growth in the use of colonoscopy [32] and consistent reductions in incidence and mortality of colorectal cancer in the United States, of which about half was recently attributed to screening [33].

Other studies of adenoma cohorts, however, have identified much lower reductions in colorectal cancer incidence associated with colonoscopy and polypectomy. Thus, three chemoprevention trials performed in the United States, with designs similar to the National Polyp Study, reported substantially greater colorectal cancer incidence rates per patient year of observation after colonoscopy and polypectomy

than found in the National Polyp Study, and could identify no reduction of colorectal cancer incidence in the adenoma cohorts compared to that expected based on reference populations [34]. Similar to the chemoprevention trials, two dietary intervention trials performed in the United States also had substantially greater incidence rates of colorectal cancer per patient year of observation than had been described in the National Polyp Study [35, 36]. Admittedly, bringing colorectal cancer rates in adenoma cohorts to that of the general population may represent success, since this cohort would be expected to have a substantially greater incidence of cancer than the general population [37]. However, the results of these studies are certainly disappointing relative to the National Polyp Study.

As noted above, more recent studies have specifically cast doubt on whether colonoscopy prevents proximal colon cancer. A case control study in Ontario identified a 67% reduction in left-sided colorectal cancer mortality associated with colonoscopy but no reduction in proximal colon cancer mortality [24]. A screening colonoscopy study performed in a single state in Germany [25] stratified patients according to whether they were undergoing their initial colonoscopy or whether they had a colonoscopy 1–10 years earlier. Compared to patients with no previous screening colonoscopy, patients who had undergone an earlier colonoscopy had a 93% reduction in the prevalence of rectal advanced neoplasms (including advanced adenomas), 71% reduction in the sigmoid colon, and 64% reduction in the descending colon and splenic flexure, but no reduction in the prevalence of advanced adenomas proximal to the splenic flexure, which occurred in the same percentage of patients in whom prevalent adenomas were found in first-time screening colonoscopies. A case control study performed in the California Medi-Cal population identified a similar trend, though there was some benefit from colonoscopy in the proximal colon [26]. Further, there was a difference in the level of protection against proximal cancers between genders. Thus, colonoscopy was associated with an 82% reduction of distal colorectal cancer in both genders, but proximal colon cancer was reduced by 64% in men and only 18% in women [26]. In the only long-term follow-up study of an actual screening colonoscopy cohort (the original screening colonoscopy cohort at Indiana University Hospital) with follow-up for nearly 20 years in 98% of screenees, colonoscopy was associated with an overall reduction in incidence and mortality of colorectal cancer of about 2/3, but 6/7 incident colorectal cancers were located in the proximal colon [38].

Failures of Colonoscopy to Prevent Proximal Colon Cancer

We are currently faced with an emerging picture in which colonoscopy effectively prevents left-sided colorectal cancer, perhaps at a level of 80%, but is less effective (and possibly is not effective) in preventing proximal colon cancers. A priori reasons why colonoscopy could fail to prevent colorectal cancer are summarized in Table 6.1.

Table 6.1 A priori explanations for failure of colonoscopy to prevent colorectal cancer

Failed detections
Incomplete intubation
Poor preparation
Limitations of technology
Suboptimal inspection technique
Incomplete polypectomy
Variation in tumor biology
Microsatellite instability (MSI)
CpG Island Methylator Phenotype (CIMP)

Table 6.2 Potential explanations why colonoscopy may provide less protection against proximal compared to distal colorectal cancer

Incomplete intubation
Preparation relatively poor in right colon
Higher prevalence of flat lesions in proximal colon
Higher prevalence of serrated lesions in proximal colon

Why should the level of protection be lower in the proximal than the distal colon? Several probable contributors to lower protection in the right colon have been described (Table 6.2), but the relative quantitative importance of these factors is currently completely uncertain.

One of these factors is likely altered tumor biology in the proximal colon (Table 6.2). Interval cancers have a higher prevalence of microsatellite instability (MSI) and of the CpG Island Methylator Phenotype (CIMP) [39]. MSI has been clearly associated with rapid transformation through the adenoma-carcinoma sequence in patients with Hereditary Non-Polyposis Colorectal Cancer (Lynch syndrome) and also occurs in sporadic proximal colon cancers, usually through hypermethylation of the MLH1 gene. This acquired inactivation of MLH1 could potentially drive some sporadic proximal colon tumors through the adenoma-carcinoma sequence more quickly. CIMP-positive tumors have not been fully established as moving through a polyp cancer sequence more quickly, but CIMP-positive tumors are believed to be the end result of serrated polyps. Optimal detection rates for serrated polyps, miss rates of colonoscopists for serrated lesions, and appropriate follow-up intervals for patients with proximal colon serrated polyps all remain uncertain at this writing. An important piece of missing information that would shed light on the contribution of altered biology to failed proximal colon cancer detection is information on whether interval cancers in the proximal colon cluster within individual endoscopists. Clustering within individual endoscopists would suggest that poor proximal colon protection against cancer by colonoscopy is fixable even with current technology. An absence of clustering of proximal colon interval cancers alone, individual colonoscopists would suggest that the problem is

fundamentally related to altered biology, and that either new colonoscopic technology must be developed or that other (noncolonoscopic) means of preventing proximal colon cancer must be developed. Recent studies that update the Canadian experience demonstrate that proximal colon protection is achieved when colonoscopy is performed by gastroenterologists [40], and when it's performed by endoscopists with high cecal intubation rates and high polypectomy rates [41]. Further, the same German investigators that found no impact of colonoscopy on the incidence of proximal colon advanced adenomas, reported that colonoscopy gastroenterologists did reduce the incidence of proximal colon cancer by more than 50% [42]. Thus, substantial protection against proximal colon cancer is achievable by high quality colonoscopy.

Certain potential contributors to poor right colon protection would appear to be correctable. Thus, some colonoscopists clearly use definitions of cecal intubation that are inappropriate, or they fail to reliably recognize the cecum when it has been intubated. The current accepted definition of cecal intubation is passage of the colonoscope tip into the cecal caput so that the medial wall of the cecum between the appendiceal orifice and the ileocecal valve can be thoroughly inspected (Fig. 6.1). It is unacceptable to see the ileocecal valve in the distance or to reach the level of the ileocecal valve with the colonoscope tip and claim cecal intubation [21].

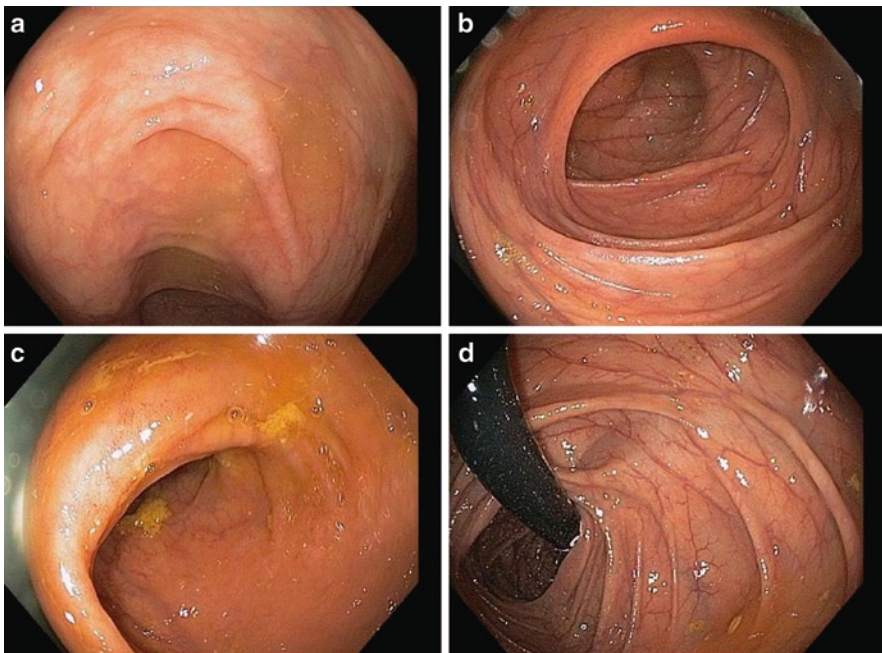


Fig. 6.1 Cecal documentation should include a photograph of the appendiceal orifice (a), and the ileocecal valve (b). If the terminal ileum is intubated, it should be photographed (c). Similarly, retroflexion in the right colon should be photo documented when performed (d). The photographs demonstrate the excellent quality of bowel preparation achieved with split dosing

Thus, the photograph of the appendiceal orifice has become increasingly important as a mechanism of documentation of cecal intubation, and a second photograph of the cecum from just distal to the ileocecal valve is advisable (Fig. 6.1). Another element that is correctable is bowel preparation, which preferentially affects the right colon. Clinical trials of bowel preparation now consistently score right colon preparation separately from overall preparation quality. The key advance in achieving high-quality right colon preparation is split dosing, in which at least half of the preparation is given on the day of the examination, usually 4–5 h prior to the time the examination is scheduled. Split-dosing is a critical aspect of the administration of preparations based on 4-L polyethylene glycol (PEG), 2-L PEG-based preparations, sodium phosphate solution and tablets, and oral sulfate solution [43–53]. Patients are typically quite willing to undergo split dosing once they are aware of its importance for polyp detection [54], and the American Society of Anesthesiology allows clear liquids to be taken up until 2 h prior to the performance of colonoscopy [55]. This recommendation is based on evidence showing that residual gastric volumes are not different in patients being allowed to drink clear liquids up until 2 h prior to examinations [55], compared to individuals who stop drinking many hours earlier. Under optimal circumstances, the colon should be free of both retained fecal debris and chyme and mucus that are produced by the colon and small bowel, and this effect is best achieved by split dosing (Fig. 6.1).

Given full cecal intubation and excellent bowel preparation, there could still be correctable detection issues in the proximal colon that could be overcome by better technology or consistent high level detection technique. In particular, certain lesions that are more prevalent in the proximal colon are also more difficult to see endoscopically and may escape current technology and/or a wide range of inspection techniques [56]. Quantitatively, the most important group of these lesions would appear to be the serrated lesions. The term serrated lesion comprises hyperplastic polyps, sessile serrated polyps (also called sessile serrated adenomas), and true dysplastic serrated adenomas now called “traditional serrated adenomas.” Though hyperplastic polyps occur in abundance in the distal colon, distal hyperplastic polyps are biologically thought to be of less importance than those in the proximal colon. A clear understanding of the importance of serrated lesions to interval proximal cancers is hampered by a number of gaps in knowledge, including the optimal expected prevalence of these lesions during colonoscopy [57], the relative importance of their size vs. number vs. histology with regard to cancer risk [58], the optimal pathologic classification of the lesions [59], and the current difficulties in creating surveillance guidelines [58] because of insufficient data from follow-up studies. Further, serrated lesions are endoscopically subtle relative to adenomas [60, 61]. They are typically pale, though if large and bulky they may develop erythematous changes from prolapse. The edges are often indiscrete, and they are not uncommonly extremely flat. In some instances, a “mucus cap” signals their presence (Fig. 6.2). Certainly, serrated lesions of substantial size and worrisome pathology are more common in the proximal colon [54].

Another group of lesions that may be more prevalent in the proximal colon, though the evidence is less clear, is flat and depressed adenomas [62–69]. Flat and depressed lesions, sometimes collectively referred to as Non-Polypoid Colorectal

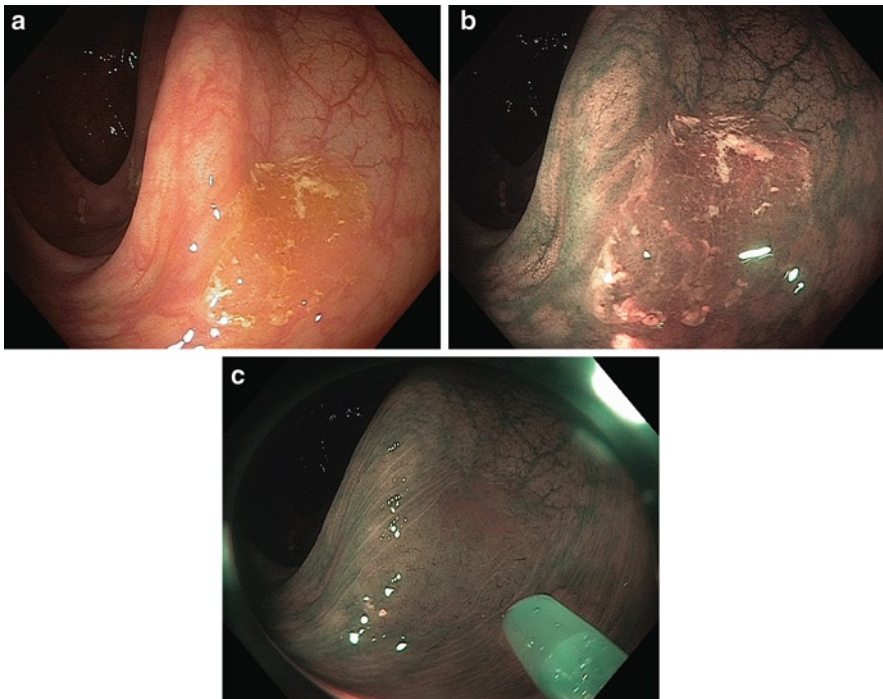


Fig. 6.2 Flat serrated lesion identified on retroflexion in the right colon (a) in white light showing mucus cap, (b) in NBI showing the mucus cap, (c) in NBI after washing the mucus cap off

Neoplasia [67], may account for about 40% of adenomas in the colon [62–69]. However, the overwhelming majority of these lesions have Paris Classification IIa [70] and have histology which is not worse than that of polypoid colorectal neoplasia [66]. The worrisome subgroup are the so-called depressed lesions, which are designated IIc and its variants (IIa+IIc, IIc+IIa) in the Paris classification and which have a dramatically high incidence of high-grade dysplasia and invasive carcinoma [62–69]. Unlike Paris Classification IIa lesions, IIc lesions are detected at a rate of one in every few hundred colonoscopies and are more common during adenoma surveillance than during screening examinations [67]. Given the surface area of several hundred human colons, detecting a single depressed neoplasm is virtually like “searching for a needle in a haystack.” Constant vigilance is needed to detect flat lesions, which are typically perceived by subtle changes in mucosal color, surface contour, loss of vascular pattern, and occasionally by edematous changes at the periphery. Studies of the prevalence of flat and depressed lesions do not typically rely on systematic chromoendoscopy [62–69] to initially detect the lesions but do utilize selective chromoendoscopy after detection to accurately characterize shape. When depressed lesions are removed endoscopically, they should be injected alongside the lesion, and an attempt should be made to remove the lesion en-bloc, with resection of a rim of normal mucosa around the lesion.

Table 6.3 Key measures for improving the quality and cost-effectiveness of colonoscopy as a CRC screening test

Bowel preparation should be given in split doses (half of the dose is given on the day of procedure)
Cecal intubation should be documented by description of landmarks and photography
All colonoscopists should document adenoma detection rates
Withdrawal times should average at least 6 min in intact colons, in which no biopsies or polypectomies are performed; this has greatest relevance to colonoscopists with low adenoma detection rates
Polyps should be removed by effective techniques, including snaring (rather than forceps methods) for all polyps >5 mm in size
Piecemeal resection of large sessile lesions requires close follow-up
In patients with complete examinations and adequate preparation, recommended screening and surveillance intervals should be followed

CRC Colorectal cancer

Note: Reproduced from [23], Table 4

Maximizing Colorectal Cancer Prevention During Colonoscopy

The essential elements of effective colonoscopic prevention of colorectal cancer are summarized in Table 6.3. Effective preparation rests on the use of split dosing, as outlined above. The cecum should be documented by notation of landmarks and photography of the appendiceal orifice. The photographs should optimally be taken from a distance that verifies the cecal strap-fold around the orifice. The terminal ileum should be photographed if entered, and the cecum should be photographed from just distal to the ileocecal valve. Retroflexion should be photographed if performed in the right colon or in the rectum.

The quality of mucosal inspection is documented by the adenoma detection rate of individual operators, which should meet currently recommended thresholds [21, 22]. The withdrawal time should be documented but is a secondary marker of the quality of mucosal inspection, since it fails to explain all variation in adenoma detection [18].

Effective polypectomy techniques should be used, and initial evidence suggests that snaring is generally more effective than forceps techniques. Snaring should be used for all polyps larger than 5 mm, though cold snaring may be adequate for some small (6–9 mm) polyps. Constant vigilance is utilized to detect not only polypoid adenomas but also flat and depressed adenomas and serrated lesions. All serrated lesions in the proximal colon should be removed. Lateral-spreading tumors (carpet adenomas), and larger sessile serrated adenomas that are removed piecemeal should undergo close endoscopic follow-up [58]. At least two follow-ups should be performed to ensure effective eradication of the polyp [71] and effective clearing of the remainder of the colon, since there is a high prevalence of synchronous adenomas and synchronous advanced adenomas in patients with large (>2 cm) lateral-spreading tumors [72].

Conclusions

Colonoscopy has become the dominant colorectal cancer screening strategy in the United States, but recent studies indicate that it is less effective in the prevention of right-sided compared to left-sided colorectal cancer. Colonoscopy is highly operator dependent with regard to adenoma detection, and measurement and documentation of the quality of mucosal inspection by individual endoscopists should be a major focus of colonoscopy screening programs. Effective colonoscopy requires high level detection of adenomas, flat lesions, and serrated lesions and constant vigilance for the rare but very important depressed lesion. Polypectomy techniques should provide effective removal and appropriate concern for safety. Effective lesion detection is facilitated by consistent high quality bowel preparation, for which the critical therapeutic step is split dosing.

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Chapter 7

New Colonoscopic Technologies for Colorectal Cancer Screening

Douglas K. Rex

Keywords Imaging • Real time histology • Resect and Discard • Technology

Introduction

Colonoscopy is an imperfect and operator-dependent technology with regard to detection of colorectal neoplasia. The evidence for operator dependency is overwhelming, and the extent of variation is alarming [1–10]. These detection problems with colonoscopy are particularly problematic, given that the technology is used for almost all colorectal cancer detection and prevention [11]. In the United States and some European countries, colonoscopy is used as a primary screening modality, and in essentially all countries it is used to evaluate other positive screening tests, including fecal occult blood testing, flexible sigmoidoscopy, barium enema, CT colonography, and in the near future serum-based markers for colorectal cancer.

New imaging technologies could improve overall cancer prevention by either highlighting or exposing lesions that are difficult or impossible to detect by any examiners using current technology, or by highlighting or exposing lesions that are missed by low level adenoma detectors, who do not use current technology to its full potential. Thus, these technologies might enhance detection by all examiners or, perhaps more importantly, they could reduce variation between examiners. As will be shown in this chapter, improving detection with imaging technology has been difficult to achieve in convincing fashion.

Another potential role for imaging technology is to provide real-time histologic analysis of detected lesions. This goal has proven easier to achieve, and a number of technologies are now ready to use for this purpose. The clinical implications are

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Table 7.1 Potential clinical uses of real-time histologic analysis

Leave distal hyperplastic colon polyps in place without resection
“Resect and discard”
Predict massive submucosal invasion of cancer (necessitating surgical resection)

several (Table 7.1). For distal hyperplastic polyps left in place, and for the “resect and discard” strategy, an endoscopic photograph would become the record of the polyp. In the “resect and discard” policy, small polyps (or diminutive polyps) have their histology evaluated endoscopically, and the lesions are then resected and thrown away [12, 13]. Postpolypectomy surveillance intervals are then based on the endoscopic histologic assessment, rather than pathology.

Technologies for Improving Detection During Colonoscopy

There are two fundamental problems for detection during colonoscopy [14]: (1) imperfect mucosal exposure (mucosa hidden on the proximal aspects of folds, flexures, valves, etc.) and (2) lesions that are endoscopically subtle, such as flat and depressed lesions or serrated lesions. These goals will be addressed separately according to technologies directed to solving these problems (Table 7.2).

Improving Mucosal Exposure

At least three technologies have been fundamentally directed at improving mucosal exposure, including wide-angle colonoscopy, cap-fitted (or hooded) colonoscopy, and the Third-Eye Retroscope (Avantis Medical Systems, Sunnyvale, CA) (Table 7.2).

Standard commercial colonoscopes have an angle of view (on the imaging lens) of 140°, which was increased to 170° as a standard feature of the Olympus EXERA 180 System (Olympus Corp, Center Valley, PA). The transition from the 140° to 170° angle of view was accomplished without loss of resolution. A tandem study comparing the 170° angle of view to the 140° scope found no improvement in adenoma detection, although it was possible to withdraw the colonoscope faster without any increase in missed lesions with the 170° colonoscope [15]. A subsequent two center U.S. randomized controlled trial involving eight endoscopists again compared the 140°–170° angle of view and found no difference in adenoma detection but overall faster withdrawal using the wide-angle scope [16]. The endoscopists in this study were actually directed to withdraw as fast as they believed they could and still allow optimal detection, an instruction to colonoscopists based on findings of earlier studies [15, 17]. There were individual endoscopists who achieved numerically greater adenoma detection with a wide-angle scope and still could withdraw faster with the instrument [16]. A theoretical model of colonoscope withdrawal on a centering line without tip deflection, based on CT colonography,

Table 7.2 Technologies for improving detection during colonoscopy

Goal	Technologies
Improving mucosal exposure	Wide-angle colonoscopy
	Cap-fitted colonoscopy
	Third-Eye Retroscope
Highlighting flat lesions	Chromoendoscopy
	High definition imaging
	Narrow band-imaging
	Fujinon intelligent chromo endoscopy (FICE)
	I-Scan
	Autofluorescence

suggested that without tip deflection the 170° angle of view increased mucosal exposure by 4% (87–91%) [18]. It is possible that users of the 140° scope compensate for this difference by tip deflection. Therefore, wide-angle colonoscopy has only been shown at the present time to produce an operator-dependent reduction in withdrawal time without an associated increase in missing. Another tandem study, using a 210° angle of view instrument with some loss of resolution, found no improvements in adenoma detection but even larger gains in the efficiency of withdrawal [17].

A number of trials have evaluated cap-fitted, or hooded, colonoscopy [19–27]. A variety of caps of different sizes, transparency, and flexibility have been utilized in these studies. Caps have also been evaluated for their effect on the efficiency of insertion and are generally considered to provide an advantage, especially for trainees [21–26]. This effect may be the result of avoidance of “redout” as the cap holds the mucosa off the tip of the colonoscope. During withdrawal, the cap is utilized to improve polyp detection by flexing it against haustral folds in order to flatten them. Two Japanese studies, by the same group of investigators, have found an improvement in adenoma detection using cap-fitted colonoscopy [19, 28]. However, the miss rates calculated in the control group were only 4 and 5% for adenomas [19, 28], substantially below the expected miss rate of >20% [1, 15, 17, 28–32]. Other studies have shown improvement in polyp detection without specific comment on adenoma detection [19–28]. A single large Asian randomized trial found that cap-fitted colonoscopy was actually associated with lower adenoma detection rates [24]. However, the two arms of the study were not controlled for bowel preparation or withdrawal time. A recent U.S. study of 100 patients performed in tandem design found improved detection of adenomas <5 mm in size using a cap device [33]. Therefore, overall results have been mixed and the benefits could be operator dependent. There appear to be few downsides of using the cap, since it does not slow insertion and the caps are inexpensive.

The Third-Eye Retroscope is a disposable catheter passed down the working channel of the colonoscope until it exits the colonoscope tip, where it automatically retroflexes. The device has an imaging lens in its tip with a complementary metal oxide semiconductor (CMOS) chip and a polarizer that prevents image glare from the colonoscope light. The retroflexed image of the colon is observed on a second monitor. In an initial study in which the investigators estimated whether individual

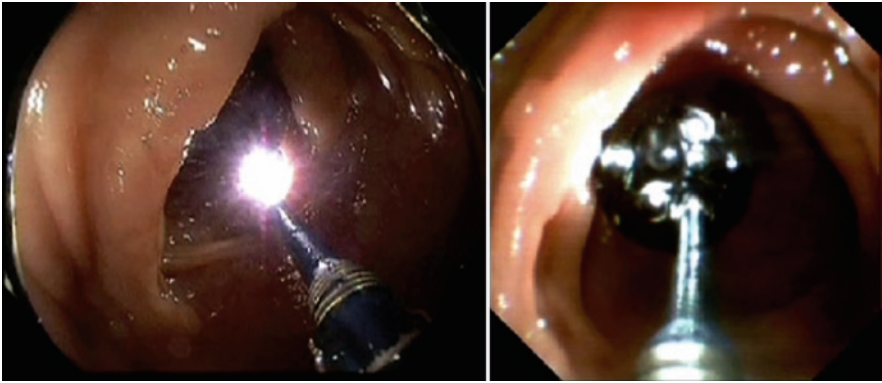


Fig. 7.1 (Left) The forward view from the colonoscope with the Third Eye Retroscope (TER) in view. (Right) The view from the TER with a small polyp on the proximal side of a fold seen in the upper left

polyps were detectable only by the Third-Eye Retroscope, there was an 11% gain in adenoma detection using the device [34] (Fig. 7.1). A randomized tandem study is currently in progress with the Third-Eye Retroscope and results are pending.

Imaging Technologies for Flat Lesions

Pancolonic chromoendoscopy (systematic dye spraying of the entire colorectum) has been evaluated in several randomized trials for its effect on adenoma detection [35–38]. Several of the trials are positive for improved detection of small adenomas, but the lesions have been small tubular lesions with low-grade histology [35–38], except for one trial with an unexpectedly high prevalence of high-grade dysplasia in tiny flat lesions [36]. Since pancolonic dye spraying is labor intensive, there is no consensus that it should be used for routine colonoscopic screening or surveillance. On the other hand, chromoendoscopy is a consideration in high-risk patients, possibly those with Hereditary Non-Polyposis Colorectal Cancer (HNPCC) or Lynch syndrome, and has a clearly established role for lesion detection in ulcerative colitis [39, 40]. In ulcerative colitis, pancolonic dye spraying can be performed with either methylene blue or indigo carmine, but some investigators are concerned about the potential carcinogenic effects of methylene blue. In the nonulcerative colitis patient, pancolonic dye spraying is typically performed with dilute (0.2–0.4%) indigo carmine [35–38].

Highlighting flat lesions can also be achieved by electronic means, sometimes referred to as electronic chromoendoscopy (Figs. 7.2 and 7.3). Each of the major endoscope manufacturers has developed a push-button operated system that is now standard equipment on their commercial colonoscopes. These systems are narrow-band

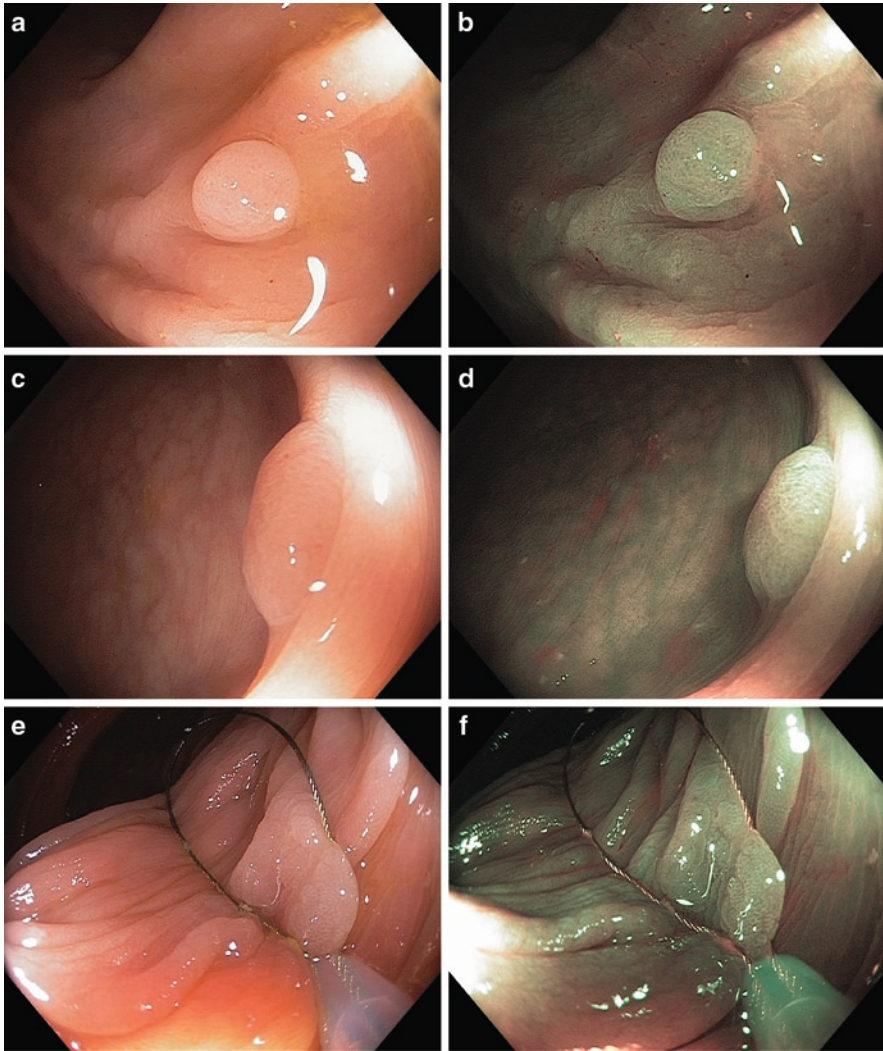


Fig. 7.2 (a–f) Hyperplastic polyps in white light (a, c, e) and blue light (NBI; b, d, f). The characteristic features are a color that is similar to or lighter than the surrounding mucosa in NBI, an absence of blood vessels (or few thin lacy vessels that course between the pits and across the polyp surface) and the “black dot” pattern seen best in NBI photographs (b) and (d)

imaging (blue light illumination or narrow band imaging (NBI)), which is utilized in current Olympus colonoscopes and post-processing imaging systems, such as the Fujinon Intelligent Chromoendoscopy System (FICE) (Fujinon, Wayne, NJ), and the I-Scan by Pentax (Morrisville, NJ). Of these, NBI is the most extensively studied. Although NBI has been positive for improving adenoma detection in some studies that have not been properly constructed, appropriately performed tandem and

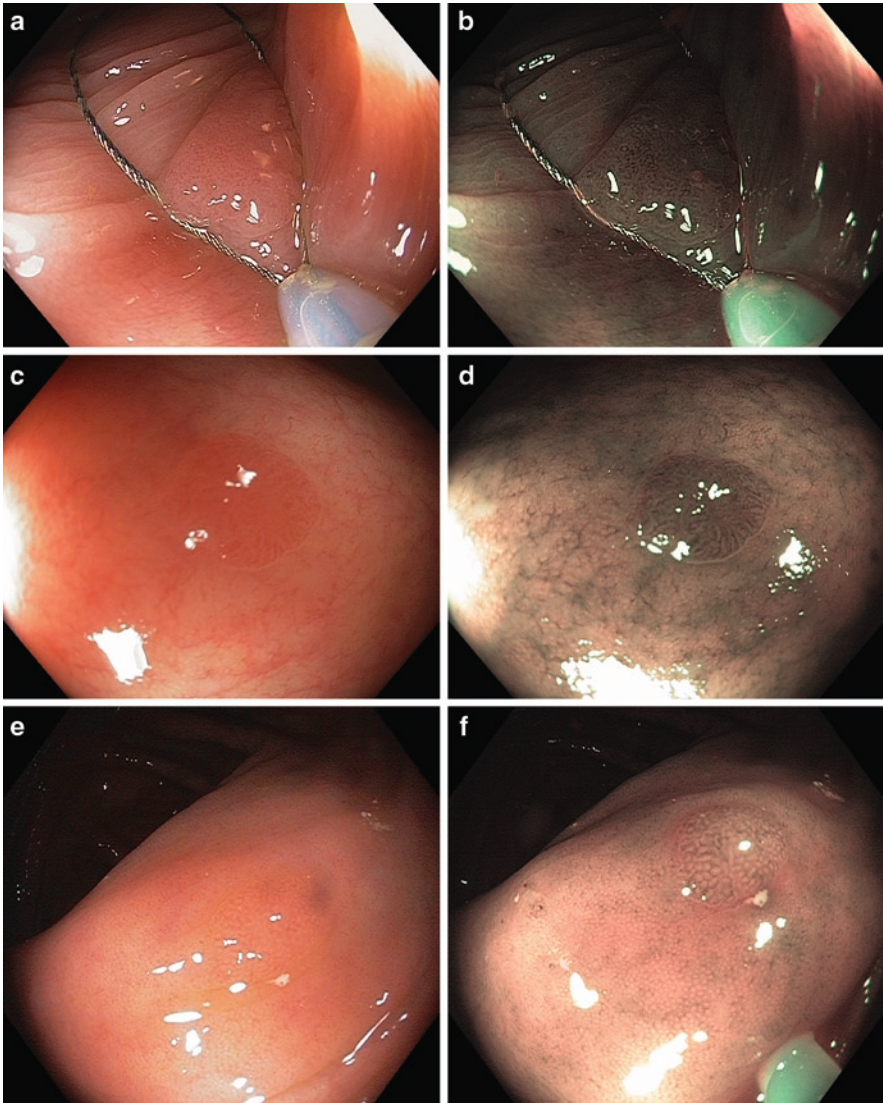


Fig. 7.3 (a–f) Adenomas in white light (a, c, e) and blue light (b, d, f) (narrow band imaging – NBI). NBI has a highlighting effect because the colon contrast between the adenoma and normal mucosa is greater than that provided by white light. The features indicating adenomatous histology are *brown in color* (created by blood vessels), the oval and tubular *white structures* (which may be pits), and the relationship of the vessels to the white structures (the vessels surround the white structures and do not continue across the polyp surface)

randomized controlled studies have been largely negative for an effect on adenoma detection [30, 41–45]. This may reflect that flat adenomas, when visualized by NBI, are invariably present when viewed in white light, and that the investigators in the study were likely primarily high level adenoma detectors. In one study in which

there was initially very poor adenoma detection with white light, NBI was initially superior to white light for adenoma detection, but the two modalities had equal performance by the end of the study [41]. This result has been interpreted as a learning effect, in which low level adenoma detectors may learn the appearance of flat lesions in white light after their initial detection with NBI. An initial randomized controlled trial testing FICE for improved adenoma detection was negative [46]; while a trial with the I-Scan post-processing method was positive [47]. Two trials have tested autofluorescence technology, which is compatible with the Olympus LUCERA system sold in Japan and the United Kingdom, but which is not currently compatible with the Olympus EXERA System sold in North American and continental Europe. Of the two trials, one was positive for improved adenoma detection [48, 49].

