Colorectal Cancer

A resident asks....

Why would a primary care doctor want to know about the genetics of colorectal cancer?

Key Points:

- About 10% of people have a family history of colorectal cancer. These people are candidates for early initiation of routine colorectal cancer screening (at age 40 instead of age 50) and might be considered for more aggressive screening strategies.
- The typical primary care practice, 2 to 8 patients (1/200 – 1/800) are from "high risk" families, with a condition called hereditary nonpolyposis colorectal cancer (HNPCC). These patients are have a high lifetime risk of colorectal cancer, with risk starting in their 20s, and have an increased risk for other cancers as well.
- Rarely, primary care practitioners will see patients with a family history of familial adenomatous polyposis (FAP). Patients who have inherited this condition are candidates for prophylactic colectomy.

Learning Objectives for Colorectal Cancer Module:

Participants will be able to:

- Understand the family history characteristics associated with increased colorectal cancer risk and with inherited colorectal cancer syndromes.
- Understand the rationale for early and more aggressive colorectal cancer screening in people with a positive family history.
- Understand the implications for patient confidentiality when family members receive care at the same health care facility.
- Understand the rationale for the claim that health care providers may have a duty to disclose information about genetic risk to family members.

CASE # 1

A resident presents a 42-year-old woman who has come for an annual exam. The resident has performed routine health maintenance, including a pelvic examination with Pap test and a clinician breast exam; a dT booster has been ordered. The patient is a non-smoker, drinks minimal alcohol, and has no known family history of breast, colorectal or ovarian cancer. The resident asks if any other preventive care is indicated.

You are aware that the patient's 50-year-old sister (who is your patient) recently underwent surgery for a small Stage 1 colorectal cancer, found as a result of routine colorectal cancer screening.

Questions for Discussion:

1. How would this information (if known to the current patient) affect your advice about preventive care?
2. What ethical concerns are raised by this case?
3. After discussing this case in a post-clinic conference, you and your colleagues realize that no one in the practice routinely counsels patients diagnosed with colorectal cancer to discuss their diagnosis with family members. Should a change be made?

CASE #1 – Discussion

1. How would this information affect your advice about preventive care?

(a) Because the patient has a first degree relative with CRC at age 50, her lifetime risk is estimated to be about 2x higher than average risk. She may be a candidate for screening starting at age 40.

About 5-10% of people have a first degree relative (parent, sibling or child) with colorectal cancer. This family history increases the risk of colorectal cancer by about two-fold compared to no family history of colorectal cancer. In addition, cancer tends to occur earlier in people with a positive family history. The cancer risk for a person at age 40 who has an affected first-degree relative is approximately the same risk as the average risk for a person at age 50 (Fuchs et al. 1994). When the relative risk is analyzed in different age groups, the increased risk is found to be more pronounced at younger ages (Fuchs et al. 1994), e.g. before 50, at a time when routine screening is not recommended. There is a consensus that routine screening should begin at age 50 for people of average risk (US Preventive Services Task Force 1996, Winawer et al. 1997, Byers et al. 1997). Thus, the risk related to family history suggests that there may be a benefit in beginning colorectal screening at an earlier age when a positive family history is present – e.g., at age 40. Winawar et al. (1997) note that: "People with a close relative (sibling parent or child) who has had colorectal cancer or an adenomatous polyp should be offered the same options as average risk people but beginning at age 40 years," and "special efforts should be made to assure that screening takes place" if the relative was affected at an early age.

RATIONALE (Winawer et al. 1997)

- Higher risk and earlier onset of cancer in people with an affected first degree relative
- Evidence for benefit of screening in average risk populations (Level I for FOBT, Level IIA for flexible sigmoidoscopy)
- Screening test performance assumed to be the same at age 40 as at age 50.

