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TOPIC HIGHLIGHT

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Familial colorectal cancer: A review

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Abstract

Familial colorectal cancer constitutes a heterogeneous group of patients in whom the underlying molecular mechanism is still unknown. Predisposition to a such neoplasms in this setting seems to be due to common low-penetrance genetic components, but the role of genetic testing in clinical practice has to be determined. Although screening guidelines in this moderate-risk population are empiric, data obtained in epidemiologic, meta-analyses and cohort studies and, more recently, the increased risk of advanced adenomas in first degree relatives who underwent screening colonoscopy support the need to include these individuals in specific screening programs. However, data to determine what test to use, how often to use and which organizational strategy to implement are needed. At present, screening uptake in this population is less than optimal; offering the opportunity to access to screening and improving screening uptake is a first significant step.

Key words: Colorectal cancer; Familial risk; Heterogeneous; Risk population; Screening uptake

Core tip: Although first degree relatives of patients with colorectal cancer have a 2- to 4- increased risk for this disease and screening guidelines are recommended in this moderate risk population, the optimal screening strategy has to be determined.

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INTRODUCTION

The heritable component of colorectal cancer (CRC) is around 35%[1]. Up to 3%-5% of all CRC are represented by the hereditary syndromes[2]. Lynch syndrome, adenomatous and hamartomatous polyposis syndromes have a Mendelian inheritance pattern. The genes responsible for these disorders have been identified and carriers of the pathogenic mutations have a high lifetime risk of colorectal and extracolonic cancers. However, syndromic CRC represents a small fraction of all CRCs. In the 25%-30% of all CRC cases the disease occurs in families without evidence for one of the known inherited syndromes.

Non syndromic or familial CRC is generally defined as clustering of CRC that is distinguished from the hereditary syndromes. Familial CRC is an heterogeneous condition that includes patients with unrecognized hereditary syndromes and patients with seemingly sporadic forms that aggregate in families. In these patients the molecular mechanism has not been established. Probably a combination of environmental and inherited genetic factors (common, low-penetrance, genetic alterations) play a role in the development of CRC in these families. Intensive colonoscopic surveillance is offered to high-risk individuals from families with Lynch syndrome[3]; reduced CRC mortality has been demonstrated in these individuals[4,5]. Colonoscopic surveillance is already offered to people with moderate risk due to a family history (FH) of CRC[6-8], but evidence supporting reduced mortality is lacking.

Table 1 Relative and absolute risk of developing colorectal cancer according to family history

Family history	Relative risk of CRC	Absolute risk of CRC by age 79
No family history	1	5%[1]
One first degree relative with CRC	2.25 (95%CI: 2.00-2.53)	11%[2]
More than one first degree relative with CRC	4.25 (95%CI: 3.01-6.08)	21%[2]
One first degree relative diagnosed with CRC before age 45	3.87 (95%CI: 2.40-6.22)	19%[2]

[1]Data from the American Cancer Society, August 2013; [2]The absolute risk of colorectal cancer (CRC) was calculated using the relative risk and the absolute risk by the age 79.

This review focuses on familial CRC. We will review the current knowledge about its genetic background and the current screening strategies in this moderate risk population. The concept of familial CRC should be considered an evolving entity. More information will become available in the next years; the knowledge of the molecular basis of familial CRC could be relevant not only to determine the optimal diagnostic and preventive approaches but also it could have prognostic implications; a better survival has been demonstrated in a prospective observational study among patients with stage Ⅲ CRC[9] and in a retrospective study[10].

GENETICS

The heterogeneous nature of non syndromic CRC suggests that the variation in genetic risk is likely to be a consequence of the co-inheritance of multiple low-penetrance variants, some of which are common. This in the so-called polygenic model of complex disease. Although the risk of CRC associated with each of these common variants is individually modest, they make a significant contribution to the overall disease burden by virtue of their frequencies in the population.

Genome-wide association studies[11-19] have identified a number of common genetic risk loci for CRC; in a recent systematic meta-analysis[20] 16 variants at 13 loci have been considered to have the most high credible association with CRC; in the same study 23 less credible variants at 22 loci were identified; the association was evaluated within a statistical and causal inference framework according to BFDP and Venice criteria[21,22]. In a recent study[23] a risk prediction model for CRC has been developed, combining age, gender, family history and information obtained from a panel using 10 common genetic variants showed to be associated with CRC susceptibility; the authors generated risk models from 44389 subjects (24395 cancers and 19994 cancer-free controls) from 7 geographically distinct populations; although individualized genetic risk prediction was not feasible, applying risk model to Scottish population identified approximately 7% of the tested subjects with > 5% predicted 10-year absolute risk of CRC; this could help to refine preventive strategies in CRC screening programs.

