RISK PROFILING: FAMILIAL COLORECTAL CANCER

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Abstract

Family history of colorectal cancer is a well-established and consistently strong risk factor for this disease. However, simply counting the number of affected relatives is an imprecise measure of colorectal cancer risk. We have reviewed current colorectal cancer screening guidelines from Australia, New Zealand, Canada, the US, and UK, and found that all, including the Australian National Health and Medical Research Council 2005 guidelines, assign people to risk categories largely based on age and rudimentary metrics of family history and recommend screening regimens. We claim that these guidelines are not sufficiently precise for a large proportion of people within these categories, as there is a substantial variation in colorectal cancer risk, even for people with the same family history, and even for people with a predisposing mutation in the same gene, or set of genes. If there was a tool to estimate individual colorectal cancer risk based on all known risk factors for the disease - personal and family history of cancer (including ages, ages at diagnoses, and genetic relationships across multiple generations), all known genetic factors (rare high-risk genetic mutations as well as common genetic variants), environmental factors and personal characteristics - then accurate prediction of future risk of colorectal cancer (personalised risk) may be possible. The development and utility of such a comprehensive risk prediction tool is important for appropriate personalised clinical management, including targeted colorectal cancer screening.

In Australia, a total of 14860 (8258 men and 6602 women) people were newly diagnosed with colorectal cancer (CRC) (12.7% of all cancer cases) and 3968 (2199 men and 1769 women) died of CRC (9.3% of all cancer deaths) in 2010, making it the second most commonly diagnosed and second most common cause of cancer-related death. On average, one in 19 men and one in 28 women will be diagnosed with CRC by age 75 years, and one in 10 men and one in 15 women will be diagnosed by age 85 years.[1] The problem with these statistics is that they are 'average' risks and therefore do not reflect the substantial heterogeneity of disease risk across the population due to varying risk factors. They apply to only a small fraction of the population.

Quantifying risk based on family history

Apart from age, family history of CRC is one of the most well-established and consistently strong risk factors for this disease.[2-4] A person with one first-degree relative (parent, offspring, sibling) with CRC (approximately 10% of the population)[5] is, on average, twice as likely to be diagnosed with CRC compared with someone without a family history (i.e. two-fold familial risk). Even a second and third-degree family history of CRC has been shown to increase the risk of disease, especially when combined with first-degree family history.[4] The younger the age at diagnosis of the affected relative, and the more closely related the affected relative, the greater the CRC risk.[4] This familial risk is partly due to genetic factors passed from parent to offspring, and partly due to environmental risk factors shared by family members. It should be noted that, none of the current CRC screening guidelines takes environmental risk factors in to account to quantify CRC risk for the population, or to formulate screening recommendations.[6-12]

In the absence of known cause for a particular family history (e.g. no predisposing gene mutation has been identified), current CRC screening guidelines from Australia, New Zealand, US, Canada and UK, assign people to risk categories of CRC based only on a combination of age and family history (table 1).[6-12] People with no personal or family history of CRC are generally defined as being at average risk, those with some family history as being at moderate or increased risk, and those with a strong family history as being at high risk of CRC. While many guidelines use basic presence or absence of family history to define risk categories, some guidelines consider the number of affected relatives, the ages at diagnoses of CRC and the degree of relationship for risk categorisation. However, even among these guidelines there are inconsistencies in definitions used for risk categorisation. For example, the variation in the criteria required to define the moderate or increased risk categories (table 1), and the variation in the recommendations provided for screening (table 2). These inconsistencies illustrate our relatively limited understanding of the familial aspect of CRC. All the existing guidelines fail to provide clear level of risk cut-offs beyond the broad and uncertain risk categories currently in use. This uncertainty constitutes a major barrier to the translation of current evidence into the most effective risk-reduction strategies.

Table 1: *Summary of family history profiles used in current guidelines to define colorectal cancer risk in the population.*

Country	Institution	Definition of family history of colorectal cancer		
		Average risk	**Moderate or increased risk**	**High risk**
Australia	National Health and Medical Research Council.[6]	*"at or slightly above average risk"* • No personal history of CRC, advanced adenoma, or chronic ulcerative colitis; and • No close relative with CRC; or • One FDR or SDR with CRC diagnosed at age 55 or older	*"at moderately increased risk"* • One FDR with CRC diagnosed before age 55; or • Two FDRs or one FDR and one SDR on the same side of the family with CRC diagnosed at any age	*"potentially high risk"* • Three or more FDRs or SDRs on the same side of the family diagnosed with CRC, or • Two or more FDRs or SDRs on the same side of the family with CRC, including any of the following high-risk features: – Multiple CRCs in a relative – CRC diagnosed before age 50 – At least one relative with endometrial, ovarian, stomach, small bowel, renal pelvic or ureter, biliary tract, or brain cancer (suspected HNPCC), or • At least one FDR with a large number of adenomas throughout the large bowel (suspected FAP), or • At least one relative identified having a high-risk mutation in APC or an MMR gene.
New Zealand	New Zealand Guidelines Group[7]	*"slightly increased risk"* • One FDR with CRC diagnosed after age 55	*"moderately increased risk"* • One FDR with CRC diagnosed before age 55, or • Two FDRs on the same side of the family with CRC diagnosed at any age	*"potentially high risk"* • Family history of FAP, HNPCC, or other familial CRC syndromes, or • One FDR plus two or more FDRs or SDRs on the same side of the family with CRC diagnosed at any age, or • Two FDRs, or one FDR plus one or more SDRs, on the same side of the family with CRC, and one such relative diagnosed with: – CRC before age 55, or – multiple CRCs, or – an extracolonic tumour suggestive of HNPCC (endometrial, ovarian, stomach, small bowel, renal pelvic, pancreas or brain cancer). • At least one FDR or SDR with both CRC and multiple colonic polyps, or • A personal history or one FDR with CRC diagnosed before age 50, particularly where CRC IHC shows absence of protein expression for an MMR gene, or • A personal history or one FDR with multiple colonic polyps.