Overall, there is not convincing evidence that adenoma detection is improved by electronic chromoendoscopy, though there could be a learning effect for low level adenoma detectors.

Technologies That Allow Real-Time Histology

Another goal of colonic imaging technology is determination of the histology of detected lesions in real time. This issue is distinct from the one discussed previously, that of initial detection of neoplasia. However, some technologies that have been studied for improvements in adenoma detection have also been studied for utility in enhancing determination of real-time histology (Tables 7.2 and 7.3). Real-time histology has traditionally been considered ineffective using white-light

Table 7.3 Imaging technologies for determination of real-time histology during colonoscopy

Technology	Manufacturer	Push button on standard colonoscopes	Adenoma vs. hyperplastic	Identify high-grade dysplasia
Chromoendoscopy with optical magnification	+++	*	Y	N
NBI with optical magnification	Olympus (LUCERA)	Y	Y	Y
NBI with high definition	Olympus (EXERA)	Y	Y	N
Fujinon Intelligent Chromo Endoscopy	Fujinon	Y	Y	N
Pentax I-Scan	Pentax	Y	Y	N
Autofluorescence	Olympus	Y	Y	N
Scope-based confocal laser microscopy	Pentax	N	Y	Y
Probe-based confocal laser microscopy	Mauna Kea Technologies	N	Y	Y
Endocytoscopy	Olympus	N	Y	Y

+ Optical magnification is available on Fujinon colonoscopes, on Olympus LUCERA models, and on specialized Olympus 160 series colonoscopes sold in the U.S., and continental Europe

*The magnification mode is pushbutton on some models

endoscopy. Certainly that conclusion is misleading, since the histology of some lesions is clearly evident in white light. For example, some red-headed pedunculated adenomas have obvious tubular or branched red structures which are blood vessels and white structures which may correspond with tubular pits. These lesions can confidently be interpreted as adenomas (Fig. 7.4). However, a subset of lesions is very difficult to interpret in white light.

The clinical implications of real-time histology are substantial (Table 7.1). First, small hyperplastic polyps in the distal colorectum are believed not to require resection because of their extremely low risk for cancer development. Leaving such polyps in place would reduce polypectomy costs and risks and reduce costs associated with pathologic assessment of polyps. A second clinical goal has been defined as the “resect and discard” policy. This has been evaluated in two prospective trials, one in the U.S. [12] and one in the U.K. [13]. The target group for “resect and discard” in the U.S. study was polyps ≤ 5 mm in size and in the U.K. study polyps ≤ 9 mm in size. The focus on diminutive or small polyps rests on the ability of all technologies to consistently determine whether polyps are adenomatous versus hyperplastic but the inability of certain technologies to identify high-grade dysplasia or villous elements (Table 7.3). Thus, polyps that are larger and which have a clinically significant prevalence of villous elements and high-grade dysplasia that would require identification by pathologic assessment are excluded from the strategy. Since U.S. guidelines for postpolypectomy surveillance incorporate villous elements and high-grade dysplasia [50], the logical focus of “resect and discard” in the U.S. is on polyps ≤ 5 mm in size. Guidelines for postpolypectomy surveillance in the U.K. do not consider villous elements or

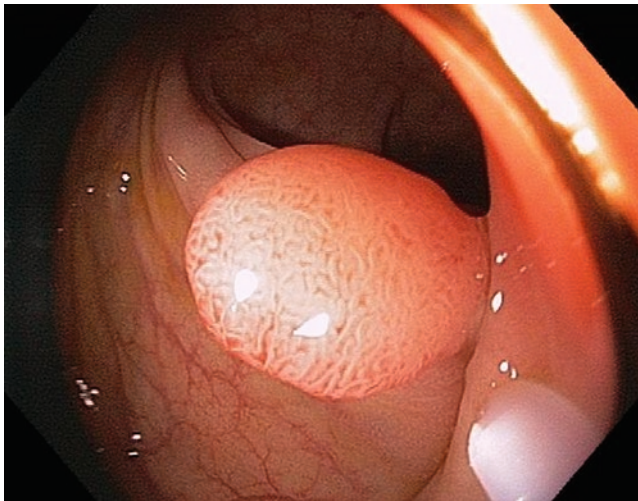


Fig. 7.4 This polyp is an adenoma. The interpretation can be made with high confidence in white light because the blood vessels (*red structures*) are easily visible, and the vessels surround tubular and oval *white structures* which may correspond to pits

high-grade dysplasia, and thus the focus of “resect and discard” in the U.K. study was polyps ≤ 9 mm in size [51].

A concept introduced in the U.S. study was that of confidence levels in interpretation [12]. Since the purpose of “resect and discard” is to identify the histology of the polyp by endoscopic assessment, resect it, and then not send it to the pathologist to reduce the costs associated with pathologic assessment, the accuracy of endoscopic assessment can be enhanced by the use of confidence levels. The use of confidence levels in selecting tests permeates clinical medicine. In the context of polyp assessment, confidence intervals imply that a high level of confidence in endoscopic assessment would allow “resect and discard” without pathology assessment to proceed; while a low level of confidence would be followed by resection and submission for pathology assessment.

Technologies available for real-time assessment of colorectal polyp histology are shown in Table 7.3. They are divided there according to their practicality as pushbutton technologies that are available in standard commercial colonoscopes versus technologies that require special capital investment in equipment.

The concept of real-time histology developed initially in Japan. Professor Kudo, using selective dye spraying and magnification endoscopy, described the pit pattern of non-neoplastic lesions, neoplasms, benign adenomas, and invasive carcinomas [52]. Although some have assumed that images seen with NBI demonstrate structures that correspond to pits, the exact origin of all of the structures visualized with NBI (with the exception of blood vessels) is not fully established.

Of all of the technologies, the best studied is NBI or blue-light illumination, which is patented by the Olympus Corporation. As noted above, Olympus markets two endoscope systems worldwide, and the LUCERA System sold in Japan and the U.K. includes optical magnification. Therefore, of the studies emanating from these countries, the accuracy typically reflects the combined effects of NBI and high-magnification [53–63]. Importantly, the recent “resect and discard” study from the U.K. did not employ the optical magnification modality [13]. Several studies from the United States have employed NBI with high-definition colonoscopy [12, 63–68], but optical magnification in Olympus colonoscopes is not available in North American and continental Europe. The EXERA systems sold in North America and continental Europe do include electronic magnification, but image expansion with this system is associated with diminished resolution. However, the EXERA system has been effective with accuracies above 90% [12], particularly in the case of polyps interpreted with high confidence [12], which has been possible for about 80% of diminutive polyps. Accuracies tend to increase with increasing polyp size [12, 63–68].

NBI with optical magnification has also been shown to allow the identification of the degree of dysplasia in adenomas in a single study [54].

The differentiation of adenomas from hyperplastic polyps using NBI relies on a series of criteria that incorporate interpretation of blood vessels and structures that may correspond to pits, although this has not yet been determined with certainty (Figs. 7.2 and 7.3). In essence, adenomas are brown in color, have short, thick blood vessels that surround tubular or oval white structures that may correspond to pits.

There is sometimes a brown shallow depression in the central portion of adenomas that is highly for specific adenomas. The brown color in the central depression is produced by numerous closely spaced punctate blood vessels. Hyperplastic polyps have either no vessels or lacy vessels that extend beyond the margins of pits and sometimes have a “black-dot” pattern that may correspond to Kudo classification Type 2 pits (Fig. 7.2).

Initial studies found that post-processing using FICE and I-Scan were also effective in differentiating adenomas from hyperplastic polyps [69, 70], but additional data are needed.

An apparent advantage for pushbutton technologies would include that they are relatively easy to learn and document by photography and presumably would not add to the cost of colonoscopy.

Other technologies, such as confocal laser microscopy [71–73] and endocytoscopy [74], require a greater investment in capital for equipment, more time for learning and performance, and therefore could increase the cost of colonoscopy. However, these technologies also provide additional information, in that they not only allow reliable differentiation of adenomas from hyperplastic polyps but also they can identify the degree of dysplasia and the presence of invasive cancer. Confocal laser microscopy is available as part of a specialized colonoscope from Pentax and also as a probe-based technology from Mauna Kea Technologies (Table 7.3).

Conclusions

For improving mucosal exposure, cap-fitted colonoscopy and the Third-Eye Retroscope warrant additional evaluation. No method that is both effective and practical for improving adenoma detection during colonoscopy has been definitely described. A number of technologies are now available that can accurately differentiate adenomatous from hyperplastic polyps in the colon, and some of these technologies can provide additional information regarding degree of dysplasia and the presence of invasive cancer. Pushbutton technologies are practical and should improve the cost-effectiveness of colonoscopy, including leaving distal colon hyperplastic polyps in place, and the development of the “resect and discard” strategy for diminutive and perhaps even small polyps.

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Chapter 8

Screening for CRC Using CT Colonography*

Brooks D. Cash

Keywords Computerized axial tomography • Radiology • Interpretation

Introduction

Air contrast barium enema (ACBE), flexible sigmoidoscopy, and colonoscopy have been used to image the colon for many years. In recent years, a number of new techniques to image the colon have been introduced and prominent among these is computed tomographic (CT) colonography (also called “CTC,” “CT colography,” or “virtual colonoscopy”). CT colonography is a high spatial resolution, low-dose CT exam of the abdomen and pelvis performed following colonic insufflation. CT datasets are reviewed on a computer workstation that generates multidimensional images of the colon (Figs. 8.1–8.3). CT colonography is extremely attractive because it is noninvasive and also relatively simple for patients to undergo and these qualities have made CT colonography a serious entrant into the field of colorectal cancer (CRC) screening.

*The views expressed in this article are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Army, Department of Defense, nor the U.S. Government.

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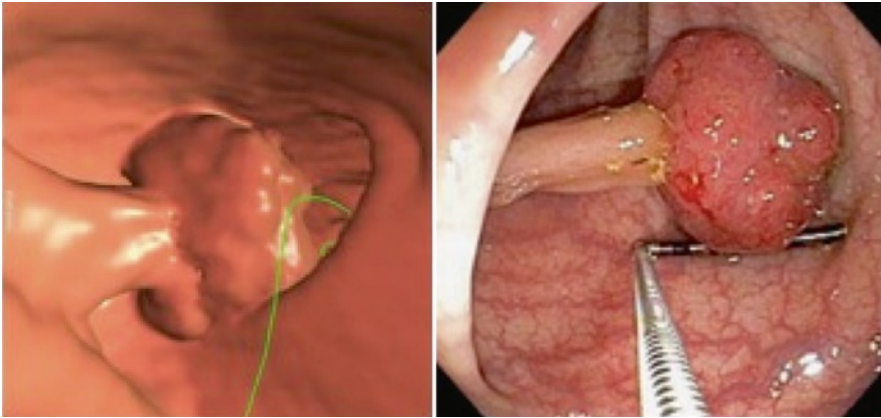


Fig. 8.1 3D appearance of a large colon polyp on CT colonography and its endoscopic correlate

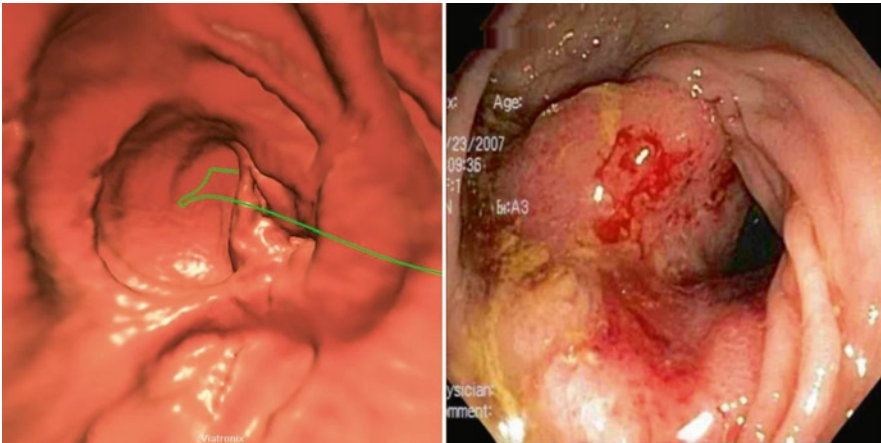


Fig. 8.2 3D appearance of an “apple-core” colon mass on CT colonography and its endoscopic correlate

Current Status of CT Colonography

Investigation of the accuracy of this technology has been underway since the introduction of CT colonography. CT colonography sensitivity has been studied extensively [1–10], with the earliest reports involving small populations at high risk for colorectal pathology and using primarily single-row scanners [11]. In these reports, the per-polyp sensitivity of CT colonography compared to colonoscopy

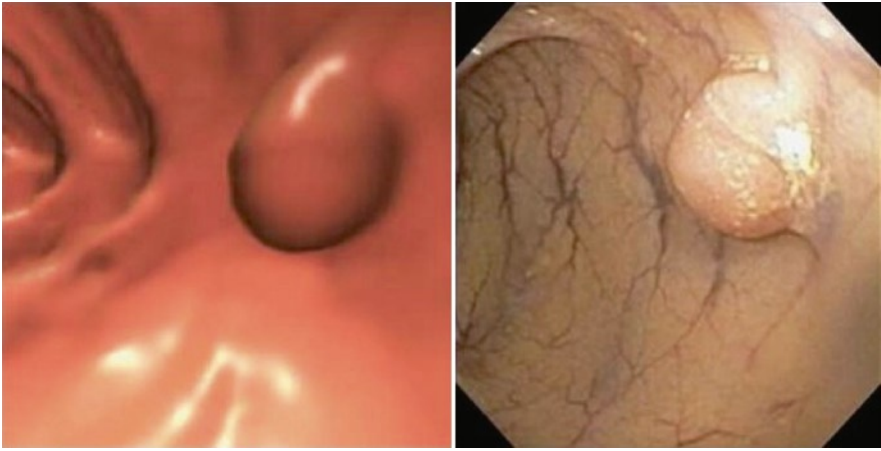


Fig. 8.3 3D appearance of an intermediate sized polyp (6–9 mm) and its endoscopic correlate

was excellent for larger lesions (in some reports up to 100%), but was poor for smaller lesions (11–55% sensitivity). These studies were extremely heterogeneous, varying in terms of patient cohorts, technical methodology, and training of CT colonographers.

As the practice of CT colonography evolved, subsequent studies demonstrated improved detection sensitivity for polypoid lesions, but continued to reveal wide variation in results. In general, the per-polyp sensitivities continued to be greatest for larger lesions and were in the following ranges: <5 mm (30–60%), 6–9 mm (45–85%), and ≥ 10 mm (60–95%). Two large, multicenter studies demonstrated that CT colonography was significantly less sensitive than colonoscopy [1, 2], a third reported similar sensitivity [10], and a fourth reported that CT colonography was more sensitive than colonoscopy for detection of lesions ≥ 10 mm [3]. Several CT colonography studies from European centers have also explored the accuracy of this test compared to colonoscopy [12, 13]. A multicenter trial of CT colonography in patients at increased risk of colonic neoplasia due to family history, personal history of adenomatous polyps, or positive FOBT concluded that CT colonography was comparable to colonoscopy performed on the same day [12]. The sensitivity of CT colonography for polyps with a diameter of 6 mm or larger was 85.3% (95% CI: 79.0–90.0%) and for polyps 10 mm or larger, 90.8% (95% CI: 84.2–95.0%). The other study compared the diagnostic accuracy of colonoscopy, CT colonography, flexible sigmoidoscopy (alone and in combination with) FOBT and FIT, in average risk, asymptomatic patients undergoing CRC screening [13]. Colonoscopy identified 100% of advanced colonic neoplasia and CT colonography identified 96.7% (95% CI: 82.8–99.9%). For polyps larger than 5 mm the sensitivity of colonoscopy was 97.8% (95% CI: 88.5–99.9%) while that of CT colonography was

91.3% (95% CI: 79.2–97.6%). The specificity observed with colonoscopy and CT colonography in this study were also comparable and both testing modalities were significantly more accurate than the other modalities tested. The specificity in all of the other studies of CT colonography mentioned above varied as well, but was generally in the 85–95% range.

A number of variables appear to contribute to the wide range of sensitivities reported for CT colonography. First, and perhaps most importantly, different technologies have been used. Not only has CT hardware varied, but so has the software used to analyze images. Among six large multicenter studies, two [1, 2] used primary 2D reading, two used a primary 3D fly-through technique [3, 13], and two used either interpretation mode as the primary method, reserving the alternative mode for problem solving [10, 12]. While results from the older studies showed that the sensitivity reported using primary 3D fly-through reading (>90% for polyps ≥ 1 cm in diameter) was far greater than that reported in studies using primary 2D reading (50–60% for polyps ≥ 1 cm in diameter), recent studies using either method have produced remarkably similar results [1–3, 10, 12, 13] (Table 8.1).

Bowel preparation methods have also varied with some studies including the use of oral contrast while others have not. An additional critical variable is the cohort of individuals examined. Some studies have included patients at high risk for colon abnormalities, while others have examined cohorts at low risk. Some studies examined highly variable cohorts. Finally, the method in which it was ascertained that lesions detected by CT colonography were accurately assessed has varied as well. Colonoscopy has typically been used as the “gold standard,” however colonoscopy does not detect all lesions, including large polyps [14–16]. Thus, its use as a “gold standard” may not be entirely appropriate. One study reported use of a “consensus” view of the colon based on the results of three different colon imaging tests as the reference standard [1], an appropriate approach in clinical trials for sensitivity and specificity, though certainly not as clinically applicable as using colonoscopy as the gold standard.

New modifications in software analysis/rendering of images – including so called “virtual dissection” [17] and computer aided diagnostics (CAD) are on the horizon [18–21]. CAD in particular appears to be a major potential advance. Volumetric data sets are generated from transverse CT sections and volumetric features characterizing polyps are computed. Polyps can then be detected by means

Table 8.1 Test characteristics: CT colonography for CRC screening in high-quality trials

References	Number of patients	Mean age	CT colonography sensitivity 6–9 mm polyps	CT colonography sensitivity >10 mm polyps
Pickhardt et al. [3]	1,233	57.8	83.6%	92.2%
Johnson et al. [10]	2,531	58.3	78.0%	90.0%
Graser et al. [13]	307	60.5	91.3% (>5 mm)	92% (>9 mm)
Regge et al. [12]	937 (Inc Risk Cohort)	60.0	85.4% (adv neoplasia)	90.8% (adv neoplasia)

of sophisticated thresholding algorithms followed by mathematical rule-based testing on the basis of feature values [22–25]. While this technique appears to hold great promise and will likely be readily integrated into reading schemes [26, 27], many issues with regard to implementing CAD into clinical practice remain.

Considerable study has also been directed at developing a minimal preparation CT colonography examination [6, 28]. It has even been suggested that it may be possible to perform CT colonography without a cathartic preparation [29]. Such an approach, if proven to be highly sensitive and safe, could revolutionize the entire field, but thus far clinically applicable large-scale trials evaluating prepless CT colonography are lacking.

Guidelines and Recommendations

Several task force and society recommendations, technology assessments, and coverage decisions pertaining to the practice of CT colonography have been released that have had an impact on the adoption of CT colonography. In May 2008, the American Cancer Society and the US Multi-Society Task Force on Colorectal Cancer (ACS/MSTF) and the American College of Radiology (ACR) released their recommendations regarding screening and surveillance for CRC and adenomatous polyps [30]. These guidelines were developed using an evidence-based approach coupled with expert opinion when “the evidence was insufficient or lacking to provide a clear, evidence-based conclusion.” For CT colonography, the authors felt that recent data suggested that CT colonography was comparable to colonoscopy for the detection of cancer and polyps of significant size when state-of-the-art techniques are applied. The expert panel concluded that there were sufficient data to include CT colonography as an acceptable option for CRC screening of average risk adults beginning at age 50 years. While the task force acknowledged that the interval for repeat CT colonography exams had not been adequately studied, it would be reasonable to repeat exams every 5 years if the initial CT colonography is negative for significant polyps. Specifically, they opined that patients whose largest polyp was 6 mm or greater should be offered colonoscopy for polypectomy. CT colonography surveillance could be offered to those patients who would benefit from screening, but either decline colonoscopy or are not colonoscopy candidates for one or more reasons.

In October 2008, the U.S. Preventive Services Task Force [31, 32] (USPSTF) released their recommendations on screening for CRC and concluded that the evidence was insufficient to assess the benefits and harms of CT colonography as a screening modality. The fact that the point estimates for the sensitivity of CT colonography for smaller adenomas in ACRIN [10] were 11% lower than in the study by Pickhardt [3] and significantly lower than estimates for optical colonoscopy obtained by using an enhanced reference standard of segmental unblinding, suggested to the USPSTF that there was uncertainty about the true sensitivity of CT

colonography for smaller adenomas. According to the USPSTF, additional uncertainties associated with CT colonography screening include potential long-term harms from CT colonography-related radiation exposure and extracolonic findings. Because CT colonography produces images of structures outside the colon, the implications of extracolonic findings that occur with CT colonography screening, including potential benefits from early disease detection as well as harms from unnecessary medical testing and anxiety, are unclear. Extracolonic findings detected by CT colonography are common, occurring in 27–69% of persons screened with this modality. The classification of extracolonic findings has varied but generally includes three types of clinical significance: high (findings that require surgical treatment, medical intervention, or further investigation), moderate (findings that would not require immediate medical attention, but would probably require recognition, investigation, or future treatment), and low (findings that would not require further investigation or treatment). Extracolonic findings of high clinical significance (for example, indeterminate solid organ masses or chest nodules, abdominal aortic aneurysms ≥ 3 cm, aneurysms of the splenic or renal arteries, or adenopathy >1 cm) occurred in 4.5–11% of asymptomatic populations, while findings of moderate clinical significance (such as renal calculi and small adrenal masses) occurred in more than 25% of cases. Since all extracolonic findings of high significance, along with some moderate findings, would require medical follow-up, these have the potential for additional morbidity and cost, as well as potential benefit.

In March 2009, the California Technology Assessment Forum (CTAF) released their analysis of CT colonography for colorectal cancer screening in average risk individuals [33]. While the Forum concluded that the accuracy of CT colonography in detecting significant colorectal abnormalities was relatively comparable to colonoscopy, that it had potential benefits including the detection of small polyps, and that it may be more acceptable to patients compared to other more invasive options, radiation exposure and identification of extracolonic lesions were identified as potential harms. The CTAF felt that it was not known whether the potential harms of CT colonography were outweighed by the potential benefits and noted that assessing the impact of the potential harms would take a longer duration of study. In addition, the CTAF concluded that whether CT colonography leads to an improvement in health outcomes had not been shown outside the investigational setting.

In May 2009, the Centers for Medicare and Medicaid (CMS) released their “Decision Memo for Screening Computed Tomography Colonography for Colorectal Cancer”, in which they concluded that the evidence was inadequate to provide coverage for CT colonography as a CRC screening test under §1861(pp)(1) of the Social Security Act [34]. The determination of whether CT colonography is an appropriate screening test under Medicare involved the consideration of test parameters and health outcomes. The CMS analysis focused on the following questions:

- Is the evidence sufficient to determine that CT colonography is a valuable screening test for CRC for average risk Medicare individuals compared to optical colonoscopy?

- Is the evidence sufficient to conclude that the use of CT colonography for CRC screening for average risk Medicare individuals improves health outcomes compared to optical colonoscopy?

CMS cited several reasons for their noncoverage decision. Since CT colonography cannot reliably detect polyps <6 mm, the impact of these polyps in the intervening screening interval of CT colonography is unknown at this point. As the percentage of participants with extracolonic findings ranged from 58 [35] to 66% [10], and since individuals undergoing screening are asymptomatic by definition, the potential impact of extracolonic findings on health outcomes needs to be determined prior to general use of this modality, according to CMS [36].

In August 2009, the Blue Cross/Blue Shield Technology Evaluation Center (TEC) released an analysis of CT colonography [37]. The TEC concluded that, bolstered by the data from several additional studies of both screening and diagnostic CT colonography, CT colonography meets the criteria to be considered an effective CRC screening test. The TEC felt that a 90% sensitivity of CT colonography for detection of polyps 10 mm or larger is consistent with an improvement in health outcomes due to detection and removal of precancerous lesions. The 86% specificity of CT colonography would result in some false-positive tests, which, in turn, would result in some unnecessary follow-up colonoscopies. The TEC also acknowledged that there are several other types of health outcomes that may differ in terms of convenience, cost, detection of unrelated health problems, and radiation exposure. It opined that these outcomes are difficult to quantify and are probably small in magnitude compared to the health benefit of identifying and removing cancer precursors from the colon.

The TEC noted the different conclusions regarding the use of CT colonography for CRC screening from various consensus groups reviewing the same evidence. The USPSTF appears to put more emphasis on the potential unknown effects of radiation exposure and workups for extracolonic findings, taking a more longitudinal perspective. The ACS/MSTF report concentrates on the capability of CT colonography to detect large polyps in a single screening visit as the principal criterion to determine colon cancer prevention, favoring screening technologies with superior single screening detection characteristics over less sensitive tests that have demonstrated efficacy with repeated screening. They concluded that based on current evidence, it appears clear that the question is no longer if or when CT colonography is ready to become a routine CRC screening test, but rather how CT colonography will be accepted and deployed into routine clinical practice in the United States.

Current Indications for CT Colonography

The breadth of current clinical indications for CT colonography is controversial (Table 8.2). Several organizations have recommended that CT colonography be considered an option for CRC screening [30, 38] while others continue to cite insufficient evidence to make such recommendations [31, 33]. Indications and opinions regarding the role for CT colonography are highlighted below.

Table 8.2 Indications for CT colonography

CRC screening of asymptomatic, normal-risk adults
Failed colonoscopy
Evaluation of colon proximal to an obstructing lesion
CRC screening in patients who refuse or who have contraindications to colonoscopy or who refuse other screening options

CRC Screening of Asymptomatic, Normal-Risk Adults

Multiple trials have examined the accuracy of CT colonography for the identification of CRC and polyps. Most of the early efforts investigated the role of CT colonography in patients who were at greater than average risk for the development of CRC or who had symptoms referable to the lower gastrointestinal tract [39–41]. A meta-analysis of 33 early studies comparing CT colonography screening to a gold standard (colonoscopy or surgery) [42], concluded that issues such as patient selection, examiner training and experience, scanner collimation and type, and mode of imaging are likely contributors to the heterogeneity observed in these trials. Recently however, several large studies examining CT colonography accuracy for detecting CRC and colon polyps in screening populations have been published [3, 10, 13]. Taken as a whole, the updated body of literature examining screening CT colonography demonstrates a sensitivity for CRC and polyps ≥ 6 mm that approaches that of colonoscopy and is superior to results obtained with other methods of screening.

The first large-scale trial of CT colonography as a CRC screening test in average risk patients was conducted in several of military tertiary care hospitals [3]. Sensitivity of CT colonography for adenomas ≥ 1 cm was 94%, compared to colonoscopy as the gold standard. This trial utilized experienced CT colonography interpreters, water soluble and insoluble contrast labeling with subsequent digital subtraction of retained stool and fluid in the colon, and relied on a primary three-dimensional interpretation of CT colonography images, all techniques which distinguished it from previous studies. Whether or not these factors were critical in the encouraging results observed in this trial remains controversial. Currently, investigators from the National Naval Medical Center in Bethesda, MD, are performing a 3,000-person study designed to validate or refute these results. Preliminary data from this trial have been encouraging, demonstrating diagnostic equivalence of CT colonography with colonoscopy for adenomas ≥ 6 mm in size [43].

More recently, results of the largest CT colonography screening trial to date were published [10]. Known as the “ACRIN II” trial (American College of Radiology Imaging Network), this study of 2,600 patients found that CT colonography had a 90% sensitivity (compared to colonoscopy) for the identification of CRC or adenomas ≥ 10 mm. The per-patient sensitivity for identifying polyps 6 mm or more in diameter was 78% with a specificity of 88%. Notably, the sensitivity for smaller lesions (particularly those in the 5–7 mm size range) was substantially lower than

for larger lesions. This study, which was in part designed to demonstrate the generalizability of CT colonography in routine practice settings and failed to accomplish this goal since the study was performed at referral centers with extensive CT colonography experience and enlisted 15 radiologist CT colonographers who were highly experienced and had to demonstrate a minimum level of proficiency by passing an entry examination prior to being allowed to participate in the trial. Readers used different CT colonography imaging processing software and a variety of interpretation methods, though all used a combination of 2-dimensional and 3-dimensional interpretation.

CT colonography has been endorsed as a primary CRC screening test by the multidisciplinary group comprised of members of the ACS, MSTF, and the ACR [30]. These guidelines recommend CTC as an acceptable screening test in asymptomatic, average risk individuals at 5 year intervals. They also recommend removal via polypectomy of every polyp ≥ 6 mm. Recently, the American College of Gastroenterology (ACG) included CT colonography among its recommended tests for CRC screening for patients unwilling or unable to undergo colonoscopy [38]. As previously mentioned, the USPSTF felt that there was insufficient evidence to assess the benefits or potential harms of CT colonography in its most recent recommendations and CMS followed suit in issuing their noncoverage decision for screening in Medicare patients in 2009 [31, 34]. Nevertheless, more than 20 states currently mandate private payer coverage for CRC screening tests in accordance with ACS guidelines (i.e., including CT colonography) [44] and the number of private insurance companies covering CT colonography for CRC screening is increasing [45, 46].

