Colorectal cancer screening in patients at moderately increased risk due to family history

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Received: November 17, 2011 Revised: May 7, 2012 Accepted: May 14, 2012 Published online: June 15, 2012

Abstract
Patients with a positive family history have an increased risk of colorectal cancer (CRC) and, in many countries, more intensive screening regimens, sometimes involving the use of colonoscopy as opposed to sigmoidoscopy or fecal occult blood testing, are recommended. This review discusses current screening guidelines in the United States and other countries, data on the magnitude of CRC risk in the presence of a family history and the efficacy of recommended screening programs, as well as ancillary issues such as compliance, cost-effectiveness and accuracy of family history ascertainment. We focus on the relatively common “sporadic” family histories of CRC, which typically imparts a mild to moderate elevation in the risk for CRC development in the proband. Defined familial syndromes associated with extremely high risks of CRC, such as hereditary non-polyposis colorectal syndrome or familial adenomatous polyposis, require specialized management approaches and are beyond the scope of this article. We will also not discuss colonoscopic surveillance in patients with a personal history of adenomas or CRC.

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Key words: Colon cancer screening; Family history; Colonoscopy; Colon polyp

INTRODUCTION
Patients with a positive family history have an increased risk of colorectal cancer (CRC) and, in many countries, more intensive screening regimens, sometimes involving the use of colonoscopy as opposed to sigmoidoscopy or fecal occult blood testing, are recommended. This review discusses current screening guidelines in the United States and other countries, data on the magnitude of CRC risk in the presence of a family history and the efficacy of recommended screening programs, as well as ancillary issues such as compliance, cost-effectiveness and accuracy of family history ascertainment. We focus on the relatively common “sporadic” family histories of CRC, which typically imparts a mild to moderate elevation in the risk for CRC development in the proband. Defined familial syndromes associated with extremely high risks of CRC, such as hereditary non-polyposis colorectal syndrome or familial adenomatous polyposis, require specialized management approaches and are beyond the scope of this article. We will also not discuss colonoscopic surveillance in patients with a personal history of adenomas or CRC.

CURRENT GUIDELINES
In the United States, the earliest national guidelines were published in 1997 by the so-called Gastrointestinal Con-
sortium, a loose collaboration of gastroenterology and oncology groups[3]. These recommendations were updated subsequently by the three major gastroenterology societies, the American Gastroenterological Association (AGA)[3], the American College of Gastroenterology (ACG)[3] and the American Society of Gastrointestinal Endoscopy (ASGE)[4], each of whom published their most recent updates in 2008, 2009 and 2006 respectively. The AGA guidelines were published under the auspices of the Multi-Society Task Force on Colorectal Cancer (which also included representatives from the ACG and ASGE) in collaboration with the American Cancer Society and American College of Radiology. Other important groups, such as the US Preventive Services Task Force, have also offered guidelines applicable to individuals with a family history of CRC[5], but these lack operational detail, e.g., they do not specify when to start screening or how long the screening intervals should be.

In general, the guidelines from the US gastroenterology groups emphasize the use of colonoscopic screening, initiation of screening before age of 50 and shorter screening intervals for high-risk individuals with a significant family history of CRC (Table 1). However, there are some important differences between the guidelines. For persons with only a family history of non-advanced adenomas in first-degree relatives (FDRs) at any age or a family history of CRC in FDRs at age >60 years, the ACG recommends only average-risk screening (starting at age 50 years), whereas the ASGE and AGA recommend initiating screening at age 40 years. In addition, while the ASGE relies heavily on colonoscopy as the preferred screening strategy in most patients with any family history, the AGA and ACG endorse the use of any acceptable screening modality (fecal occult blood testing, sigmoidoscopy or colonoscopy) in patients with less significant family histories. In the US, almost all public and private insurance plans cover CRC screening in patients with a family history of CRC, usually in the form of screening colonoscopy. With regard to Medicare, screening colonoscopy every 2 years is covered for so-called “high-risk” patients, a vaguely defined group that can include any person with a first-degree or second-degree family history of CRC or “polyp”.

From an international perspective, the World Gastroenterology Association presented comprehensive CRC screening guidelines in 2007[6]. These guidelines tailor the approach to each country, which is assigned to one of six “chains” based on the epidemiology of CRC and economic resources available. For patients with a family history, screening colonoscopy every 5 years is recommended for countries in the upper socioeconomic tiers, while less expensive but still effective measures are recommended in countries with limited health care resources or endoscopic capacity. The Asian Pacific consensus guidelines published in 2008 also endorse early-onset screening in patients with a family history[7]. In addition, national guidelines are available for certain individual countries outside of the US, in particular Britain and Canada[8-10], Germany and Poland already have large-scale screening colonoscopy programs, while many countries with national health insurance systems cover some CRC screening measures, most commonly fecal occult blood testing. In general, guidelines from other countries place less emphasis on the widespread use of screening colonoscopy and rely more on less expensive modalities, such as sigmoidoscopy or fecal occult blood testing[10].

