Screening and Surveillance for Colorectal Cancer
Part of the Couriculum

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Internal Medicine Grand Rounds
University of Texas Southwestern Medical Center at Dallas
September 15, 2006

This is to acknowledge that Dr. Harford no financial interests or other relationships with commercial concerns related to this program. Dr. Harford will not be discussing off-label uses in this presentation.

Introduction

It is estimated that colorectal cancer (CRC) mortality could be reduced by 28%-60% and CRC incidence reduced by 17%-54% if we could screen 75% of the eligible population [1]. Screening participation rates of this order have been achieved for cervical and breast cancer. However, the most recent National Health Interview Survey and the Behavioral Risk Factor Surveillance System survey found that less than 45% of adults aged 50 or older had any CRC screening within the recommended time intervals [2-4]. Awareness of the importance of CRC screening and participation in screening are increasing. Efforts are being made to identify, study, and address obstacles to increased participation [5, 6].

Screening, Surveillance, Normal Risk and Increased Risk

Screening is the testing of a group considered to be at normal risk of a disease in order to discover those at increased risk. By convention, persons are considered to be at normal risk of CRC if they are ≥ 50 years of age and have no other risk factors. Surveillance is the testing of persons known to be at increased risk of a disease. A variety of screening options are considered acceptable for persons at normal risk of CRC, but colonoscopy is generally recommended for persons at increased risk. Thus, assessment of risk is the first step in screening and surveillance for CRC.

Risk factors for CRC

Age

Since 95% of cases of CRC present in persons ≥ 50 years old, it is generally recommended that screening begin at age 50. CRC risk continues to increase with advancing age from 50/100,000 at age 50, to 250/100,000 at age 70, to 400/100,000 at age 80. The prevalence of cancer and large adenomas at screening colonoscopy increases with age. However, the difficulties and risks of colonoscopy also increase with age. The risk of death from causes other than CRC increases with age. Thus, the net benefit of CRC screening is substantially less for elderly persons than for middle-aged persons in overall good health [7-9]. There is no consensus regarding an age at which CRC screening should be discontinued. It seems reasonable to discontinue screening if estimated life expectancy is less than 5 years.

Symptoms and signs

Patients who are ≥ 50 years of age who report visible rectal bleeding of any type, who have an unexplained persistent change in bowel habits, or who are found to be iron deficient should be referred for colonoscopy.

Family history

About 25% of cases of CRC are associated with a family history. Colonoscopy rather than ordinary screening should be considered in patients with a positive family history. About 2%-3% of cases of CRC are associated with Lynch Syndrome (also termed Hereditary Non-polyposis Colorectal Cancer or HNPCC). Physicians should be aware of both the classic and attenuated presentations of Lynch Syndrome and familial adenomatous polyposis (FAP). The family history should elicit not only cases of colon cancer, but also other cancers associated with the Lynch Syndrome, such as ovarian and endometrial cancer, along with the age of the affected person at the time of diagnosis. A

conscientious effort is necessary to obtain a complete family history. It is often necessary to advise the patient to make inquiries of other family members [10].

Gender, obesity, smoking, and alcohol intake
Male gender, obesity, current smoking, and heavy intake of alcohol are associated with risk, but have not been incorporated into screening guidelines [11-14].

Other risk factors
Patients with a personal history of CRC, adenomatous polyps, or inflammatory bowel disease (IBD) of more than 8-10 years duration are at increased risk of CRC and should be referred for colonoscopy.

SCREENING PATIENTS AT NORMAL RISK

Stool Testing

Fecal Occult Blood Testing (FOBT)

Prospective, randomized trials have established the effectiveness of guaiac-based FOBT screening. In the Minnesota U.S. trial rehydrated Hemoccult® slides were used, and 10% were positive. In patients screened yearly there was a 33% reduction in CRC mortality after 13 years and a 20% reduction in incidence after 18 years. Thirty-eight percent of patients screened yearly had colonoscopy at some point [15, 16]. In the U.K. and Danish trials patients were screened every other year with non-rehydrated slides [17-19]. Fewer slides were positive (1-4%) and fewer patients (5%) had colonoscopy. CRC mortality reduction was 15% in the United Kingdom (U.K.) trial and 11% in the Danish trial. In the Danish study mortality reduction was higher (43%) among patients who completed all 9 rounds of screening over the 18 years of the study. These patients represented about 27% of those initially randomized to the screening arm of the study [19].