Other experts also recommend more aggressive screening. For example, the **American Cancer Society** (Byers et al. 1997) recommends early screening when a first degree relative has had colorectal cancer or an adenomatous polyp before age 60; initiation of screening is recommended either at age 40 or 10 years before the youngest case in the family, whichever is earlier. The screening strategy recommended is a *full colon screen* every 5 years.

(b) It is appropriate to ask about additional family history as well, because additional affected second-degree relatives (grand-parents, aunts, uncles) would raise the possibility of an inherited colorectal cancer syndrome.

Two rare conditions account for most high risk colorectal cancer families: **Familial Adenomatous Polyposis** (**FAP**) and **Hereditary Nonpolyposis Colon Cancer** (**HNPCC**) (See **Table 1** for prevalence and lifetime risk; See **Table 2** for summary of FAP and HNPCC). FAP is diagnosed by the presence of multiple colon polyps. HNPCC is diagnosed by pedigree characteristics, after FAP has been ruled out. The pedigree criteria that suggest an inherited risk of colorectal cancer include:

- Multiple relatives with colorectal cancer
- Sequential generations affected
- One or more family members affected at an early age (e.g. before age 60)
- Other cancers that are associated with a genetic predisposition, especially uterine (endometrial) cancer
- Multiple primary tumors – e.g., two or more colorectal neoplasms

It is important to recognize that other cancers besides colorectal cancer can be important clues to HNPCC; focusing only on colorectal cancer may miss some families. Other HNPCC-associated cancers include endometrial cancer (~40% lifetime risk in HNPCC) and cancers of the ureter/renal pelvis and small bowel (Vasen et al. 1999).

Identification of an inherited colorectal cancer syndrome has implications for prevention strategies and genetic testing (see Discussion below).

2. What ethical concerns are raised by this case?

The patient is apparently unaware of her sister's diagnosis. This may indicate that her sister does not wish to disclose her cancer diagnosis. Yet the information may be important to the resident's patient as a basis for early initiation of colorectal cancer screening. The ethical concerns include:

- Obligation to protect the confidentiality of the sister's medical condition
- Obligation to provide the best care recommendations to the resident's patient

These obligations are potentially conflicting, and may be more difficult to address because of the teaching role of the attending physician.

Confidentiality

Physicians are obligated to respect the confidentiality of medical information. In this case, the attending physician has information that may be of value in the care of the resident's patient, but s/he is not free to make it known to that patient without permission. The attending physician may choose to contact the sister recently diagnosed with CRC in order to discuss with her the potential value of sharing her diagnosis with her sister. This conversation will enable the attending physician to determine whether information about the diagnosis was withheld or whether it was simply not apparent to the patient with CRC that her medical history would be relevant to family members.

Potential duty to disclose

If there is agreement that the resident's patient should have CRC screening, on the basis of her sister's diagnosis of CRC at age 50, then the health care providers (attending and resident) may have an obligation to ensure that the family history and its implications are disclosed. Family members may also have an obligation to share information that could affect the health care decisions of their relatives. This putative duty **assumes that an action can be taken on the basis of the disclosed information that will improve health outcome.** There is no duty to

disclose family history if it will not lead to a specific action – thus, if the resident's patient were herself over 50 and already a candidate for CRC screening on the basis of age, this case would not raise the same concerns. Similarly, if a health care system reviewed the current evidence on CRC screening and decided on a screening policy that did not include early screening on the basis of a family history of CRC, it could argue against the need for the affected sister to disclose her cancer diagnosis. However, this conclusion would run counter to two published practice guidelines (Winawer et al., 1997; Byers et al., 1997).

3. *After discussing this case in a post-clinic conference (following a discussion with the patient's sister and subsequent disclosure of the family history), you and your colleagues realize that no one in the practice routinely counsels patients diagnosed with colorectal cancer to discuss their diagnosis with family members. Should a change be made?*

If the members of the practice agree that early CRC screening should be offered to those with a family history of CRC, it follows that patients with CRC should be encouraged to discuss their diagnosis with family members, together with its implications for early screening of family members.