Finally, there is now published data regarding the use of CT colonography screening in Medicare-eligible patients. A description of the experience from the University of Wisconsin [47] compared the results of CT colonography in 577 average risk patients between the ages of 65–79 years to those obtained in the general screening population with a mean age of 56.9 years and found, not surprisingly, that Medicare aged patients were more likely than the general screening population to harbor advanced colonic neoplasia (7.6 vs. 3.2%, $p < 0.001$) and to progress to colonoscopy based on CT colonography findings (15.3 vs. 7.9%, $p < 0.001$). Older patients were more likely than younger patients to have significant extracolonic findings (15.4 vs. 10.3%, $p < 0.012$) but were not more likely to undergo additional diagnostic testing for these extracolonic abnormalities. Another series described the outcomes of 1,410 Medicare-eligible aged patients (83.4% Caucasian, 58.2% female, mean age 72.7 years) undergoing CT colonography for primary CRC screening or polyp surveillance [48]. Thirteen point five percent had findings on CT colonography suggestive of intracolonic pathology of which 8.2% were C2, 4.6% were C3 and 0.7% were C4, according to the C-RADS CT colonography reporting scheme. Advanced colonic neoplasia, defined as adenomas ≥ 10 mm, villous or high-grade histology, or cancer, occurred in 8.5% of this cohort. The frequency of progression to colonoscopy was 13.8%. For the EC portion of the examination, likely unimportant (E3) findings were noted in 22.5% and were most commonly attributable to the cardiac, renal, and pulmonary systems. Only 3% had potentially

important (E4) EC findings on CT colonography. When known coronary artery disease was categorized as an E2 finding, the prevalence of E3 lesions fell to 13%. Thus, it appears that, in response to CMS concerns, results obtained with CT colonography in the Medicare-eligible population are comparable to those observed in general screening populations.

Failed Colonoscopy

Incomplete colonoscopic examination occurs in 2–5% of colonoscopic examinations, usually secondary to patient discomfort or uncooperativeness, anatomic irregularities (tortuosity, strictures, excessive looping), or inadequate colon preparation [49]. Air contrast barium enema (ACBE) has traditionally been the test of choice for patients in whom colonoscopy could not be completed. However, ACBE may be difficult to perform immediately after a failed colonoscopy, and barium coating of the colon wall is sometimes suboptimal after certain colon preparations. Several studies have evaluated the use of CT colonography after failed colonoscopy. In one, CT colonography and ACBE had comparable results in 10 patients after incomplete colonoscopy [50]. In another study, CT colonography was performed within 2 h after incomplete colonoscopy in 40 patients, all of whom either had lower gastrointestinal symptoms or who were at increased risk of CRC [51]. Among the 26 patients who underwent both CT colonography and ACBE in this study, CT colonography was better tolerated ($p < 0.001$) and CT colonography was judged to adequately reveal 96% of colonic segments compared to 91% for ACBE. Thus, failed colonoscopy is a widely accepted indication for CT colonography and is endorsed for this indication by multiple guideline issuing authorities including CMS, the ACS, MSTF, ACR, and the ACG [30, 38]. For Medicare aged patients, CT colonography after failed colonoscopy is a covered benefit by CMS.

Evaluation of Colon Proximal to an Obstructing Lesion

Several studies have evaluated the results of CT colonography for examination of the colon proximal to an obstructing lesion and current CRC screening guidelines recommend examination of the colon proximal to a CRC lesion because synchronous neoplastic lesions are found in 5–8% of patients diagnosed with CRC [52, 53]. One study evaluated 29 patients without acute bowel obstruction in which the colonoscope could not be advanced proximal to the obstructing lesion [9]. In this trial, findings on CT colonography were compared to findings from preoperative ACBE and/or colonoscopy. CT colonography identified 100% of occlusive CRC as well as 24 proximal colonic polyps and two synchronous proximal adenocarcinomas. Four patients underwent preoperative ACBE that failed to adequately evaluate the proximal colon while CT colonography adequately examined the proximal colon in all of these patients, one of whom had a synchronous CRC. In another study of 19 patients

with distal, occluding CRC [54], CT colonography identified all 19 distal lesions as well as 22 lesions proximal to the obstruction, including two adenocarcinomas. ACBE was attempted, but was unsuccessful in 5 patients while CT colonography adequately demonstrated the proximal colon in all 5 of these patients.

Colonic strictures due to radiation therapy, previous surgery, inflammatory bowel disease, or NSAIDs can also prevent complete colonoscopy. CT colonography has been shown to permit adequate visualization of the proximal colon in these patients as well. To date, no trials have specifically examined the role of CT colonography in a uniform population of patients with colonic strictures due to a single etiology, but in one prospective study [55] of patients with a history of abdominopelvic surgery and/or radiation (41 patients) and controls (20 patients), CT colonography was judged to be successful in all patients. Although clinical outcomes, such as CT colonography sensitivity were not reported, the data suggest that CT colonography is safe and feasible in this population.

CRC Screening in Patients with Contraindications to Colonoscopy or Who Refuse Other Screening Options

Minimal data are available regarding the use of CT colonography as a screening test in patients with contraindications to colonoscopy (e.g., coagulopathy, intolerance to sedation) or who refuse other screening options. However, this is a critical area in which CT colonography may be beneficial. The recently updated ACG CRC screening guidelines include CT colonography as a screening test for in patients who fit these criteria [38].

Contraindications for CT Colonography

CT colonography has few contraindications (Table 8.3). However, it should not be performed in patients for whom perforation is a concern. In addition, CT colonography should probably not be performed immediately after failed colonoscopy in patients who had polyps removed or large biopsies taken during the incomplete colonoscopy due to the possible increased risk of perforation resulting from the required colonic insufflation with CT colonography. Specific clinical circumstances exist in which endoscopic examination is preferred to CT colonography. These include, but are not limited to, situations in which the pretest probability of identifying colonic abnormalities is increased, such as patients with symptoms of organic gastrointestinal disease, patients with familial colon cancer syndromes, or patients with inflammatory bowel disease in whom mucosal sampling for dysplasia is recommended [56].

The maximum age at which to cease CRC screening with CT colonography is subject to many of the same concerns as screening with colonoscopy. A recent analysis of screening colonoscopy in the elderly found that the gain in life expectancy

Table 8.3 Contraindications to CT colonography

Relative contraindications	Absolute contraindications
Symptomatic acute colitis	Routine follow-up of inflammatory bowel disease
Acute diarrhea	Hereditary polyposis or nonpolyposis cancer syndromes
Recent acute diverticulitis	Evaluation of anal canal disease
Recent colorectal surgery	The pregnant or potentially pregnant patient
Symptomatic colon-containing abdominal wall hernia	
Recent deep endoscopic biopsy or polypectomy/mucosectomy	
Known or suspected colonic perforation	
Symptomatic or high-grade small bowel obstruction	

was only 15% that observed in a younger population [57]. Additionally, the USPSTF recently recommended that routine CRC screening of patients over the age of 75 be discontinued given questions about its overall cost effectiveness [31]. It seems reasonable that since the diagnostic accuracy of CT colonography approaches that of colonoscopy, that the age to cease population-based CRC screening with CT colonography should also be 75 years. As with all diagnostic testing, however, the approach to each patient will require individualization, taking into account the general health and desires of the patient as well as the results of prior screenings.

Qualifications and Training of Personnel

CT Scanning

CT scanning should be performed by ARRT-certified radiologic technologists. Prior to CT acquisition, adequate colonic inflation is confirmed using a CT scout. Suboptimal colonic distention can result in falsely negative CT examinations [58], so personnel performing CT colonography need to be facile with equipment and techniques to ensure adequate distention. Therefore, a program that demonstrates technologist expertise in review of CT scout images is required.

Skill and Training to Interpret CT Colonography

The ACR practice guidelines [59] for performing and interpreting diagnostic CT requires licensed medical practitioners to have a thorough understanding of the indications for CT as well as a familiarity with the basic principles and limitations

of the technology. They should have a thorough understanding of the technology and instrumentation as well as radiation safety. With respect to CT colonography in particular, the ACR [60] recommends that the supervising and interpreting physicians should have reviewed at least 50 cases in one or more of the following formats:

1. Formal hands-on interactive training on CT colonography interpretation
2. Supervision with a CT colonography-trained physician(s) acting as a double reader
3. Correlation of CT colonography and endoscopy findings in patients who undergo both procedures

In 2009, the ACR released updated guidelines in which they specify qualifications for interpretation of CT colonography based on clinician training in CT radiology [56]. For clinicians not previously trained in the performance and interpretation of CT of the abdomen and pelvis, the ACR recommends the following to qualify as a CT colonography interpreter:

1. Completion of an ACGME approved training program in their respective specialty in which they practice, plus 200 h of Category I CME in the performance and interpretation of abdominal-pelvic CT. Supervision, interpretation, and reporting of 500 CT cases, at least 100 of which must be abdominal-pelvic CT during the past 36 months in a supervised situation.
2. Education regarding patient preparation, bowel insufflation, and CT image acquisition.
3. Formal hands-on interactive training using dedicated CT colonography software, including the interpretation, reporting, and/or supervised review of at least 75 endoscopically confirmed CT colonography cases using primary 2D and/or primary 3D search with routine problem-solving techniques.

These criteria would appear to be most applicable to interpreters who interpret both the intracolonic and extracolonic portions of the CT colonography examination. Despite the intensive study and evolution that CT colonography has undergone over the last decade, the extent of training for gastroenterologists to accurately read CT colonography has not been defined. The relevance of abdominopelvic CT training for CT colonography interpreters who only evaluate the intracolonic portion of the examination is unknown, but likely minimal. The most recent version of the GI Core Curriculum specifies that gastroenterology trainees should use CT colonography in order to become familiar with the appearance of cancer as well as understand the indications, contraindications, advantages and disadvantages of this technique relative to other radiology and nonradiology techniques to examine the colon [61].

As studies like the ACRIN II trial [10] most likely represent technologically advanced comparisons performed by experts, there is a valid concern that if the relative sensitivity of CT colonography compared with colonoscopy is only 90% in the hands of experts, it may be lower when the procedures are performed by “everyday” specialists. Certification criteria for participation in the ACRIN II trial required that each participating radiologist submit confirmation

of having interpreted at least 500 CT colonography examinations or having participated in a specialized 1½ day training course in CT colonography performance and interpretation. In addition, all participating radiologists in this trial were required to pass a qualifying examination in which they achieved a detection rate of at least 90% for polyps measuring 10 mm or greater in diameter in a reference image set [10].

A number of studies have examined the variability of the “learning curve” associated with interpretation of CT colonography findings. In one, with two blinded teams made up of a radiologist and gastroenterologist [62], it was found that increasing experience (after reading 25 cases) led to enhanced specificity and reduced interpretation times. In another study examining reader training at 25, 50, 75, and 96 case intervals, sensitivity improved after reading 50 cases while optimal sensitivity (92% for target lesions) was achieved after interpreting 75 cases [63]. Thomeer et al. [64] reported similar findings at the 75 case threshold, although this study used only two readers with limited prior experience in reading CT colonography. Bodily et al. [65] evaluated the performance of non-radiologists (medical students and radiologic technologists) after training using a teaching file of 50 cases followed by blind interpretation of 50 cases with colonoscopic correlation (30 positive, 20 negative). The nonradiologists performed similarly compared to radiologists with improvement in performance after reading 100 cases.

Two recent publications indicate that personnel without previous training in abdominopelvic CT interpretation can interpret CT colonography accurately after appropriate training. In one report, seven novices (six medical students and one abdominal imaging fellow) received intensive training that included 1 day of training similar to that provided to staff radiologists as well as computer self-assessment modules, reading assignments, expert observation, and independent evaluation of CT colonography training cases [66]. Posttraining evaluation documented performance similar to that reported in previous CT colonography clinical trials involving expert CT colonography interpreters [3, 10, 12, 13]. Furthermore, a recent report demonstrated that gastroenterologists detected lesions by CT colonography with an accuracy comparable to that of highly trained radiologists [67]. In this study, the most accurate gastroenterology readers had undergone formal training in CT colonography, underscoring the value of such training.

Response to training, however, is unpredictable. In one study, three radiologists (GI radiology consultant, research fellow, and trainee) with no prior experience in CT colonography were tested on 100 cases [68]. Feedback and training was given after the first 50 cases and performance and reporting times were compared for these and then 50 subsequent datasets. Prior experience of gastrointestinal radiology enhanced the ability to read CT colonography; however, competency could not be assumed after direct training with the database of 50 cases. In another study, inexperienced CT colonography readers (<50 cases read) who completed a CT colonography training module performed better than experienced CT colonography readers with a sensitivity of 70 vs. 47% in detecting lesions ≥ 10 mm [1]. Slater et al. studied the diagnostic performance amongst six readers (4 residents, 2 subspecialty gastrointestinal radiologists) without prior CT colonography training in reading 20

cases (32 polyps) [69]. Overall untrained reader sensitivity was poor with marked individual variation and the overwhelming majority of missed polyps were due to failure of detection (82–95%).

Exam and Equipment Specifications

The spectrum of CT colonography practice may vary widely depending upon the clinical indication and available equipment, but adherence to standards for all portions of the exam are required to achieve reproducible results.

Colonic Preparation

Most regimens employ a cathartic agent in addition to a colonic stimulant (usually bisacodyl tablets or suppositories). Polyethylene glycol electrolyte solution is a nonabsorbable, osmotically balanced preparation that is safe, results in little fluid shifting during administration, and is commonly used prior to CT colonography and colonoscopy. Oral sodium phosphate based agents have fallen out of favor recently due to concerns about nephrotoxicity [70]. Magnesium citrate is a milder saline cathartic preparation, which performs similarly to polyethylene glycol for CT colonography when combined with fecal tagging agents [71]. Polyethylene glycol results in increased fluid within the colon compared to oral sodium phosphate preparation [72], but this generally is not a diagnostic dilemma if the patient is scanned in two positions to permit redistribution of colonic fluid. The selection of a cathartic agent will depend on patient factors as well as endoscopist preferences. Patient factors include underlying conditions that lead to contraindications for electrolyte shifts, fluid shifts, or phosphate ingestion.

Tagging of colonic fluid and stool can be achieved with oral contrast agents prior to the CT exam. Fecal and fluid tagging may permit identification of submerged polyps and reduce false-positive exams due to residual stool [73]. Use of fecal and fluid tagging is not mandatory if the patient is adequately cleansed with cathartics and scanned in two positions, as both fluid and stool generally move with repositioning [8], and is impractical when CT colonography is performed following incomplete endoscopy. Stool tagging is generally achieved with ingestion of a barium suspension; fluid tagging is performed using an iodinated oral contrast agent. Compliance with fecal and fluid tagging regimens can be challenging for some patients. CT colonography performed without bowel purgation cleansing is a promising extension of the CT colonography technique in which small amounts of tagging agents are ingested 1–2 days prior to the examination in order to allow digital subtraction of labeled stool and fluid without a large volume catharsis [74–77]. A recent study from the Netherlands did show excellent and comparable accuracy of a limited preparation CT colonography to a subsequent lavage prepared colonoscopy in patients with positive occult blood tests [78]. This technique,

however, cannot currently be recommended as no large clinical studies in a screening population have validated its performance, but it is reasonable to expect that continued technical and procedural refinements in the future may lead to “prep-less” CT colonography.

Colonic insufflation is performed prior to CT acquisition using air or carbon dioxide (the latter may reduce postprocedure cramping) [79]. Glucagon, a spasmolytic agent, does not increase colonic distention, but may improve patient comfort [80, 81]. Colonic insufflation with automated insufflators results in improved colonic distention compared to manual insufflation [82]. Automatic insufflators may also be safer owing to preset ramped flow rates and automatic venting at predetermined intracolonic pressures [83].

CT Acquisition Technique

Following review of an initial CT scout, high resolution CT is performed in the supine and prone positions. Scanning the patient in two positions is mandatory, to permit redistribution of colonic fluid and air, and improves the detection of colonic polyps compared to a single position [8, 84].

While submillimeter slice thicknesses are possible with 64-slice CT systems, utilization of such slice thicknesses results in datasets of thousands of images, increases image noise, and will result in increased radiation dose if noise is held constant. Numerous phantom experiments have demonstrated that polyps 6 mm or greater in size can be detected using slice thicknesses of 3 mm or less, with narrower slice thicknesses potentially increasing lesion conspicuity [85–87]. Several large patient studies employing 2.5 or 3 mm slice thickness have demonstrated acceptable performance for detecting polyps 6–9 mm in size [3, 7, 88]. Unlike routine abdominal CT, which identifies solid organ abnormalities using differences in X-ray attenuation between soft tissue structures, CT colonography identifies colonic polyps and cancers by exploiting the attenuation difference between these soft tissue lesions and intracolonic air. The resulting larger attenuation gradient permits CT colonography exams to be performed at much lower radiation doses. Scanning at lower dose (i.e., lower mAs settings, higher pitch) increases image noise and complicates visualization of extracolonic structures, but does not compromise the detection of colorectal polyps and cancers 5 mm or greater in size. The radiation dose for CT colonography exams using supine and prone acquisitions in published CT colonography protocols averages 8 mSv [89], compared to the barium enema which has an estimated effective dose of 4.0 mSv in males and 8.8 mSv in females [90]. The tube current used to achieve doses similar to barium enema varies depending upon scanner model and other acquisition parameters, but should be within this range for average sized patients undergoing routine CT colonography exams. The American College of Radiology practice guidelines for CT colonography recommend a kVp of 120 kV and a tube current of <100 mAs for routine CT colonography exams in adult patients [56]. Even more recent estimates

of dose delivery associated with CT colonography place the effective dose between 1 and 2 mSv [12, 91].

Recent articles have heightened the concern regarding radiation delivery by CT scans and subsequent cancer risk later in life [92, 93]. These estimates, which are based on modeling rather than direct observation, extrapolate the outcomes observed in populations such as atomic bomb survivors and the Chernobyl incident to the risk of cancer incidence in patients exposed to medical radiation. The underpinnings of these risk estimates is the “linear no-threshold” (LNT) theory of radiation-associated risk which holds that exposure to ionizing radiation (IR) increases carcinogenic risk linearly and that carcinogenic effectiveness remains constant irrespective of dose and dose-rate. There continues to be a significant debate among the health physics community regarding the LNT theory and whether it can be applied to the low-dose and very low-dose IR delivery that occurs in most settings of medical radiation delivery [94]. There are multiple lines of evidence that actually contradict the LNT, but these remain controversial. Generally agreed upon limitations regarding the extrapolation of risks for patients undergoing CT scanning include the lack of epidemiological data from which accurate models can be developed, the unknown effects of low-dose IR or very low-dose IR on cellular defense mechanisms, the ability of these amounts of IR to induce chromosomal damage, and the factors that may increase or decrease risk on an individual level. Brenner recently considered the risk of radiation exposure to the public, based upon typical CT acquisition parameters and extrapolated cancer risks based on atomic bomb survivors of all ages who had whole body exposures of a mean of 20 mSv and concluded, based on the low doses of radiation delivered with CT colonography, the advanced age of patients undergoing the examination for screening purposes, the proven performance characteristics of the examination, and the prevalence and incidence of adenomas and CRC that the risk–benefit ratio favors CT colonography compared to no screening [95].

When characterization of solid organs is necessary (e.g., to evaluate a potentially significant extracolonic finding or to stage an obstructing colon cancer), intravenous contrast with normal dose settings should be employed. Intravenous contrast may also be used to characterize polyps (e.g., to distinguish polyp from stool, as a salvage procedure in the setting of excess colonic fluid). In these circumstances normal dose settings are also appropriate so that the attenuation of colonic lesions can be accurately assessed [96].

CT Colonography Interpretation and Polyp Reporting

Intracolonic Findings

All intracolonic findings should be examined and reported, and any segment not adequately evaluated should be documented. All large masses and lesions that compromise luminal caliber should be communicated. The size and location of colorectal

lesions should be reported, with appropriate images annotated or described. Descriptive features of polyps and masses should include morphologic features (sessile, pedunculated, flat), location (rectum, sigmoid, descending, transverse, ascending colon, cecum), and lesion attenuation (soft tissue attenuation and fat).

One of the most controversial areas involving CT colonography has to do with the reporting of polyps. General agreement exists that all polyps ≥ 10 mm should be reported, and the patient referred to endoscopic polypectomy, since 10–25% of these lesions may harbor high-grade dysplasia or cancer [97]. However, great controversy about reporting and/or management of subcentimeter polyps discovered at CT colonography exists [98–101]. In the CT colonography reporting and data system (C-RADS) consensus proposal, 6 mm was suggested as the minimum size for reporting polyp lesions [102]. This viewpoint was endorsed by the European Society of Gastrointestinal Radiology in a recent consensus statement that recommended polyps 4 mm or smaller be ignored [103]. The practice guidelines of the ACR for the performance of CT colonography in adults state that polyps ≥ 6 mm should be identified and reported [56]. Current ACG recommendations state that patients with polyps ≥ 6 mm and patients with three or more polyps of any size should be offered colonoscopy and polypectomy [38]. The ACG also recommends that polyps of any size detected with moderate to high confidence should be reported, since patients and referring physicians deserve to be aware of the test results and there is evidence that patients and physicians would like to know about small polyps found at CT colonography [104].

We simply do not know enough about the risk of cancer arising from diminutive (< 5 mm) or small (6–9 mm) polyps. The majority of published research indicates that these risks are likely to be extremely small, though clearly not zero. A recent analysis of data from the Clinical Outcomes Research Initiative (CORI) showed very low rates of advanced neoplasia in diminutive polyps [105]. In this analysis, advanced neoplasia was seen in 1.7% of nearly 4,000 diminutive polyps. Cancer, with a statistical prevalence of 0% in this analysis, was seen in 1 of these polyps. The prevalence of advanced histology in small polyps was 6.6% (5.3% excluding serrated adenomas) and the prevalence of cancer was 0.2%. Other studies suggest higher rates of advanced lesions in small polyps. In a study of nearly 2,000 adenomas, 5.6% of adenomas ≤ 10 mm were advanced and 0.4% harbored cancer [106]. It should be recognized, however, that colonoscopy misses approximately 25% of diminutive polyps so the actual prevalence of advanced lesions in people undergoing colonoscopy may actually be higher than these estimates [107]. Do CRC arising after “normal” colonoscopies represent “missed” lesions that simply evolved into cancer or do these incident CRC follow a different neoplastic pathway? As we have recently seen, colonoscopy may not offer us as a complete protection from colon cancer as we once thought [108]. It should also be recognized that the debate as to what sized polyp should be used as a threshold to proceed to colonoscopy after CT colonography revolves around a very small and quite subjective 1–2 mm difference and is not predicated on any known *behavior* of diminutive and small polyps. Until that information is clarified this debate will likely continue without clear resolution.

Extracolonic Findings

Extracolonic findings (many of which are incidental findings) are common. In a recent systematic review involving 3,488 patients, 40% of the patients had one or more abnormality [73]. Extracolonic cancers were detected in 2.7 and 0.9% had an aortic aneurysm. Approximately 1–2% of patients will have highly important findings requiring medical or surgical intervention [109, 110]. A recent analysis of outcomes from two large CT colonography centers that included more than 10,000 patients undergoing screening CT colonography [111]. Unsuspected cancer was found in 0.56% and included CRC, identified in 0.21%, as the most common type of malignancy. In published clinical trials, the incidence of extracolonic findings far surpasses the incidence of colorectal lesions larger than 5 mm in size [10, 112–114], but it should be recognized that the vast majority of these extracolonic findings are not clinically significant and require no medical workup. Predictions regarding the impact of extracolonic findings on the “cost of CTC” have varied widely due to the heterogeneous nature of assumptions and analyses employed. More complete knowledge regarding the societal “cost” of not screening for CRC must be incorporated into models and arguments related to the impact of extracolonic findings on CT colonography.

Potential for Increased Screening Uptake

Despite the widely acknowledged benefits of CRC screening for reducing the incidence and mortality of CRC, patient adherence to screening guidelines remains poor and continues to lag behind screening for other cancers with recent summaries indicating that only 50–60% of average risk individuals are compliant with current screening guidelines [115]. Barriers to undergoing colonoscopy have been well enumerated and include psychological barriers, inadequate education regarding the risk of CRC and the available screening options, lack of healthcare provider recommendations, and limitations in access to care [116]. The time commitment required to undergo a colonoscopy, inconvenience for the required escort, and possible lost revenue or productivity are additional potential reasons that individuals avoid undergoing this important preventive health test.

If newer CRC screening tests have comparable performance attributes, but are perceived as less noxious than colonoscopy, there is a possibility that such tests could ultimately increase CRC screening adherence and have a positive impact on the morbidity and mortality of CRC. While the impact of disruptive technologies such as CT colonography will take several years to appreciate, perception and compliance with these tests can be measured. We recently investigated why patients chose CT colonography rather than other readily available methods (primarily colonoscopy) of CRC screening in 250 consecutive, average risk individuals in our open access system. The most common reasons for choosing CT colonography were convenience (33.6%), primary care provider recommendation (13.6%), and the

perception of safety of the examination (10.8%). More importantly, we asked patients, “If CT colonography were not offered at Bethesda Naval Hospital as an option for colon cancer screening, would you still have undergone colon cancer screening with colonoscopy?” Thirty-seven percent (91/250) of patients responded that, given that scenario, they would not have undergone CRC screening with colonoscopy while 62% (155/250) indicated that they would have undergone CRC screening with colonoscopy [117]. Obviously the generalizability of this data is limited, but it should serve as an indication that the development and deployment of a high-quality alternative to colonoscopy has the potential to get people off the screening sidelines.

Integration of CT Colonography with Colonoscopy

Approximately 10% of patients undergoing screening CT colonography receive a recommendation to proceed to colonoscopy due to intracolonic polyps or mass lesions identified on CT colonography. Since it is well recognized that the preparation required for colonoscopy is one of the most disliked aspects of colonoscopy, it is preferable to perform diagnostic colonoscopies on the same day as the CT colonography. In our experience, only 40–50% of patients with a “positive” CT colonography elect to undergo colonoscopy on the same day, even though they realize that another bowel preparation will be required. Thus, with a capacity of 15–20 CT colonography examinations per day, the endoscopy schedule remains largely unaffected. When same-day colonoscopies are needed, they can be performed on a space-available basis, typically after the completion of morning procedures in a previously booked endoscopy room, in an available endoscopy room, or over the lunch hour. We have found that performing CTC from 06.30 AM to 12.30 PM permits the rapid disposition of any CT colonography patients proceeding to colonoscopy prior to beginning afternoon procedures. While our model may not be applicable to some practices in the nonacademic or nonmilitary setting, there are civilian private practices where same-day CT colonography and colonoscopy have been successfully bundled together with promising results.

Conclusions

CT colonography is an emerging diagnostic modality for CRC screening that has shown diagnostic yields for intracolonic neoplasia similar to that obtained with colonoscopy in large, methodologically rigorous clinical trials. Based on its performance characteristics, it is a reasonable assumption that CT colonography represents the second best option for CRC screening after colonoscopy in terms of diagnostic accuracy. As such, it is currently endorsed as an appropriate screening modality by several prominent guideline issuing organizations such as the American

Cancer Society, American College of Radiology, American Gastroenterological Association, Blue Cross Blue Shield Technology Evaluation Center, and the American College of Gastroenterology. There are differences and controversy, however, as to the exact role of CT colonography in CRC screening and other organizations have not endorsed this test for average risk CRC screening. CT colonography has been granted a Category I CPT code by the AMA RUC and is gaining increasing support as a screening option via third-party payers. Establishing a CT colonography center is a time, labor and capital intensive process and requires close coordination between medical specialties. The ideal model appears to be one whereby a same-day colonoscopy option is offered for positive CT colonography examinations. Participation in the existing CT colonography registry maintained by the American College of Radiology should be encouraged and maintenance of clinical competencies should be carefully monitored and documented. Divergent opinion with regard to the importance of radiation from CT colonography as well as extracolonic findings and their effects on the overall costs and utility of the test continues to be a major impediment to widespread adoption of CT colonography but emergent data in the Medicare aged population appears to suggest that these concerns can be minimized. Additional research is needed to determine if CT colonography will lead to increased participation in CRC screening programs but there is evidence to suggest that this may be the case. CT colonography may also prove to be a very useful platform through which we can gather important information regarding polyp natural history. This information could have widespread and important implications for the practice of colonoscopy and help guide decisions regarding polyp resection and primary as well as secondary prevention of CRC.

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Chapter 9

Noninvasive Screening Tests

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Keywords Fecal occult blood test • Immunochemical • Fecal DNA

Introduction

During the past 2 decades, colorectal cancer (CRC) incidence and mortality rates in the United States have declined in part due to screening. The most recent Behavioral Risk Factor Surveillance System (BRFSS) survey data posted on the CDC website indicate that, in 2008, 52% of adults aged 50 years or older had a fecal occult blood test (FOBT) within the previous year or a lower endoscopy (sigmoidoscopy or colonoscopy) within the previous 5 years [1]. In fact, the majority had either a sigmoidoscopy or colonoscopy (42.3% of respondents), while just 15.3% were screened with a stool test [1]. In 2006, 60.8% of respondents to the same survey reported having had an FOBT within the year preceding the survey or a lower endoscopy within the preceding 10 years, an increase from 56.8% in 2004, 53.9% in 2002, and 53.1% in 2001 [2, 3]. These surveys show that while lower endoscopy screening has increased (43.4% in 2001, 44.8% in 2002, 50.1% in 2004, and 55.7% in 2006), FOBT screening has declined (23.5% in 2001, 21.6% in 2002, 18.5% in 2004, and 16.2% in 2006) [2, 3]. The 2000 National Health Interview Survey (NHIS) found that 49.7% of adults ≥ 50 years never had CRC testing; only 37.1% were current for their CRC screening [4]. In 2003, the NHIS survey reported higher rates of colonoscopy screening (32.2% in men and 29.8% in women) than FOBT screening (16.1% in men and 15.3% in women) or sigmoidoscopy screening (7.6% in men and 5.9% in women) [5]. In general, self-reported CRC screening rates from all national surveys, which are probably overestimates of actual screening, have increased from less than 25% in the late 1980s to about 60% in 2006, mainly due to increased use of screening colonoscopy [6].

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In 1998, the NHIS survey found that 37.1% of men and 30.2% of women had undergone recent CRC screening (FOBT within 2 years or lower endoscopy within 3 years), while 66.9% of women had a mammography within the preceding 2 years and 79.9% of women had a Pap smear test within the preceding 3 years [7]. In 2005, the NHIS survey reported that 67% of women had a mammogram in the 2 previous years, 78% of women had a Pap smear in the 3 previous years, 17% of adults aged 50 years or older had an FOBT in the 2 previous years, and 50% of adults ≥ 50 years had ever undergone a screening lower endoscopy [8]. Breast and cervical cancers screening participation is still ahead of CRC screening, with 76% of women current with mammography and 82.9% current with Pap smear according to the 2008 BRFSS survey (compared to 52% for CRC screening) [1]. The variation in uptake among colorectal, breast, and cervical cancers screening has many determinants, including the nature of screening tests, their availability, the health service context, and the invitee's personal characteristics [9]. Adequate uptake is critical for screening programs to affect mortality rates in order to reproduce the results seen in randomized trials. Access to care alone is insufficient to ensure appropriate levels of screening; patients need simple and reliable mechanisms to engage healthcare professionals in order to understand screening, pros and cons of different modalities, and how to complete the screening [6]. The performance characteristics of the screening tests are undoubtedly a key factor in physicians' recommending the tests, and in patients subsequently undergoing those tests. Mammography sensitivity is in the range of 77–95%, with a specificity of 94–97% [10]. Conventional Pap smear sensitivity is about 73%, with a specificity of 92–96% [11]. A discussion of the characteristics of the various FOBTs, fecal DNA assays, and current status of serum/plasma DNA and protein markers for CRC screening follows.