Advantages of FOBT are accessibility, safety, and low initial costs, but sensitivity and specificity are limited. Sensitivity of a single 3-day FOBT is about 25% for CRC or advanced adenomas [20]. Sensitivity improves with repeated testing, but high participation rates are difficult to sustain [19]. The positive predictive value (PPV) of unrehydrated FOBT for CRC is only 5% to 18% and the PPV for either CRC or large adenomas it is 20 to 40% [21]. In research trials compliance rates of 60-70% with initial testing have been reported, but in clinical practice it is generally lower. In a study of U.S. Veterans, 51% of patients completed mailed FOBTs [22]. Compliance with repeated testing is lower. In the U.K. study, only 38% of subjects completed all the FOBTs offered. Physicians often do not follow recommended guidelines for FOBT screening [23]. Screening should not be done by testing stool obtained by digital rectal examination (DRE). The sensitivity of a DRE FOBT is only 5%. A negative result has little predictive value, although a positive DRE FOBT has the same PPV for CRC as a positive 3-sample FOBT [24, 25]. All patients with any positive FOBT (including a DRE FOBT) should be referred for colonoscopy. In one study only 34% of patients with a positive FOBT received a complete colon examination (colonoscopy or DCBE). Physicians too often inappropriately repeat positive FOBTS or fail to refer patients for evaluation [26].

FOBT in patients on warfarin

The positive predictive value (PPV) of FOBT for CRC among patients on warfarin (8.5%) is not significantly different from that among patients not on warfarin (10.5%). It is not necessary to discontinue warfarin for FOBT [27].

FOBT after colonoscopy

There is little information regarding the use of FOBT after colonoscopy. In one study, no cancers were found in 183 normal-risk patients referred for a positive FOBT who had colonoscopy within the past 5 years. The authors concluded that it was prudent to suspend FOBT for 5 years after negative screening colonoscopy [28]. In contrast, in another study of higher-risk patients (history of CRC or polyps, positive family history) in a colonoscopy surveillance program were offered off-year FOBT. Of patients who participated, 7% had a positive FOBT, and 25% of those were discovered to have CRC or an advanced polyp. The authors concluded that it was reasonable to offer at least one FOBT between surveillance colonoscopies [29].

Fecal Immunochemical Tests (FITs)

Guaiac-based FOBTs may be false positive in the presence of dietary plant peroxidases, meat, and upper GI blood loss. They may be falsely negative in the presence of peroxidase inhibitors such as vitamin C. FITs detect only human hemoglobin in stool, do not require dietary restrictions, and have higher specificity than guaiac-based tests [30, 31]. The American Cancer Society recommends FITs as more user-friendly than guaiac-based FOBTs [32].

Fecal DNA Tests

Exfoliated DNA from colonic neoplasms contains multiple genetic abnormalities. Human DNA can be isolated from stool and analyzed [33]. A DNA stool test (PreGenPlus®, Exact Sciences) is commercially available. In a large study of normal-risk patients, the sensitivity of fecal DNA was only 52% for CRC, compared to 13% for FOBT, and only 15% for advanced adenomas, compared to 11% for FOBT [34]. Currently, the sensitivity of fecal DNA testing is not substantially better than the sensitivity of guaiac-based stool tests. The cost of fecal occult blood tests is high. Until the sensitivity improves and cost is reduced, this methodology, although promising, cannot be recommended [31, 35].

Fiberoptic Sigmoidoscopy (FFS)

Case control studies show that FFS screening reduces mortality from rectosigmoid cancer by 50%-80%, and overall CRC mortality by 30%-45%. Risk reduction persists for 5-10 years [36-38]. Several ongoing large, prospective randomized studies will provide more information. The United Kingdom FFS Trial was initiated in 1993. One-time screening FFS was offered between the ages of 55 and 64. The results of this trial will not be available for several years [39, 40]. The Italian (SCORE) trial is a similar smaller study [41]. In the U.S. PLCO (prostate, lung, colon, ovarian) trial, about 155,000 men and women aged 55 to 74 have been randomized to CRC screening by FFS every 3 years or to usual care, and will be monitored until 2015 [42]. The preliminary reports from these trials have provided important information. Participation rates have been 60%-80%. CRC has been

found in 0.3%-0.54% and advanced adenomas in 4%-6%. About 5%-10% have been referred for colonoscopy. Complications have been rare (< 1/1000) [39, 43, 44].

Hyperplastic polyps are common in the distal colon, but do not signal an increased risk of CRC. The risk of advanced neoplasms is also small with single small adenomas. Referral for colonoscopy may not be mandatory for patients with single small adenomas [45, 46].