SCREENING

Many studies have demonstrated that first degree relatives (FDRs) of patients with CRC have a 2- to 4-fold risk of developing this neoplasm compared with the general population. A first degree relative is a family member who shares at least 50% of their genes with a particular individual in a family (*i.e.*, parents, offspring and siblings). The familial risk is directly related to the number of FDRs affected and inversely related to the age of youngest FDRs. In Table 1 the pooled estimates of CRC risk among FDRs according to a meta analysis are reported[24] and the absolute lifetime risk has been calculated; similar estimates were reported in two other meta analyses[25,26]. In a study[27] from the Utah population database, including 2327327 persons with ⩾ 3 generation family histories and 10556 CRC cases, familial relative risk was calculated for various constellations of family risk of CRC. The authors demonstrated that increased number of affected FDRs influences risk much more that affected SDRs or TDRs. However, when combined with a positive first-degree family history, a positive second- and third-degree family history can significantly increase risk. In familial colon cancer, there is evidence of an anticipation phenomenon; in individuals with affected FDRs, CRC arise 10 years earlier than those without FH[28,29]. These associations have been demonstrated also for colorectal adenomas; the familial risk of CRC with adenoma in a FDR[24] is 1.99 (95%CI: 1.55-2.55). In a case-control study[30], an increased risk of large adenomas was associated with a history of large adenomas in relatives (OR = 2.27; 95%CI: 1.01-5.09); however, a systematic review about the risk for CRC in individuals with a family history of adenomatous polyps raised methodological limitations about the studies analyzed[31].

Based on these studies, most scientific societies[6-8] recommend that screening in FDRs should be more aggressive than that recommended in average risk population, starting at a younger age than average-risk population (Table 2); screening is recommended also in FDRs of individuals with advanced colorectal adenomas[6-8]. Although evidence of anticipation exists in individuals with affected FDRs, thus justifying the onset of screening at a younger age, there are no data that suggest differences in natural history between sporadic and familial non syndromic CRC.

These recommendations are empiric, but further evidence supports the need to include these individuals in specific CRC screening programs. Many studies focused on the risk of CRC[24]; a lesser number of studies addressed the risk of finding adenomas in this popula-

Table 2 Screening guidelines in familial colorectal cancer

	ACG[6]	ASGE[7]	USMTF[8]
First degree relative with CRC diagnosed at age < 60 or two or more first degree relatives	Colonoscopy at age 40 or 10 yr younger than affected relative; if normal repeat every 5 yr	Colonoscopy at age 40 or 10 yr younger than affected relative; if normal repeat every 5 yr	Colonoscopy at age 40 or 10 yr younger than affected relative; if normal repeat every 5 yr
First degree relative with CRC diagnosed at ⩾ 60	Same as average risk	Colonoscopy at age 40 or 10 yr younger than affected relative; if normal repeat every 10 yr	Screening should be at an earlier age (40); individuals may choose to be screened with any recommended form of testing
Second- or third-degree relatives with CRC	-	As average risk individuals	-

CRC: Colorectal cancer; ASGE: American Society for Gastrointestinal Endoscopy; ASG: American College of Gastroenterology; USMTF: US Multi-Society Task Force.

Table 3 Colonoscopy-based screening controlled studies: Risk of advanced adenomas

Design	Age (yr)	No relatives/no controls	AA in relatives/AA in controls	OR	95%CI	Ref.
Prospective, case-control	40-74	185/370	10.8%/4.9%	2.5	1.1-5.4	[32]
Prospective, case-control	40-50	228/220	5.3%/2.3%	2.56	0.87-7.47	[33]
Prospective, cross-sectional	45-75	1252/765	11.3%/6.3%	2.41	1.69-3.43	[39]
Prospective, cross-sectional	40-70	374/374	7.5%/2.9%	3.07	1.50-6.30	[42]

AA: Advanced adenomas; OR: Odds ratio.