The sensitivity and specificity of a screening test are usually interrelated (i.e., increases in one results in decreases in the other) and define the test's overall accuracy [12]. Before these parameters are determined, the reliability of the test (how well repeated measurements of the test, by the same provider or not, yield similar results) should be established. However, a reliable and accurate (excellent sensitivity and specificity) test does not necessarily imply an optimal screening test. An ideal test should also be reasonably priced, widely available, easily accessible, convenient, minimally or noninvasive, safe, and acceptable to the target population [12, 13]. The clinical utility of the test is measured as predictive values (positive and negative), which are dependent on the underlying prevalence of disease in that target population. The potential harm of the test should be minimal, whether it is physical (risks of the test itself), psychological, behavioral, or social (i.e., employability and insurability) [14]. Inappropriate application or interpretation of screening tests can deprive people of their perceived health, trigger unnecessary and potentially harmful diagnostic testing, and waste valuable healthcare resources [15]. All of these factors, along with patient preference, influence implementation of, and participation in, screening programs, particularly CRC screening where an array of possible screening tests is available. With the selection of a particular CRC screening test over others for an individual or a group, several trade-offs are at play between test characteristics, benefits, risks, and costs.

Guaiac-Based Fecal Occult Blood Testing (FOBT)

Test Mechanism

The performance of tests that examine stool for the purpose of screening for CRC depends on the constituents of feces. The constituents are the result of leakage, secretion, or exfoliation of products from the tumor or as a consequence of its presence [16]. Hemoglobin is the prototype of leaked products in the stool of individuals with CRCs or adenomas. Guaiac-based fecal occult blood testing (g-FOBT) is contingent on the presence of hemoglobin in the stool. g-FOBT has been the mainstay of CRC screening for more than 40 years. The most commonly used brands of g-FOBT in the United States are Hemoccult II and Hemoccult II SENSE (Beckman Coulter, Inc., California).

g-FOBT detects the peroxidase-like activity of heme in the stool [17]. Each test consists of three cards impregnated with guaiac. Two samples from the same stool are smeared on the two panels of a single card. Since microscopic bleeding from colorectal neoplasms is intermittent, three separate bowel movements should be examined, with two slides for each one. A developer containing an alcoholic solution of hydrogen peroxide is then added as an oxygen donor. In the presence of pseudoperoxidase activity from heme/hemoglobin in stool, the oxidation of guaiac occurs, inducing a blue color change.

g-FOBT reacts to any peroxidase activity in the feces, including bleeding from the upper GI tract, dietary heme, and plant peroxidases [18]. False-positives can result from non-neoplastic lower GI bleeding, such as hemorrhoids or angiodysplasias, but also from upper GI bleeding sources, as heme remains relatively stable during transit through the GI tract. False-positive results can also arise from consumption of red meat, poultry, and fish, as well as some raw fruits and vegetables such as melons, turnips, and horseradish. Conversely, false-negatives occur with intake of vitamin C supplements or high levels of foods containing vitamin C. Thus, it has been recommended to refrain from ingesting all these items for 3–5 days prior to testing. Withdrawal of nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, has also been advocated for 7 days to reduce (but not prevent) nonspecific bleeding. In a study by Ahlquist et al., subjects who did not refrain from taking NSAIDs during stool collection had a Hemoccult positivity rate of 5.2%, vs. 3.3% for those who did, a significant increase in the false-positivity rate ($p < 0.0001$) [19].

Tests Characteristics

g-FOBT specificity has been shown to decrease by 3–7% points if dietary restrictions are not followed [20]. Hemoccult II SENSE is the most likely g-FOBT to be influenced by diet because of its high sensitivity to peroxidase activity. But some

dietary restrictions could be relaxed if test development is delayed for at least 72 h: this allows unrestricted consumption of peroxidase-rich fruits and vegetables, since plant peroxidases degrade within this time period [21]. Also, recent studies [22, 23] and newer recommendations indicate that use of low-dose aspirin might not interfere with g-FOBT results [24].

Guaiac test reactivity can be augmented by rehydrating the slide before development [20]. In the Minnesota study, Mandel et al. observed a greater-than fourfold increase in positive results with rehydration of the slides, from 2.4 to 9.8% [25]. Sensitivity increased from 80.8 to 92.2%, but specificity dropped from 97.7 to 90.4%. A marked deterioration of the positive predictive value (PPV) resulted, falling from 5.6 to 2.2%. For this reason, rehydration of Hemocult is not recommended in the American College of Physicians guidelines [26].

The screening sensitivity of g-FOBT has been evaluated in several trials. In the Veterans Affairs Cooperative study, Lieberman et al. recruited 2,885 subjects with a mean age of 63 years to undergo complete colonoscopy, before which they did 3-card Hemocult II testing. All cards were rehydrated before development. Advanced colonic neoplasia was defined as adenomas 10 mm or more in diameter, adenomas with at least 25% villous component, and adenomas with high-grade dysplasia or invasive cancer. With 73 positive g-FOBTs among the 306 subjects with advanced neoplasia, single application test sensitivity was only 23.9%. Sensitivity improved to 35.6% for detecting invasive cancer or high-grade dysplasia and improved further to 50% for the sole detection of invasive cancer. One-time screening sensitivity for any neoplasia was 11.7% and only 7% for small tubular adenomas. With a false-positive rate of 6.4%, one-time g-FOBT is therefore not useful in identifying patients with small adenomas. The study also found an association between the number of positive test cards and the likelihood of advanced neoplasia.

In a review of eight prospective blinded studies of nonhydrated Hemocult test against colonoscopy as the reference standard in asymptomatic nonreferred populations, Ahlquist assessed the sensitivity of one-time screening among a total of 13,472 subjects [20]. With 41 positive g-FOBTs among 159 cancers, he reported an overall spot sensitivity of 26% for invasive cancer. Only 36 of 302 large adenomas were Hemocult positive, which translated into a trivial sensitivity of 12%. It is important to note that sensitivity for single digital g-FOBT exam is even worse; among 3,121 asymptomatic tested subjects, Collins et al. found its sensitivity to be just 5% for advanced neoplasia [27].

Ahlquist et al. evaluated the performance of nonhydrated g-FOBT in a group of 1,217 patients undergoing surveillance after curative resection of CRC [19]. The study also assessed the accuracy of g-FOBT in a large group of their first-degree relatives that included 12,312 subjects. In the postresection group, Hemocult II sensitivity was 26% for cancer, and only 13% for all polyps 1 cm or larger, irrespective of histology. Overall specificity was 95.3%. The negative predictive value (NPV) for cancer was 98.4%, but the PPV was only 8.2%. In the group of relatives, the PPV was 4.2% for cancer and 16.7% for polyps. The estimated Hemocult II sensitivity for cancer based on follow-up of a subgroup of 900 subjects was 25% at 3 years.

One-time testing with either Hemocult II or Hemocult II SENSEA (without rehydration) was compared in a group of 8,104 subjects 50 years of age or older [28]. Performance was evaluated by identifying the screened patients found to have neoplasms (CRC or polyps 1 cm or larger in diameter) in the 2 years after screening. Sensitivity for carcinoma was 37.1% with Hemocult II, and more than twice that with Hemocult II SENSEA (79.4%). For neoplasms as defined above, sensitivity was 32.4% and 71.2% with Hemocult II and Hemocult II SENSEA respectively. The improved sensitivity of Hemocult II SENSEA occurred at the cost of a nearly 10% drop in specificity (86.7% vs. 97.7% for carcinoma; and 87.5% vs. 98.1% for neoplasms). The PPV was similarly affected: for cancers, 6.6% vs. 2.5%; and 23.2% vs. 9.2% for advanced neoplasms (Hemocult II and Hemocult II SENSEA respectively). Allison et al. estimated that Hemocult II SENSEA would result in 111 additional colonoscopies to detect 1.8 more CRCs in every 1,000 people screened [28].

In a large group of 4,404 subjects (analyzed subgroup of more than half) enrolled from 81 sites, Imperiale et al. reported an even lower sensitivity for Hemocult II in detecting cancer [23]. Subjects were at average risk for CRC, with a mean age of 69.5 years. Hemocult II was performed after dietary and medications restrictions were suggested, with three cards developed without rehydration. All analyzed subjects completed colonoscopy. Hemocult II sensitivity was only 12.9% for cancer, and 10.8% for advanced neoplasia. Specificity was 95.2%, comparable to reported Hemocult II specificity of 88–98% [18, 20].

In a German study comparing different modalities of CRC screening in about 300 subjects, g-FOBT data was available for 276 subjects [29]. All were over 50 years of age and at average risk for CRC cancer. Advanced neoplasia was detected in 46 lesions (only one carcinoma). Sensitivity for advanced neoplasia was 20%, specificity was 89.6%; NPV was 91.8% and PPV was only 16.1%.

Mortality Reduction

Despite its limited sensitivity for advanced neoplasia and cancer, annual or biennial g-FOBT testing has been shown to reduce mortality from CRC in several large randomized controlled trials (RCT). The landmark trials have been conducted in Minnesota, USA [25, 30]; Nottingham, UK [31]; Funen, Denmark [32, 33]; Göteborg, Sweden [34, 35]; and France [36]. All trials have evaluated the effect of serial or programmatic screening with g-FOBT (Hemocult or Hemocult II), but with variations in methodology. In the American and Swedish trials, most specimens were rehydrated, whereas no rehydration was performed in the trials from the UK and Denmark (Table 9.1). Screening was biennial in these last two RCTs; the Minnesota study included both an annual and biennial arms; while in the Swedish trial, subjects were screened two to three times only at various intervals (three different cohorts). The ages of screened subjects ranged between a lower limit of 45 and 50 years and an upper limit of 74–80 years, except in the Swedish trial where all enrolled subjects

Table 9.1 Summary of randomized controlled trials of g-FOBT screening

Reference	Country	Test type interval	Study duration	Mortality reduction (%)
Mandel et al. [25]	USA	Rehydrated Hemoccult-II annual	13 years	33
Hardcastle et al. [31]	UK	Biennial Hemoccult-II	18 years	21
Kronborg et al. [32]	Denmark	Biennial Hemoccult-II	8 years (range 4–14 years)	15
Lindholm et al. [35]	Sweden	2–3 rounds of Hemoccult-II	10 years	18
Faivre et al. [36]	France	6 rounds of Hemoccult-II	13 years	30
			9 years from last screening	16
			11 years	16

were aged 60–64. Combined, these four RCTs involved more than 300,000 people. The reduction in CRC mortality in these trials ranged between 12 and 33%.

In the Minnesota trial, nearly 46,000 subjects were randomized to annual screening, biennial screening, and control groups (about a third in each group) [25]. The annually screened group completed 75% of the screening offered, and the biennially screened group completed 78% of eligible screenings. After 13 years of follow-up, CRC mortality was reduced by 33% in the annual group (with 46% of subjects compliant with all screenings); but was only reduced by 6% (not statistically significant) in the biennial group compared to controls (60% were fully compliant in the biennial group). After 18 years of follow-up, the annual screening group CRC mortality reduction was unchanged, but the biennial screening group CRC mortality was significantly reduced by 21% [30].

In the Nottingham study, about 150,000 individuals were followed up for a median of 7.8 years [31]. Half constituted the intervention group and the other half the control group. In the screening group, 38% completed all required FOBTs, and 40% did not complete any FOBT test. The cumulative reduction in CRC mortality in the screening group was 15%.

In the trial from Denmark, about 60,000 participants were evenly randomized to the screening or control groups [32]. CRC mortality reduction was 18% after 10 years of follow-up, similar to that of the UK study. Compliance was 67% in the first screening round, with 92–94% completing each subsequent round compared to the preceding round. Follow-up after 13 years and seven biennial screening rounds showed a reduction in CRC mortality, with a relative risk of less than 0.70 in those adhering to the program [33]. The risk of death from CRC was overall reduced to 0.85 (95% CI=0.73–1.00) in the screening group relatively to the control group (intention-to-treat analysis).

In the Swedish trial, all inhabitants of Göteborg aged 60–64 were recruited to the study, with about 34,000 subjects in each group [34]. After a prevalence screening (63% compliance) and only one rescreening (60% compliance), with a median follow-up of 8.3 years, there was a 12% relative risk reduction in CRC mortality

(CRC mortality risks of 0.35/1,000 in the intervention group vs. 0.40/1,000 in the control group, based on preliminary data at the time) [37]. Two of the three study cohorts underwent later a second rescreening (64% compliance), and mean follow-up was extended in all cohorts to 15.5 years, with a mean of 9 years from the last screening [35]. A 16% reduction of CRC mortality was found with this subsequent follow-up (CRC mortality risks of 0.53/1,000 in the intervention group vs. 0.64/1,000 in the control group) [35].

In the French trial, a population-based study, 91,199 individuals aged 45–74 years were allocated to either six rounds of biennial FOBT screening or no screening. The first round was in 1988/1989 and last round in 1998. Acceptability of the test was 53% for the first screening and varied from 53.8 to 58.3% for subsequent rounds. Positivity rates were 2.1% initially averaged 1.4% subsequently. The PPV was 11.5% for CRC and 16.8% for large adenomas (≥ 1 cm). After 11 years of follow-up, CRC mortality was significantly lower in the screening group compared with the control group (mortality ratio, 0.84; 95% CI, 0.71–0.99), and was even lower in persons who complied with at least one round of screening (mortality ratio, 0.67; 95% CI, 0.56–0.81).

All of these RCTs, regardless of technique, age group, screening interval, and number of screening rounds, have shown a significant reduction in CRC mortality with serial g-FOBT. Meta-analysis of four of the trials shows a 16% relative risk reduction in CRC mortality, which was 23–25% among those who actually attended screening [37, 38]. In addition, the Minnesota trial identified a significant reduction in CRC incidence after an 18-year follow-up period [39]. About 91% of the study participants were still followed up at that point. CRC incidence was significantly reduced in both intervention groups compared to controls: a 20% decrease was observed in the annually screened group (relative risk=0.80 (CI, 0.70–0.90)); and a 17% decrease was found in the biennially screened group (relative risk=0.83 (CI, 0.73–0.94)). These figures may be an underestimate of the true reduction, since compliance with all screening rounds was less than 50%, and because of a hiatus in screening for about 4 years during the study period (between 1982 and 1986).

Population-Based Screening Programs

Participation rates in the RCTs of g-FOBT have ranged between 53 and 67%, whereas rates have been lower in other studies [24]. While 25–40% of participants in clinical trials do not complete scheduled testing over the years, adherence to repeat testing in clinical practice is uncertain [40]. The disadvantages and limitations of g-FOBT account for part of this limited compliance, including low sensitivity, which necessitates repeated interval testing, the burden of dietary and drug restrictions, and the inconvenience of the collection process. Among average-risk participants in a screening program, 2–5% will have a positive g-FOBT result [41]. While the false-positive rates have varied, the annual consequential cost has been estimated at several billion dollars in the United States [42].

Over the past few years, the results of population-based CRC screening programs have been published, proving that g-FOBT screening is applicable and beneficial at the level of the general population. In addition to the study by Faivre et al. discussed previously, Denis et al. in 2007 reported the outcomes of the first round of a screening program in the Haut-Rhin district in eastern France [43]. Residents aged 50–74 were invited to participate, in collaboration with their general practitioner. The only restrictions applied to the amount of aspirin and vitamin C intake. Participation rate was 55.4%, and was higher in women (57%) than in men (53.7%). The overall g-FOBT positivity rate was 3.4%. Of those, 87.9% underwent colonoscopy as recommended, with 51.2% of these detecting cancers or polyps. The number of colonoscopies needed to detect an advanced neoplasm was 3.2 overall, was higher in women ($n=4.9$ compared to 2.5 in men) and decreased as age increased. Cost circa 2006 was estimated at 29.3 € (approximately \$44) per screened person and 13,466 € (approximately \$20,000) per cancer detected.

In 2009, Steele et al. published the findings of three rounds of biennial g-FOBT population-based screening in Scotland [44]. This was carried out in three Scottish National Health Services Boards, with a total population around 1.3 million. All individuals aged 50–69 were invited to participate. Participation rates were 55, 53, and 55.3% in the first, second, and third rounds respectively. Positivity rates declined with each round: 2.07% at first round, 1.9% at the second, and 1.16% at the third round. Compliance with colonoscopy was 85.5, 89.5, and 81.3% in the consecutive rounds. The PPV for cancer was 12% in the first round, 7% in the second round, and 7.5% in the third round. At follow-up, true interval cancers (i.e., those who had a negative g-FOBT result) accounted for 30.1% of CRC diagnosed within 2 years of the first round, and 36.9% of cancers diagnosed within 2 years of the second round.

The three population-based CRC screening programs confirm the feasibility of FOBT screening outside of research settings, with diagnostic yields and participation rates comparable to those of the RCTs.

Immunochemical Fecal Occult Blood Tests

Test Mechanism

Immunochemical fecal occult blood tests (i-FOBT) were first introduced in the early 1990s to improve specificity and eliminate the need for dietary restrictions required for g-FOBT. Current available tests include, among others, HemeSelect, FlexSure OBT, and InSure [45]. These tests are also referred to as fecal immunochemical tests (FIT). This latter nomenclature is preferred by some “to emphasize that this test is much more than an update of old technology” [46].

FITs use one or more monoclonal and/or polyclonal antibodies that specifically detect the intact globin protein portion of human hemoglobin [45]. If hemoglobin

is present in the stool, the labeled antibody will attach to its antigens, resulting in a positive test. This test does not require intact human hemoglobin for reactivity [18]. These tests do not react with nonhuman hemoglobin or with plant peroxidases, thereby obviating the need for dietary restrictions prior to testing. In addition, since the globin protein is rapidly degraded by upper gastrointestinal enzymes, blood from the upper GI tract is not detected by i-FOBT, making it more specific for bleeding of colorectal origin. Thus, aspirin and NSAIDs-induced upper GI bleeding does not interfere with FIT, precluding the need to withdraw these medications before testing [21, 24].

Test Characteristics

Sensitivity of one-time screening with FIT ranges between 60 and 85% for CRC, and is only 20–50% for advanced adenomas [40]. Morikawa et al. published the results of a large retrospective analysis of data collected between 1983 and 2002 evaluating the test characteristics of one time FIT in asymptomatic 21,805 persons aged 40 years or older (mean age of 48 years; 72% men) [47]. All subjects underwent colonoscopy within 1 or 2 days of i-FOBT (Magstream 1000/Hem SP). FIT was positive in 1,231 patients (5.6%). Invasive cancer was detected in 79 patients, and advanced neoplasia was found in 727 subjects. Sensitivity of FIT was 65.8% for cancer, and was 27.1% for all advanced neoplasia, with specificities of 94.6 and 95.1% respectively. FIT was less sensitive in detecting localized cancer than advanced cancer (sensitivity of 52.8% in Dukes' stage A, 70% in stage B, and 78.3% in stages C and D). Also, FIT was less sensitive in detecting proximal neoplasia than distal neoplasia (16.3 and 30.7% respectively).

In another Japanese study, Nakama et al. evaluated the sensitivity and specificity of 1, 2, and 3 day FIT [48]. This prospective study involved 4,611 asymptomatic adults over the age of 40, of whom 18 patients were found to have CRC. All subjects underwent colonoscopy after being tested for three consecutive days by an FIT (Monoheam). Sensitivity for cancer was 55.6% for 1-day testing, 83.3% for 2-day testing, and 88.9% for 3-day testing, with respective specificities of 97.1, 96, and 93.9%. Analysis showed a significant difference in sensitivity for cancer between 1-day and 2-day testing, as well as between 1-day and 3-day tests, but not between 2-day and 3-day sensitivity nor between 1-day and 2-day specificity. The authors suggested a 2-day method for FIT based on their results.

In addition to eliminating the need for diet and drug restrictions, FIT allows a simpler sampling technique, and most versions require less than three fecal samples as recommended for g-FOBT. Rather than using a wooden spatula, FIT uses probes or brushes. !nsure offers the convenience of a long-handled brush used to brush the surface of the stool inside the toilet bowl; the brush is then dabbed on a test card [18]. These enhancements have been shown to significantly improve participation in screening. Cole et al. randomized 1,818 subjects into three cohorts screened either with Hemoccult Sensa, FlexSure or !nsure [49]. Participation increased by

28% by removing diet and drug restrictions, and by 30% by simplification of sampling with !nsure; the combination resulted in an overall 66% increase in participation. The same group reported that the !nsure brush technique was preferred by 82.6% of subjects (over FlexSure), while sensitivity and specificity for cancer and adenomas did not differ between the two tests [49].

Quantitative FIT

The test characteristics of FITs can be adjusted by varying the threshold for globin detection in the feces, although few are approved for quantitative use. This quantification enables to set a cutoff for positivity to correspond to a desired sensitivity/specificity ratio based on a particular population needs and resources. Smith et al. showed that altering the threshold of !nsure positivity in a screening population could preserve cancer detection rate, while lowering the false-positive rate [50]. Quantification is based on the principle that as stool hemoglobin concentration increases, there is a continuous increase in the likelihood of finding neoplasia [24]. Determining the cutoff must allow an acceptable positivity rate; since a positivity rate of 2% significantly decreased mortality in the g-FOBT RCTs, Young and Cole suggest that a positivity rate equal or higher than 2% will achieve similar or better results with quantitative FIT [24]. The flexibility provided by quantification could allow national health programs to calibrate CRC screening based on the availability of colonoscopy. In addition, quantification may allow providing patients with specific information about their risks for cancer and advanced neoplasia.

Levi et al. evaluated the characteristics of a quantitative FIT for detecting clinically significant neoplasia in a 1,000 consecutive ambulatory patients [51]. These subjects were scheduled for elective colonoscopy either for evaluation of gastrointestinal symptoms or for being at high-risk of CRC neoplasia. Each subject provided three FIT samples, the highest value of which was compared with colonoscopy findings. Specimens were processed by the OC-MICRO instrument (Eiken Chemical Co., Tokyo, Japan). The threshold for a positive test was varied in increments of 25 ng of hemoglobin/mL of stool from 50 to 150 ng/mL. Colonoscopy identified clinically significant neoplasia in 91 individuals: 17 had cancer (of whom 16 were Dukes' stage A or B) and 74 had advanced adenomas. Mean fecal hemoglobin concentration increased with the colonoscopy findings, with nonoverlapping confidence limits, supporting the principle of FIT quantification: values ranged from 25 to 45 ng/mL for subjects with no neoplasia (mean 35 ng/mL); from 44 to 115 ng/mL for those with nonadvanced adenomas (mean 79 ng/mL); from 315 to 654 for those with advanced adenomas (mean 485 ng/mL); and from 697 to 1,477 ng/mL for cancer (mean 1,087 ng/mL). At the usual threshold of 100 ng/mL, test sensitivity and specificity for cancer were 88.2 and 89.7% respectively, and for all clinically significant neoplasia 61.5 and 93.4%, respectively. At the lower threshold of 75 ng/mL, test sensitivity and specificity for cancer were 94.1 and 87.5% respectively, and for all clinically significant neoplasia 67 and 91.4%, respectively.

Based on the very small difference in specificity between the 100 and 75 ng/mL thresholds, the authors suggested using the 75 ng/mL threshold, along with three FIT samples. Since the study population was not an asymptomatic average-risk cohort, direct evidence to extrapolate the findings to the screening setting is lacking. However, the early and curable spectrum of disease, as well as the disease prevalence encountered in this study population, are both comparable to the screening setting.

Fraser et al. assessed the quantification of hemoglobin in feces collected on a single card collection device (*hema-screen* DEVEL-A-TAB, Immunostics) [52]. This simple card collection was assayed by immunoturbidimetry, on a SENTiFOBT analyzer (Sentinel Diagnostics, Milan, Italy). This Scottish study population consisted of 376 participants who had a positive g-FOBT result. Median hemoglobin concentration was 13.5 ng/mL for persons with no colorectal neoplasia, 15.2 ng/mL for those with low-risk adenomas, 65.6 ng/mL for those with high-risk adenomas, and 168.9 ng/mL for cancer. The difference was statistically significant between persons with high-risk adenomas or cancer as compared to the other groups. But there were large dispersions of values among each group, with concentrations overlapping between the groups. Sensitivity and specificity were evaluated at different cutoffs between 25 and 100 ng/mL; the authors suggested a threshold of 26.7 ng/mL for optimal sensitivity/specificity ratio based on their analysis; however, this threshold requires independent validation in a separate sample of persons. While this study supports a simpler quantitative FIT collection card method, more importantly it reinforces the potential benefit of quantification with FIT, where the hemoglobin threshold could be adjusted to fit the clinical and economic settings.

FIT vs. g-FOBT

Performance of FIT and g-FOBT has been compared in several trials. In one of the first trials, Allison et al. compared HemeSelect, a FIT, to both Hemoccult II and Hemoccult II SENSE [28]. As previously mentioned, this study involved more than 8,000 individuals. Sensitivity for cancer was 68.8% with HemeSelect, in a similar range to that of Hemoccult II SENSE (79.4%), but double that of Hemoccult II (sensitivity of 37.1%). Specificity for cancer was 94.4% with HemeSelect, which was numerically higher than Hemoccult II SENSE (86.7%) and but slightly lower than Hemoccult II (97.7%). Compared to Hemoccult II, HemeSelect detected 1.3 times more cancers and required 34 more colonoscopies per 1,000 people screened, whereas Hemoccult II SENSE detected 1.8 times more cancers but required 111 more colonoscopies due to its reduced specificity. Thus, HemeSelect detected more cancers (and large polyps as well) without increasing the need for colonoscopy as much as Hemoccult II SENSE.

Guittet et al. compared the performance of a quantitative FIT (Immudia/RHPA, processed with Fujirebio Magstream 1000 automated device) with nonrehydrated Hemoccult II [53]. The study involved 10,673 average-risk individuals aged

50–74 years; only those with either a positive g-FOBT or FIT were referred for colonoscopy, therefore allowing only a relative comparison between these two fecal tests. Three stools were analyzed for Hemoccult II in the standard fashion, whereas two fecal samples from 2 different days were tested for FIT. The positivity threshold for FIT ranged from 20 to 75 ng/mL. Of 886 (8.3%) subjects with at least one positive FOBT, 711 (80%) underwent colonoscopy, with results available for 644 patients (91%), of whom 21 had cancer and 149 had high-risk adenomas. At the cutoff of 20 ng/mL, FIT detected 1.5 times more cancers, and 3 times more advanced neoplasia; but the false-positive rates were 2.88 and 2.68 times higher, respectively. Raising the cutoff to 50 ng/mL, FIT detected 1.36 times more cancers and 2.33 times more advanced neoplasia; the ratio of false-positive rates was 1.28 for cancer and 0.99 for advanced neoplasia, showing no loss in specificity for the latter. Raising the cutoff further to 75 ng/mL, FIT detected 1.14 times more cancers, and 1.9 times more advanced neoplasia, with lower false-positive rates than g-FOBT (ratio of 0.94 for cancer and of 0.67 for advanced neoplasia). This study shows that FIT has better relative test characteristics than g-FOBT, with a gain that is more important for advanced adenomas than for carcinomas. Once again, it also illustrates the benefit of quantitative FIT in determining the positivity threshold so that the balance between sensitivity and specificity may be optimized.

The high sensitivity g-FOBT, Hemoccult II SENSEA, has been compared to FIT in several trials. Wong et al. reported the results in 135 consecutive subjects referred for colonoscopy who also submitted three samples of both Hemoccult II SENSEA and FlexSure OBT [54]. Sensitivity, specificity, and PPV for significant neoplasia (CRC or adenomas ≥ 1 cm) were 91, 70, and 18% respectively with Hemoccult II SENSEA, and were 82, 94, and 47% respectively with FlexSure OBT. Similar results were reported by Levi et al. in 151 patients undergoing colonoscopy who also submitted three samples of both Hemoccult II SENSEA and OC-MICRO [55]. Sensitivity, specificity, and PPV for significant neoplasia were 75, 34, and 12% respectively with Hemoccult II SENSEA, and were 75, 94, and 60 respectively with OC-MICRO. As compared with OC-MICRO, 4 times more colonoscopies were required with g-FOBT to identify one significant neoplasia because of the lower specificity of the highly sensitive g-FOBT. Smith et al. also compared Hemoccult II SENSEA with !nsure in 2,512 subjects, of whom 2,351 were asymptomatic individuals undergoing screening [56]. !nsure's true positivity rate for cancer was 87.5% overall as compared to 54.2% for Hemoccult II SENSEA. For advanced adenomas, true positivity rate was 42.6% with !nsure and 23% with the highly sensitive g-FOBT. Again, this last study shows a better performance of FIT compared to Hemoccult II SENSEA.

Van Rossum et al. compared the participation rate and test performance of Hemoccult II and FIT with an intention-to-screen analysis [57]. This prospective Dutch study involved 20,623 asymptomatic individuals aged 50–75 years, who were randomized to the g-FOBT or FIT groups. Invitations were sent by mail to 10,301 subjects to submit three Hemoccult II samples, and to another 10,322 subjects to submit one FIT sample: OC-Sensor (Eiken Chemical Co, Tokyo, Japan). The positivity cutoff of OC-Sensor was fixed at 100 ng/mL as recommended by the

manufacturer, and no variation in quantification was applied. All participants with a positive FOBT were referred for a colonoscopy. The participation rate difference was 12.7% in favor of FIT (46.9% vs. 59.6%, $p < 0.01$). Positivity rates were 2.4 and 5.5% in the g-FOBT and FIT groups, respectively. Cancers and advanced adenomas were detected 2.5 times more in the FIT group: 145 (1.4%) vs. 57 (0.6%) (absolute difference = 0.8%, $p < 0.01$). Cancer detection rate was 0.2% ($n = 24$) with FIT and 0.1% ($n = 11$) with g-FOBT (absolute difference = 0.1%, $p < 0.05$). In the g-FOBT group 103 colonoscopies were performed, and in the FIT group 280 subjects underwent colonoscopy. But as FIT detected more cancers and advanced adenomas, the number needed to screen according to intention-to-screen to find an advanced adenoma or carcinoma was 181 for g-FOBT and 71 for FIT, and to find one cancer was 936 for g-FOBT and 430 for FIT (no statistical difference). The results of this study highlight the superiority of FIT for detecting cancers and advanced adenomas, whereas g-FOBT significantly underestimated the prevalence of these lesions and generated a lower participation rate.

In the previously mentioned study from Germany by Graser et al. [29], where all 307 average-risk subjects underwent colonoscopy, both g-FOBT and FIT had a low PPV for advanced neoplasia: 16.1% and 17.8%, respectively. Prior to colonoscopy, subjects provided three stool samples on 3 consecutive days for g-FOBT; and two samples from the same stool for FIT (FOB Gold immunoturbidimetric latex assay, Sentinel Diagnostics, Italy). Sensitivity for advanced neoplasia was better with FIT: 32%, vs. 20% with g-FOBT. Specificities were 89.6 and 85.8%, respectively, for g-FOBT and FIT, while the respective NPVs were 91.8 and 92.9%.

While the studies are heterogeneous with respect to study population, specific tests compared, and surrogate outcomes for CRC mortality, the overall results show that FITs are better than guaiac-based FOBTs because of greater sensitivity, higher detection rates, and higher specificity. FITs have the additional potential advantage of allowing for tailoring the threshold for various clinical circumstances. On balance, FITs are superior to gFOBT and should replace gFOBT wherever it is being used for CRC screening.

Comparative Performance of Various FITs

The performance of six different qualitative FITs was evaluated by Hundt et al. in a prospective study conducted between January 2006 and December 2007 in Germany [58]. A total of 1,319 individuals, all of whom underwent colonoscopy, were enrolled from 20 gastroenterology centers. All were at average-risk for CRC, with a mean age of 63 years; half of the study participants were men. Advanced adenomas were diagnosed in 130 subjects (10%). Participants provided one Hemoccult card and collected stool in a container, which was frozen and sent to the study processing central laboratory. Stool from the container was used to test the six FITs: Bionexia FOB-plus, DIMA, Germany; Bionexia Hb/Hp Complex, DIMA, Germany; PreventID CC, Preventis, Germany; immunoCARE-C, CAREdiagnostica,

Germany; FOB advanced, Ulti Med, Germany; and QuickVue iFOB, Quidel, San Diego, California. The study compared the performance characteristics of Hemocult and these six qualitative FIT for the detection of colorectal adenomas (cancers were excluded from analysis as it was diagnosed in only 11 patients). The positivity rate for g-FOBT was 4.5%, while that for the FITs ranged from 5.8 to 46.4%. Sensitivity of g-FOBT was lowest at 5.4%, and was 9.4% for advanced adenomas. Sensitivities of the FITs for detection of advanced adenomas varied widely from 25.4% (immunoCARE-C) to 71.5% (Bionexia Hb/Hp Complex). Specificity of g-FOBT was 95.9%, and ranged from 58.8 to 96.7% among the FITs. Only immunoCARE-C and FOB advanced had specificities over 90%: 96.7 and 92.9%, respectively, with sensitivities of 25.4 and 26.9% respectively. Overall, immunoCARE-C and FOB were the two best-performing tests. While this study demonstrates that g-FOBT is inferior to various FITs, it underscores the large differences in diagnostic performance among FITs, and the importance of evaluating a particular FIT before it is implemented for CRC screening.