FFS can be done with modest preparation, inconvenience, and little risk. It provides substantial and durable risk reduction. By training non-gastroenterologists and providing dedicated facilities, large scale screening has been done successfully in the U.K. and in by Kaiser Permanente of California [40, 47]. On the other hand there are problems with the use of FFS for screening. Few U. S. primary care providers do a substantial number of FFS, and there are few trained non-physician endoscopists [23, 48]; reimbursement for FFS does not cover the cost [49]; only part of the colon is examined and about 2%-5% of patients with negative FFS examinations will have CRC or an advanced adenoma proximal to the reach of the sigmoidoscope, and over the last several decades. This number may increase since there has been a proximal shift in the distribution of CRC [50-52].

Fiberoptic Sigmoidoscopy combined with FOBT

The American Cancer Society endorses FFS every 5 years combined with yearly FOBT as an acceptable CRC screening strategy. Studies suggest that the primary benefit is due to FFS, and that FOBT adds little to a FFS screening program [53, 54].

Colonoscopy

There have been no controlled, randomized, prospective studies of colonoscopy in reducing CRC mortality, but indirect evidence is very strong. Case-control studies from Italy and from the Veterans Administration showed risk reductions of 50%-65% [55, 56]. The National Polyp Study was not designed to address the use of colonoscopy for screening but CRC incidence was reduced by about 75% in the group followed by colonoscopy after initial polypectomy, compared to a reference group [57, 58]. The feasibility of colonoscopy for primary screening has been established by 2 large studies. In the VA Cooperative Study #380, the entire colon was examined in 98% of patients. Major complications occurred in 0.3% of cases, with no perforations and no deaths attributable to colonoscopy. CRC was found in 1%, and advanced adenomas in 9.5% [59, 60]. A study in women (CONCeRN) was done in tandem with the VA Cooperative Study. The prevalence of advanced polyps was lower among women in this study (5%) than among the men examined in the VA Cooperative Study [61]. In another study, colonoscopy was used to screen 1994 normal-risk patients $\geq$ 50 years old enrolled in a corporate health plan. The entire colon was examined in 97% of cases. CRC was found in 0.5%. Advanced adenomas were found in the distal colon in 3% and in the proximal colon in 2.5% of patients [62].

A substantial proportion of physicians and patients believe that colonoscopy is the most effective screening strategy. Some experts and expert panels strongly endorse "colonoscopy first" [63-65]. Others do not believe that the available evidence supports this

recommendation [40]. The U.S. Preventive Services Task Force concluded that "it is unclear whether the increased accuracy of colonoscopy compared with alternative screening methods ... offsets the procedure's additional complications, inconvenience, and costs" [66]. CRC risk reduction is greater with colonoscopy than with screening FOBT or FFS, but is probably closer to 50%-60% than the 75%-90% extrapolated from the National Polyp Study [37, 55]. Although colonoscopy is accurate, recent studies comparing state-of-the-art CT colonography and colonoscopy suggests that up to 12% of lesions ≥ 10 mm may be missed by colonoscopy [67]. Purging for colonoscopy is unpleasant. The use of sedation requires patients to take an entire day from their normal activities. The cost of colonoscopy is prohibitive for many patients who do not have insurance. It is not clear whether there is adequate colonoscopy capacity in the U.S for the purpose of screening. The demand for colonoscopy has increased with Medicare coverage, public education, and celebrity endorsement [68, 69]. If a colonoscopy first strategy were adopted, there might be sufficient colonoscopy capacity to maintain a steady state, but "catching up" would take a number of years. Even if overall colonoscopy capacity is adequate, capacity and access are clearly not adequate for significant groups and health care systems in the United States. Many Veterans Affairs Medical Centers have found that current colonoscopy capacity is inadequate to meet increased demands generated by successful implementation of FOBT surveillance programs [1, 70].

Double Contrast Barium Enema (DCBE)

DCBE every 5 years is endorsed as an alternative method of CRC screening by the American Cancer Society and the GI consortium [32, 71]. There no direct evidence that DCBE is effective. The accuracy of DCBE is much lower than colonoscopy. Sensitivity of DCBE for lesions ≥ 10 mm is about 50% [72, 73]. The main advantage of DCBE is the fact that it is widely available and does not require sedation. DCBE can be used after incomplete colonoscopy, and significant neoplasms may be found in 3-5% of such cases [74, 75].