Methods to accomplish the task of informing family members are unresolved. Geneticists often send a letter to the patient, encouraging him/her to share the information with family members. The practice could potentially aid in this effort by producing a fact sheet about CRC risk and screening, for distribution to family members. The outcome of such efforts has not been studied.

In addition, while an argument for early screening of relatives can be made, many questions remain concerning the prevention approach. These questions can serve as the basis for seminar discussions, focused on (1) the extent to which each question is supported by current evidence and (2) what additional studies would best answer the unresolved questions. They include:

1. Is the natural history of colorectal cancer the same in people with and without a family history of colorectal cancer?

2. Can data from average-risk populations over age 50 be used to predict screening test performance when screening is begun at age 40 in people with a positive family history?
3. What is the net benefit, in reduced morbidity and mortality, from early screening of people with positive family history?
4. How should family history data be obtained? Is cancer in more distant relatives important?
5. Should additional measures be promoted for people with an increased risk of colorectal cancer – e.g., lifestyle risk factors; folate supplementation?
6. If family history is used to predict risk, will false reassurance and decreased screening occur among people without a family history of colorectal cancer?
7. How does a strong family history and thus increased risk impact the performance characteristics of differing screening strategies that are now variously recommended?

For further information, see Potter (1999) for discussion of epidemiology of colorectal cancer risk and Winawer et al. (1997) for detailed discussion of colorectal cancer screening.

CASE # 2

A resident presents a new patient, referred by the gastroenterology service. She is a 28-year-old woman who recently underwent a subtotal colectomy for right-sided colorectal cancer. Her presenting symptom was lightheadedness secondary to anemia, which is now corrected. The tumor was contained within the wall of the bowel and no additional cancer therapy was recommended. She is otherwise in good health. She is scheduled for annual surveillance of the rectal stump.

Question for Discussion:

1. What additional information do you request from the resident?

CASE #2 – Discussion

1. What additional information do you request from the resident?

By virtue of her very early age of onset, this patient is likely to have an inherited predisposition to colorectal cancer, now manifested in her diagnosis. Presumably she does not have FAP, because no description of multiple polyps (>100) was noted in the GI referral, but this point should be confirmed. With FAP ruled out, the most likely diagnosis is HNPCC. Genetic testing may be indicated, and consideration of additional surveillance, e.g. for endometrial cancer, may be indicated. In addition, family members are at risk for HNPCC, and may benefit from intensive colorectal cancer screening.

Genetic testing

HNPCC is associated with mutations in five genes (MSH2, MLH1, MSH6, PMS 1, PMS2), all involving DNA repair functions known as "mis-match repair" – that is, genes that code for proteins involved in repairing DNA replication errors that occur during cell division. Testing is currently available for mutations in MSH2 and MLH1, which account for the majority of identifiable mutations responsible for HNPCC. Genetic testing within a family can distinguish those who may benefit from early and intensive colorectal screening from those who have not inherited the familial cancer predisposition. This risk information may also be helpful in making other life decisions.

An important caveat about genetic testing for HNPCC is limited sensitivity – mutations cannot be found in all affected families. Therefore, the optimal testing strategy is as follows:

1. Test one or more affected relatives
2. If a mutation is identified, testing can be offered to unaffected individuals, to determine whether they have inherited the mutation and therefore the cancer predisposition
3. If no mutation is identified in an affected individual, then the testing for that family is deemed "uninformative." In that case, all at-risk individuals in the family need to continue

screening appropriate to high risk individuals, because testing cannot determine who has inherited a predisposition to cancer and who has not.

Why test an affected relative first?

If a mutation cannot be identified in an affected family member, further testing will be non-informative and should not be pursued. However, if a mutation can be identified in an affected relative, both negative and positive test results will be informative in unaffected family members.

