Colon Cancer: Exactly Who is at Risk?

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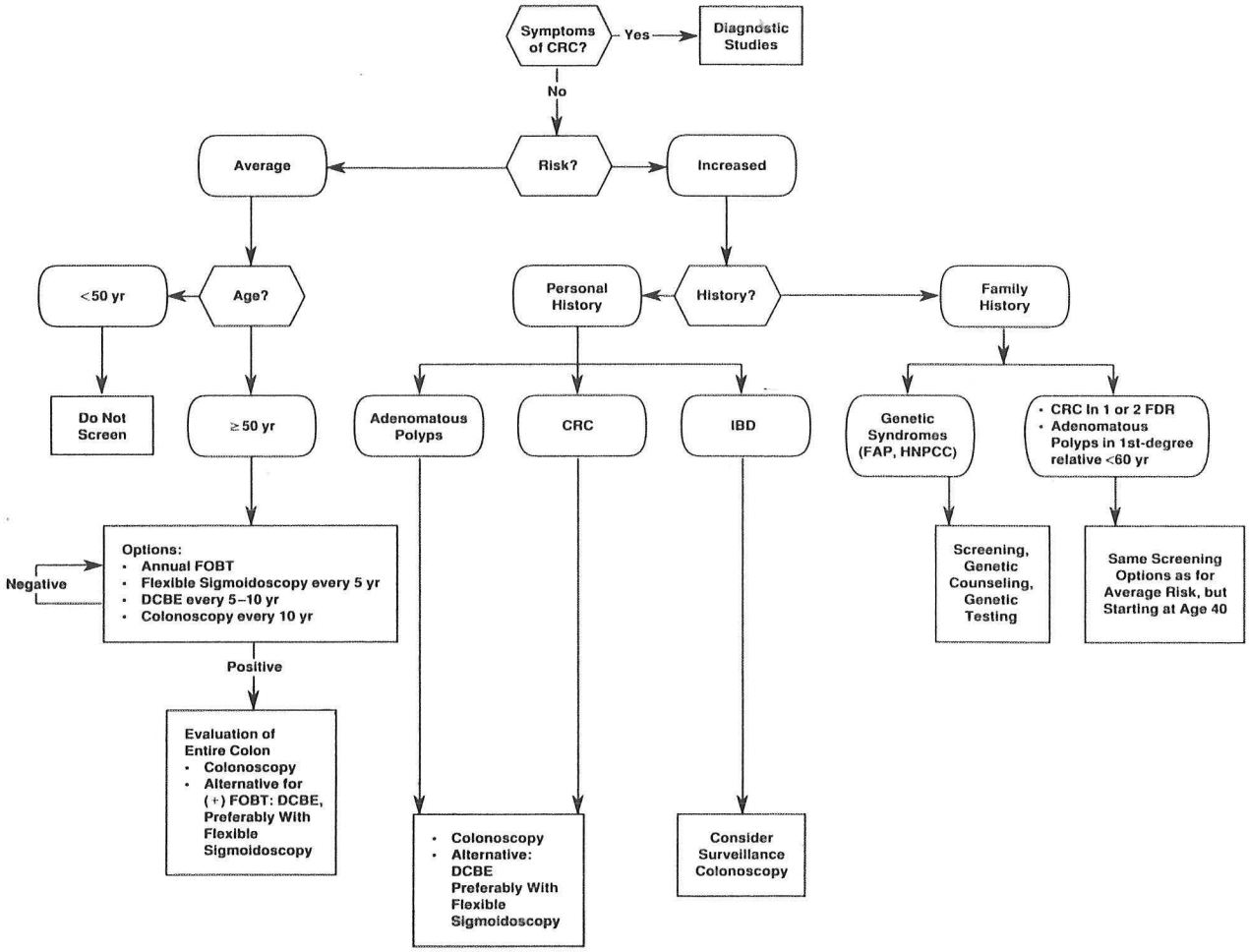

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INTRODUCTION

Cancer of the colon is a preventable disease. Good clinical studies, painstakingly carried out over the past twenty five years, have unambiguously shown that mortality from this disease can be reduced by at least two thirds by widespread application of currently available screening techniques and secondary prevention of the cancer.[1] Although primary prevention, through such simple interventions as diet modification, vitamin supplementation or chronic NSAID use might yet prove to reduce the incidence of colon cancer_[2], the gist of this grand rounds will be to examine risk factors and screening techniques that can be put to use now to secondarily prevent colon cancer.