CT colonography (CTC)

Multidetector CT scanners and improved software make it possible to construct high-resolution 3-dimensional images of the colon and to "fly–through" the colon, creating a view analogous to colonoscopy ("virtual colonoscopy"). In one report, expert radiologists using advanced techniques detected polyps ≥ 10 mm with a sensitivity of 94% and specificity of 96% [76]. However, in another report, CTC as practiced in the general medical community was found have a sensitivity of only 55% for polyps ≥ 10 mm [77]. CTC is safe and no sedation is needed. CTC can detect polyps missed on optical colonoscopy [67]. Important extraluminal abdominal conditions may be detected [78]. Problems remain to be resolved. Sensitivity is unacceptably low without optimal techniques and expert interpretation. Incidental extraluminal abnormalities can be expected in about 5-10% of cases and create difficult management problems [78, 79]. Patient acceptance may not be better for CTC than colonoscopy unless the need for purging is eliminated. Fecal tagging and digital subtraction may make this possible [80, 81]. The polyp cutoff size used to refer patients for colonoscopy has important implications. At 10 mm, about 10% of screened patients will be referred, whereas at 6 mm, about 30% will be referred [76]. It is not clear whether it is prudent to follow patients with polyps between 6

mm and 9 mm in size [82-84]. CTC has a role for patients at high risk of CRC who cannot have colonoscopy and for those patients in whom colonoscopy is incomplete [85].

Cost Effectiveness and Cost Savings

The cost-effectiveness of CRC screening compares favorably to that of other well-accepted cancer screening programs. A review for the U.S. Preventive Services Task Force concluded that no one CRC screening strategy is clearly more cost-effective than others. Recommendations for one strategy over another cannot be made on the basis of cost effectiveness [86]. Except perhaps over an extended time frame, CRC screening does not result in net cost savings [1, 87].

American Cancer Society Guidelines

The American Cancer Society (ACS) guidelines for CRC screening indicate that, beginning at age 50, both men and women at normal or average risk for colorectal cancer should follow one of the following screening options listed below [32].

- FOBT or FIT every year. For FOBT or FIT, a take-home, multiple-sample kit should be used. FOBT tests done in the doctor's office following digital rectal examination are not recommended. There is no justification for repeating FOBT in response to an initial positive finding. Toilet bowl FOBTs are not recommended. FITs are more patient-friendly and are likely to be equal or better in sensitivity and specificity.
- FFS every 5 years
- FOBT or FIT every year plus FFS every 5 years. FFS together with FOBT is preferred compared with FFS alone or FOBT alone
- DCBE every 5 years
- Colonoscopy every 10 years.

SURVEILLANCE FOR PATIENTS AT INCREASED RISK

Positive Family History

About 25% of cases of CRC are associated with a positive family history. A small number are associated with well-defined hereditary colon cancer syndromes such as Lynch Syndrome (2-3% of cases), familial adenomatous polyposis (FAP) (< 1% of cases), and the hamartomatous polyposis syndromes (< 0.1% of cases). Uncharacterized cases have been termed Common Familial Colon Cancer. A family history should be obtained not only for CRC, but also for other Lynch Syndrome cancers. Common Familial Colon Cancer is also associated with a history of adenomatous polyps. Family histories are often inadequate for cancer screening. In one survey, a cancer family history was obtained in 68% of patients, information about specific relative and type of cancer in 61%, and age at diagnosis in 39% of patients. Only 17% of patients who met criteria for early onset breast cancer were referred for genetic counseling [10].

<u>Common Familial Colon Cancer</u>

Numerous studies have documented the relative risk (RR) of CRC according to family history. This information is summarized in Table 1.

Table 1.Relative Risk of CRC According to Family History

Family History	Relative Risk
One first-degree relative with CRC	2-3
Two first degree relatives with CRC	3-4
One first-degree relative with CRC diagnosed at age ≤ 50 years	3-4
One second or third-degree relative with CRC	1.5
Two second-degree relatives with CRC	2-3
One first-degree relative with an adenoma diagnosed at age ≤ 50 years	2

In general, colonoscopy should be used for surveillance of patients with a positive family history. Most guidelines recommend starting surveillance before age 50 years, and repeating colonoscopy more often than every 10 years. Guidelines differ on whether to take into account relatives who develop CRC at ≥ 60 years, second-degree relatives, or relatives with polyps. Guidelines from the American Cancer Society (ACS), the GI Consortium (GIC), and the American College of Gastroenterology (ACG) are summarized in Table 2 below [32, 63, 71].

Table 2. Recommendations for Screening According to a Family History of Polyps or CRC

- *One first-degree relative with CRC or adenoma(s) diagnosed at age ≥ 60 years*
  - ACS: Screening as for average risk
  - GIC: Screening as for average risk, but beginning at 40 years old
  - ACG: Colonoscopy every 10 years, starting at 40 years old

- *One first-degree relative with CRC or adenoma(s) diagnosed at ≤ 60 years or multiple first-degree relatives diagnosed at any age*
  - ACS: Total colon examination (colonoscopy or ACBE) every 5-10 years, starting at 40 years old or 10 years younger than the youngest affected relative
  - GIC: Colonoscopy every 5 years, starting at 40 years old or 10 years younger than the youngest affected relative
  - ACG: Colonoscopy every 3-5 years, starting at 40 years old or 10 years younger than the youngest affected relative (no statement on polyps).