Counseling

Genetic testing involves potential risks as well as benefits. Knowledge of an inherited predisposition may cause anxiety and family distress, and may also pose a risk of stigmatization and discrimination in access to insurance or employment (Hudson et al. 1995, Rothenberg 1995). Appropriate protection of privacy must be considered. There is expert consensus that individuals contemplating genetic testing should have pre-test counseling, to ensure the opportunity to consider these issues carefully prior to making a decision, and post-test counseling, to ensure that the results are understood (Geller et al. 1997). However, few studies have assessed the efficacy of genetic counseling, and the scope of personal and social risks posed by genetic testing has not been studied systematically.

Cancer screening in HNPCC

For people who do not have colorectal cancer:

> "People with a family history of colorectal cancer in multiple close relatives and across generations, especially if cancer occurs at a young age, should receive genetic counseling and consider genetic testing for hereditary nonpolyposis colon cancer (HNPCC). They should be offered an examination of the entire colon every 1-2 years starting between the ages of 20 and 30 years and every year after age 40 years" (Winawer et al. 1997).

RATIONALE

- High lifetime risk of colorectal cancer, and increased proportion of proximal tumors, in people from families meeting the pedigree criteria suggestive of HNPCC

- Risk increased by age 21
- Genetic tests positive in only about 60%-70% of families
- Some observational data suggest a shortened polyp to cancer interval in HNPCC

Endometrial cancer screening

An expert panel recommends endometrial cancer screening for women with HNPCC, on the basis of expert opinion (Burke et al. 1997). The rationale is the high lifetime risk of endometrial cancer (estimated to be ~ 40%), high sensitivity of available screening tests, and excellent clinical outcome when treatment is instituted early. Suggested screening methods include transvaginal ultrasound and endometrial sampling.

Table 1.
Genetics of Colorectal Cancer: Prevalence and Risk

Genetic Category	Estimated Prevalence	Estimated Lifetime Risk of Colorectal Cancer	Other Increased Cancer Risks
No family history of CRC	9/10	4-6%	
Affected first degree relative	1/10	8-12%	
HNPCC	1/200-1/800	80%	Endometrial cancer (estimated lifetime risk of ~ 40%); ovary, ureter/renal pelvis, brain, small bowel, hepatobiliary tract and skin (sebaceous tumors)
FAP	1/8000	close to 100%	Stomach & small bowel

Table 2.
Inherited Colorectal Cancer Syndromes

Familial adenomatous polyposis (FAP):

Prevalence: 1/8000
Mode of inheritance: Autosomal dominant
Accounts for ~ 1% of CRC cases
Lifetime CRC risk: Close to 100%, mean onset age 40
Diagnosis: >20 (usually >100) colorectal polyps, detectable at puberty or in early adulthood by sigmoidoscopy or colonoscopy (sigmoidoscopy is usually sufficient to make the diagnosis)
Treatment of choice (based on expert opinion and limited observational data): subtotal colectomy (leaving the rectum intact) followed by periodic sigmoidoscopy to evaluate the rectal area for evidence of cancer
Genetic testing: A test for mutations in the APC gene is positive in about 80%-85% of families with FAP

Hereditary nonpolyposis colon cancer (HNPCC):

Prevalence: 1/200 - 1/800
Mode of inheritance: Autosomal dominant
Accounts for ~ 5% of CRC cases
Lifetime CRC risk about 80%, mean onset age 44. Lifetime risk of endometrial cancer about 40%; other reported cancers in HNPCC families include ovarian and cancers o f the ureter/renal pelvis, brain, small bowel, hepatobiliary tract and skin (sebaceous tumors**)**
Recommended screening (based on expert opinion and limited observational data): colonoscopy starting in the 20s; endometrial screening (with ultrasound or endometrial aspirate) in affected females
Genetic testing: HNPCC is caused by mutations in 5 genes, MLH1, MSH2, PMS1, PMS2, and MSH6. Testing is available for mutations in MLH1 and MSH2, which account for the majority of identifiable mutations. The overall estimate of sensitivity for such testing in HNPCC is approximately 60-70%.

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