EPIDEMIOLOGY

In the US, approximately 20% of CRC cases occur in patients with a first-degree family history of CRC. Because CRC is the third most common cancer in the US, 5%-10% of the general population have a first-degree family history of CRC[11-13] and almost 30% have a first- or second-degree relative (SDR) affected by CRC[14]. CRC is similarly prevalent in many other countries. Thus, recommendations on screening persons with a family history of CRC have widespread ramifications.

FAMILY HISTORY OF CRC

Based on mostly case-control or cross-sectional data, it is clear that a positive family history of CRC confers an increased risk for the development of CRC[13-21]. The few studies that did not show a significant increase risk were uncontrolled, small or of poor quality[22]. Most studies attribute the increased risk to earlier initiation of adenoma formation, but one study also showed that family history is associated with increased adenoma growth rates[23]. Large registry studies have confirmed that the risk of CRC in those with a family history is brought forward by about 10 years compared with those without a family history, implying that screening should start earlier in the former group[24]. However, there is some doubt as to whether or not screening recommendations should be different for those with relatives who developed CRC younger than 60 vs those whose relatives developed CRC at an older age. In one study, the former group did not demonstrate a higher incidence of advanced neoplasia on screening colonoscopy compared to the latter[25].

The increased risk associated with a family history of CRC has been investigated by several meta-analyses[26-28]. The earliest review included 27 studies and reported a relative risk of 2.25 if a patient has a FDR with CRC and 4.25 if there are multiple FDRs with CRC[28]. Another meta-analysis summarized data from 33 studies, showing that the elevated relative risk in the proband decreased as he or she aged, from 3.73 at age 40 years to 1.59 at age 70 years[29]. No difference was found between the impact of male and female affected relatives, nor between rectal vs colon cancer[29]. According to the most recently published meta-analysis, which summarized data from 59 studies, the absolute cumulative risk for CRC development between age 40-75 years is 4.7% for those with at least one affected SDR and 9.6% for those with at least one affected FDR[27]. It is suggested that the risk...
Many studies have reported that the risk of colorectal adenoma development is also increased in the presence of a family history of CRC[20-30], with a meta-analysis of 13 studies concluding that the overall relative risk was 1.7[31].

Many families have complex combinations of affected FDRs, SDRs and/or third-degree relatives (TDRs). A study using a large population database from Utah recently demonstrated that the risk changes with different constellation patterns of affected relatives (Table 2)[32]. In the presence of FDR family history, affected SDRs and TDRs can further increase risk to the proband. However, second- or third-degree family history alone increases the risk in the proband only slightly, to a clinically insignificant degree. The data also showed that risk is increased to 4.97 in those with both parents afflicted with CRC, and that older age of diagnosis (up to 70 years old) does not negate the increased risk in those with affected FDRs.

FAMILY HISTORY OF COLORECTAL ADENOMAS

Patients with a family history of colorectal adenomas also appear to exhibit increased risk[34,35], although some experts have expressed concerns that case-control studies reporting odds ratios purporting to reflect an increased risk of CRC in relatives of those with adenomas may actually be evaluating the reverse risk[36]. However, there is probably a true increase in risk, as evidenced by one prospective cohort study that showed an increased prevalence of large adenomas or CRC in FDRs of patients with large adenomas[37]. According to a meta-analysis, the relative risk of developing CRC in those with a family history of adenomas is 1.99[38]. The new ACG guidelines recommend only average-risk screening for patients with a family history of non-advanced adenomas. In contrast, the ASGE and AGA guidelines advise more aggressive screening regimens for patients with a family history of adenomas (of any size)[28,39]. Guidelines from countries outside the US generally do not recommend more aggressive screening for those with only a family history of adenomas[39].