Familial Adenomatous Polyposis (FAP)

FAP is an autosomal dominant syndrome caused by germline mutations in the APC gene. Fifty percent of affected patients develop adenomatous polyps by age 15 and 95% by age 35. From 100 to thousands of polyps may be found. The average age at diagnosis of CRC is about 35-40 years, and the lifetime risk of CRC approaches 100%. FAP accounts for less than 1% of all CRC cases [88].

The clinical presentation of FAP patients presents no diagnostic problems except in attenuated syndromes. Testing for APC gene mutations is commercially available and should done first on an affected family member. A specific mutation can be found in about 70% of cases. When the test is positive, other family members can be screened for the same mutation. Those with negative tests can be reassured that they do not have FAP

with a certainty approaching 100% and should be offered normal-risk screening. If a specific mutation is not found in an affected family member (about 30% of cases), the responsible mutation may not be detectable by current techniques. In such cases, the genetic testing is uninformative and not helpful. Family members must have endoscopic screening. Generally, FFS can be used rather than colonoscopy (except in attenuated FAP), since many polyps occur throughout the colon, including the rectum.

Colonoscopic surveillance recommendations from the GI Consortium and the ACG for FAP patients with uninformative genetic testing are summarized in Table 3 [63, 71].

Table 3. Recommendations for colonoscopic surveillance of FAP patients with uninformative genetic testing

- GIC: FFS every year beginning at age 10-12 years
- ACG: FFS every 1-2 years at age 10-12 years. If screening is negative by age 40 years, relatives can revert to normal risk screening. Older unscreened relatives of FAP patients should have colonoscopy.

When FAP is confirmed either by genetic testing or by endoscopy, total colectomy should be recommended because the lifetime risk of CRC is close to 100%. If a subtotal colectomy is done, the rectal remnant must be screened every year by FFS. Upper GI endoscopy should be done every 1-3 yrs to screen for gastric or periampullary adenomas.

Attenuated polyposis syndromes related to the APC gene

There are several syndromes related to the APC gene. Affected patients present with fewer polyps and at a later age than those with classic FAP.

Attenuated FAP (AFAP) is a variation of FAP in which mutations occur in the 5' end (first 5 exons), the 3' end, or in exon 9 of the APC gene. Ten to 100 adenomas are found and there may be rectal sparing. Compared to classic FAP there is a 10-20 year delay in onset of CRC, but lifetime risk is still very high. Gastric and duodenal adenomas are common. Colonoscopy, rather than FFS, should be used for screening. Depending on the number of polyps and the rate of polyp development, patients may be managed by frequent colonoscopic surveillance and polypectomy, or by colectomy. Endoscopic surveillance of the stomach and duodenum is recommended. Genetic testing can be done as for FAP [89, 90].

I1307K mutations in the APC gene cause genetic instability predisposing to a second downstream stop codon mutation, leading to an attenuated FAP phenotype. The risk of CRC, breast cancer and several other cancers is increased about twofold. The mutation is carried by about 6% of Ashkenazi Jews and in 28% of Ashkenazi Jews with CRC [88]. Patients should be managed with surveillance colonoscopy and polypectomy.

MYH gene mutations may cause an autosomal-recessive polyposis syndrome. MYH is a base-excision repair (BER) gene. Inheritance of two mutated alleles causes G:C to T:A mutations throughout the genome, leading to secondary APC gene mutations. Patients with FAP-MYH polyposis present with 15-100 adenomas. Unlike attenuated FAP,

transmission is not vertical (no history in parents or children), and there is no germline mutation in the APC gene. The incidence of CRC is 40-50% at a mean age of 43-58 years [91, 92]. A few patients have presented with early onset CRC with and fewer than 15 polyps [92]. Genetic testing is done first by mutation-specific testing because 80% of affected persons have one of 2 specific MYH mutations. If one of these is present, then sequencing is done to identify the other mutated allele [91-94].