BACKGROUND

Each year in the USA 134,000 patients are diagnosed with colon cancer and about 55,000 patients will die of the disease.[3] Over the past ten years, despite an ageing population, the incidence of the disease has declined modestly, an encouraging fact perhaps attributable to widespread use of polypectomy and prevention of overt cancer. Nonetheless, the number of deaths has remained constant and colon cancer remains the second leading cause of death by cancer in the country (behind breast cancer in women and lung cancer in men). At 55,000 deaths per year, colon cancer mortality now exceeds death by homicide and motor vehicle collisions.

As shown in Table 1, the lifetime risk of developing colon cancer in the USA is about 5% and the lifetime risk of dying from it is 2.5%.[4]

Table 1. Familiar Statistics

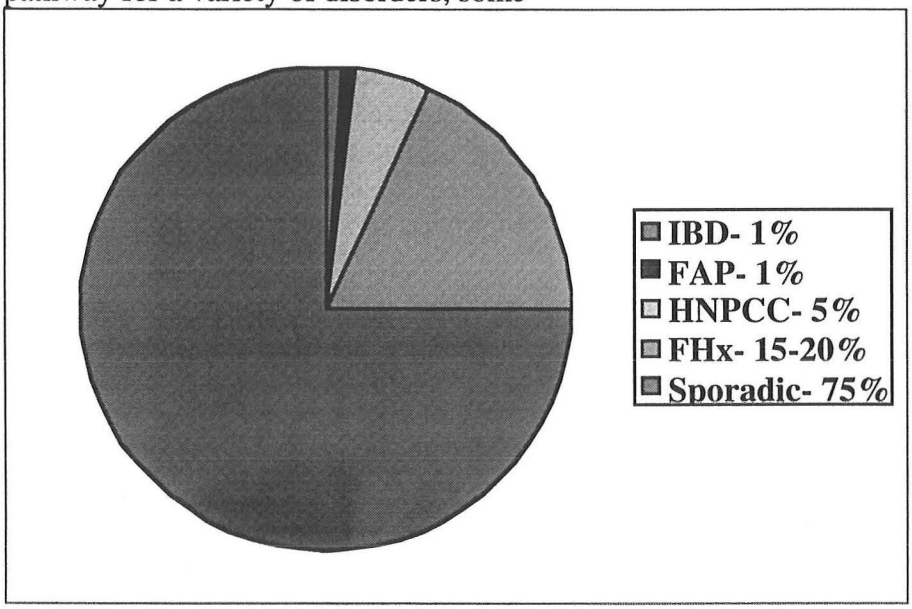
- 134,000 new cases of colon cancer per year
- 55,000 deaths from colon cancer per year
- CRC is the second leading cause of death by cancer
- Lifetime risk of developing colon cancer is 5.0%
- Lifetime risk of dying from colon cancer is 2.5%
- Prognosis is largely determined by the clinical stage at the time of diagnosis
- Adenoma to carcinoma sequence takes 8-10 years

Criteria for screening for any disease
To justify screening for a particular disease, the prevalence of the disease must be high enough to balance the risk and cost of screening, or if the disease is rare, the screening test must be utterly safe and inexpensive.[5] An example of the former is screening for breast cancer which has a lifetime incidence of about 12%, thereby justifying the risk and cost of mammography. The rare condition of phenylketonuria, which is screened for by a simple neonatal urine dipstick, is an example of the latter. In both of these examples, the second criteria for screening is met, namely, that the prognosis must be improved by early detection of the disease.

Colon cancer as a model for screening
Colon cancer meets both of these criteria. The lifetime incidence of death from colon cancer of 2.5% is well within the range to justify screening and the likelihood of surviving a diagnosis of colon cancer is critically dependent on the stage of the cancer at the time of diagnosis. The five year survival for stage I to IV of colon cancer is 95%, 70%, 45% and < 5% respectively.[6]
In addition, screening for colon cancer has a benefit not available for breast cancer screening in that the premalignant lesion can, in most cases, be identified and removed thereby preventing the cancer from developing in the first place.[7] Adenocarcinomas of the breast (and adenocarcinomas of the prostate for that matter) arise from a clone of dysplastic tissue imbedded in a solid organ. Even if the premalignant lesion can be identified, surgery is needed to remove the lesion.
With respect to colon cancer, the adenoma arises from the surface colonic epithelium, a single layer of cells which is entirely visible during colonoscopy. When the adenoma has expanded to a size of only two millimeters in diameter (still weighing < 10 mg), it is readily visible as a plaque or protuberance on the otherwise flat colonic epithelium and can be easily removed. As the adenoma continues to grow, the muscular action of the colon tries to push the adenomatous polyp downstream, as it would a piece of adherent stool. As a result, the adenoma comes to resemble a ball of neoplastic tissue attached to the colon mucosa by a stalk- a pedunculated polyp. If there is any premalignant neoplasm more amenable to removal than a pedunculated polyp, then I don't know about it. Thus, for these reasons, colon cancer would seem to be a disease ideally suited for screening and secondary prevention.[8]