The differences in the analytical performance among FOBTs were emphasized in a laboratory study from Massachusetts General Hospital [59] in which 71 stool samples sent to the clinical laboratory for various testing indications were used to compare five different FOBTs, including one g-FOBT (Hemocult SENSE) and four FITs: Polymedia OC-Auto Micro FOB (an instrument-read test; Polymedco, NY), QuickVue iFOB (Quidel, CA), Clearview Ultra FOB (Inverness Medical, MA), and Hemocult ICT (Beckman Coulter, CA). Significant differences in the reported package insert analytical sensitivity were observed among the five tests. In addition, the sensitivities calculated by the authors differed from those reported by the manufacturer, particularly for Hemocult SENSE and QuickVue FOB. The percent of positive samples ranged from 8.5 (Polymedia FOB) to 42.2% (QuickVue FOB). In 31 cases (43.7%), a discrepant result was obtained for at least one of the five methods. While the samples tested in this study did not fully match the types of specimens typically obtained for CRC screening, the study highlights the importance of selecting an adequate and properly evaluated FIT to utilize in a screening setting, particularly in light of the wide spectrum of performance features of these tests.

Haug et al. assessed the performance of two quantitative enzyme-linked immunosorbent assay (ELISA)-based FITs for detection of adenomas in the same cohort of subjects [58]. The characteristics of these two quantitative tests (RIDASCREEN Haemoglobin and RIDASCREEN Haemo-/Haptoglobin Complex, R-Biopharm AG, Germany) were compared to each other and to the qualitative tests mentioned above. Positivity cutoff levels were varied from 2 $\mu\text{g/g}$ of stool (manufacturer-recommended threshold) to 14 $\mu\text{g/g}$ of stool. Sensitivities for advanced adenomas ranged from 40 to 23.9% at the different cutoff levels for the hemoglobin test, and from 33.1 to 11.5% for the hemoglobin-haptoglobin test. Respective specificities ranged from 89.6 to 97.4%, and from 90.9 to 98.6%. The cutoff levels for a specificity of about 95% were selected for each test for further comparison (6 $\mu\text{g/g}$ of stool for hemoglobin and 4 $\mu\text{g/g}$ of stool for hemoglobin-haptoglobin). Corresponding sensitivities for advanced adenomas were 33.1% for hemoglobin and 23.9% for hemoglobin-haptoglobin. In addition, at the various levels of specificity

observed for the qualitative tests, the ELISA-based quantitative FIT showed similar sensitivities for advanced adenomas compared with these qualitative FITs. Thus, diagnostic performance of the quantitative hemoglobin FIT was better than the combination quantitative FIT; it was comparable to that of the qualitative tests, but allows the flexibility of determining positivity threshold.

Hol et al. compared g-FOBT (Hemoccult II) and FIT (OC-Sensor micro; Eiken Chemical Co., Japan) at different cutoff levels in an average-risk, screening-naïve Dutch population, aged 50–74 years [29]. A total of 10,011 individuals were randomized to g-FOBT group (three cards, no rehydration) or FIT group (single specimen, positivity analysis at 25 g/mL increments between 50 and 200 ng/mL) between November 2006 and November 2007. Subjects with a positive FOBT were referred to colonoscopy (in the FIT group, for all levels ≥ 50 ng/mL). Participation rate was higher in the FIT group (62%) than in the g-FOBT group (50%). Positivity rate was 2.8% for g-FOBT, while it ranged for FIT from 8.1% at a threshold of 50 ng/mL to 3.5% at a 200 ng/mL threshold. The most important decrease in FIT positivity rate was seen between threshold values of 50 and 75 ng/mL (8.1% vs. 5.7%). At all tested thresholds, FIT detected more advanced neoplasms than did Hemoccult II: g-FOBT 1.2%; FIT at 50 ng/mL 3.2%; FIT at 75 ng/mL 2.7%; FIT at 200 ng/mL 2.1%. No significant difference in CRC detection rates was found between the two tests. The number needed to screen to find one advanced neoplasm favored FIT at all thresholds. For g-FOBT, the number needed to scope to detect one subject with advanced neoplasia or CRC was 2.2 and 10.3, respectively. This was better than FIT at a threshold of 50 ng/mL (2.4 and 14.1, respectively); but was similar to FIT at the threshold of 75 ng/mL (2.0 and 11.6, respectively); while the number needed to scope at a threshold of ≥ 100 ng/mL was lower for FIT than for g-FOBT. This study shows that FIT outperforms g-FOBT at all tested thresholds, with higher participation and advanced adenomas detection rates. In addition, quantification allowed the authors to establish the optimal positivity threshold to avoid an excess of unnecessary colonoscopies. They suggested a threshold of 75 ng/mL, as the number needed to scope at this value was essentially similar to that of g-FOBT, while achieving a detection rate more than twice that of Hemoccult II. It is worth noting that this cutoff was identical to the one recommended by Levi et al., as described above [51].

Additional results from the Dutch study were published when Hol et al. reported the findings in a third group randomized to flexible sigmoidoscopy as compared to the two FOBT groups [60]. The positivity threshold for FIT was fixed at 100 ng/mL per the manufacturer's instructions, resulting in a positivity rate of 4.8% and an advanced neoplasia detection rate of 2.5%. Independent predictors of higher participation rates with FIT screening were female sex and age 60–64 years. The PPV of g-FOBT for advanced neoplasia was 45.2% (9.7% for CRC) and that of FIT was 53.3% (10.2% for CRC), with no statistically significant difference. However, the detection rate for advanced neoplasia was significantly higher with FIT as compared to g-FOBT (OR, 2.0; CI 1.3–3.2), after adjusting for age and sex. The diagnostic yield of advanced neoplasia per 100 invited subjects was also significantly higher with FIT (1.5; CI 1.2–1.9) than with g-FOBT (0.6; CI 0.4–0.8; $p < 0.001$). The authors reiterated their preference of FIT over g-FOBT for screening.

Sequential Stool Testing

Although using FIT as a preferred screening stool test over g-FOBT is supported by several comparative studies, a sequential occult blood screening strategy has been evaluated because of the potential cost savings. Fraser et al. reported their findings on a two-tier approach in two trials involving subjects from the Scottish Bowel Screening Program [61, 62]. In both studies, subjects with a positive g-FOBT were invited to participate while awaiting colonoscopy. In the first trial [61], two stool samples for FIT were collected (Instant-View, Alfa Scientific Designs, CA), and results were classified as both samples negative (N/N), one negative and one positive (N/P) and both positive (P/P). Among 800 participants, 22% were N/N, 16% N/P, and 62% P/P. Seven hundred and ninety five of these participants had colonoscopy data. CRC was found in less than 1% of both the N/N and N/P groups, while 8% of the P/P subjects had CRC. Advanced adenomas were present in 1% of the N/N individuals, 10% of the N/P subjects, and 24% of those P/P. In the second study [62], stool for FIT was collected with one simplified card (hema-screen DEVEL-A-TAB; positive at 50 ng/mL of hemoglobin). Among 1,124 invited individuals, 558 participated and 556 of those had colonoscopy. FIT was positive in 254 subjects (negative in 302). CRC was diagnosed on colonoscopy in 18.5% of FIT-positive subjects, and in just 0.7% of those FIT-negative. Advanced adenomas were present in 21.3% of the FIT-positive participants and in only 4% of those FIT-negative. In both studies, colonoscopy results revealed that FIT was highly sensitive for CRC among subjects with positive g-FOBT (95% and 95.9%); while sensitivity for advanced neoplasia was 90.1% in the first trial and 87.8% in the second. The authors concluded that this two-tier approach would reduce the demand for colonoscopy without significantly reducing the sensitivity of a screening program.

Implementing FIT Screening

Overall, FIT appears superior to g-FOBT as far as performance and acceptability. As it specifically binds human hemoglobin, FIT eliminates the need for dietary and drug restrictions. This advantage, along with more simplified sampling methods, has resulted in higher participation rates. Results are generally more reliable as FIT typically undergoes development in the laboratory setting, where analysis is automated, with ensuing improvement in reproducibility and quality control. The ability of FIT to generate quantitative test results offers a major advantage over g-FOBT, allowing optimal positivity threshold value determination for screening programs based on given needs and available resources. In addition to greater adherence, FIT results in higher detection rates both for advanced adenomas and carcinomas. In fact, as detailed above, its sensitivity is higher than g-FOBT, without a significant drop in specificity (and higher specificity than high-sensitivity g-FOBT).

With g-FOBT proven to be effective in reducing CRC mortality in several RCTs, it is reasonable to assume that annual FIT screening would lead to at least a similar reduction in CRC mortality. Data on CRC mortality reduction deriving from FIT screening are available from Japan, where mass screening with FIT was introduced in the mid 1980s. In a case–control study published in 1995, Saito et al. reported a significant reduction in CRC mortality by FIT screening (screening at 1 year: odds ratio=0.40, 95% CI=0.17–0.92; screening at 2 years: odds ratio=0.41, 95% CI=0.20–0.82) [63]. More recently, Lee et al. reported the results of their large-scale population-based prospective cohort study [53], which included 42,150 Japanese men (48%) and women (52%), of whom 7,179 (17%) had undergone FIT screening. The cohort was followed for a 13-year period. Compared to the unscreened group, and after adjustment for potential confounding factors, CRC mortality was reduced by 72% in the screened subjects (RR=0.28, 95% CI=0.13–0.61). Overall CRC incidence did not differ significantly between the two groups, but incidence of advanced CRC, defined by invasion of the muscularis propria or deeper (T2–T4 in the TNM Classification), was reduced by 59% in the screened group (RR=0.41, 95% CI=0.27–0.63). Cost concerns with FIT are raised as more societies are advocating its use over g-FOBT. But one Chinese study comparing g-FOBT, FIT, and a sequential testing, either with 2-day or 3-day sampling, showed that FIT with two-sample testing had a lower relative cost per cancer detected than either g-FOBT or the sequential testing [21].

Current Guidelines (Table 9.2)

At this time, the American College of Gastroenterology (ACG) recommends annual FIT as the preferred CRC detection test when CRC prevention tests are declined [64]. The most recent US Preventive Services Task Force (USPSTF) statement recommends an annual high-sensitivity g-FOBT or an annual FIT when fecal testing is performed for CRC screening [2]. The latest joint guideline from the American Cancer Society (ACS), the US Multi-Society Task Force on Colorectal Cancer (MSTF), and the American College of Radiology (ACR) also recommend for CRC detection either annual highly sensitive g-FOBT or annual FIT [65].

Table 9.2 Guidelines for fecal-based screening tests and testing intervals

	ACS/MSTF/ACR (2008)	USPSTF (2008)	ACG (2009)
Hemoccult II	Not recommended	Annually (<i>unclear recommendation</i>)	Not recommended
Hemoccult II SENSA	Annually	Annually	Annually (<i>alternative test</i>)
FIT	Annually	Annually	Annually (<i>preferred test</i>)
Fecal DNA	Yes: interval uncertain	Not recommended	Every 3 years (<i>alternative test</i>)

But while highly sensitive g-FOBT will detect more clinically significant neoplasia than conventional g-FOBT, the lower specificity will likely make any g-FOBT-based screening more costly than a FIT screening strategy because of a higher rate of false-positive tests.

Fecal DNA Testing

Background

Like other cancers, CRC is a disease of mutations in genes that regulate cell growth and survival. Mutations that contribute to CRC pathogenesis are either inherited (i.e., germ line mutations) or acquired (i.e., somatic mutations). CRC develops through one of three pathways – chromosomal instability, microsomal instability, and gene promoter methylation, also known as the CpG island methylator phenotype (CIMP) pathway [66, 67]. While there is overlap among the pathways, they inactivate different tumor suppressor genes and stimulate different oncogenes.

Searching for markers of neoplasia in stool is based on studies showing that tumor cells and DNA are shed into the colonic lumen where they combine with fecal material, and that specific mutated genes can be isolated from stool consistent with a neoplasm somewhere in the gastrointestinal tract. During the early part of the previous decade, investigators examined several different mutations for their presence in the stool of persons with colorectal neoplasia. Some of these studies, the mutations examined, and their test characteristics are shown in Table 9.3 [68–72].

A Multicomponent Fecal DNA Assay

Concurrent with these efforts were those from several groups of investigators who were working in collaboration with EXACT Sciences, Inc. (“EXACT”). Four

Table 9.3 Selected early studies of fecal DNA testing

Reference	Panel components	Sensitivity for CRC (%)	Specificity (%)
Dong et al. [68]	P53, K-ras, BAT-26	71	–
Traverso et al. [69]	APC	57	100
Traverso et al. [70]	BAT-26	37	100
Calistri et al. [71]	P53, K-ras, APC, 5 MSI markers, long DNA	62	97
Müller et al. [72]	Hypermeth of SFRP2	77–90	77

CRC colorectal cancer

Table 9.4 Studies of a multicomponent assay for fecal DNA testing: version 1

Reference	Sensitivity		Specificity
	Cancer	Advanced adenomas	
Ahlquist et al. [73]	91% (20/22)	82% (9/11)	93% (26/28)
Tagore et al. [74]	63% (33/52)	57% (16/28)	96% (204/212)
Syngal et al. [75]	63% (43/68)	26% (6/23)	NA
Brand et al. [76]	69% (11/16)	NA	NA

NA not available

preliminary studies involving a multicomponent assay developed by EXACT showed a cancer sensitivity of 62–91%, advanced adenoma sensitivity of 27–82%, and specificity of 93–96% [73–76]. However, all four studies involved patients with advanced, symptomatic cancers (Table 9.4). This limitation begged the question of how the multicomponent assay would be performed in the screening setting. Therefore, EXACT conducted a multicenter study to compare the test characteristics of its fecal DNA panel vs. guaiac-based Hemoccult II for the detection of CRC (TNM stages I–IV) and CRC and high-grade dysplasia (TNM stages 0–IV) in average-risk, asymptomatic adults aged 50 years or older [23]. In this landmark study, subjects were required to provide a stool sample for DNA analysis, complete Hemoccult II testing (3 cards, 6 panels), and under colonoscopy to the cecum, which served as the reference standard against which both stool-based tests were compared. Fecal DNA was isolated from stool and analyzed for 21 point mutations involving K-ras, APC, and p53; BAT-26, which is a marker of microsatellite instability; and a DNA integrity assay (“DIA”), which is a marker of disordered apoptosis. If any of the 23 components of the assay was positive, the test was interpreted as positive.

Of 4,404 enrolled persons, 2,507 were analyzed, including all persons with CRC ($n=31$), high-grade dysplasia ($n=40$), other advanced adenomas ($n=347$), and 1,423 persons with no polyps. Fecal DNA detected 16 of 31 (51.6%; CI, 35–68%) CRCs compared with 4 of 31 (12.9%; CI, 5–29%) for Hemoccult II ($P=0.003$), and it detected 29 of 71 (40.8%; CI, 29–53%) persons with TNM Stages 0–III disease, as compared to just 10 of 71 (14.1%; CI, 7–24%) for Hemoccult II. Fecal DNA detected 18.2% of advanced neoplasia as compared with 10.8% for Hemoccult II ($P=0.001$). Among persons with no polyps of any kind, the two tests were comparable: 94.4% for fecal DNA and 95.2% for Hemoccult II [23].

The results of the trial were considered disappointing by many because of the numerically higher sensitivity achieved in preliminary studies. Examination of the individual test components revealed that the DIA component of the assay was non-functional during the study, whereas it had performed consistently well during the preliminary studies. It was later determined that the reason for DIA’s failure was because of competition for breakdown of apoptotic DNA by bacterial endopeptidases, a problem that was solved by addition of an EDTA-containing buffer that inactivated the bacterial enzymes and improved DNA stabilization.

Given the lessons of the multicenter study, EXACT produced a second generation assay with improved DNA stabilization, and improved DNA isolation, which was accomplished by moving from a bead-based to a gel-based platform. Perhaps more importantly, new markers were identified, including HTML and methylation of the vimentin gene. These markers, along with the original ones, were tested on the stool collected from 40 patients with CRC and 122 controls with totally normal colonoscopy [77]. After exploring various combinations of old and new markers, it was found that the combination of DIA and vimentin provided the best results, with sensitivity of 88% and specificity of 82% [78]. This combination of markers was then validated in a subsequent study involving 42 subjects with CRC and 241 controls. With the same thresholds for positivity, sensitivity maintained itself fairly well at 86%; however, specificity fell to 73%. When the thresholds were optimized based on the data from both studies, sensitivity was 83% and specificity 82%.

In 2008, the NIH-funded counterpart study to EXACT's multicenter study was published [67]. This study was a multicenter, cross-sectional study involving 4,482 average-risk adults. It compared two fecal DNA tests with two occult blood tests for the outcome of screen-relevant neoplasia, defined as curable-stage cancer (i.e., stages I–III), an adenoma larger than 1 cm, or an adenoma with high-grade dysplasia. The two fecal DNA tests were the multicomponent assay (fDNA-1) and the combination of APC, K-ras, and vimentin (fDNA-2); the two occult blood tests were guaiac-based Hemoccult II (HOII) and Hemoccult SENSa (HOS). The main results from this study are shown in Table 9.5. The sensitivity of fDNA-1, the original multicomponent assay, was even lower than in the multicenter study. Both occult blood tests had a sensitivity that was comparable to fDNA-2, and all had very comparable specificities. Perhaps most striking was the sensitivity of fDNA-2 for screen-relevant neoplasia, as it detected 46% of adenomas that were 1 cm or larger, as compared with just 10% for HOII and 17% for HOS; however, as might be expected, the high sensitivity came at the cost of lower specificity, which was 84% [79].

Other Fecal DNA Markers

Several studies have looked at a variety of DNA mutations as markers for various degrees of colorectal neoplasia in hopes of identifying a sensitive and specific

Table 9.5 Results of NIH-sponsored trial of fecal DNA vs. hemoccult for detection of screened relevant neoplasia and colorectal cancer

Test	N	Sensitivity % (95% CI)		Specificity (%)
		Screen-relevant neoplasia	Colorectal cancer	
Hemoccult II	2,497	11 (6–16)	48 (30–67)	98 (98–99)
Hemoccult-Sensa	2,497	21 (15–27)	68 (49–83)	97 (96–97)
Fecal DNA test 1	2,497	20 (14–26)	25 (5–57)	96 (95–97)
Fecal DNA test 2	217	40 (32–49)	58 (36–80)	84 (76–92)

From Ahlquist et al. [79]

screening test for CRC. Some of these studies have used newer methods to detect low-abundance gene mutations, as fecal DNA testing must overcome the biological challenge of a very low proportion of mutant DNA molecules from colorectal neoplasms. These enhanced methods include single base extension, allele-specific polymerase chain reaction (PCR), BEAM-ing (beads, emulsification, amplification, and magnetics), and digital melt curve (DMC) assay. Other studies have examined new markers of colorectal neoplasia, such as gene hypermethylation, which is frequently involved in CRC pathogenesis. A few of the more recent and arguably more relevant studies are described here.

Zou et al. used a DMC assay to quantify low-abundance mutations in stool samples and compared this test with other approaches [80]. The DMC assay combines rapid gene scanning properties of melt-curve technology [81–83] with the extremely sensitive quantitative capacity of digital PCR [70, 84]. In the first of two studies, the DMC detected known mutations in 28 (90%) of 31 CRC stool samples and in 6 (75%) of 8 advanced adenomas samples [80]. In the second study, the DMC assay detected 16 (59%) of 27 archived samples from persons with advanced adenomas that contained K-ras mutations, as compared with just 7% using Hemocult II, 15% using HemocultSensa, and 26% using the EXACT Sciences K-ras assay [80]. Respective specificities were comparable at 92, 92, 92, and 100%. These findings warrant further study of the DMC assay as a fecal DNA screening tool.

Using a novel single-step modification of DNA with sodium bisulfate and fluorescence PCR methodology, Nagasaka et al. examined methylation of RASSF/SFRP2 promoters in 296 fecal samples from a variety of Japanese patients, including 152 with colorectal tumors [85]. The assay identified one or more methylated markers in fecal DNA from 75% of patients with CRC and in 44% of patients with advanced colorectal adenomas, as compared with 10.6% of controls with no gastrointestinal neoplasia or inflammation. These markers were also present in 57% of persons with gastric cancer.

Using a gene expression array-based strategy, Glockner et al. examined methylation of a potential tumor suppressor gene, tissue factor pathway inhibitor 1 (TFPI2), to detect CRC [86]. After identifying aberrant methylation of TFPI2 in 97% of adenomas and 99% of CRCs, they explored this marker's potential for early detection of CRC using a stool-based assay in patients with nonmetastatic CRC and colonoscopy-negative controls. TFPI2 methylation had a cancer sensitivity of 76–89%, adenoma sensitivity of 21%, and a specificity of 79–93% [86]. Further study of this epigenetic marker is warranted.

A highly sensitive method for detecting methylated DNA, Methyl-BEAMing technology enables absolute quantification of the number of methylated molecules in a sample, and is able to detect as few as one methylated molecule in nearly 5,000 unmethylated molecules in DNA from plasma and fecal samples [87]. Using methylated vimentin as a biomarker in plasma samples, methyl-BEAMing detected 59% of CRCs and with a specificity of 93%. On fecal samples, it detected 41% of 22 CRCs and 45% of 20 advanced adenomas [87]. Applying this method to other genes that become methylated in CRC would improve the sensitivity of this technique.

What Is the Place of Fecal DNA Testing in Colorectal Cancer Screening?

The most recent guidelines are inconsistent with regard to fecal DNA testing for CRC. The ACS-MSTF-ACR guidelines recommend it at a 5-year interval as one of two “cancer detection” tests [65]. The American College of Gastroenterology recommends it, but does not specify a testing interval [64]. The USPSTF does not recommend it because the Task Force was unable to weigh risks and benefits of the test [2].

Fecal DNA testing has several issues to address. First, only two studies have assessed its performance in the screening setting. All of the other studies have compared specimens from CRC cases with (usually) controls with no neoplasia detected on colonoscopy. While it is not realistic to expect each candidate marker or panel of markers and each assay method to be tested in the screening setting, an acceptable “level” of study rigor has not been identified. Second, a testing interval has not been firmly established. EXACT’s PreGenPlus is recommended every 5 years, but there are no empirical data supporting this testing interval. Modeling studies have suggested reasonable reductions in CRC incidence and mortality, but colonoscopy and FOBT dominate fecal DNA in these analyses [88, 89]. Third, the test performance of fecal DNA is currently no better than FITs or high-sensitivity gFOBTs, yet the cost of fecal DNA is substantially greater than FOBTs. Last, management of the patients with a positive fecal DNA test and “negative” colonoscopy is uncertain. Should the colonoscopy be repeated? If so, when? Should other testing be performed looking for cancers of the upper digestive and respiratory tracts? These and other issues serve as rich substrate for further investigation.

Blood-Based Screening Tests

Background

Perhaps the ultimate screening test for CRC is a blood test that identifies persons who have either current advanced neoplasia or increased life-time risk for it. Multiple studies have attempted to identify such a test, although a reliable serum biomarker for advanced neoplasia has yet to be described. While some studies have measured DNA markers, the majority of studies involve proteomics, which is the study of protein expression in biologic samples. The use of proteomics for cancer detection involves identifying biomarkers – either individual proteins or proteomic patterns (also known as “expression signatures”) – that discriminate between persons with and without cancer or advanced colorectal neoplasia. The overarching goals of proteomic analysis are to identify differences in protein expression that correlate with different disease states and to identify one or more (protein) biomarkers that have distinct quantitative differences between clinically relevant groups.

Table 9.6 Findings of selected studies on molecular blood tests for detection of colorectal neoplasia

Studies	Markers	Sensitivity, % (n)		Specificity, % (n)
		Cancer	Adenoma	
<i>DNA in plasma</i>				
Diehl, 2005	APC mutations	67 (16/22)	9 (1/11)	100 (33/33)
Grutzmann, 2008	Methylated Septin 9	58 (73/126)	18 (3/17)	90 (165/183)
Lofton-Day, 2008	Methylated Septin 9	69 (92/133)	–	86 (154/179)
deVos, 2009	Methylated Septin 9	69 (62/90)	–	85 (132/155)
Li, 2009	Methylated vimentin	59 (48/81)	–	93 (102/110)
Lee, 2009	Methylation of 10 genes	86 (210/243)	75 (48/64)	92 (254/270)
<i>Proteins in serum or plasma</i>				
Liu, 2006	Mass spec profile	95 (70/74)	–	95 (333/351)
Habermann, 2006	C3a-desArg	97 (57/59)	86 (31/36)	94 (30/32)
Hurst, 2007	MMP-9	78 (74/95), combined	–	76 (35/46)
Leman, 2007	CCSA-3, CCSA-4	100 (28/28)	78 (14/28)	96 (51/53)
Waigenbach-Brunagel, 2008	CCSA-2	89 (24/27)	20 (4/20)	84 (106/127)
Kim, 2009	S100A8	41 (36/88), combined	–	95 (20/21)
	S100A9	45 (40/88), combined	–	95 (20/21)
	CEA	22 (19/88), combined	–	100 (21/21)

As with the literature on fecal DNA, most of the studies involving serum biomarkers are case–control studies, which usually do not sample the entire spectrum of diseased or nondiseased subjects. In addition, case–control studies are prone to bias and chance and, particularly when the number of candidate markers exceeds the number of study subjects, require independent validation on a separate sample of subjects [90].

Table 9.6 summarizes the results of selected studies within the past 5 years. Studies involving DNA include distinct mutations or methylation of one or more genes [87, 91–95]. Among these studies, cancer sensitivity ranges from 59 to 87%, while specificity ranges from 86 to 100%. Sensitivity for large adenoma, which has been much less studied, ranges from 9 to 75% [91, 92, 94]. Studies involving protein markers demonstrate greater variation with respect to both the kinds of markers and types of assays. Cancer sensitivity ranges from 89 to 100%, while specificity ranges from 77 to 100% [96–101]. Adenoma sensitivity, which has been much less studied, ranges from 20 to 86%. For both DNA and protein markers, more data are needed on sensitivity and specificity of curable-stage lesions: stages 1 and 2 CRC with or without advanced adenomas.

Several methodological challenges to molecular marker research have been well described [90, 102]. In general, successful biomarker discovery will require a well-characterized study population with appropriate spectra of cases and controls; high-quality samples that are acquired and processed in a uniform fashion; a reliable

analytic platform; and independent validation, preferably by independent groups of investigators. Future biomarker researchers and consumers of this body of literature will have to consider carefully these requirements when designing and evaluating subsequent studies in this area.

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Chapter 10

Removal of Difficult Colon Polyps

Jerome Wayne

Keywords Sessile adenoma • Flat adenoma • Chromoendoscopy • Non-lifting sign

Difficult colon polyps are not necessarily large, such as those over 2 cm in diameter, but may be relatively small but flat, or may be in a difficult or inaccessible area of the colon. These polyps include lesions that require special maneuvers for their removal.

Sessile polyps are usually considered to be somewhat difficult to remove, with the larger diameters falling into the “very difficult” category which require advanced polypectomy techniques. Some pedunculated polyps may also require advanced techniques, especially when the head is so large that it is difficult to see around the head of the polyp to seat the snare around its stalk. Most polyps in the colon are sessile, and many of these will be located in the right colon, from the hepatic flexure to the cecal caput. Pedunculated polyps, with a pedicle of pulled-out mucosa and submucosa caused by the constant action of peristalsis in the colon’s attempt to evacuate the polyp, are usually located in the sigmoid colon. In spite of the contractility of the rectum, large sessile polyps may grow in the rectum without a pedicle.

Most colon polyps can be removed through the colonoscope [1]. Studies have shown that removal of colon polyps markedly decreases the incidence of colorectal cancer [2]. Sessile polyps less than 15 mm in diameter rarely present a problem for their removal, and they are often resected with one application of the snare providing total polypectomy with a single snare application unless they are flat, which may make them difficult to remove. Polyps over 15 mm in diameter, however, should not be ensnared with one application of the snare loop, since the thin colon wall may be bunched up underneath the polyp as the snare is being closed, capturing the muscularis propria within the wire loop. If this occurs, the entire thickness of the wall can be transected as electrocautery current is applied. The situation in the colon is completely different from that in the stomach and esophagus where the

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muscular wall is quite thick in relationship to the mucosa and submucosa and will not “buckle” and bunch up under the snare as the loop is closed around the polyp. In the colon, the thickness of the wall varies from 1.4 to 2.3 mm in diameter throughout the entire colon, including the sigmoid [3, 4]. The studies by EUS have demonstrated that there is no “thick area” in the sigmoid colon where the endoscopist can feel complacent in snare application because of the perceived notion that the sigmoid is much thicker than the right colon.

In order to prevent the bunching up of deeper layers of the colon wall within the snare loop as it is closed, injection of fluid into the submucosa will markedly increase the thickness of the submucosal layer and prevent entrapment of the muscularis propria and serosa. The amount of injected fluid may vary from a few cc to 30 or more cc. The object is to place a significant amount of saline beneath the polyp to elevate it in its entirety above the normal mucosal plane. The injected solution also serves to prevent deep thermal injury as electrocautery current is applied.

It is useful to classify polyps according to a specific nomenclature since this permits endoscopists who read the report and across the world to be able to know the type of polyp that was removed. In the United States, most endoscopists perform colonoscopy and report that a “large (25 mm) sessile polyp was removed.” However, this does not give any information on the height of the polyp, whether one portion was depressed, whether there was an elevated portion associated with a flat portion, or whether the polyp was smooth or irregular in its surface configuration. Even for the description of a “flat polyp,” the use of the term “flat” is relatively nonspecific, as mentioned by Bourke [5].

A recent update to an accepted system of nomenclature appeared in late 2009 [6]. This system describes polypoid lesions as sessile or pedunculated with the definition of sessile as a polyp that is over 2.5 mm in height. These are called type Is and Ip or the combination is Isp. Nonpolypoid adenomas (Type II) are less than 2.5 mm in height and there are three categories of these nonpolypoid colorectal neoplasms (NP-CRN): slightly elevated, flat, and depressed with descriptors of a, b, or c, respectively. All these are often referred to as “flat.” “Carpet adenomas” are defined as type II lesions over 10 mm in diameter and have been given the name of laterally spreading tumors (LSTs) which can be granular or nongranular in appearance. Morphology appears to be important in determining the malignant potential of polyps; flat lesions that are depressed or flush with the mucosal surface and nongranular LSTs all have a significantly higher risk of containing high-grade dysplasia. The vast majority of polyps are sessile, with most pedunculated polyps being found in the left colon, where peristalsis is strong and tends to pull on polypoid protrusions, resulting in a pedicle formation.

Benign or Malignant?

Once a lesion has been recognized, and its size determined, the next decision that must be made is whether the polyp is benign or malignant. There are few criteria that can be used to make the determination as to whether any particular colonic lesion is malignant.

A question that arises is whether to perform a biopsy and then bring the patient back for polypectomy based on the subsequent results of biopsy or to depend on the visual impression of whether the polyp is benign. There are no published studies on the visual criteria which can be applied to a polyp to determine the presence of malignancy; however, endoscopists in a tertiary referral center [7] have stated that a benign polyp does not have any of the following features: ulceration, induration, or friability. A publication [8] stated that malignant polyps may be visually recognized by the following criteria: a shallow depression in a flat polyp or a scooped-out area like the capital letter “C” in the center of an otherwise benign-appearing polyp, multiple irregular nodules, large size, or by spontaneous bleeding. Japanese endoscopists have noted that large flat polyps were usually benign, and that invasive carcinoma is seen in elevated sessile polyps [9, 10]. The morphology of polyps becomes important, since there is general consensus that flat polyps that tend to spread laterally rarely contain cancer.