Lynch Syndrome

Lynch Syndrome (hereditary non-polyposis colorectal cancer) is an autosomal dominant syndrome due to a germline mutation in one of the DNA mismatch repair (MMR) genes, most commonly MSH2 or MLH1, less commonly MSH6 or PMS2. MMR mutations accumulate at a very high rate. Errors are more likely in non-coding DNA sequences with multiple repeats (microsatellites), leading to microsatellite instability (MSI).
Lynch Syndrome is associated with 2-3% of all cases of CRC. The lifetime risk of CRC is up to 70%. Colorectal cancers present at an early age, are often right sided, and have characteristic histology. Synchronous and metachronous CRCs are common. There is an increased risk of a number of tumors of certain other organs [95, 96].

Table 4. Lynch Syndrome-Related Tumors

Colon and rectum
Endometrium
Ovary
Stomach
Pancreas
Ureter and renal pelvis
Biliary tract
Small bowel
Sebaceous adenomas, keratoacanthomas (Muir-Torre variant)

Physicians should suspect and evaluate for Lynch Syndrome when the family history includes CRC and/or other Lynch Syndrome-related tumors presenting at an early age and in several members of the family. The Amsterdam II Criteria are used to identify potential Lynch Syndrome families.

Table 5. Amsterdam II Criteria

- Three relatives with a Lynch-syndrome associated tumor, one of who is a first-degree relative of the other two,
- Involving at least 2 successive generations;
- One or more cases diagnosed before the age of 50 years
- Not due to familial adenomatous polyposis
- Tumors verified by pathologic examination [97]

The Amsterdam Criteria cannot be used to exclude the possibility of Lynch Syndrome. Affected families may not fulfill Amsterdam Criteria, particularly if the family under consideration is small.

Physicians should also consider Lynch Syndrome in patients who present with CRC with certain clinical characteristics defined by the Revised Bethesda Criteria {373,383). In this circumstance the resected tumor should be tested for microsatellite instability (MSI). This can be done on fixed and archived tissue samples. If the tumor is MSI-high, it can be testing further by staining for MMR gene products (see below).

Table 6. Revised Bethesda Guidelines for Testing Colorectal Tumors for MSI

- CRC diagnosed in a patient who is less than 50 years old
- Presence of synchronous or metachronous CRC or other Lynch Syndrome-associated tumors, regardless of age
- CRC with MSI-high histology* diagnosed in a patient who is less than 60 years old
- CRC diagnosed in one or more first-degree relatives with Lynch Syndrome-associated tumor, with one of the tumors diagnosed at younger than 50 years old
- CRC or Lynch Syndrome-associated tumor diagnosed in two or more first or second-degree relatives, regardless of age.

* MSI-high history refers to one or more of the following features: right-sided location, mucinous/signet-ring differentiation, solid-cribiform growth pattern, tumor-infiltrating lymphocytes, Crohn disease-like lymphocytic reaction

The median age of presentation of CRC and other tumors in Lynch Syndrome may be later than previously appreciated. In a recent report the median age of CRC was 54 years in men, but 70 years in women. The median age of endometrial cancer was 62 years {309}. It has been suggested that Lynch Syndrome should be considered in 0.5 to 1% of all patients presenting for CRC screening, and in 10-15% of all patients presenting with CRC [98]. In one study, 19% of sequential CRC patients met Bethesda guidelines, but only 17% of those were referred for genetic testing [99].

Genetic Testing for Lynch Syndrome

Genetic counseling should be offered to any patient considered for genetic testing. If resected CRC tissue is available, it may be tested for MSI. An alternative tissue test is immunohistochemistry (IHC) staining for the protein gene products of MSH2, MLH1, and MSH6 [88, 98]. Both tests are commercially available, and can be done on fixed tissue. MSI or IHC testing should be done on patients meeting the Bethesda Guidelines. If the tumor is found to be MSI-high or if IHC testing shows absence of MMR gene product the patient should be tested for a germline MMR mutation.

About 60% of patients meeting the Amsterdam II Criteria will have a MMR gene mutation. If a germline mutation is identified, family members at risk can be screened for that mutation. A negative result effectively rules out Lynch Syndrome. Those who do not carry the germline mutation can be reassured and offered normal-risk screening. Those found to carry the germline mutation must be offered intensive surveillance. If a germline mutation is not identified in an affected family member, genetic testing is not helpful, since not all mutations producing Lynch are currently detectable. In this situation, all potentially affected family members must be offered intensive colonoscopy

surveillance. Surveillance should be started at age 25 years, or 10 years younger than the youngest affected family member, and should be repeated every 1 to 3 years. After 40 years of age, or whenever polyps are detected, colonoscopies should be done yearly. Intensive surveillance has been shown to reduce CRC mortality by 65% [71, 100]. Prophylactic colectomy should be strongly considered in confirmed mutation carriers who are unwilling or unable to undergo surveillance. Total or subtotal colectomy should be done if CRC is found, since the risk for metachronous CRC is up to 40%. If subtotal colectomy is done, yearly screening of the rectal segment should continue, as the risk of rectal cancer is about 1% per year [101].