ETIOLOGIES OF COLON CANCER

Cancer of the colon is not a homogeneous disease having a single cause. Rather, it is the final common pathway for a variety of disorders, some clearly due to inherited mutations and others due in part to inherited traits, and still others due to environmental factors.[9]



As shown in Figure 1, of the total of 134,000 new cases of colon cancer diagnosed each year, about 1% occur in association with chronic inflammatory bowel disease, usually ulcerative colitis. [10]Another 1% occur as result of the adenomatosis polyposis coli (APC) mutation which causes familial adenomatous polyposis (FAP) a misnomer since in one third of the cases, the disorder presents as a new mutation without any family history. About 5% result from the inheritance of a mutation in one of several DNA mismatch repair genes which presents with early cases of colon cancer, endometrial cancer, ovarian cancer, gastric cancer or renal pelvis tumors. This syndrome goes by the cumbersome name of hereditary nonpolyposis colon cancer syndrome or HNPCC.[11]

In 15 to 20% of cases, one or more first degree relatives (parents, siblings or children) are also known to have colon cancer implying that several genetic factors may be involved. For purposes of discussion, these cases are referred to as having a "positive family history", though the specific gene defects are unknown.[9]

A striking aspect of Figure 1 is that fully 75% of all new cases of colon cancer arise in the absence of any identifiable risk factor, other than age. These cases have been termed "sporadic colon cancer". It is likely that in the future, the proportion of cases termed sporadic will diminish as new genetic or environmental factors are identified.[11] *For the time being however, a clinician must bear in mind that three fourths of the cases of colon cancer he sees will have arisen in patients with absolutely no identifiable risk factor.*[4]

STRATEGY OF COLON CANCER SCREENING

Figure 1 has profound implications for the design of screening strategies. As a general rule, the first step in screening for a disease is to "risk stratify" the population and then focus resources on those individuals within the population deemed to be at high risk. Such a strategy has the advantage of producing a higher yield of patients with the disease; but with respect to colon cancer, such a strategy would miss three fourths of the cases.

Colon cancer screening would seem to warrant a two pronged approach- risk stratification based on age, personal medical history and family history with division of the population into an "average risk group" and a "high risk group".[1] Both groups are screened, but the high risk group receives more intensive screening. The majority of the sporadic cases of colon cancer will be captured through screening of the average risk group and at the same time, the higher yield of colon cancer from intensive screening of the high risk group justifies the added risk and cost. The disadvantage of such a strategy lies in its complexity. Clinicians must learn to "risk stratify" their patients, and the patients must be made to understand why some of them are offered "better" screening than others, sometimes within a spousal unit. Nonetheless, the complexity is justified on the basis of improved efficiency. Today, less than one fourth of the people in this country are being screened for colon cancer, but the number is expected to increase dramatically and rapidly.[12] Medicare, as of 1998, has agreed to pay for colon cancer screening and the other health care payers are (reluctantly) following suit. They will, however, insist on optimum efficiency in how this vast sum of money is spent.[13] Since intensive screening is undeniably more costly than nominal efforts at screening, a critical determinant of cost effectiveness lies in the exact definition of "average risk" and "high risk".

Table 2. Risk Factors for Colon Cancer

- Age > 50
- Inflammatory Bowel Disease
- Adenomatous Polyposis Coli
- Hereditary Non-Polyposis Colon Cancer Syndrome
  - must Amsterdam criteria be met?
  - can genetic tests exclude HNPCC?
- Family History of CRC
  - first degree relatives only or any relatives?
  - number of relatives?
  - age at diagnosis of relative?
- Family History of Polyps
  - age at diagnosis of relative?
  - size and type of polyp?
- Personal History of CRC
- Personal History of adenomatous polyp
  - size and type of polyp?

RISK STRATIFICATION

Age

If the incidence of colon cancer is plotted as a function of age, there is a clear increase in both men and women beginning at age 50.[1] The incidence continues to double with each successive decade and shows no evidence of a plateau. *Accordingly, the age of 50 has been generally accepted as the beginning of "average risk" for colon cancer. In the absence of any personal medical history (such as inflammatory bowel disease) or any family history of colon neoplasia, individuals less than 50 are at "low risk" and should not be screened for colon cancer.*

Inflammatory Bowel Disease

Patients with longstanding chronic inflammatory bowel disease have a markedly increased incidence of colon cancer. [14] The risk is directly proportional to both the anatomic extent of the disease and the duration of the disease, topping out with a lifetime incidence of about 25%. Most of these cancers occur in patients with chronic ulcerative colitis, though a small fraction have occurred in patients with Crohn's colitis. Unlike the situation in all other types of colon cancer in which the tumor arises from an adenomatous polyp, [15] in these patients, the tumor arises from flat area of adenomatous epithelium exhibiting severe dysplasia on histologic examination. Accordingly, screening (or more properly, surveillance) should be performed by colonoscopy with multiple random biopsies at periodic intervals (every one to two years). A barium enema will fail to detect the flat dysplastic lesions and fecal occult blood testing will always be positive due to the colitis itself.