tion[32-44]; there is a particular risk of advanced adenomas progressing to invasive cancer; a 2.6%-5.7% annual transition rate was calculated[45]. Advanced adenomas are defined as those larger than 10 mm and/or with high-grade dysplasia and/or with villous component. Colonoscopy-based screening studies in relatives of individuals with CRC detected advanced adenomas of screened individuals ranging from 3.3%[41] to 21.3%[40]; the majority of these studies lack of a control group of average risk individuals undergoing screening colonoscopy. In Table 3 controlled studies are reported[32,33,39,42]; in three of them[32,39,42] a 2.5-3.0 fold increased risk of advanced adenomas in individuals with family history undergoing screening colonoscopy has been found in multivariate analysis when compared with those without family history; the lack of significance found in fourth study[33] could be due do to the different age range of relatives (from 40- to 50 years of age), that is lower than the age range of the relatives considered in the other studies. Some predictors of adenomas such as increasing age[32,34,36,39,42], male sex[34,37-40] and strength of family history[32,34,36] have been identified with a 1.5- to 3.0-fold increased risk; this information could help to refine screening recommendations.

A further evidence derives from screening programs carried out in average risk individuals; in fecal occult blood test positive individuals the risk of advanced adenomas is increased in those with family history (OR = 1.53, 95%CI: 1.27-1.83) versus those without family history[46]. In colonoscopy-based screening studies[47] family history of colorectal cancer was associated with a higher risk of advanced neoplasms (OR = 2.5; 95%CI: 1.5-4.2). Although controlled studies with mortality endpoints are lacking, a 16 year prospective follow-up study in 1124 individuals at "moderate-risk" (*i.e.*, not fulfilling Amsterdam criteria) because of family history of CRC was carried out in a tertiary referral family cancer clinic in England[48]. These individuals underwent colonoscopy every 3-5 years, the number of cases of CRC observed (4 *vs* 26.5; RR = 0.15, 95%CI: 0.08-0.30) and the number of death from CRC (2 *vs* 10.7; RR = 0.19, 95%CI: 0.10-0.38) was significant lower than expected.

Although some evidence supports screening in these individuals, controversy exists whether people with family history should be managed in specific screening and with specific surveillance protocols. European guidelines recommend that in absence of hereditary syndromes, individuals with positive family history should not be excluded from CRC screening programs[49].

It is unclear which organizational strategy should be used in this at moderate risk population. Opportunistic screening has been evaluated in many observational studies[50] using mailed survey and telephone interviews. These studies have evaluated colorectal screening practices, including use of screening test, adherence to guidelines and barriers against screening in these individuals. A recent meta-analysis[51] evaluated 17 studies, accounting for a total of 13269 individuals with a family history of CRC; pooled screening participation levels were calculated for each screening modality; fecal occult blood testing, sigmoidoscopy-based and colonoscopy-based screening participation were respectively 25% (95%CI: 12-38), 16% (95%CI: 7-27) and 40% (95%CI: 26-54). Colonoscopy uptake among FDRs is less than 40% even if they are invited to screening[32,37,52], but in an organized screening program from Italy[53], the colonoscopy uptake among

725 invited to screening was significant higher than those not invited (78% *vs* 8%, $P < 0001$). Randomized controlled trials are needed[54] to evaluate systematic interventions promoting adherence to CRC screening among FDRs. Many factors have been identified as predictors of screening participation in this individuals; a recent systematic review[55] included 10 relevant papers according to reviewer's inclusion criteria; the review revealed that receiving recommendation from a clinician, the strength of family history and the relationship with the affected relative are associated with screening uptake.

It remains to be clarified what screening test to use; no prospective controlled studies have compared different screening tests in this population. In a multicenter prospective, double-blind study[56] on 595 FDRs with CRC submitted to screening colonoscopy, fecal immunochemical testing demonstrated a high diagnostic accuracy for CRC; using receiver-operating characteristic curves, area under the curve (AUC) was 0.96 (95%CI: 0.95-0.98); for advanced adenomas diagnosis AUC was 0.74 (95%CI: 0.66-0.82).

Economic issues should also be considered before implementing screening programs in these individuals; using the MISCAN-COLON model, a microsimulation model designed to evaluated costs and outcomes of CRC screening, the authors[57] compared colonoscopy screening of all individuals (colonoscopy every 10 years starting at age 50) with three family history-based screening programs (colonoscopy every 10 years starting from age 40; colonoscopy every 5 years starting from age 40 and colonoscopy every 5 years starting from age 50); the cost-effectiveness of family history based screening programs varied from $18000 to $51000 per life year gained.

CONCLUSION

Although the evidences of the studies are still incomplete and screening strategies are controversial in this moderate risk population, we suggest that screening colonoscopy at age 40 should be recommended especially in those with a CRC diagnosed at age < 60 or with more first degree relatives affected in the family.

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