There have been no controlled studies of intensive screening for other common Lynch syndrome tumors. Nevertheless, screening for endometrial and ovarian cancer been recommended, beginning at age 30-35 and repeated every 1-2 years. When fertility is no longer desired, prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy should also be considered, particularly if colectomy is to be done. In families in which gastric cancer or urinary tract cancer has been identified, surveillance gastroscopy, renal ultrasound, and bladder cytology should be considered, although there is no proof of benefit [96].

Attenuated Lynch Syndrome

About 10% of cases of Lynch Syndrome are caused by mutations in MSH6. A closely related gene, MSH3, can partially compensate for mutations in MSH6. Cancers occur about 10-20 years later than in classic Lynch Syndrome, but by the age of 70, the cumulative risk of CRC is about 70% in men. By the same age, the risk of CRC in women is only 30%, but the risk of endometrial cancer reaches 70% [102].

Other hereditary syndromes associated with CRC

Several other rare hereditary syndromes are associated with an increased risk of CRC. These are discussed briefly below. For a more complete discussion, the reader is referred to an excellent recent review [95].

Peutz Jeghers is an autosomal dominant syndrome that leads to perioral pigmentation and histologically distinct gastrointestinal polyps. These occur predominantly in the small bowel but may occur anywhere in the gut. Mutations in the STK11 tumor suppressor gene can be identified in 60% of cases. Clinical features are usually diagnostic. Benign complications of the polyps such as small bowel obstruction or bleeding occur at an early age. The lifetime risk of CRC is 40%, and of breast cancer >50%. Patients are also at increased risk of a number of other tumors, including gastric, pancreatic, small bowel cancer, ovarian, uterine, cervical, testicular, and pulmonary. Screening colonoscopy is recommended every 3 years starting when symptoms present or in the late teens [98]. Screening gastroscopy and small bowel examination are also recommended every 2 years starting at age 10.

Juvenile polyposis is an autosomal dominant syndrome. It should be suspected if more than 3 juvenile polyps are found in the colon, or if juvenile polyps are found in other areas of the gut. Mutations have been identified in the MADH4 (SMAD4), and BMPR1A

genes. Mutations are not familial in 25% of cases. Genetic studies may be helpful, as juvenile polyps also occur sporadically, and the clinical features are not otherwise diagnostic. Benign complications of the polyps may occur in young children. The lifetime risk of CRC is 60% and mean age of presentation is 34 years. Patients are also at increased risk of gastric, small bowel, and pancreatic cancer. Screening colonoscopy is recommended every 3 years as well as screening gastroscopy and small bowel examinations every 2 years starting at 15 years of age [98].

Inflammatory Bowel Disease (IBD)

The risk of CRC is increased in chronic ulcerative colitis (UC) and in Crohn colitis. With extensive colitis (involving the colon proximal to the splenic flexure) the risk of CRC is about 5% after 10 years, 20% after 20 years, and 40% after 25 years. Risk is lower in patients with left-sided colitis. No appreciable increased risk occurs with ulcerative proctitis. The risk of cancer is further increased in patients with severe inflammation, sclerosing cholangitis, or a family history of CRC [103, 104]. The risk of cancer may be reduced up to 40 to 75% by the regular use of sulfasalazine or mesalamine [103, 105, 106]. Folic acid supplementation should be added if sulfasalazine is used. This preventive measure should receive as much emphasis as surveillance [106].