If colitis involves the entire colon, then colonoscopic surveillance should commence after eight years of disease. If colitis involves only the left colon, then surveillance should commence after fifteen years of disease.

Adenomatous Polyposis Coli (APC or familial polyposis)

APC is inherited as an autosomal dominant trait with >95% penetrance. Phenotypically, hundreds or even thousands of adenomatous polyps develop throughout the colon beginning at puberty. If the colon is left in place, virtually all of these individuals will develop colon cancer, most in their twenties or thirties. Treatment is total proctocolectomy. Screening in patients with suspected APC (usually on the basis of an affected parent or sibling) consists of a flexible sigmoidoscopy beginning at puberty. Genetic testing for the APC mutation is available, and if positive, confirms the diagnosis and relatives can be counselled [16] and screened with the genetic test.[17] If an APC mutation is not identified, then the genetic test is uninformative and relatives need to be screened with flexible sigmoidoscopy. Clinicians should bear in mind that one third of APC patients present as a new germ-line mutation (which they can pass on to their offspring) without any prior family history of APC.

Hereditary Non-Polyposis Colon Cancer Syndrome (HNPCC)

HNPCC is also inherited as an autosomal dominant trait with a penetrance of about 80%. Most, and perhaps all of these cases are due to inheritance of a mutation in one of the five known DNA mismatch repair genes.[11, 18] Phenotypically, the disease presents with the early onset of adenomatous polyps predominantly in the right colon. These adenomas may develop into cancer within three years, much faster than the usual eight to ten year "dwell time" of a sporadic adenoma. The average age at diagnosis of colon cancer is 48 (some patients in their twenties) and 70% of the tumors are in the right colon.

In addition to colon cancer, HNPCC patients may also develop early onset malignancies at other sites including the endometrium [19] (about 40%), ovary, stomach, hepatobiliary system and renal pelvis. These other tumor organ sites have been termed HNPCC related cancers.

Table 3. Diagnostic Criteria for HNPCC

Amsterdam criteria:

- -three of more relatives with colon cancer
- -one patient a first degree relative of another
- -two generations with cancer
- -one cancer diagnosed below age 50

Bethesda criteria:

- -Amsterdam criteria are met, or
- -two HNPCC related cancers (colon, endometrial, ovarian, gastric, renal), or
- -undifferentiated right-sided colon cancer before age 45, or
- -signet cell colon cancer before age 45, or
- -adenoma before age 40

When HNPCC was first being described as a distinct clinical syndrome, investigators met in Amsterdam and developed strict criteria for the diagnosis of HNPCC. These criteria served a useful purpose for the investigators, insuring that all pedigrees probably did indeed have an autosomal dominant mutation accounting for the clustering of cancers. Unfortunately, the Amsterdam criteria are so strict that many patients with the mutation are excluded from the diagnosis because their family size is too small to meet all of the criteria.

The so-called Bethesda criteria [20] expand the definition of HNPCC to include a) HNPCC related cancers at two or more sites in the same patient, b) very early onset undifferentiated or signet cell colon cancers (age less than 45) and c) very early onset adenomas (age less than 40). With the addition of the Bethesda criteria, the clinician has a much more sensitive and practical means of diagnosing HNPCC.[21]

Despite the development of more clinician-friendly criteria, we still need a more definitive means of confirming and excluding HNPCC. As will be discussed in detail later, the surveillance program for HNPCC is intense and costly.[22] A

20 year old member of an HNPCC family, if the disease cannot be reliably excluded by a genetic test, will undergo *thirty* surveillance colonoscopies by the time they are 60 years old, even though their chance of inheriting the trait is only 50%.