Biopsies are notoriously erroneous for the diagnosis of invasive carcinoma within a polyp because the depth of tissue obtained is usually limited and because high-grade dysplasia on biopsy (which used to be called noninvasive carcinoma or carcinoma in situ) is histologically identical to invasive carcinoma and whether invasive is present depends on the pathologist seeing tumor cells crossing the muscularis mucosa, a depth of biopsy unusual in routine biopsy techniques. In addition, the amount of tissue sampled by biopsying a large polyp represents only a fragment of the total polyp volume submitted for histopathology. Most colonoscopists base the decision as to whether a large polyp is benign or malignant on the visual impression when it is identified. If the visual assessment is that the polyp is benign, the decision for removal should be based on other visual criteria such as size and accessibility; if it looks like it can be removed, an attempt should be made to resect it without a biopsy for “confirmation.”

There is a general reluctance among endoscopists to remove large polyps because of the possibility of invasive carcinoma. One report [11] stated a 40% incidence of invasive carcinoma in large polyps, but this finding was based on the pathologist’s finding of carcinoma in surgical specimens that were sent to the pathology laboratory, not polyps that were removed endoscopically. Endoscopically resected polyps, which meet the visual criteria of being benign, will actually have an incidence of about 10–15% of invasive malignancy. When the decision is made by the endoscopist to attempt removal of large polyps, it is necessary to obtain the patient’s agreement to repeated endoscopy sessions and follow-up endoscopies. Complete resection of large sessile polyps may require more than one session and, since high rates of local recurrences are reported, it is mandatory to confirm complete removal by follow-up examinations.

Chromoendoscopy

If there is concern about the extent of a polyp or the presence of carcinoma, chromoendoscopy may be of assistance to the visual impression by the endoscopist. Chromoendoscopy refers to the process in which tissue stains or dyes are applied to

the gastrointestinal mucosa through an endoscope to detect or enhance the appearance of abnormalities. The application of dye on the surface is used to characterize those abnormalities and to delineate their margins. Chromoendoscopy is simple, safe, and may be combined with magnification endoscopy. Although commonly used in Japan [12], it has not been widely used in the USA and Europe.

Tissue stains are classified into three categories: absorptive, reactive, and contrast types. Absorptive stains are actively absorbed into the mucosal cells. Examples of this type of stain are Lugol's solution and methylene blue. Lugol's iodine solution has been used primarily in the upper digestive tract. Methylene blue is taken up by absorptive cells and enters the cytoplasm. The absence of staining usually indicates neoplastic changes. Patients may notice blue–green discoloration of urine and stools after use of this agent. Staining is evident within 2–3 min and begins to fade after 15–20 min, but persists up to 24 h.

Crystal violet stains the margins of the crypts on the mucosal surface, allowing very clear definition of the mouths of these pits. Complete mucus removal by washing with water is required for accurate staining and diagnosis. Kudo et al. [13] describe five types of pit patterns as seen with chromoendoscopy which correlate with histologic diagnosis. These pit patterns require a magnification endoscope to delineate their specific characteristics.

Reactive stains such as Congo red identify cellular products, an example of which is the change in color of a pH indicator. This stain changes color from red to dark blue/black in the presence of acid with a $\text{pH} < 3$. A combination of Congo red and methylene blue has been used to highlight colonic neoplastic lesions which tend to bleach the dyes sprayed on their surface.

Contrast stains are not absorbed, but they highlight surface topography by pooling in mucosal crevices and depressions. The primary contrast stain used in the colon is indigo carmine dye (ICD) with a concentration of 0.1–0.8%.

ICD is most commonly applied via a spray catheter passed through the endoscope. It has been given orally, with a large volume lavage electrolyte preparation solution. The problem with this total colon-staining method is the inability to recognize mucosal pathology, such as inflammatory reactions, which rely on visual identification. When ICD is delivered through a spray catheter or flushed through the biopsy channel, any overlying material and mucus should be washed off with a strong flush of water.

The main use for chromoendoscopy with and without magnification endoscopy has been for the detection, characterization, and delineation of polyps and neoplasms. Since most sessile and pedunculated polyps and most carcinomas are obvious without using chromoendoscopy, its main application has been for flat adenomas, and in some instances, to define tumor depth in attempts to clarify the possibility of endoscopic resection (Fig. 10.1a, b). There may be a role for applying dye spray to the normal-appearing mucosa around an obvious neoplastic lesion in order to better define the margins of a sessile polyp if endoscopic resection is considered. The subcategory of “lateral spreading polyp” refers to polyps that are relatively flat, over 10 mm in diameter and grow superficially. These may be easily overlooked during colonoscopy and may be a challenge to remove completely. They may be seen more easily by chromoendoscopy [14].

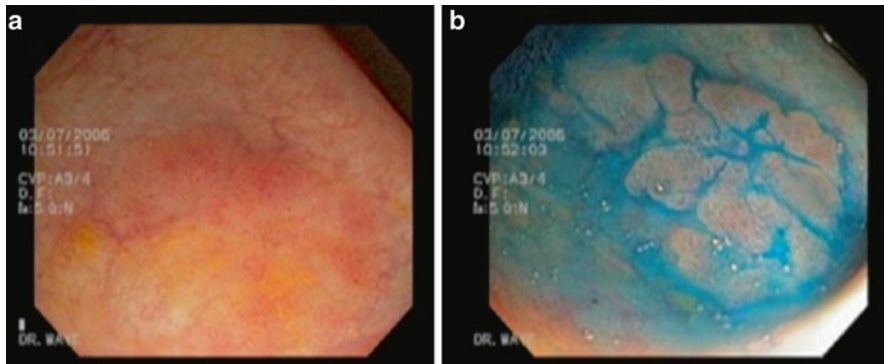


Fig. 10.1 (a) Chromoendoscopy. Patchy discoloration of the colonic mucosa. (b) The area after spraying with a dilute solution of methylene blue which brings out the flat colon polyp (Paris type 0-IIb). Final diagnosis: tubular adenoma

Narrow band imaging is an electronic method of changing the visual surface characteristics of the colon. Here, narrow bands of the white light spectrum are utilized to enhance the vascular pattern of the mucosal surface. These are generally narrow bands of light in the blue/green range and can be used to identify the superficial vascular nature of a polyp or to detect polyps in the colon. This technique is useful, quicker (requiring pressing a button on the endoscope), and less time-consuming and less “messy” than the application of dye spray techniques.

General Criteria for Removal

If the polyp appears to be benign on endoscopic visual examination, the average endoscopist (as compared to experts) must then consider certain criteria for its removal. If any of these are present, the endoscopist will have considerable difficulty in its removal. This, however, does not mean that gastroenterologists should not attempt removal of polyps that are beyond the size of these criteria. Many large polyps can be removed in piecemeal fashion with an eventual good result after multiple sessions of polypectomy. Criteria for polyps that will be difficult to remove are: (1) the polyp occupies more than one-third the circumference of the colon wall; (2) the polyp crosses over two haustral folds; (3) the polyp encircles and actually involves the base of the appendix; (4) the polyp is in a difficult location. A polyp which extends more than one-third the circumference of the colon wall will create a large mucosal defect if it is removed. It is possible that polyps of this size could be removed by an expert endoscopist, but even the expert may elect to send such a patient for surgical resection rather than face the possibility of multiple

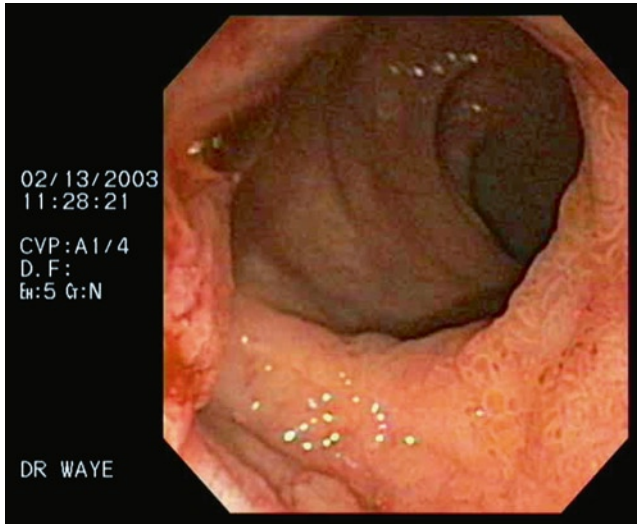


Fig. 10.2 Polypectomy requiring multiple sessions. A circumferential flat polyp in a patient who had multiple unsuccessful surgical procedures performed for removal of this polyp. A combination of snare polypectomy and argon plasma coagulator (APC) fulguration destroyed this polyp over multiple sessions spanning 4 years. This was a tubulovillous adenoma. Paris type 0-IIa and 0-IIb. Final diagnosis: villous adenoma

colonoscopic examinations, particularly if the colonoscopic approach to the polyp was extremely difficult and demanding (Fig. 10.2). Gastroenterologists need to become more familiar with the techniques of difficult polypectomies, since the advent of the computerized tomographic colonography will certainly discover more polyps and more large polyps than have been seen in the past. Polyps that cross over two haustral folds present another problem in their total removal, since it may be almost impossible to remove the entire polyp, especially the portion that lies in the valley expands between two haustral folds. Polyps that involve the appendiceal orifice may extend into the appendix and, although this phenomenon is rare, total removal of this type of polyp is problematic.

Does the Patient Need Hospitalization?

Once a decision has been made that the lesion is benign, and that there is a possibility for its removal by using advanced polypectomy techniques, the decision should be then directed toward whether the polyp should be removed at the time that

it is seen. There are only a few reasons why polypectomy may be performed to a subsequent time, or to another location. These occasions are:

- The patient is on anticoagulants
- The patient is poorly prepped (?)
- The patient has an implanted pacemaker/defibrillator

The vast majority of polyps that fall in the category of those needing “advanced polypectomy” can be performed in an ambulatory setting, even in an office remote from the hospital. This does not mean that a special “ambulatory surgical center” be utilized for polypectomy, but that it can be done in a well-equipped office remote from a hospital location.

In a center in Australia, 90% of patients who were scheduled for surgical resection of polyps avoided the need for surgery. In the removal of 193 difficult polyps from 174 patients, only 20 bed days were used and that was because of endoscopic complications. All of the patients were treated in an ambulatory basis and the procedural success rate was 95% [15]. To put this issue in perspective, the rate of immediate complication is so low in colonic polypectomy, even in large polyps, that it seems unnecessary to hospitalize any patients for removal of polyps by the technique of endoscopic mucosal resection (EMR). The literature supports the concept that all polyps that are endoscopically resectable by EMR can be successfully managed in an ambulatory situation or even in an office remote from the hospital.

Equipment for Polypectomy of the Difficult Polyp

Before embarking on any advanced polypectomy procedures, the full array of accessory equipment should be available. There is no need for any other items, except perhaps for the argon plasma coagulator (APC) in addition to ensuring that these standard accessories are readily accessible if the need for them arises.

- Colonoscope, standard or pediatric [16, 17]
- Large snare and small snare (a rotatable snare is not necessary)
- Electrosurgical unit
- Needle injector
- Retrieval basket
- Epinephrine 1:10,000
- Pure carbon surgical marker (SPOT)
- Aspiration trap for recovery of polyp fragments
- Various solutions for submucosal injection prior to polypectomy and for dye spray
- Endoclips
- Endoloops (optional)

Broad-Based Polyp (Is or IIa,b,c, LST)

The polyp with a wide attachment to the colon wall may be resected with one application of the wire snare if the base is less than 1.5 cm in diameter whether or not the height is over 2.5 mm. The polypectomy is considerably easier if the polyp is located at the 5–6 o'clock position in the field of view. If it is in the 9 or 12 o'clock position, polypectomy is extremely difficult. Rotation of the shaft of the colonoscope and movement of the dial controls can reposition the colonoscope into a favorable approach for endoscopic resection (Fig. 10.3a, b). The endoscopist should consider piecemeal polypectomy of any polyp whose base is greater than 1.5 cm [18] (Fig. 10.4a, b). During the technique of piecemeal polypectomy, an attempt should be made to place one edge of the wire snare at the junction between adenoma and normal mucosal wall [19]. The other limb of the wire loop can be maneuvered over a substantial portion of the polyp, but not extending to encompass the entire polyp unless it is less than 15 mm in diameter. The tip of the snare sheath should then be advanced to the edge of the polyp nearest the endoscope. Aspiration of air will collapse the colon as the snare is closed slowly. The endoscopist's attention should be directed toward the tip of the wire snare as it moves over the mucosal surface behind the polyp when the slide bar is being retracted. Direct vision is an important adjunct to ascertain whether a portion of normal mucosa is caught within the snare tip or if the tip slides over the mucosa and engages on the far margin of the polyp. This assessment is important, but may not be possible in all instances of piecemeal polypectomy. If one is not sure as to whether the wire loop contains extra tissue, the sheath should be jiggled to and fro as mentioned previously, while observing the colon wall to assess whether the wall in back of the polyp moves along

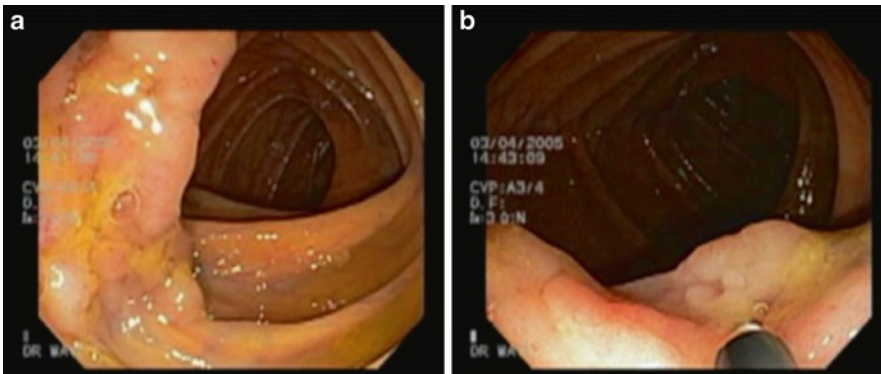


Fig. 10.3 (a) Position of the polyp. A polyp at the 9 o'clock position is extremely difficult to remove (Paris type 0-Is and 0-IIa). Final diagnosis: tubulovillous adenoma. (b) With manipulation of the shaft and dial controls, polyps can be brought to a more favorable position to the 6 o'clock position since that is where the instrument channel is directed. A needle injector is placed into the polyp for creating the saline lift

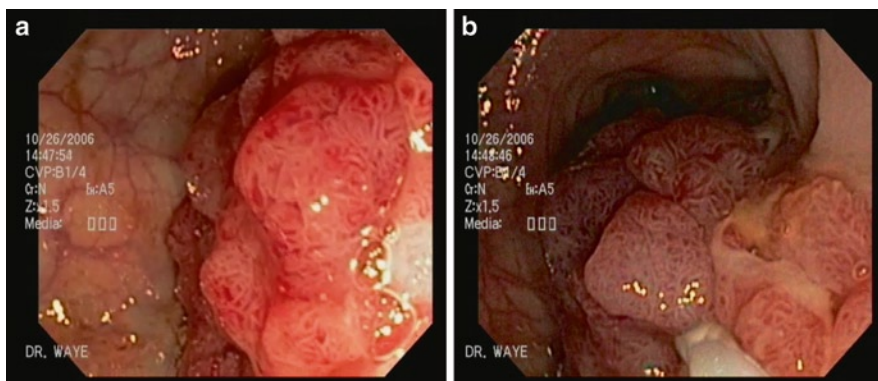


Fig. 10.4 (a) Piecemeal polypectomy. A large sessile polyp filled the lumen of the colon (Paris type 0-Is). Final diagnosis: tubulovillous adenoma. (b) The snare is placed around a portion of the polyp to debulk it in piecemeal fashion so that the base can be located and treated. This polyp was completely removed with multiple snare applications

with the polyp. After the wire is closed upon the desired portion of the polyp, the sheath should be lifted slightly away from the wall, tenting it toward the lumen to separate the mucosa from submucosa. This will limit the depth of thermal injury when current is applied because the local zone of heating has a lessened chance of damaging the muscularis propria and serosa as the layers are pulled away from each other.

Large right colon polyps with a clamshell configuration may present with only the most distal portion being visible to the endoscopist. In fact, even though the most distal portion of polyp may be removed endoscopically, there often is a portion of the polyp on the proximal aspect of the fold that may not be visible. This area can be seen by performing a retroversion maneuver in the right colon. This maneuver is best accomplished using a pediatric colonoscope, with a short “nose,” and a shorter bending radius than the standard colonoscope. With the instrument straightened, and the tip in the cecum, retroversion is performed by markedly deflecting the up/down control and advancing the instrument to push the angulated tip bending section into the caput increasing the angle of deflection similar to rectal retroversion. Once the turn has been made, it is usually necessary to markedly adjust the right/left control to permit visualization of the colonoscope shaft in the U-turn mode. Often, pulling back the endoscope shaft with a clockwise torque will complete the turning maneuver. Polyps can be removed in the retroversion mode, but all the intraluminal events are upside down and backward from the usual control functions, since the instrument is now in a 180-degree opposite view than on straightforward colonoscopy. However, saline may be injected, the snare may be utilized, and the APC can all be passed through the accessory channel in the retroverted scope.

A gastroscope can also be used for removal of polyps in a tortuous sigmoid colon, laden with diverticuli. The short nose and acute angulation capability usually

permit accurate positioning of the scope and snare to perform polypectomy when the standard adult colonoscope is unable to see the polyp and snare into the proper configuration.

It may be possible to promote volume reduction of polyps by injecting epinephrine into the polyp prior to resection. It has been reported [20] that a significant reduction in polyp volume could be achieved by injecting adrenaline into large polyps prior to polypectomy. Volume reduction was associated with no complications or bleeding. In the description of the method, 4–8 mL 1:10,000 epinephrine was injected into the head of a polyp at 2–4 sites. After immediate blanching of the head, 2–4 mL of epinephrine should again be injected into the stalk of a polyp in two or more sites. A delay of several minutes (3–5 min) was recommended to maximize the polyp volume reduction. This technique deserves further investigation.

The Nonlifting Sign

In general, malignant tumors should not be removed using the submucosal fluid injection method. If a polyp fails to elevate (the “nonlifting sign”), it may be an indication of infiltration by cancer into deeper tissues, limiting the expansion of the submucosal layer [21, 22]. Although deep or superficial needle placement may be the cause for failure to raise a bleb under a polyp, a submucosal bulging or bleb on one side of a polyp in response to injection without any visible elevation of the tumor itself (or only minimal elevation of one portion) is a clue that there is fixation into the submucosa (Fig. 10.5a–c). This phenomenon may also be caused by a prior attempt at polypectomy with healing and scarring of the mucosa and submucosa, preventing their separation by fluid injection. Japanese endoscopists [23] have reported that flat polyps that are granular and tend to spread laterally (LSTs) have a low incidence of malignant degeneration. There is a theoretic possibility that injection through a malignant tumor may cause tracking of cancer cells into and even through the bowel wall. The risk of this happening is minimal, with experience gained from direct percutaneous needle aspiration of malignant tumors in other sites throughout the body. In the latter instances, the risk of tumor tracking is 1 in 10,000 to 1 in 20,000 cases [24].

Any tumor which can be elevated with submucosal injection of fluid may be totally removed by endoscopic resection, even if invasive cancer is found on tissue examination. The ability to elevate a tumor indicates that there is no deep fixation, or only a limited degree of fixation to the submucosal layer, with the probability of complete removal [25].

Configuration

Flat polyps are commonly encountered, with the morphological description promulgated in Japan; their previous definition is: a mucosal lesion with a flat or slightly rounded surface combined with a height of less than half the diameter of

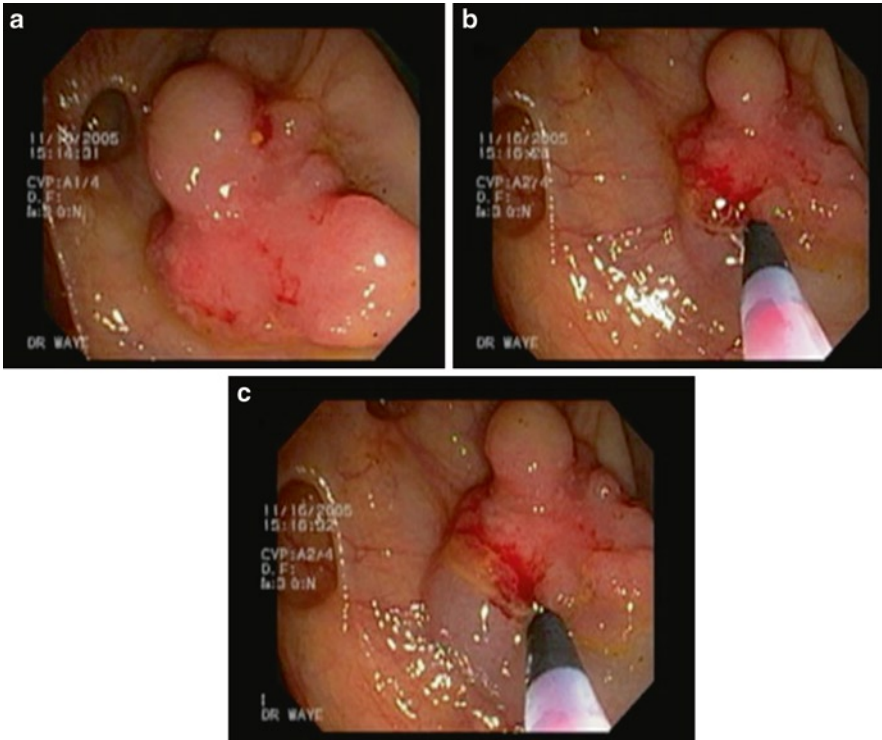


Fig. 10.5 (a) Nonlifting sign. A sessile polyp with a central indentation suspicious for malignancy. Paris type 0-Is. (b) Saline is injected at the edge of the polyp, but with a small amount of saline the polyp does not elevate, instead a submucosal bleb of fluid is seen below the polyp. (c) After further injection of saline, the polyp still does not elevate while the submucosal bleb continues to enlarge. This polyp was partially removed and revealed invasive adenocarcinoma

the lesion. Sessile lesions were defined as raised with no distinct stalk when the diameter does not exceed twice the height [26, 27]. These older definitions have been replaced by the Paris Classification [6]. The extremely flat polyp, like a postage stamp on the wall (IIb), may be difficult to approach under any circumstances (Fig. 10.1a, b). Saline injection may raise up the entire area and elevate the polyp on a saline plateau, making it impossible to capture the polyp with the snare because there is no edge which the snare wire can grasp as it closes. This type of polyp configuration should be removed without prior submucosal injection since that may flatten the surface so that air aspiration will not be of benefit because the whole area is infiltrated and the polyp will not raise up as air is suctioned. Air aspiration alone will elevate the lesion in the absence of a submucosal injection: open the snare over the polyp, keep it flat on the wall, aspirate air, and remove relatively small portions of tissue in order to prevent closing the snare on the full thickness of the colon wall. Removal of air with the open snare loop in place will

collapse the distended colon causing the polyp footprint to decrease while the colon circumference also decreases. As mentioned before, as the footprint becomes smaller, the polyp volume does not change so it rises up into the open snare making capture easier. It is necessary for the operator to visually confirm that the snare entraps only mucosa during these closures. For flat polyps, a monofilament snare may be helpful as it is more rigid than braided wire and will more readily close around a flat polyp.

Removal of Air to More Easily Capture a Polyp

Removal of air from the colon not only decreases the diameter of the colon, but also decreases its length, in a similar fashion to taking the air out of a long toy balloon. As air is removed from the colon, the circumference decreases and the diameter gets smaller. A sessile polyp whose base may fill $\frac{1}{4}$ of the lumen will also decrease its footprint on the colon wall, but since the volume of the polyp has not decreased, the polyp will actually raise up into the open snare which has been placed over the polyp before air is aspirated. The removal of air just prior to closing the snare around the polyp is of great benefit, as the lesion often jumps up into the snare as air is withdrawn.

Endoscopic Submucosal Dissection (ESD)

Endoscopic submucosal dissection (ESD) was developed in Japan [28] for removal of large gastric lesions which were not amenable to EMR either because of their size, the difficulty with resecting a specimen in multiple pieces (the margins cannot be readily determined), or because the lesion is bound down to deeper tissues such as occurs with prior EMR attempt or with superficial invasive carcinoma. It has been applied to colonic lesions where large colon neoplasms could be totally excised with one specimen. However, the technique of ESD is more time-consuming than EMR, there is a higher rate of complications (up to 5% of ESD application of the colon results in a perforation), and a longer length of hospitalization after applying this technique.

The technique of ESD is similar to EMR except that the submucosal space is the plane in which tissue is dissected. This requires special electro-surgical equipment and one large specimen is obtained as opposed to EMR where multiple fragments of tissue are accumulated. The indications for ESD are: a sessile colorectal tumor whose size is more than 20 mm, and with a morphology of protruded sessile (Is or Isp) or superficial types IIa, IIa+IIc. The technique is suited for resection of colon adenoma or carcinoma with invasion only down to the superficial submucosa. ESD is also performed for a lesion with submucosal fibrosis that could not be removed by conventional EMR even if the size of the lesion was less than 20 mL.

The technique [29, 30] is usually performed using a regular colonoscope. A transparent hood is affixed to the tip of the endoscope and the elevation of the tumor is performed with multiple injections of hyaluronic acid solution (to increase the length of time that the injected solution remains in the submucosa). Various short tip “knives” are used such as a hook knife, or a flex knife. The border of the tumor is delineated by chromoendoscopy. Frequently, small marks are made at the periphery of the tumor so that, once ESD has been started, the marks will readily indicate the outline of the polyp. The fluid infiltrated mucosa is then incised near to but not directly on the edge of the polyp. A hemircumferential incision is made around the polyp and electrocautery current is used to burrow into the submucosal space undermining the entire polyp. Patients are regularly hospitalized for several days after ESD because of the high rate of bleeding and perforation. The perforation rate is 5–7% and is higher for rectal tumors (up to 15%). When perforation is detected by endoscopy, these patients are treated only by endoscopic clipping without surgery. The rate of postoperative hemorrhage is approximately 1%. One of the major advantages of ESD for colorectal tumors is that a high rate of en bloc resection can be achieved. Despite its longer procedure time and higher perforation rate, ESD results in higher en bloc resection and curative rates compared with EMR [31].

Bleeding During Polypectomy (Immediate Bleeding)

If bleeding obscures vision during piecemeal polypectomy, the blood may be dispersed by squirting water through the biopsy channel or through a dedicated water channel on more advanced endoscopes. Mild bleeding may be controlled by continuation of piecemeal polypectomy where cautery of the next segment may heat seal the bleeding vessels at the previously cut edge. For more persistent bleeding, a 1:10,000 solution of epinephrine can be injected into the site of bleeding to promote hemostasis, clips may be applied, or a thermal modality can be used such as the APC, Bicap, or heater probe. A randomized study has been reported [19] to affirm the utility of epinephrine in the submucosal injection solution in preventing immediate bleeding, but the control group showed an unusual number of polyps (9%) that bled after polypectomy. Similar techniques are applied for bleeding during ESD, but a special coagulating forceps is frequently used for hemostasis.

The Argon Plasma Coagulator

After piecemeal resection of sessile polyps, there are often (in about 28% of piecemeal polypectomies) small fragments of tissue left at the intersections of snare loop application and at the edges of the polypectomy site. These usually will, with healing, reform as viable but small polyps. Immediately following snare polypectomy,

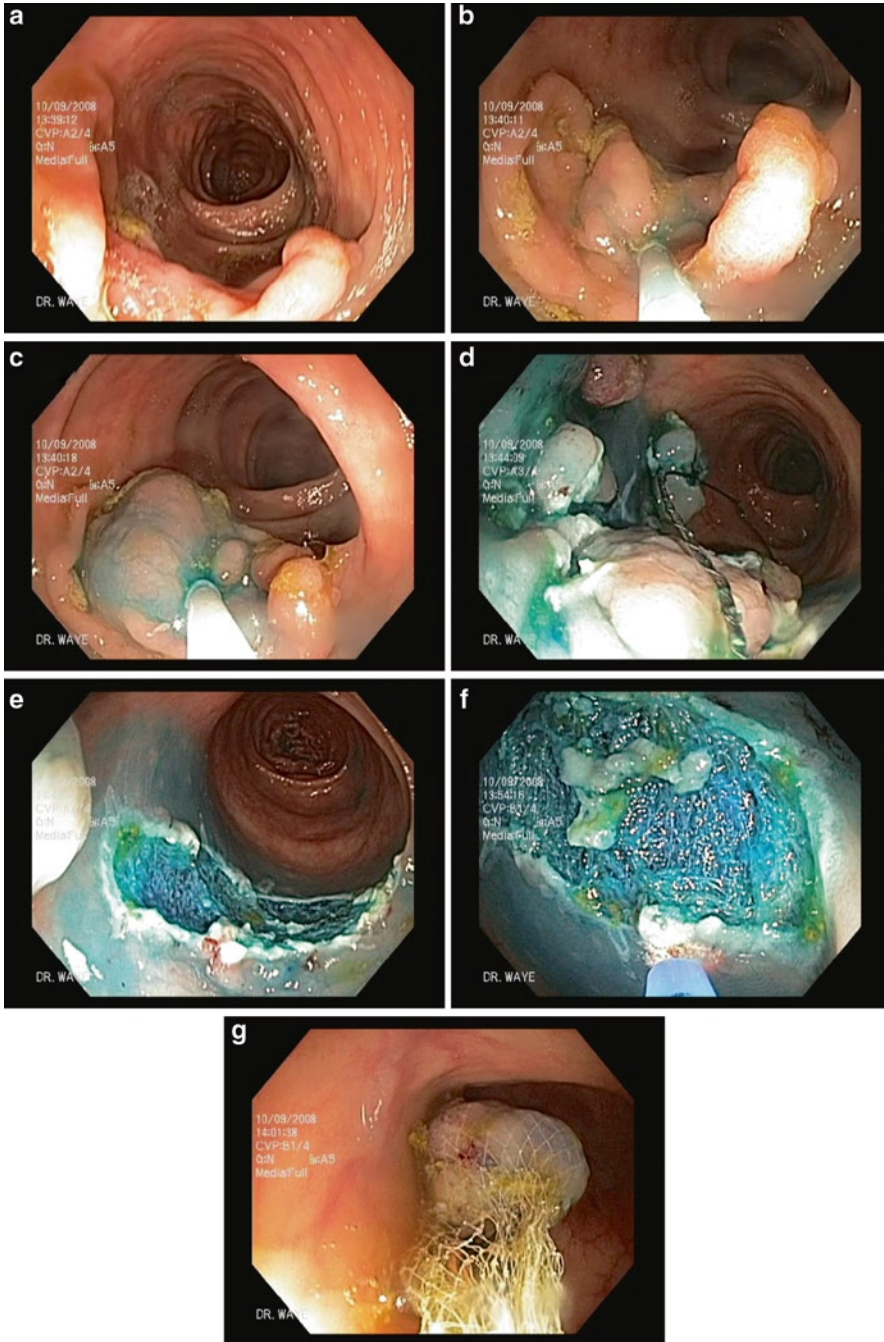
these can be destroyed by using a thermal energy source, such as a Bicap electrode, heater probe, or APC [32] (Fig. 10.6a–g). There are no series that have reported on the first two, but articles on the APC have shown that its use on the polyp base to ablate residual tissue will decrease the recurrence rate [33–35].