In IBD, dysplasia may precede the development of CRC. The object of surveillance in IBD is to discover those patients at highest risk of CRC by detection of dysplasia with systematic biopsies, as well as to discover CRC at an early stage. Several small case-control studies have shown improved Duke's stage and lower CRC incidence among patients with UC who have surveillance colonoscopies [103, 107, 108]. There is no information regarding surveillance in Crohn's colitis [71]. Surveillance colonoscopy should begin after 8-10 years of extensive colitis and after 15 years of left-sided colitis. Patients with sclerosing cholangitis should begin surveillance upon diagnosis. Colonoscopies should be done every 1 to 3 years, increasing frequency with increasing duration of disease. Surveillance colonoscopies should be avoided during periods of active colitis. Four biopsies should be taken every 10 cm. Strictures and mass lesions other than pseudopolyps should be biopsied [71, 109, 110]. Patients found to have high grade dysplasia (HGD), multifocal low grade dysplasia (LGD), or dysplasia associated with a lesion or mass (DALM) are at high risk of CRC. In one study 42% of patients with HGD and 16% of patient with LGD were found to have CRC at the time of colectomy. Of patients with LGD who were followed, 32% progressed to HGD or CRC [111]. If biopsies are read as indefinite for dysplasia, the frequency of surveillance should be increased to every 6 months. There is substantial variability in the interpretation of dysplasia among pathologists. A reading of LGD or HGD should be confirmed by an expert pathologist. Given the probability of sampling error, a finding of definite dysplasia cannot be mitigated by repeat colonoscopy with negative biopsies. Patients with IBD may develop sporadic tubular adenomas. When an apparent adenoma is encountered during surveillance colonoscopy, it should be removed, and biopsies of the surrounding mucosa should be obtained. Tubular adenomas with only low-grade dysplasia with no dysplasia in surrounding mucosa do not appear to be markers of CRC risk over short intervals and can be considered sporadic adenomas rather than DALM [71]

Surveillance after Removal of Adenomatous Polyps or Colorectal Cancer

Adenomatous Polyps

Surveillance colonoscopy after removal of adenomatous polyps has 2 objectives: to detect and remove polyps missed during the first colonoscopy and to detect and remove new polyps. The overall incidence of advanced neoplasms 3 years after initial colonoscopy is about 3% [57]. Studies have established factors that can be used to stratify this risk. These are summarized in Table 7.

Table 7. Risk Factors for Subsequent Advanced Neoplasms after Initial Colonoscopy and Polypectomy

- Adenoma ≥ 10 mm
- Multiple adenomas (≥ 3)
- Advanced histology (villous, high-grade dysplasia)
- Proximal location of adenoma
- Older age at diagnosis of adenoma(s)
- Family history of CRC in a parent

Hyperplastic polyps are not considered a risk factor for subsequent advanced adenomas. Patients who have removal of large sessile polyps at the index colonoscopy should have a follow-up colonoscopy within 6 months in order to insure complete excision [112].

Guidelines for surveillance after polypectomy are generally consistent, but differ in some details. Guidelines from the American Cancer Society and the GI Consortium are summarized in Table 8 [32, 71].

Table 8. Intervals for Colonoscopic Surveillance after Polypectomy

American Cancer Society

- Single adenoma ≤ 10 mm: 3-6 years. If follow-up colonoscopy is negative, revert to average risk surveillance
- Single adenoma ≥ 10 mm or ≥ 3 adenomas or advanced histology: 3 years. If follow-up colonoscopy is negative, repeat in 3 years, and if negative again, revert to average risk surveillance

Gastrointestinal Consortium

- 1-2 adenomas < 10 mm: 5 years
- Single adenoma ≥ 10 mm or ≥ adenomas or advanced histology: 3 years. If follow-up colonoscopy is negative, continue surveillance colonoscopy every 5 years.

Surveillance colonoscopy is frequently overused. In one survey, 50% of endoscopists recommended surveillance within 3 years after removal of one small adenoma, and many after finding only hyperplastic polyps [113, 114].

Colorectal cancer

When CRC is discovered, the entire colon must be examined for the presence of synchronous neoplasms. This can be done before resection or within 6 months after resection if obstruction precluded complete examination initially. Surveillance

colonoscopy after resection of colorectal cancer is done to detect local recurrence and metachronous neoplasms. Early surveillance after resection for colon cancer differs from that after resection for rectal cancer. The rate of local intraluminal recurrence of colon cancer is quite low (about 3%). Most local recurrences are extraluminal, are best detected by surveillance CEA and CT, and are rarely resectable for cure. The American Society of Colon and Rectal Surgeons, the AGA Consortium, and the American College of Gastroenterology recommend that the first surveillance colonoscopy be done 3 years after resection if the entire colon was cleared perioperatively [71, 112, 115]. Frequent early colonoscopy for intraluminal recurrence of colon cancer offers no overall survival benefit [116]. The risk of local recurrence after resection of rectal cancer differs according to the technique of resection. Recurrence rates after excision by blunt dissection are as high as 45%, but less than 10% after total mesorectal excision, and as low as 2.4% if pre-operative radiotherapy is followed by total mesorectal excision [117]. If blunt dissection is used it is prudent to recommend FFS every 6 months for the first 2 years [118]. Endoscopic ultrasound has been used for surveillance after resection of rectal cancer, and early detection of recurrences has been reported, but a survival benefit has not been proven [119].

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Colorectal Cancer Screening and Surveillance
Harford, WV
Surgical Oncology Clinics of North America 2006; 15: 1-20
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