Genetic Test for HNPCC

Two molecular approaches are used to test for the mutations that result in HNPCC. The more indirect approach [23] is to test extracts from the tumor itself for its ability to facilitate the amplification of unstable segments of genomic DNA known as microsatellites. If a DNA mismatch repair gene is mutated, then the microsatellite exhibits instability on amplification and the test is deemed positive for microsatellite instability (MIS). *Unfortunately, the test lacks specificity for HNPCC.* Although MIS is the "molecular signature" of HNPCC with approximately 90% of such tumors exhibiting MIS, about 15% of sporadic colon cancers also show MIS, presumably through somatic mutation of a DNA mismatch repair gene in the tumor. Since HNPCC tumors are much less common than sporadic cancers, the majority of random tumors that test positive for MIS will actually be sporadic lesions. If the pre-test probability for HNPCC is high, then the utility of MIS testing is greatly improved (i.e. the predictive value of a positive MIS test for HNPCC is acceptably high). MIS testing can be recommended if one of the following criteria are met: a) one or more first degree relatives of the index case had colon cancer or endometrial cancer, b) the index colon cancer occurred before the age of 50 or c) multiple sites of colon cancer or endometrial cancer in the index case.[20]

A second, more direct approach is to laboriously sequence each of the five DNA mismatch repair genes (MSH2, MLH1, PMS1, PMS2 or MSH6). About half of the mutations are in MSH2 with MLH1 the next most common site. *Unfortunately, the test lacks sensitivity for HNPCC.* Between 30 and 40% of Amsterdam criteria positive HNPCC patients do not have an identifiable mutation in any of the mismatch repair genes.[24] This means that the laborious genetic test, which costs about $2,400, cannot reliably exclude HNPCC; thus, the "possible HNPCC" patient must still undergo repetitive colonoscopies if the genetic test is negative. If it is positive, he enters colonoscopic surveillance but his relatives can be reliably screened with the genetic test alone.[25]

A recent report [26] from Vogelstein's lab has shown (in a relatively small group of 22 HNPCC patients) that a mutation can be identified in 100% of the cases by segregating chromosome pairs into cell lines (in effect, converting diploid to haploid for the individual chromosome in question) and testing for the mutation in the cell line.

If it turns out to be true that the sensitivity and specificity of genetic testing for HNPCC can be increased to 100%, then the cost, risk and burden of screening for this disease will have been dramatically reduced. In the meantime, for purposes of risk stratification, patients who meet the Bethesda criteria for HNPCC should be considered at "high risk".

Family History of Colon Cancer

Between 15 and 20% of all colon cancers occur in patients who can identify at least one other first degree relative who also had colon cancer.[27] This statistic, which greatly troubles many healthy patients who have a relative with colon cancer, must be placed in perspective. Assuming that an average person has two parents and one sibling (n=3, number of relatives), and that the lifetime incidence of colon cancer is 0.05 (5%), then one would expect that the probability of <u>not</u> having at least one relative with colon cancer is:

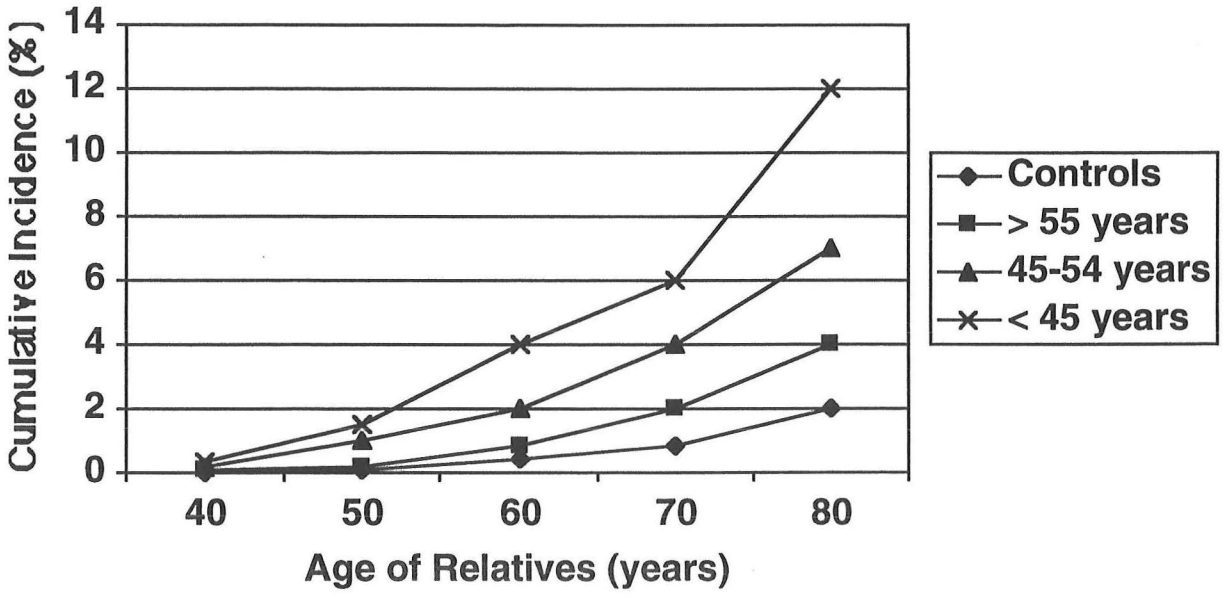
$$(1 - 0.05)^3 = .86 \text{ or } 86\%$$

Thus, almost 15% of all people will, if their relatives live long enough, have at least one first degree relative who had colon cancer, *even if the cancers occur randomly like a lighting strike*. If multiple siblings are available, then the probability increases further. Put another way, the fact that 15 to 20% of colon cancers occur in the setting of a positive family history is not all that different from the 14% that would be expected if the cancers occurred purely at random.