Table 1  Colorectal cancer screening guidelines for patients with a family history[2-4]

| Family history | ACG | ASGE | AGA |
|----------------|-----|------|-----|
| 2 FDRs with neoplasia | 40  | Colonoscopy | 5  |
| 1 FDR with CRC < 60 | 40  | Colonoscopy | 5  |
| 1 FDR with CRC > 60 | 50  | Any | Average risk |
| 1 FDR with adenoma < 60 | 50  | Any | Average risk |
| 1 FDR with adenoma > 60 | 50  | Any | Average risk |
| 2 SDRs with CRC | -  | -   | -   |

Table 2  Relative risk of colorectal cancer occurrence in a proband associated with different constellations of family history[32]

| No. of FDRs with CRC | No. of SDRs with CRC | No. of TDRs with CRC | Relative risk (95% CI) |
|----------------------|---------------------|---------------------|-----------------------|
| 1                    | 0                   | 0                   | 1.76 (1.65-1.89)      |
| 2                    | -                   | -                   | 3.01 (2.66-3.38)      |
| 0                    | 2                   | -                   | 1.20 (1.05-1.38)      |
| 1                    | 1                   | -                   | 2.12 (1.90-2.35)      |
| 1                    | 2                   | -                   | 2.31 (1.80-2.93)      |
| 0                    | 1                   | 2                   | 1.33 (1.13-1.55)      |

FDR: First-degree relative; SDR: Second-degree relative; TDR: Third-degree relative; CI: Confidence interval; CRC: Colorectal cancer.

Efficacy of Screening

In general, the yield of colonoscopy for detecting colorectal neoplasia is high in FDRs of patients with CRC[47-49] in many cases higher than that seen in matched patients without a family history[41-46]. However, there have been occasional studies reporting low yield[50], while some have disputed the usefulness of initiating screening at age 40 years[46].

The efficacy of screening colonoscopy at reducing CRC incidence and mortality specifically in patients with a family history has been well documented in non-randomized studies[47,48]. There have also been many large studies that included patients with and without a family history, showing improvement in CRC incidence and mortality with screening; however, none of these studies stratified results specifically for patients with a family history.

Compliance with Screening Recommendations

Surveys show that many primary care providers and gas-
troenterologists recommend screening colonoscopy starting at age 40 years for high-risk patients[50], while adherence to screening recommendations is variable in relatives of patients with CRC[50,53]. In general, African Americans with a family history are less likely to undergo appropriate screening than whites with a family history[53]. One study suggests that awareness of family history and increased risk can serve as a motivating factor for undergoing CRC screening[53]. In a recent study, we retrospectively reviewed the most recent 161 screening colonoscopies performed at our hospital involving patients with a family history of CRC in a FDR[54]. We found that 103 (64%) had not been referred for screening in compliance with guideline recommendations. Specifically, 92 (57%) had delayed initiation of screening (i.e., screening was started at an age much later than that recommended by the guidelines), 5 (3%) had premature initiation of screening, and 6 (4%) had screening with the wrong modality. Of cases involving delayed screening initiation, in 15 (16%) the patient was not under the care of a primary care provider at the time screening was supposed to have started, in 3 (3%) the patient refused screening despite recommendations by the primary care provider, and in 26 (28%) the patient was older than the recommended age by the time CRC was discovered in their relatives (usually siblings). The remaining patients had no discernible reason and it can surmised that many of these were not referred for screening appropriately because of knowledge defects in their primary care providers with regard to screening guidelines.

COST-EFFECTIVENESS

A decision analysis study showed that the cost-effectiveness of screening for the presence of a family history of CRC ranged from $18,000 to $51,000 per life-year gained[55]. There have been no cost-effectiveness studies that directly analyzed patients with a family history of CRC but because almost all cost-effectiveness studies have concluded that screening average-risk patients is cost-effective[56], it is likely that screening patients with a family history of CRC, in whom the prevalence of CRCs and neoplasia is higher, will be cost-effective.

ACCURACY OF FAMILY HISTORY REPORTING

For screening to be effective, the accuracy of any CRC family history must be assured. Several studies have looked at the reliability of patient self-reporting of family history, showing accuracy rates of 57%-83% for positive FDR history and 98%-99% for negative family history; as might be expected, accuracy for self-reporting of family history in SDRs or TDRs was lower (27%-67%)[57-60]. The accuracy of family history of colorectal adenomas is even more problematic. Subjects may not be aware of the size or histology of polyps found in relatives, thus making it difficult to derive accurate family histories of adenomas. For this reason, the ACG recommends that a family history of “polyps” should be treated as a family history of advanced neoplasia only if there is reasonable certainty that the polyp in the affected relative was indeed an advanced neoplasm, based on patient recall or medical records[59].

CONCLUSION

In conclusion, family history of CRC is a well established risk factor for CRC development in the proband and more aggressive screening regimens for such high-risk patients are well supported by available evidence and appear to be cost-effective. Compliance with current guidelines is still suboptimal and may be affected by under-reporting of positive family histories. These findings emphasize the importance of ongoing measures to improve screening compliance in high-risk patients.

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