The APC is not a laser, and the only similarity between the APC and the argon laser is the name “argon.” In the APC, inert argon gas is delivered into the intestinal lumen through a small catheter which resembles the sheath of a polypectomy snare. An insulated wire runs through the catheter and ends just before the tip of the catheter. Once the wire is activated using a footswitch, the flowing argon gas becomes electrically energized (called the argon plasma) and a spark is formed from the tip of the sheath to the intestinal wall. This is a noncontact thermal modality which does not require the probe to touch the tissue at any time during its activation. Since the argon plasma delivery system is utilized in a monopolar mode, an electrical return plate must be placed onto the patient’s skin, similar to monopolar electrosurgical therapy.

The delivery of energy depends on electrically activated plasma. The monopolar circuit is completed as a spark is produced which contacts the bowel wall. If the tip of the catheter is pointed into the lumen or is several centimeters from the target tissue, no spark occurs and inactivated and inert argon gas escapes harmlessly into the colon lumen. It is necessary to monitor the patient’s abdominal distention by having an assistant gently palpate the abdomen during each activation of the APC. Since this modality is not a laser, it requires no special protection for personnel during its use.

The depth of coagulum is variable and can, to a large extent, be controlled by the duration of application and the total energy delivered [33, 36]. During use of the heat-producing APC, the generated spark desiccates tissue. With the low power output settings used in the colon (40 or 25 W with the ERBE VIO) and avoidance of prolonged single site spark application, the spark will only jump a few millimeters from the tip of the probe to the bowel wall with a burn depth of approximately 1 mm. The APC can safely treat the base of a polypectomy site to ensure total ablation of adenoma, once piecemeal polypectomy has been performed. The longer the transfer of energy is directed to one area of the colon wall, the deeper will be the thermal damage. To prevent a deep burn, the tip of the probe should be kept in

Fig. 10.6 (a) Piecemeal polypectomy. A broad-based hemicircumferential polyp. A polyp of this size should be elevated with saline for safe polypectomy. The final diagnosis was a tubulovillous adenoma, Paris type 0-Is and 0-IIa and 0-IIb. (b) A needle injector is placed into the center of the polyp for fluid injection. (c) Part of the polyp is elevated. Multiple injections of saline were also given into other parts of this polyp. (d) Parts of the polyp have been removed. The wire snare is poised to encircle the middle portion of this polyp. (e) The polypectomy site is clean following piecemeal polypectomy. The *blue* color is due to methylene blue added to the saline solution which produces a contrast between the polyp and the fluid-filled submucosa. (f) The APC destroys small remnants of polypoid tissue at the base and edges of the polypectomy site. (g) The fragments of polypoid tissue that were resected in piecemeal fashion are collected within the Roth basket for retrieval



motion during activation. Because of the ability to maintain a superficial depth of thermal injury, the APC can be successfully used to “paint” a large area of flat adenoma or residual tissue at the base of a polypectomy site without damage to deep layers of the colon wall.

Plastic Cap on Endoscope

To assist in removal of flat sessile polyps, a plastic cap may be attached to the colonoscope tip, with a preloaded snare placed at the mouth of the cap [37, 38]. The cap is similar to that used for esophageal variceal banding. Once the polyp elevated with a submucosal injection fluid has been aspirated into the cap, a sizable portion of the mucosa can be removed using coagulation current. This technique has received the acronym “EMRC,” for Endoscopic Mucosal Resection with Cap. Caution is urged for using this technique above the peritoneal reflection because of the risk of full-thickness resection when the entire wall of the colon is aspirated into the cap [39]. Full suction cannot be applied, nor should the aspirated tissue fill the cap before transection. A large volume submucosal fluid cushion is necessary for safety [37]. Endoluminal full-thickness resection using a rigid instrument can be performed [40] to remove sessile and/or malignant polyps in the rectum. This technique may offer a better alternative to endoscopic piecemeal resection or resective surgery in selected cases of rectal tumors. However, it does not allow for lymphadenectomy and has therefore a limited use in malignant lesions.

Accessories

Two interesting accessories should be available for the endoscopist who performs advanced polypectomy. These are the endoloop and the endoclip. Endoloop is a detachable nylon snare loop that can be placed over a lesion (such as a pedunculated polyp) like a wire snare and tightened with a one-way silicone-rubber stopper. The stopper prevents opening of the loop once it has been closed. This loop can be used for additional hemostasis during or after polypectomy. The loop is most often employed for large polyps with a thick pedicle. After placement close to the bowel wall, polypectomy is performed above the loop-ligature. The fully assembled endoloop, with an accompanying oversheath (to permit the soft nylon loop to be delivered through the instrument channel), is of the same size as a snare. Once extruded from the end of the delivery system, the loop is maneuvered around the head of a polyp under direct vision. The loops spontaneously slough in 4–7 days, and endoscopy following detachment of the loops shows residual shallow ulcers. The loop and carrier device (HX-20) are manufactured by Olympus, Japan. The loop, being relatively floppy, is difficult to place over the head of a large polyp, but is more easily applied after polypectomy if the pedicle appears to ooze blood

following transection [10]. There is one report of using two standard snares (for lower cost than the nylon loop) to prevent hemorrhage after removal of thick-stalked polyps [34, 41]. One wire snare is tightened on the stalk and held closed with a clamp as the colonoscope is withdrawn; a second snare transects the polyp above the ligating snare which sloughs in a few days. The combination of epinephrine injection and endoloop in these large pedunculated polyps may be useful.

Mucosal clips have been available for several years and are currently manufactured by three companies. These small tweezer-like devices (or tripods) are useful for marking mucosal lesions and have been used to identify the distance reached by the colonoscope, as well as to mark edges of tumors prior to expandable metal stent placement. The expandable clips may also be used for hemostasis. The clips are especially useful for bleeding from flat polypectomy sites, but have also been used successfully to stop arterial pulsatile bleeding from the severed stalk of pedunculated polyps [35, 42]. It is possible to apply a clip onto the base of a pedunculated polyp close to the bowel wall and snare the polyp above the clip using standard snare techniques. It is important that the wire snare does not touch the metal clip, lest an aberrant current pathway be activated, with a potential burn of the colon wall. The clips spontaneously dislodge within several days. There is controversy concerning their use to prophylactically prevent postpolypectomy bleeding [36, 41, 43, 44]. Clips have also been used to seal a small postpolypectomy perforation [42, 45].

Localization of Polypectomy Site

After polypectomy has been completed, it may be necessary to place a permanent identification marker at the site of polypectomy so that the exact site of the lesion can be identified on subsequent colonoscopic examinations, or if the polyp is found on histologic examination to harbor malignancy, a permanent marker is desirable to guide the surgeon to the area of polypectomy for subsequent resection. This permanent marker was previously made with a sterilized solution of diluted India ink, but has subsequently been replaced by a solution of pure carbon in suspension that is prediluted and premeasured so that it can be injected directly into the submucosal space for identification purposes [46]. This special "surgical marker," if injected at the polypectomy site, will permanently stain the mucosa by depositing carbon particles into the submucosal area. This marker is readily identified on the mucosal surface by the endoscopist and on the serosal surface by the operating surgeon. The previous injections with sterilized India ink created minimal problems after injection, but the new carbon particle suspension has not been reported to have any deleterious effects.

It is important to ensure the carbon particles are deposited into the submucosal space, resulting in a visible elevated blue/black bleb under the mucosa. Oftentimes, the needle is inserted into the colon wall, and the injected solution flows out through the needle tract into the lumen and does not result in a permanent stain. Therefore, no mark is identifiable by the endoscopist who may subsequently examine the colon, or the surgeon who is dismayed at not finding the injected marker.

It has been suggested [47] that saline be injected into the submucosa prior to injection of the surgical marker to ensure that the surgical marker is indeed injected into the submucosal space by directly injecting into the previous saline bleb. This does ensure that the injection has been made in the proper space. Once injected, the carbon particles are permanently contained in the submucosa and do not disappear for the lifetime of the patient.

Retrieval of Specimens

Large sessile colon polyps that are removed from the rectum and sigmoid may be retrieved using suction on the tip of the endoscope. If a large fragment of polyp is being withdrawn, the suction at the tip of the instrument as applied through the small suction channel may not be sufficient to hold the polyp onto the instrument as it is withdrawn through the anal canal. These large fragments may be removed by resnaring and pulling the polyp fragment up against the faceplate of the instrument and then removing the instrument with gentle pressure as the patient is asked to bear down in a defecatory attempt.

Polyps in the proximal colon are more difficult to retrieve. A single large piece can be resnared and withdrawn during scope removal or one large fragment can be suctioned onto the tip of the scope and withdrawn using continuous suction. Since the suction channel is only 3.2–3.8 mm in diameter, it is small in relation to a large polyp fragment and the force of suction may not be significant to maintain adherence during retrieval through a tortuous sigmoid colon.

If the fragments are small and the polyp is relatively soft and pliable, they can be removed by suction and compression of the pieces in an attempt to deliver them through the suction channel of the colonoscope. If suction is used, a multicompartimented trap with mesh compartments can be successfully employed to collect the polyp fragments and prevent them from traveling into the large suction chamber ordinarily used to collect aspirated material.

An alternative is to cut larger pieces into smaller segments for suction retrieval through the accessory channel. This is accomplished by using the snare to “cold-cut” the free pieces into the size that can be aspirated.

The Roth basket is an especially useful tool for retrieval of fragments of right colon polyps [48]. The basket resembles a wire snare with a soft nylon net attached to its perimeter. This can be placed over polyp fragments, and upon closure, the fragments are trapped within the basket. Reopening the basket repeatedly will permit the entrapment of several more pieces while retaining the original fragments within a slight redundancy of the net which forms a pouch. This basket may also be employed for removal of large rectal polyps when it is not possible to bring them through the anal canal since it permits a large amount of tension on the basket.

If the resected polyps (or fragments) disappear from view, they have been influenced by the pull of gravity. Squirt water through the accessory channel, and if a stream is seen to puddle nearby or fall into the distance, advance the scope to the

first pool of fluid where the polyp(s) will be found. If vision is blurred during water instillation, fluid is washing over the lens and flowing along the side of the scope: withdraw to the fluid pool to locate the polyp.

What are the Limits of Colonoscopic Polypectomy?

If passage to the right colon has been difficult and a large sessile polyp is encountered with a broad attachment that would require several attempts at piecemeal resection, the wisest approach may be to suggest surgical resection (Fig. 10.7) to avoid the necessity for repeated difficult colonoscopies with repeated difficult polypectomies. The risk-benefit ratio will depend on the location of the polyp, the degree of difficulty in accessing the lesion, its size, and the comorbidities of the patient.

A carpet-like polyp which extends over several centimeters (IIa, LST) may not be amenable to endoscopic resection and require surgical extirpation. An attempt can be made to fulgurate the surface of such polyps with the APC, shank of the monopolar biopsy forceps, a Bicap probe, or with the laser. It is unusual to be able to destroy flat adenomas because of the superficial depth of tissue injury by these thermal probes. However, these may be best approached by ESD.

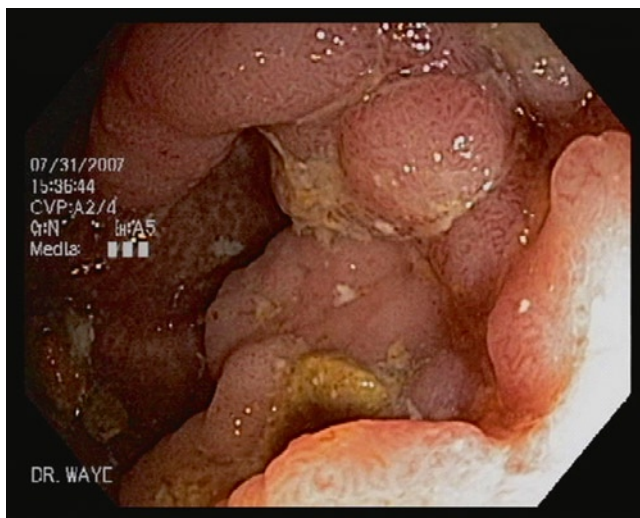


Fig. 10.7 Polyp not removed. This extensive cecal polyp was sent for surgery. It involves over 50% of the cecal caput and extends onto the lower lip of the ileocecal valve. Part of the polyp could not be visualized because it was partially hidden by the ileocecal valve. A retroversion maneuver to view the portion of the polyp below the ileocecal valve could not be accomplished. Paris type 0-Is

The advent of laparoscopic-assisted right hemicolectomy may markedly impact the inclination of adventurous colonoscopists to attempt removal of large polyps. The ease of laparoscopic resection may make a significant difference in the willingness of the patient and endoscopist to embark on the repetitive number of colonoscopies required to ablate a large and difficult right colon polyp. Some reports [49] mention that patients having laparoscopic resection of large polyps may be discharged in 24 h, but others [50] report complications with this approach and state that an average hospital stay is 6 days. Both the risks and benefits of an aggressive endoscopic approach will need to be reevaluated.

For the average endoscopist, polyps that extend more than one-third the circumference of the colon are usually not amenable to endoscopic resection, nor are polyps that extend across two intrahaustral septae. When the basal attachment crosses two intrahaustral septae in its longitudinal dimension, endoscopic resection is often not possible since the adenoma in the valley between two folds cannot be shaved off due to its inaccessibility. The advanced endoscopist may be able to inject fluid into the submucosa beneath the polyp in the valley and cause it to rise up sufficiently to ensnare, but this may not always be possible. The extensive polyps will always prove difficult to resect endoscopically and are surely the ones in need of advanced polypectomy techniques.

The Malignant Polyp

Resecting a portion of a malignant polyp may aid the diagnosis by providing a large tissue fragment for histopathological analysis, but no attempts should be made to remove an obviously malignant sessile polyp, which can be characterized by friability, ulceration, and its typical “waxy” appearance. Even if these large polyps appear to be benign, about 10–15% will have invasive cancer [38]. When polyps are removed in piecemeal fashion, the histological assessment of margins and depth of invasion of malignant cells can be problematic. In a review article [51], Hassan et al. defined a positive resection margin when malignant cells were present at the margin or if the line of resection was doubtful for malignant cells, and as negative when a cancer-free margin was reported. The probability of residual malignancy following polypectomy of malignant polyps (those with malignant cells that have invaded beyond the muscularis mucosa) can be generally divided into low- and high-risk groups. The risk groups are determined by the probability of residual cancer cells at the site of polypectomy, lymph node metastases or distant metastases. Malignant polyps at low risk have: a margin of resection at the base that is clear of malignant cells; is well or moderately well differentiated; no invasion of vascular or lymphatic channels; and the endoscopist’s estimate that a total resection has been accomplished. The high-risk group has: tumor at the resection margin; poor differentiation of malignant cells; vascular and/or lymphatic invasion; and/or visible residual tumor at the resection site.

A review of clinical outcomes based on a comprehensive literature search concerning follow up of malignant polyps details the patient outcomes according to the various risk factors [51]. It should be noted that a positive resection margin has a high risk of residual cancer (30.4%) compared to 2.8% with a clear resection margin. Vascular or lymphatic vessel invasion also portends a high rate of lymph node metastasis.

Pedunculated malignant polyps have a much better outcome than sessile with the exception of lymph node metastases being about the same incidence as sessile malignant polyps. Local disease, defined as residual disease at the polypectomy site and/or recurrent disease on follow-up examination, was reported in 1 of 295 (0.3%) low-risk patients compared with 40 of 230 (17.4%) high-risk cases.

Not all patients whose malignant polyps have met the criteria for high-risk polyps will have poor outcomes. At most, about one third will have a positive resection margin, recurrent disease, lymph node metastases, or distant metastases. The decision of surgery should not only take into account the histopathology factors, but also need to put into the decision algorithm the patient's general health status, the risk of surgical mortality, and the knowledge that about two thirds of patients who have poor histological criteria in their malignant polyps will survive without surgery.

Safety and Complications

Once the decision has been made to do the polypectomy, various outcome questions arise. Among these is the safety of the procedure. The major risks of any polypectomy are bleeding and perforation. It would seem that the complication rate would be related to the size of the polyp, but that does not appear to be true. The published rate of complications is that bleeding occurs in 1.4% of polypectomies, and perforation in 0.3% of cases. In a series of removal of large polyps, there was only one perforation [52]. Conio et al. [38] reported that during resection of 139 large sessile polyps (86 in the right colon), bleeding occurred during the procedure in 15 cases, all of whom were successfully treated endoscopically. No perforations were seen, and 12% had malignant polyps. Another report [53] of the removal of 147 large polyps (half of which were sessile) stated that 2 perforations occurred and had surgical repair, and 8 had bleeding that was controlled endoscopically. Bleeding during polypectomy was successfully handled in 10% of Kanamori's series [54] and ranged from 2% [52] to 24% [8] of polypectomies. No patients in either series required surgical intervention. Older age and large polyps located in the cecum appear to be predictive of a tendency to bleed. Most postpolypectomy bleeding can be treated endoscopically [55, 56], but a small number may require a surgical approach.

A recent article from France discussed the EMR technique for removal of 34 tumors larger than 4 cm. Thirty-four percent of tumors were type Is, 58% type IIa, 4% type IIb, and 4% type IIc. In two cases, procedural bleeding occurred and was managed endoscopically. One small perforation was successfully treated with clips.

Recurrence of tumor was seen in only three patients (12% of these procedures), and all these patients eventually had their polyps removed with repeat endoscopic examinations [57]. In a paper from Malaysia, EMR resulted in only a 7.2% recurrence rate all of which was subsequently eradicated by repeat EMR [58]. In another article of removal of 151 large colorectal polyps, only six patients had a recurrence of adenomatous tissue during the first endoscopic control at the site of the previous polypectomy and 2.3% of patients had a late recurrence detected at 12 months follow-up. All the recurrences were successfully treated endoscopically [56].

Postpolypectomy syndrome was only rarely reported in a few series of patients [59]. This syndrome refers to signs and symptoms of peritoneal inflammation due to thermal injury to the deep serosal layers at the site of polypectomy. It usually responds to conservative measures.

Perforations as a result of removal of large colon polyps are unusual [38, 53], but not all require surgery as some will respond to intravenous antibiotics [55]. Although the usual concept holds that older patients may tolerate endoscopy less well than younger patients, it has been demonstrated that age as an independent risk factor does not increase the incidence of perforation in therapeutic endoscopy.

One of the obvious problems with piecemeal polypectomy of large colon polyps is the polyp with invasive carcinoma. If any fragment contains cancerous cells, it is not possible to tell which portion was at the base of the polyp, and therefore, a decision should be made as for any patient having invasive carcinoma in an adenoma. Most of the patients who have large right colon polyps are elderly, and decisions should be made based on the patient's comorbidities, the probability of recurrent tumor, and the risk of nodal metastasis or distant metastases. Even with a large sessile polyp, where carcinoma invades down to the resection margin, the incidence of residual nodal or distant metastasis is less than 100% and is probably closer to 15%. Therefore, in the patient who is elderly and/or of a poor operative risk, the risk of a surgical resection must be balanced against the probability of that patient dying from metastatic cancer. This decision must be based on the patient's general condition, the extent of carcinoma, and whether the endoscopist felt that the entire tumor was removed at the time of polypectomy.

Summary

Submucosal injection polypectomy is a safe and effective method for removal of sessile polyps. By paying attention to detail, raising a sufficient submucosal bleb of fluid, aspiration of air, keeping the snare loop parallel to the mucosal surface, and following accepted piecemeal polypectomy techniques, removal of large polyps throughout the colon is possible in a high percentage of patients [13, 15].

A recent report [15] stated that 90% of difficult polyps could be removed endoscopically and avoiding surgery. There were no perforations in this series of 174 patients and the cost savings over surgery were about \$7,000 per patient. In a pro-and-con debate [60], it was determined that endoscopic resection is safe and feasible

in the removal of large polyps [61], but that the skill level of gastroenterologists needs improvement since many large polyps referred for surgery could be removed by the surgeon during a repeat colonoscopy and many surgeries could be avoided [62, 63].

The welfare of the patient is the most important factor in the approach to the difficult polyp. If the impending polypectomy has a high risk of complication or the endoscopist is concerned that the lesion is too large or cannot be approached in a safe manner, polypectomy should not be performed. The risks and benefits to the patient must be evaluated in any polypectomy, especially when dealing with the difficult polyp [64].

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Chapter 11

Screening for Colorectal Cancer in the Elderly

Charles J. Kahi

Keywords Life expectancy • Screening decision • Elderly

Screening for colorectal cancer (CRC) in the elderly involves complex decision-making at the interface of gastroenterology, general internal medicine, geriatric medicine, public health, and medical ethics, and represents a unique and controversial issue in the modern health care landscape. Unlike starting and continuing screening, considerable uncertainty remains regarding the upper age limit, or appropriate set of circumstances, which would allow elderly patients to forgo CRC screening. This chapter will review issues pertaining to screening for CRC in elderly patients, including benefits and harms of screening, impact of screening on patient survival, and decision-making by patients and health care providers.

The Broad Perspective

CRC remains the third most common cancer, and second leading cause of cancer death in both sexes in the United States [1]. Age is an important risk factor for the development of CRC and its precursor lesion, the adenomatous polyp [2]. The incidence of CRC rises from 26.7 cases per 100,000 at ages 45–49, to 48.8 cases at ages 50–54 years, and exceeds 400 cases after the age of 80 [3]. By contrast, CRC is considerably less common in patients younger than 50, as illustrated by a study that reported no CRCs and a 3.5% prevalence of significant polyps in 906 patients aged 40–49 undergoing screening colonoscopy [4]. While the starting age for screening is relatively well defined, there are no data from randomized controlled trials to guide the decision to stop screening. Three randomized controlled trials of fecal occult

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blood testing (FOBT) enrolled patients aged up to 80 years [5–7], a case-control study of screening flexible sigmoidoscopy included patients aged up to 91 years [8], while the upper age limit in the National Polyp Study was 88 years [9]. However, elderly patients constituted small subgroups in the aforementioned studies, and it is not clear whether they benefited from screening to the same degree as younger patients. The proportion of elderly patients among all those undergoing CRC screening in the U.S. is not known with precision; however, it is likely to increase as the U.S. population ages. For example, an analysis of 146,457 patients in the Clinical Outcomes Research Initiative (CORI) database showed that patients 70 years or older accounted for 26.6% of colonoscopy examinations, while patients older than 80 accounted for 6.5% [10]. The extension of Medicare coverage to screening colonoscopy in 2001 has led to an increase in the number of elderly patients undergoing this procedure [11]. The number of persons aged 80 years and above was over 13 million in 2000, representing 4.65% of the total population and an increase of 17% since 1990 [2], and this has been paralleled by an increase in life expectancy [4]. Thus, there is a growing cohort of elderly patients who are potentially eligible for CRC screening; however, currently available resources, including the U.S. gastroenterology workforce, are not able to meet the demands of screening and surveillance for all those eligible [12]. This is the case specifically for colonoscopy, which is considered the final common pathway for CRC screening modalities.

Yield and Risks of Colonoscopy in the Elderly

Several studies have quantified the yield and risks of colonoscopy in the elderly. In a retrospective study of 117 patients at high risk for colorectal neoplasia, Khanna [13] reported a 28% prevalence of CRC in the subgroup older than 80. Bat et al. [14] reviewed the findings and complications of 436 colonoscopies done on patients older than 80. The prevalence of CRC was 29% when the indication for the procedure was evaluation of rectal bleeding, compared to 10% for all other indications ($p=0.04$). In another retrospective review of 1,199 consecutive colonoscopies performed on 1,112 patients aged 80 years and older, the prevalence of cancer was 3.7% [15]. Two advanced adenomas and no cancers were found in the subgroup of patients who underwent colonoscopy for screening (86 colonoscopies, 7% of total), and there were 8 (0.6%) reported major complications. Three other retrospective studies [16–18] reported similar results and showed that the yield of colonoscopy was highest in patients with symptoms, particularly bleeding. Colonoscopy was also reportedly safe, with rates of postprocedural hemorrhage and perforation ranging from 0 to 0.7% [14, 16–18]. By contrast, a retrospective review of 915 patients aged 50–100 years who underwent colonoscopy for screening or symptomatic indications reported an increasing prevalence of advanced neoplasia including CRC with age, and increased risk for neoplasia among subjects undergoing screening colonoscopy; however, the subgroup of patients who were older than 80 was relatively small ($n=53$, 5.8%) [19].

Collectively, these studies show that colonoscopy is feasible and relatively safe in elderly patients, with high yield for colonic neoplasia. However, this conclusion in and of itself does not greatly inform decisions to stop screening. In these retrospective studies, most patients were at higher risk for colonic neoplasia due to the presence of symptoms (rectal bleeding, weight loss, abdominal pain, anemia), or a prior personal history of CRC or inflammatory bowel disease, hence the findings may not be applicable to asymptomatic patients who choose to undergo screening. The studies were retrospective reviews from single institutions, raising the concern for selection bias and incompleteness of data, particularly regarding under-reporting of complication rates. More importantly, these studies are limited by the fact that they did not assess the survival time of elderly patients after undergoing screening or surveillance. The increased prevalence of colonic neoplasia after a certain age does not, alone, justify subjecting patients to the risks of colonoscopy, especially if these patients ultimately die relatively soon after screening from unrelated causes. In addition, setting an upper age limit as an absolute rule to stop screening for everyone can disqualify the relatively “young” elderly with a long life expectancy [20–23]. In practice, performing colonoscopy in elderly patients may not be as straightforward as in younger patients: there is a higher rate of poor bowel preparation, the procedure takes longer to complete, and the risk of incomplete and aborted procedures is increased [24–26].

Recent studies have allowed more direct determination of colonoscopy risks in the geriatric population: in one study, 53,220 Medicare beneficiaries age 66–95 years who underwent outpatient colonoscopy (10% for screening) were identified, and the rate of serious GI complications (bleeding and perforation), and cardiovascular events resulting in a hospitalization or emergency department visit within 30 days after colonoscopy compared with matched beneficiaries who did not undergo colonoscopy [27]. Patients undergoing colonoscopy had a higher risk for adverse gastrointestinal events than their matched group, and the rate increased with age. Quantitatively, the overall unadjusted risk per 1,000 procedures was 0.6 for bowel perforation, 8.7 for postpolypectomy hemorrhage, and 19.4 for cardiovascular events. The risk of adverse events was higher for patients undergoing polypectomy, and for those with specific comorbid conditions (history of stroke, chronic obstructive pulmonary disease, atrial fibrillation, or congestive heart failure) [27].

Life Expectancy and Screening Outcomes

The essence of screening is to prolong life through prevention or early detection of cancer. In the case of CRC, randomized trials of FOBT show that differences in CRC-specific mortality between screened and unscreened individuals do not appear until at least 5 years after screening has occurred [5–7]. Thus, screening for CRC should ideally be targeted to elderly patients with a life expectancy of at least 5 years. Older patients or those with significant comorbidity may not derive significant

benefit, or prolongation of life from undergoing screening, because competing risks for death may outweigh the benefits of screening.

Earlier modeling studies have attempted to explore the relation between CRC screening and life expectancy in elderly individuals, often with conflicting findings. A model based on data from the National Center for Health Statistics and Surveillance Epidemiology and End Results Survey (SEER) reported that starting at age 50, screening throughout life has a maximum potential life expectancy benefit of 28 days for colon cancer, and stopping fecal occult blood testing at age 75 would result in 9 lost days of life, compared to 5 lost days at age 80 [28]. The authors concluded that 80% of the benefit of CRC screening was achieved before the age of 80 years. However, some of the study assumptions were that the benefit of screening persisted unchanged throughout life, and that there was no harm associated with screening. Its findings also conflicted with the conclusions of an earlier study, which suggested that screening for CRC may be cost-effective for the elderly throughout life [29].

A framework developed by Walter and Covinsky has been often used both to guide individualized cancer screening decisions in older patients and as a basis for modeling studies [30]. The framework is based on quantitative estimates of life expectancy, risk of CRC death, and screening outcomes, and reveals substantial variation in the likelihood of benefit for patients of similar ages with varying life expectancies. Patients with life expectancies of less than 5 years were unlikely to derive any survival benefit. The framework also addressed the potential harms of screening, such as the detection of CRC cases which would not have become clinically significant, particularly in the setting of decreasing life expectancy [30]. A recent model [31], based on the same framework [30], examined the risks and benefits of screening in patients aged 70–94 years with varying health status using annual fecal occult blood tests, flexible sigmoidoscopy every 5 years, or colonoscopy every 10 years. As expected, the benefit of screening varied with age, life expectancy, and screening modality, with colonoscopy screening having the greatest benefit but the highest risk of complications [31]. Interestingly, the potential for screening-related complications was greater than the estimated benefit in those patients aged 70 years and older [31]. These studies, based on mathematical models and cost-effectiveness analyses, may be useful to guide health care policy, but can be challenging to use in clinical practice, especially when making decisions for individual patients.

More recent studies have attempted to clarify the clinical implications of these models by addressing the relationship between prevalence of colon neoplasms and impact of screening on life expectancy, and the long-term outcome of patients after screening [32–34]. Lin et al. reported the results of a cross-sectional study involving 1,244 asymptomatic individuals in three age groups (50–54 years [$n=1,034$], 75–79 years [$n=147$], and ≥ 80 years [$n=63$]) who underwent screening colonoscopy [34]. The prevalence of neoplasia was 13.8% in the 50–54-year-old group, 26.5% in the 75–79-year-old group, and 28.6% in the group aged 80 years or older. However, despite the higher prevalence of neoplasia in elderly patients, the mean extension in life expectancy was significantly lower in the group aged 80 years or older (0.13 years) compared to the 50–54-year-old group (0.85 years) [34]. Gross et al. extended the question of impact of screening on survival by determining the

degree to which life expectancy after diagnosis of an early-stage CRC varies according to age or comorbidity [32]. The authors found that life expectancy was strongly related to age and the burden of chronic illness after cancer diagnosis, with patients with several chronic medical conditions having a lower gain in life expectancy associated with early-stage CRC diagnosis than counterparts without such conditions [32]. In other words, the comorbidity burden in some older patients may decrease their life expectancy to a point that they may not experience one of the benefits of CRC screening, which is the detection of CRC at an early, and potentially treatable, stage.

The long-term outcomes and predictors of mortality of elderly persons after colonoscopy have also been reported. In a retrospective cohort study of 404 persons aged 75 years or older who underwent colonoscopy, the prevalence of advanced neoplasms was 15% [33]. There were 167 deaths (41%); the mean overall survival was 4.1 ± 0.1 years (median 5.95 years). A symptomatic indication for colonoscopy was not predictive of death. Mortality was predicted by age (hazard ratio 1.16 for each year increase beyond age 75 years, 95% CI 1.07–1.3, $p=0.0003$) and Charlson score (hazard ratio 8.3 for each point increase, 95% CI 1.4–48.5, $p=0.02$). The median survival of patients aged 75–79 years was >5 years if the Charlson score was ≤ 4 . Among patients aged 80 years and older, the median survival was <5 years regardless of Charlson score. In other words, in this cohort of elderly patients, age and comorbidity (but not procedure indication) were predictors of death, and the protective effect of younger age lessened as comorbidity increased [33], with most patients aged 80 and older unlikely to live long enough to derive a survival benefit from CRC screening.

Screening Decisions

As discussed in the previous sections, the benefit of screening for CRC may be offset by age and increased comorbidity in certain patients. It therefore follows that assessments of life expectancy by clinicians should drive screening decisions in elderly patients, and allow tailoring of CRC screening to individuals who are most likely to benefit. However, available data point to significant discordances between CRC screening decisions and appropriateness based on patient factors. Fischer et al. examined the records of 500 consecutive primary care patients at a single VA hospital to determine the appropriateness of FOBT screening [35]. Overall, 35% of the patients had at least one reason that the FOBT was inappropriate, most commonly a life-limiting comorbidity [35]. The same investigator subsequently studied the relationship between patient comorbidity and FOBT screening using a national sample of veterans, and found no consistent significant association between comorbidity (measured by the Charlson score) and the use of FOBT, except in the sickest 1% of patients [36]. Similar observations have been reported in younger individuals with significant comorbidity. For example, Sultan et al. examined the relationship between CRC screening, self-reported health status

(measured by the 36-Item Short-Form Health Survey), and comorbidity (measured by the Kaplan-Feinstein Index) in a cohort of veterans aged 50–64 years [37]. Screening rates were high among patients with moderate (44.9%) and severe (45.8%) comorbidity. In the 60–64-year age group, high screening rates for patients with poorer health were observed. Fifty-two patients died during the 5-year follow-up, of which 37 (71.2%) had undergone screening for CRC [37]. A recent study by Walter and colleagues confirmed the discrepancy between life expectancy and receipt of CRC screening, with healthy older patients not receiving screening and older patients with significant comorbidity receiving it [38]. The authors assessed the VA and Medicare claims of 27,068 veterans 70 years or older for receipt of a CRC screening test (FOBT, colonoscopy, sigmoidoscopy, barium enema), and found that the rate of screening was only 47% for patients with no comorbidity (5-year mortality, 19%), and 41% for patients with severe comorbidity (5-year mortality, 55%) [38].