If a patient is unduly concerned about their risk of colon cancer based on a family member with the illness, they can be reassured that they have a 90% chance of never getting the disease. Nonetheless, a family history of a first degree relative (FDR) with colon cancer does increase risk for the disease. With one FDR with colon cancer, the age adjusted incidence of colon cancer approximately doubles. It is still low (<0.2%) but the relative risk is 2. Put another way, colon cancers occur ten years earlier, on average, in patients with a FDR. The incidence of colon cancer in a patient at age 40 with one FDR with the disease is the same as an average 50 year old.[28]

Second degree relatives (grandparents, aunts and uncles) share only one fourth of the alleles with the patient, so the genetic effect of polygene traits is greatly diluted and the relative risk is barely detectable. *For purposes of risk stratification, second degree relatives are ignored (unless they contribute to an HNPCC pedigree).*

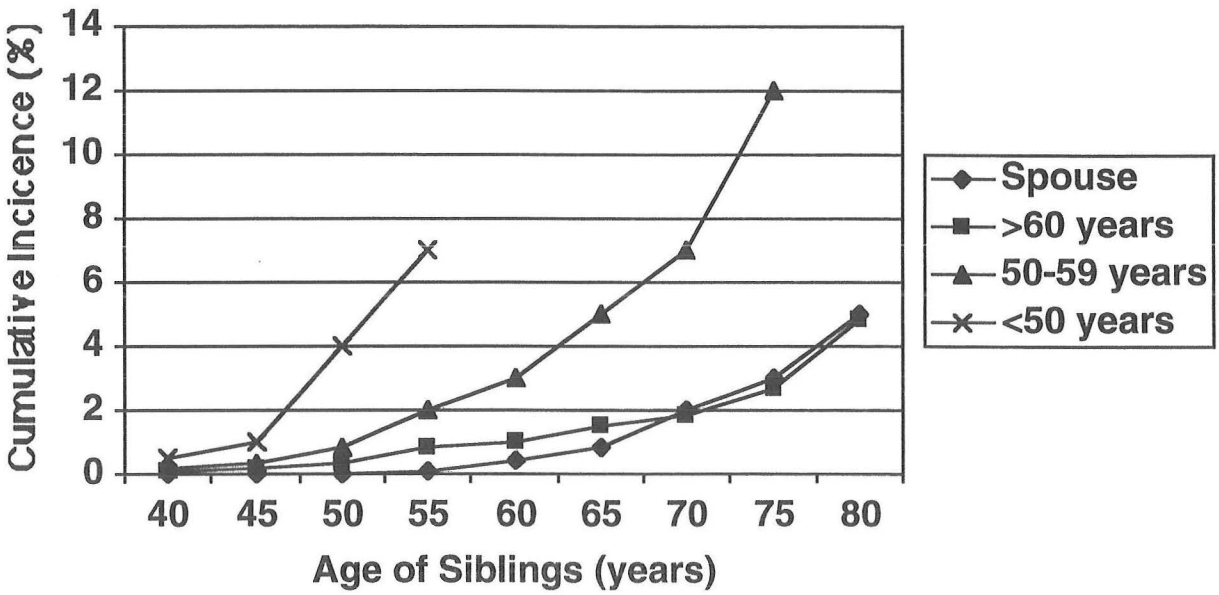
Figure 2. Risk of Colon Cancer in Relatives by Age at Diagnosis of Proband with Colon Cancer.



Having a first degree relative with colon cancer imposes a small risk of getting colon cancer yourself, but having a first degree relative who got colon cancer at a young age imposes a very substantial risk of getting the disease yourself. As shown in Figure 2, the cumulative incidence of colon cancer is plotted as a function of age in four groups of relatives, segregated according to the age at which the proband developed colon cancer.[29] The control group represents relatives of people who never got colon cancer. If the colon cancer in the proband occurred late in life, after age 55, then the relative risk was about 2. If the colon cancer occurred between 45 and 54, the relative risk increased to 3.5 and all the way to 6 if the cancer occurred at age less than 45.

For purposes of risk stratification, any first degree relative with colon cancer places the patient in the "high risk" group, but special consideration is given to those individuals who have two or more first degree relatives with colon cancer, or one first degree relative who developed colon cancer at age less than 60.

Figure 3. Risk of Colon Cancer in Siblings by Age at Diagnosis of Proband with Polyps



Family History of Polyps

In a pattern analogous to colon cancer, a family history of adenomatous polyps in first degree relatives also increases the relative risk of getting colon cancer. [30] As shown in Figure 3, the cumulative incidence of colon cancer is plotted as a function of age in four groups of siblings, segregated according to the age at which the proband developed an adenomatous polyp.[31] The control group in this study were the spouses of the probands who had a polyp. If the polyp in the proband was discovered after the age of sixty, then the relative risk was the same as the control group. However, if the adenomatous polyp developed before the age of 60, then the incidence of colon cancer was dramatically increased.

For purposes of risk stratification, an adenomatous polyp in a first degree relative, diagnosed before the age of 60 places the patient in a "high risk" group. Adenomas in relatives diagnosed beyond the age of 60 appear to have little risk.

SCREENING RECOMMENDATIONS

The following recommendations represent, with very minor embellishments added by me to rectify minor inconsistencies, the consensus of a number of national organizations.[1] These include: American Gastroenterological Association, American College of Gastroenterology, American Society for Gastrointestinal Endoscopy, Crohn's and Colitis Foundation of America, Oncology Nursing Society, Society of American Gastrointestinal Endoscopic Surgeons. The American Society of Colon and Rectal Surgeons and the American Cancer Society have also endorsed these recommendations, though their guidelines include the language of "moderate risk" and "high risk", which are lumped together in the other societies' guidelines as "high risk".[32] A number of governmental organizations have also had a major role in the development of these recommendations. The Agency for Health Care Policy and Research funded the initial phase of the guideline development including the appointment of a multidisciplinary expert panel. The Office of Technology Assessment performed the cost-benefit analysis and the Health Care Financing Administration carefully followed the proceedings to insure that Medicare reimbursement policies closely matched the recommendations.

Table 4. Average Risk Patients: Only Risk is Age > 50

FOBT yearly
or
Flexible Sigmoidoscopy every five years
or
Both of the above
or
Air Contrast Barium Enema every 5-10 years, FOBT yearly if negative
or
Colonoscopy every 10 years

Table 5. Inflammatory Bowel Disease

Surveillance colonoscopy every 1 to 2 years after 8 years of pancolitis

Surveillance colonoscopy every 1 to 2 years after 15 years of limited colitis

Do not offer FOBT

Do not offer double contrast barium enema or flexible sigmoidoscopy

Table 6. Adenomatous Polyposis Coli

Yearly flexible sigmoidoscopy beginning at puberty

Genetic testing for APC mutation and genetic counselling

Chemoprevention until colectomy

Table 7. Hereditary Nonpolyposis Colon Cancer (HNPCC)

Surveillance colonoscopy every 1 to 2 years beginning at age 25

Surveillance colonoscopy yearly beginning at age 40

Annual screening for endometrial and ovarian cancer beginning at age 25

Annual urinalysis beginning at age 25

Consider upper endoscopy in families in which gastric cancer has occurred

Table 8. Family History of CRC or Adenoma

Family History- one first degree relative with CRC > 60

Offer average risk screening beginning at age 40

Strong Family History- two first degree relatives with CRC > 60
or
-one first degree relative with CRC or adenoma < 60

Offer average risk screening beginning at age 40, and gently insist

Consider offering screening colonoscopy

SUMMARY

1. Using existing screening techniques, the mortality of colon cancer could be reduced by at least 70%.

2. Each "life saved" by screening would live, on average, an additional eight years.

3. Given the imprecision of underlying assumptions such as polyp dwell time, colonoscopy complication rates, the natural history of small adenomas, etc., a cost-effectiveness analysis does not favor one screening modality over another, but the lifetime investment in screening for colon cancer will range from $250 to $1200.

4. Currently, less than one fourth of patients at risk are being screened for colon cancer.

5. The greatest benefit for the patient is achieved with the first colonoscopy at which time the largest polyps are removed.

6. Ongoing, repetitive surveillance colonoscopies, which are usually either normal or only small adenomas are removed confer little benefit but add greatly to the cost.

7. Enormous cost reductions could be achieved if the natural history of small adenomas were better known (most studies suggest that they pose little risk).

8. A reliable (meaning sensitive and specific) genetic test for HNPCC is needed that can effectively exclude or confirm the diagnosis.

9. Virtual colonoscopy (computerized tomographic colonography) holds promise as a screening modality if the sensitivity and specificity continue to improve and if more of the analysis can be performed by super-computers, thus reducing physician time and lowering costs.