These large database studies have been complemented by surveys aimed to describe providers' experiences and practice patterns regarding screening for CRC in elderly patients. One such study surveyed 183 VA healthcare providers using clinical vignettes that varied by patient age (75, 80, or 85 years), comorbidity, and past CRC screening history [39]. Ninety-five percent of providers stated they would recommend screening for a healthy 75-year-old compared to 66 and 39% for a healthy 80 and 85-year-old, respectively (p -values <0.0001). Providers were more likely to recommend screening for a 75-year-old with moderate congestive heart failure (CHF) versus severe CHF (61 vs. 15%, OR 9.0 [95% CI 5.8–14.0], $p < 0.0001$) and more likely to recommend screening for an 80-year-old with prior colonoscopy within the preceding 10 versus 5 years (42 vs. 23%, OR 2.6 [95% CI 1.9–3.5], $p < 0.0001$). A substantial minority of respondents (range 15–21%) reported they would screen a 75-year-old with an active malignancy, severe CHF, or severe chronic obstructive pulmonary disease (COPD). The conclusion was that while patient age, comorbidity, and past CRC screening history were incorporated into CRC screening recommendations for elderly veterans, a substantial proportion (up to 21%) of these recommendations was inappropriate [39]. Other surveys have shown comparable findings. Lewis et al. surveyed a group of resident physicians at a university internal medicine program, and reported that their life expectancy estimates and screening recommendations for hypothetical 75 and 85-year-old women patients with varying health states showed moderate agreement with life table estimates, their recommendations for CRC screening varied appropriately according to patient life expectancy and health state, but that there was significant reported uncertainty about the potential benefit of screening [40]. Conversely, Cooper et al. surveyed 884 primary care physicians to determine their recommendations for CRC screening using FOBT and sigmoidoscopy in four pairs of clinical vignettes that varied by patient age (65 or 75 years) and comorbidity (none, mild, moderate, and severe). Physicians were more likely to recommend screening with FOBT rather than sigmoidoscopy, regardless of patient age and comorbidity, and many providers recommended screening with FOBT in inappropriate circumstances, such as a patient with a terminal malignancy [41].

The reasons for inappropriate screening, that is screening which is not targeted to elderly patients most likely to benefit, are incompletely understood. The decision to screen, or not to screen, is complex and requires taking into account several interrelated variables in addition to chronological age and estimated life expectancy, including functional status, past screening history, patient preference, system factors such as clinical reminders and quality of care measures, and individual physicians' experience and practice [39]. There is evidence that organizational pressures, such as the use of performance measures to increase the rates of screening, can lead to the unintended consequence of increasing the rate of inappropriate screening in elderly patients with limited life expectancy [42]. The oversimplification of the benefits of CRC screening, and erroneous misperceptions that its benefits are universal, may also contribute to elderly patients making poorly informed screening decisions [42]. Recently, the United States Preventive Services Task Force (USPSTF) issued updated recommendations for CRC screening [43]. Using two microsimulation models, investigators commissioned by the USPSTF found that continued screening in 75-year-old persons after consecutive negative screenings since age 50 added little benefit, because individuals who had been adequately screened since age 50 were unlikely to have a missed adenoma at their last screening (or a new adenoma since the last negative screening) that would develop into CRC [44]. The authors also reported that stopping at age 75 after consecutive negative screenings since age 50 provided almost the same benefit as stopping at age 85, but with substantially fewer colonoscopy resource use and decreased risk for complications [44]. Based on the results of the decision analytic models, the USPSTF stated "...Despite the increasing incidence of colorectal adenomas with age, for individuals previously screened the gain in life-years associated with extending screening from age 75 to 85 was small in comparison to the risks of screening people in this decade. For adults who have not previously been screened, decisions about first-time screening in this age group should be made in the context of the individual's health status and competing risks, given that the benefit of screening is not seen in trials until at least 7 years later. For individuals older than age 85, competing causes of mortality preclude a mortality benefit that outweighs the harms" [43]. Limitations of these guidelines are that the analysis used chronologic rather than comorbidity-adjusted life expectancy, which limits applicability since health and functional status is an important factor in the decision to stop screening, and the appropriate selection for screening of elderly patients aged between 75 and 85 who have not been previously screened remained unclear.

The uptake and impact of these guidelines on clinical practice are yet to be determined; however, they are an important step in defining "stop rules," and reducing the uncertainties regarding CRC screening in the elderly. Ultimately, as expressed by Walter and colleagues, "given the heterogeneity of the elderly population, there is no evidence of one age at which potential benefits of screening suddenly cease or potential harms suddenly become substantial for everyone," and decisions to screen or not should be based on health status, benefits and risks of the screening test, and patient preference [45].

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Chapter 12

Chemoprevention

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Keywords Nutrition • Fiber • Antioxidants • Aspirin • Statins

Introduction

Colorectal cancer is a common malignancy in the United States with nearly 150,000 new cases identified annually. Nearly 50,000 people are expected to die this year from colorectal cancer in the US [1]. Several factors likely contribute to the development of colorectal cancer, including genetic markers and environmental exposures. While heritable disorders, such as FAP and HNPCC or Lynch Syndrome, have been identified that add increased risk for the development of colorectal cancer, most cases are sporadic, without an identifiable family history. With increased attention to screening programs, colorectal cancer-related death rates have been declining, yet it remains the number two cancer killer in the United States. Because of this, much work has been done to identify factors that place people at increased risk of colorectal cancer and to find agents that may minimize this risk. Much of this research has been focused on nutrition and nutritional status and its role in cancer prevention. More recently, the idea of chemoprophylaxis using anti-inflammatory and other pharmaceutical agents has been explored. This chapter will discuss both of these areas and how they might affect colorectal cancer risk.

Nutrition

Nutrition and nutritional status are important factors for colorectal cancer development. The National Cancer Institute recommends a diet low in fat and high in fiber, fruits, and vegetables in an effort to prevent the disease. A true effect for dietary

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modifications has been difficult to establish; however, and what effect is present is likely small. Given the overall prevalence of the disease, though, even a small risk reduction without side effects may translate into a large societal benefit.

Obesity

Obesity, defined as a BMI >30 , has been associated with an increased risk for a number of cancers. Several large cohort studies have examined the effect of obesity on colorectal cancer risk. In the Health Professionals Follow-Up Study, 51,529 male health professionals between the ages of 40 and 75 were followed prospectively for 6 years. It was noted that those in the highest quintile for BMI had a relative risk of developing colorectal cancer of 1.82 (95% CI: 1.14–2.19, $P < 0.001$) vs. those in the lowest quintile [2]. The data also supported an increased risk of colon cancer with increasing waist circumference and waist-to-hip ratios. Subsequently, the NIH-AARP Diet and Health Study examined the relationship between colorectal cancer and BMI in a group of both men and women. A total of 517,144 men and women in the US between the ages of 50 and 71 were followed prospectively for 5 years. Again, those in the highest BMI range were found to have an increased risk of developing colorectal cancer with a multivariate hazard ratio of 2.05 (95% CI, 1.45–2.91, $P < 0.0005$) [3]. The data were similar for both males and females. When analyzed by tumor type, the data revealed an increased risk for colon but not rectal cancer. More recently, a systematic review and meta-analysis of prospective studies utilized 221 datasets and included 282,137 incident cases [4]. This study concluded that a 5-kg/m² increase in BMI was associated with an increased risk of colon cancer in men (RR 1.24; 95% CI, 1.20–1.28, $P < 0.001$), rectal cancer in men (RR 1.09; 95% CI, 1.06–1.12, $P < 0.001$), and colon cancer in women (RR 1.09; 95% CI, 1.06–1.12, $P < 0.001$). The risk of rectal cancer in women attributable to BMI was not found to be significant.

Given the difficulties associated with such studies, no randomized, prospective trials examining the direct effects of weight loss on colorectal cancer risk. Abundant data suggest that increased physical activity, a marker for weight loss, is associated with decreased risk of colorectal cancer [5].

The mechanism by which obesity increases risk of colorectal cancer is likely related to insulin-like growth factor 1 (IGF-1). Obesity leads to insulin resistance and hyperinsulinemia. This subsequently leads to decreased levels of insulin-like growth factor binding protein 1 levels and, eventually, increased circulating IGF-1. IGF-1 has been shown to be carcinogenic, acting both to promote the survival of transformed and mutated cells that would normally undergo apoptosis as well as encouraging cell growth [6]. Increased levels of leptin associated with obesity may also account for some of the increased risk of colorectal cancer but the evidence is not as strong [7].

The overall association of obesity to colorectal cancer has led many to examine different dietary and nutritional elements that may have an independent effect. Several examples of these include animal proteins including red meat and processed meats, fruits and vegetables, fiber, calcium and vitamin D, folate, and antioxidants.

Red Meat and Processed Meats

Population data suggest that nations with higher incidence of colon cancer generally have higher consumption of red meats [8]. This has been seen prospectively as well. In the Cancer Prevention Study II, 148,610 adults aged 50–74 year were followed for 10 years. Overall, 1,667 incident cases of colorectal cancer were identified. Higher consumption of red meat was found to be associated with an increased risk of rectal cancer with a relative risk of 1.71 (95% CI, 1.15–2.52, $P=0.007$) [9]. Similar results were found in a European population in the EPIC cohort [10]. Recently, a large meta-analysis examining 15 studies that included 1,042,824 participants and 7,367 incident cases was performed [11]. The overall relative risk for colorectal cancer was 1.28 (95% CI=1.15–1.42) for subjects in the highest category of red meat consumption vs. the lowest. This association was noted to be stronger for rectal cancer than colon cancer. The overall relative risk for colorectal cancer was 1.20 (95% CI=1.11–1.31) for subjects in the highest category of processed meat consumption vs. the lowest. This association was stronger for distal cancer than proximal cancer.

There are several reasons why red meats and processed meats may relay increased risk of colorectal cancer. It has been noted that cooking meat at a high temperature forms heterocyclic amines and polycyclic aromatic hydrocarbons that are carcinogenic [12]. Furthermore, N-nitroso compounds are formed in red meat endogenously and can be carcinogenic. Further evidence suggests that heme iron in red meat increases cell proliferation in the mucosa through lipoperoxidation and cytotoxicity of fecal water that could then lead to carcinogenesis. Additionally, high protein and high calorie diets may increase IGF-1 signaling, which, as we have seen, is associated with an increased risk of colorectal cancer. Overall, the effect of red and processed meats is likely secondary to the presence of animal protein and not its fat contents, as low fat diets have not been shown to decrease the risk of colorectal cancer [13].

Fruits and Vegetables

Eating fresh fruits and vegetables is encouraged because of their general health benefits. In terms of the colon and rectum, fruits and vegetables prevent constipation (via fiber) and decrease exposure time with carcinogens. They provide vitamins and micronutrients that may disrupt carcinogenic pathways as well as nondigestible material that colonic bacteria ferment into short chain fatty acids that may affect differentiation, apoptosis, and epigenetic regulation of gene expression.

In the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), 3,057 cases with at least one histologically verified adenoma of the distal large bowel were compared with 29,413 control subjects. In this study, diets rich in fruit, deep-yellow vegetables, dark-green vegetables, onions, and garlic were found to reduce risk of colorectal adenoma, a precursor to colorectal cancer [14].

Epidemiological data regarding the effects of fruits and vegetables on colorectal cancer itself, however, are mixed. Case control studies have generally shown stronger evidence than prospective cohort studies, although the results are still weak [15]. These discrepancies may be related to recall and selection biases in case-control studies as well as an underestimation in cohort studies because of imprecise dietary measurements and limited variety of diets within each cohort. A recent meta-analysis of prospective cohort studies was performed that examined 756,217 participants with 5,838 incident cases over a period of 6–20 years [16]. The pooled relative risk of colon cancer for the highest vs. the lowest quintiles of total fruit and vegetable intake was not found to be significant (RR=0.91, 95% CI 0.82–1.01, $P=0.19$). When broken down by site of cancer, however, there was a significant effect of total fruits and vegetables on distal colon cancers with a relative risk of 0.74 (0.57–0.95, $P=0.02$). There is debate in the literature as to whether certain types of fruits and vegetables or organically grown crops are more likely to reduce the risk of colorectal cancer. There is some evidence that plants rich in polyphenolic compounds, which are thought to be more abundant in organic rather than industrially grown foods, exhibit strong chemoprotective activity [17].

Fiber

Dietary fiber is thought to have numerous effects on the GI tract in general and the colon specifically. It has been studied in a variety of gastrointestinal conditions including diverticular disease, irritable bowel syndrome, antibiotic-associated diarrhea, and inflammatory bowel disease [18]. The effect of dietary fiber on colonic adenomas and colorectal cancer has also been well described. In terms of adenomas, several randomized trials have been performed with varying results. Recently, a Cochrane meta-analysis was performed to further evaluate this question [19]. Overall, the study concluded that there was no evidence that increased dietary fiber intake is associated with a decreased risk of colonic adenomas (RR-1.04, 95% CI 0.95–1.13, $P=0.4$). The effect of dietary fiber on colorectal cancer risk itself has also been evaluated and again there has been mixed results. In the European EPIC cohort, fiber intake was found to be inversely related to CRC incidence (RR-0.75, 95% CI 0.59–0.95, $P=0.006$) [20]. In the American Nurses Health Study, there was found to be no association between intake of dietary fiber and colorectal cancer risk (RR-0.95, 95% CI 0.73–1.25, $P=0.59$) [21]. A recent meta-analysis was therefore performed for further evaluation [22]. In this analysis, 13 cohort studies were examined and included 7,328,414 person years with 8,081 incident cancers. The results suggested that there was a slight effect of increased fiber intake on preventing colorectal cancer (RR-0.84, 95% CI 0.77–0.92, $P=0.002$); however, this effect was diminished and no longer significant when adjusting for other risk factors (RR-0.94, 95% CI 0.86–1.03, $P=0.75$).

Calcium and Vitamin D

Several lines of evidence suggest that increased intake of calcium and dairy products likely reduce the risk of colorectal cancer. Several epidemiological studies from various populations including American [23], Swedish [24], and Finnish [25] men have shown an inverse relationship between dietary calcium and dairy intake and colorectal neoplasia. Two recent larger cohort studies including both men and women have suggested similar results. In a combined analysis of the Nurses' Health Study and the Health Professionals Follow-Up Study, 87,998 women and 47,344 men were followed for a total of 10–20 years [26]. The results pointed to an inverse association between higher total ($>1,250$ vs. <500 mg/day) calcium intake and distal colon cancer. Multivariate analysis, however, revealed that this finding was restricted to those with a higher intake of vitamin D. In an analysis of The NIH-AARP cohort, 3,383,377 person years were evaluated [27]. Dairy food and calcium intake were again found to be inversely associated with cancers of the digestive system in both men and women, especially colorectal cancer. A recent pooled-analysis of ten cohort studies showed similar findings. After analyzing 534,536 subjects with 4,992 incident cancers, an inverse relationship was noted between higher levels of milk intake and colorectal cancer (RR-0.85, 95% CI 0.78–0.94, $P<0.001$) as well as total calcium intake and colorectal cancer (RR-0.78, 95% CI 0.69–0.88, $P<0.001$).

Given the interaction between calcium and colorectal cancer risk, calcium supplementation has been evaluated as a means of decreasing colorectal cancer risk. In the Calcium Polyp Prevention Study, 930 subjects with an adenoma identified on index colonoscopic evaluation were randomized to receive either 1,200 mg of calcium daily or placebo [28]. Repeat colonoscopies were performed at 1 and 4 years after randomization to evaluate the rate of adenoma recurrence. The data revealed a recurrence rate of 31% in the calcium group and 38% in the placebo group (adjusted risk ratio 0.81, 95% CI 0.67–0.99, $P=0.04$). This effect has been duplicated in two recent meta-analyses [29, 30]. Furthermore, the protective effect of supplemental calcium appears to extend several years past the treatment period [31]. Due to the vast evidence for its use and relatively little documented harm, the American College of Gastroenterology currently recommends calcium supplementation to decrease risk of colorectal adenoma recurrence [32]. The overall effect of calcium supplementation on the risk of colorectal cancer is less well established. In the Women's Health Initiative, 36,282 postmenopausal women were randomized to receive either 1,000 mg Calcium+ 400 IU of Vitamin D daily or placebo for 7 years [33]. The results indicate that the incidence of colorectal cancer did not differ significantly between the two groups. The authors point out that the lack of effect may have been due to a follow-up period that was too short or a dose of calcium that was too low.

It is not clear how calcium offers protection from the development of colorectal cancer. Several possible mechanisms include reducing epithelial cell proliferation directly or through calcium sensing receptors in the colon [34], by binding

secondary bile acids and ionized fatty acids and preventing their effects on proliferation [35], or by inducing apoptosis of tumorigenic cells [36].

Furthermore, there seems to be a functional relationship between calcium and Vitamin D that may have an implication for colon cancer prevention. Vitamin D is known to activate calcium channels in the small intestine and colon [37]. It also has receptor-dependant mechanisms that lead to effects in the nucleus of several cell types. Vitamin D acts principally through interaction with VDR, a member of the steroid receptor superfamily. VDR binds to calcitriol and induces a configurational change. VDR then heterodimerizes with retinoid X receptor and this complex binds to vitamin D responsive elements in the nucleus. This interaction induces gene transcription leading to cell cycle arrest, differentiation, and apoptosis.

One important observation regarding the interaction between calcium and Vitamin D originates from post-hoc analyses of the Calcium Polyp Prevention Study. The data showed that most of the effect of calcium in lowering adenoma recurrence rates occurred in subjects who had baseline levels of serum Vitamin D above the median with little effect in subjects with lower levels [38].

Epidemiological data regarding the effect of Vitamin D specifically on colorectal cancer risk are mixed. Most of these studies have evaluated the effect of dietary Vitamin D on cancer risk. Most Vitamin D, however, is obtained through direct exposure to sunlight rather than dietary sources. In fact, an inverse association between solar radiation exposure by geographic region and overall age-adjusted cancer mortality has been identified [39]. The sum of endogenous production and exogenous ingestion of Vitamin D can be estimated by measuring serum 25-hydroxy-vitamin-D levels. In a nested-cohort study of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort using 1,220 incident cancers, the effect of circulating 25-(OH)-D levels on colorectal cancer was evaluated [40]. The data suggest that there is an inverse relationship between 25-hydroxy-vitamin-D levels and colorectal cancer risk.

Folate

One-carbon metabolism is involved in DNA replication and repair as well as the synthesis of S-adenosylmethionine that is utilized in methylation reactions. Low concentrations of one-carbon related nutrients such as folate, B6, B12, and riboflavin, therefore, may potentially promote carcinogenesis. Folate is a compound that is found in green, leafy vegetables, fruits, cereals, grains, nuts, avocados, lentils, beans, and meats. Its exact mechanisms in relation to colorectal carcinogenesis are unclear but available evidence points to a direct role. Alcohol use confers increased risk of colorectal cancer, and this may be mediated by interfering with folate availability [41]. Known genetic variations in folate metabolism impart different incidences of colorectal cancer as well. For example, the MTHFR C677T mutation homozygosity, which leads to reduced enzymatic activity, confers a decreased risk of colon cancer [42].

Epidemiological data regarding the effect of folate on colorectal cancer have been mixed. In the Nurses Health Study, higher folate intake was inversely related to colorectal cancer risk (RR, 0.69, 95% CI, 0.52–0.93) [43]. However, in the Women's Health Study, total folate intake was not significantly associated with the risk of colon cancer (RR, 1.16, 95% CI, 0.76–1.79) [44]. The interaction between folate and colonic adenoma risk has also been evaluated.

In a combined analysis of the Nurses Health Study and the Health Professionals Follow-Up Study, 25,474 subjects with 895 adenomas were identified. The results suggested that high dietary folate was inversely associated with the risk of colorectal adenoma in both women (RR=0.66, 95% CI 0.46–0.95) and men (RR=0.63, 95% CI 0.41–0.98) [45]. Responding to this data, several randomized, placebo-controlled trials of folate supplementation on colorectal adenoma recurrence were performed. In the Aspirin/Folate Polyp Prevention Study, 1,021 subjects were randomized to receive folic acid 1 mg/day, with or without aspirin, or placebo, with or without aspirin, in a 3×2 block design for 3 years [46]. The results indicated that folate supplementation was not associated with a reduced risk of recurrent colorectal adenomas (RR 1.13, 95% CI, 0.93–1.37, $P=0.23$). Surprisingly, those in the folate supplementation group were found to have a higher rate of noncolorectal cancers, specifically prostate cancer with a rate of 7.3% in the folate group and 2.8% in the placebo group ($P=0.01$). Similar findings were identified in a European trial [47]. In the United Kingdom Colorectal Adenoma Prevention Trial (ukCAP), 939 subjects were randomized to receive folic acid 0.5 mg/day, with or without aspirin, or placebo, with or without aspirin, for 3 years. Again, the results indicated that there was no reduction in colorectal adenoma recurrence in the folate supplementation group (RR 1.07, 95% CI, 0.85–1.34). In this study, however, there was no difference identified between the groups in terms of noncolorectal cancers. Few studies have evaluated the effect of folate supplementation on colorectal cancer risk. In a recent meta-analysis of these trials, however, folate supplementation was not shown to be associated with a decreased risk of colorectal cancer [48].

Antioxidants

Antioxidants inhibit oxidative DNA damage that may lead to cancer development. As such, they have been targeted as possible agents for chemoprophylaxis. Selenium is the best studied of these antioxidants. Several epidemiological studies have shown an inverse association between selenium and overall cancer incidence. In the NHANES III survey, a significant mortality benefit was identified in those with higher serum selenium levels [49]. This benefit extended to selenium levels of 130 ng/mL; however, increased mortality was seen in association with levels >150 ng/mL. Data from a randomized trial examining the effect of selenium supplementation on skin cancer were found to reduce the incidence of, and mortality from, cancers at several sites including the colorectum [50]. It is important to note, however, that selenium was not found to be protective for the incidence of basal or

squamous cell, the primary outcome in the study. Long-term follow-up of the same data suggested a decreased risk of adenomatous polyps in the selenium supplementation group, but this was not statistically significant [51]. A subgroup analysis did reveal a reduction in the risk of colorectal adenomas in subjects with low baseline levels of selenium, or who were smokers. This idea was looked at more closely in a combined analysis of three adenoma prevention trials, the Wheat Bran Fiber Trial, the Polyp Prevention Trial, and the Polyp Prevention Study [52]. Pooled analysis revealed that subjects with selenium levels in the highest quartile had lower odds of developing a new adenoma compared to those in the lowest quartile (OR 0.66, 95% CI 0.50–0.87, $P=0.006$). Randomized trials utilizing antioxidants other than selenium have shown mixed results, and a recent meta-analysis examining these studies showed no overall benefit to antioxidant supplementation [53].

The effect of antioxidants in the colon and rectum has also been evaluated in FAP. In a small study involving 36 patients with FAP who had previously undergone prophylactic colectomy with ileorectal anastomosis, subjects were randomized to receive either 3 g/day of Vitamin C or placebo [54]. The results were mostly negative with only a significant decrease in rectal polyp area at one follow-up interval in the treatment group compared to the placebo group. There was no effect on the overall number of polyps. A later study utilizing a three-arm trial including placebo, a Vitamin C and E cocktail, and fiber supplementation also showed no significant effect of vitamins vs. placebo [55].

Pharmaceuticals

Aspirin

Aspirin inhibits cyclooxygenase, which then leads to the conversion of arachidonic acid to prostaglandins and eicosanoids. Aspirin also has other effects including inhibition of NF- κ B, activation of p53, and catabolism of polyamines. Because of this multitude of effects, aspirin has been well studied in colorectal cancer chemoprevention. Two large cohort studies have evaluated the effect of ASA on the incidence of colorectal adenomas. In the Health Professionals Follow-Up Study, 47,900 males were followed for 4 years and a significant risk reduction was identified for ASA users vs. non-ASA users for overall adenomas (RR-0.77, 95% CI 0.63–0.95) [56]. In the Nurses Health Study, 121,701 women were followed for 10 years and again, a significant risk reduction was identified for ASA vs. non-ASA users (RR-0.75, 95% CI 0.66–0.84) [57]. Several randomized controlled trials have been conducted to evaluate the use of ASA on colorectal adenoma risk. Three studies specifically have evaluated the effect of ASA in patients with prior adenomas. In the Aspirin/Folate Polyp Prevention Study, 1,121 patients with recently resected adenomas were randomized to receive placebo, ASA 81 mg, or ASA 325 mg daily for 3 years [58]. In this study, low dose ASA was associated with reduced risk of

recurrent adenomas, but not high dose ASA. In the APACC Trial, 272 patients with recently resected adenomas were randomized to receive placebo, ASA 160 mg, or ASA 300 mg daily for 4 years [59]. High dose ASA was associated with reduced risk of recurrent adenoma, but not low dose ASA. In the UK Colorectal Adenoma Prevention Trial, 945 subjects with recently resected adenomas were randomized to receive either placebo or ASA 300 mg daily for 3 years [47]. In this trial, ASA was found to reduce the risk of recurrent adenoma as well. A recent meta-analysis of these data sets as well as those from a trial evaluating adenoma recurrence in patients with prior colorectal cancer has been performed [60]. The pooled risk ratio of any adenoma for any dose of aspirin vs. placebo was 0.83 (95% CI, 0.72–0.96). The individual effect of high and low dose could not be adequately evaluated because of heterogeneity. The effect of ASA on colorectal cancer risk has been more inconsistent, likely secondary to inadequate follow-up intervals. In the Nurses' Health Study, long-term data were collected involving ASA use and colorectal cancer incidence for 20 years [61]. The benefit of ASA in preventing colorectal cancer was not observed until more than 10 years of use. The benefit also appeared to be dose related with more substantial effects limited to higher doses of ASA. Randomized controlled trials examining colorectal cancer prevention involving either lower doses of ASA or short-term follow-up have also been mixed, but a recent combined analysis of long-term data from two trials involving higher dose ASA correlates with cohort studies [62]. This analysis suggests the use of 300 mg of ASA or more daily for 5 years is protective, with a latency period of about 10 years. The harms associated with long-term high dose ASA, including increased risk for GI bleeding, especially associated with higher doses, increased risk of GI symptoms (nausea, dyspepsia), and increased risk of hemorrhagic stroke have prevented their adoption as chemoprophylaxis for average risk populations.

Recently, there has been evidence that the protective effect of ASA may be specific for tumors that over-express COX-2 [63]. In a combined analysis of the Nurses Health Study and the Health Professionals Follow-Up Study, incident cancers were evaluated for COX-2 expression. Aspirin status was then looked at for these cancers. Regular aspirin use was found to significantly decrease the risk of colorectal cancer for tumors that over-express COX-2 but not for tumors with weak or absent expression (COX-2 Tumors: RR 0.64, 95% CI 0.52; Other Tumors: RR 0.96, 95% CI 0.73–1.26). This work led to an increased interest in COX-2 inhibitors and other NSAIDs as potential agents for chemoprophylaxis.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Cyclooxygenase 2 (COX-2) Inhibitors

Cohort data suggest a protective effect of NSAIDs on colorectal cancer and adenoma risk [64]. In the Nurses Health Study, which measured colorectal cancer risk, use of ≥ 2 tablets of a non-ASA nonsteroidal anti-inflammatory drug (NSAID) per week for 20 years was found to have a protective effect (RR 0.79, 95% CI,

0.64–0.97). In the Polyp Prevention Study, which measured recurrent adenoma risk, any NSAID use for 4 years was found to be protective (RR 0.64, 95% CI 0.48–0.85). Three large randomized controlled trials evaluating the effect of COX-2 inhibitors on adenoma recurrence have also been performed. In the APC Study, 2,035 patients with prior adenomas were randomized to receive Celecoxib 200 mg BID, Celecoxib 400 mg BID, or placebo and were followed for 3 years [65]. A significant risk reduction was found for both doses relative to placebo. In the PreSAP Trial, 1,561 patients with prior adenomas were randomized to receive Celecoxib 400 mg daily or placebo and were followed for 3 years [66]. Again, a significant reduction in recurrent adenoma risk was found for Celecoxib vs. placebo. In the APPROVe Trial, 2,587 patients with prior adenomas were randomized to receive Rofecoxib 25 mg daily or placebo and were followed for 3 years [67]. A significant risk reduction was again seen, suggesting the effect was consistent across COX-2 inhibitors. Unfortunately, these trials revealed a significant increase in cardiovascular events including myocardial infarction for those taking COX-2 inhibitors and therefore their use as chemoprophylaxis cannot be supported.

The use of NSAIDs in FAP has been evaluated as well. Early small studies indicated that Sulindac significantly decreased the number of polyps in patients who had undergone prophylactic colectomy with ileorectal anastomosis [68]. Another small study showed similar results in both patients with previous colectomy and those without [69]. Long-term follow-up of this same group revealed a large ratio of patient dropout (5 out of 12) but of the seven that remained on Sulindac therapy, six were free of polyps at a mean follow-up period of 76.9 ± 27.5 months [70]. One trial has evaluated Sulindac therapy for the primary prevention of adenomas in FAP. A total of 41 young subjects with FAP genotype but who had yet to develop polyps were randomized to receive either 75 or 150 mg of Sulindac twice daily or placebo for 4 years. There was no significant difference between the groups in terms of development of adenomas [71]. COX-2 inhibitors have also been evaluated in FAP. In a trial of 77 patients with FAP who were randomized to receive either 100 mg of Celecoxib twice daily, 400 mg of Celecoxib twice daily, or placebo, a significant reduction in the number and burden of colorectal polyps was observed in the high dose Celecoxib group [72].

Statins

Another class of drugs that has been evaluated as potential agents for chemoprevention of colorectal cancer is statins. Statins have been shown to reduce carcinogen-induced colon cancers in rodent models as well as decrease proliferation and induce apoptosis in colon cancer cell lines. Their proposed mechanism of action is through interruption of isoprenylation of intracellular proteins. Epidemiological evidence showing their effect, however, has been sparse. A meta-analysis of randomized controlled trials as well as observational studies was recently performed [73]. No effect was found across randomized control studies or cohort studies, and there was

a modest risk reduction found for statins in case-control studies. A recent pooled analysis of three adenoma recurrence prevention studies also showed no effect from statins (RR 1.03, 95% CI 0.87–1.23) [74].

Hormone Replacement Therapy (HRT)

In the Nurses' Health Study, data were collected on hormone replacement therapy (HRT) and adenoma and colorectal cancer risk [75]. Fifty nine thousand and two postmenopausal women were evaluated, and 470 incident cancers and 838 incident adenomas were identified. Current use of hormones was associated with decreased colorectal cancer risk in general as well as a decrease in the risk of large (>1.0 cm) adenomas. Subsequently, the Women's Health Initiative evaluated colorectal cancer risk in a randomized trial of HRT. In the estrogen only arm, there appeared to be no effect of estrogen compared to placebo [76] and a recent long-term follow-up of the WHI data confirmed the lack of effect [77]. Initial observations from the estrogen + progestin arm revealed a decreased risk of colorectal cancer in subjects taking HRT (HR 0.63, 95% CI, 0.43–0.92) [78]. Closer evaluation of this data revealed that cancers diagnosed in women who took estrogen and progestin were diagnosed at a more advanced stage than those with placebo [79]. However, this effect was not evident when examining long-term follow-up data from the same trial [80].

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