10. In a fragmented health care delivery system such as we have (uninsured, Medicare, Medicaid, managed care, indemnity insurance and self pay), decisions regarding colon cancer screening must, of necessity, take account of financial resources.

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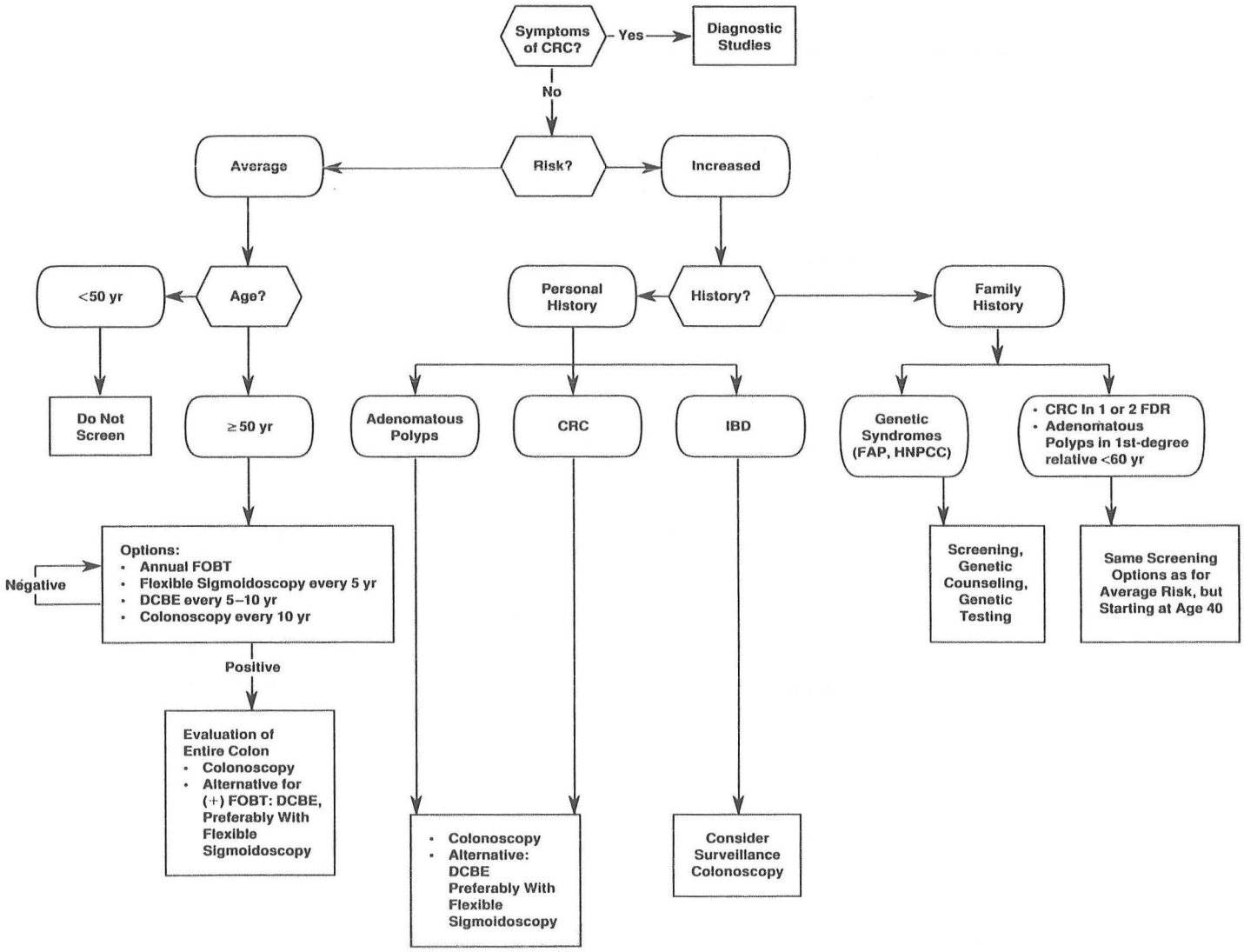
APPENDIX A. Screening algorithum (from reference 1)



APPENDIX B. Medicare Reimbursement for colon cancer screening (useful ICD9 and CPT codes)

FOBT (CPT 91065)- once every 12 months, after age 50

Screening Flexible Sigmoidoscopy (CPT 915153)- once every 48 months, after age 50

Screening Colonoscopy for high risk patient (CPT 915155)- once every 24 months
requires supporting diagnosis of either:
V160- family history of malignant neoplasm GI tract
V185- family history of certain other specified conditions, digestive tract
V1272- diseases of digestive tract, colonic polyps, or,
any code for chronic colitis

Screening Colonoscopy, not high risk (915215)- NO MEDICARE REIMBURSEMENT