Country	Institution	Definition of family history of colorectal cancer		
		Average risk	Moderate or increased risk	High risk
USA	American Cancer Society, US Multi-Society Task Force on Colorectal Cancer, and American College of Radiology[8]	*"average risk"* • No family history of CRC[87]	*"increased risk"* • One FDR with CRC or adenoma diagnosed before age 60, or • Two or more FDRs with CRC or adenoma diagnosed at any age • One FDR with CRC or adenoma diagnosed at age 60 or older, or • Two or more SDRs with CRC. [87]	*"high risk"* • FAP: genetic diagnosis of FAP or suspected FAP without genetic testing evidence, or • HNPCC: genetic or clinical diagnosis of HNPCC or people at increased risk of HNPCC,[87] or • Inflammatory bowel disease, chronic ulcerative colitis and Crohn's colitis.
Canada	Canadian Task Force[9]	"*at normal risk"* • Not defined in the statement paper.	• One or two FDRs with CRC	*"at above-average risk"* • FAP: Multiple adenomatous polyps throughout the colon; polyps first appear after puberty; and other lesions including gastric and duodenal polyps, desmoid tumours, osteomas and retinal lesions. • HNPCC: defined by Amsterdam Criteria-II88 • Family history: More than two FDRs with CRC, but do not meet criteria for HNPCC.
	Canadian Association of Gastroenterology and Canadian Digestive Health Foundation[10]	*"at average risk"* • No family history of CRC	• One FDR with CRC or adenoma diagnosed after age 60, or • Two or more SDRs with CRC or adenoma at any age • One FDR with CRC or adenoma diagnosed at before age 60, or • Two or more FDRs with CRC or adenoma at any age	*"high risk"* • HNPCC: defined by Amsterdam Criteria-II88; or • FAP; or • AAPC or AFAP
UK	British Society of Gastroenterology and Association of Coloproctology for Great Britain and Ireland[12]	• No family history of CRC	*"high-moderate risk"* • Three relatives# with CRC in first-degree kinship,* at least one is a FDR of the consultand, none diagnosed before age 50, or • Two relatives## with CRC in first-degree kinship,* at least one is a FDR of the consultand, both diagnosed before age 60 or their mean age before 60. *"low-moderate risk"* • One FDR with CRC diagnosed before age 50, or • Two FDRs with CRC diagnosed at age 60 or older.	*"high-risk"* • At-risk HNPCC: fulfills Amsterdam Criteria-II88; or untested FDR of proven MMR gene mutation carrier • MMR gene mutation carrier • One FDR with MSI-H CRC and IHC shows absence of MSH2, MSH6 or PMS2 protein expression; MLH1 loss and MSI specifically excluded. • At-risk FAP: member of FAP family with no mutation identified) • MAP: MUTYH-associated polyposis.

AFAP, attenuated familial adenomatous polyposis; AAPC, attenuated adenomatous polyposis coli; APC, adenomatous polyposis coli; CRC, colorectal cancer; FAP, familial adenomatous polyposis; FDR, first-degree relative; IHC, immunohistochemistry; SDR, second-degree relative; MMR, mismatch repair; MAP, MUTYH-associated polyposis; MSI, microsatellite instability.

*First-degree kinship: first-degree relatives of each other

#Combinations of three affected relatives in a first-degree kinship include: a parent and a blood-related aunt/uncle and/or grandparent; OR two siblings/one parent; OR two siblings/one offspring; OR both parents/one sibling.

##Combinations of two affected relatives in a first-degree kinship include: a parent and grandparent; OR >2 siblings; OR >2 children; OR child and sibling.

Ages at diagnosis are quoted in years.

Table 2: *Summary of colorectal cancer screening recommendations for asymptomatic adults, by country and category of risk.*

Country	Institution	Title	Recommendations by category of risk		
			Average risk	**Moderate or increased risk**	**High risk**
Australia	National Health and Medical Research Council	*The prevention, early detection and management of colorectal cancer (2005)*[6]	• FOBT/FIT every 2 years starting at age 50 • Flexible sigmoidoscopy every 5 years starting at age 50	• Colonoscopy every 5 years starting at age 50, or 10 years earlier than the youngest age at diagnosis of CRC in the family, whichever comes first	• Genetic counseling; Refer to CRC specialist to plan appropriate surveillance and management. • FAP: Flexible sigmoidoscopy every 1-2 years, from age 12–15 to 30–35 until polyposis develops. If no polyposis develops, flexible sigmoidoscopy every 3 years after age 35 and change to population screening after age 55. • HNPCC: Colonoscopy every 1-2 years, starting at age 25, or 5 years earlier than the youngest age at diagnosis of CRC in the family, whichever comes first.
New Zealand	New Zealand Guidelines Group	*Guidance on Surveillance for People at Increased Risk of Colorectal Cancer (2011)*[7]	• FIT every 2 years starting at age 50 (Same strategy as for those with no FDR with CRC and no personal history of CRC, adenomas, or inflammatory bowel disease)[89]	• Colonoscopy every 5 years starting at age 50, or 10 years earlier than the youngest age at diagnosis of CRC in the family, whichever comes first	Refer to • a cancer genetic service or the New Zealand Familial Gastrointestinal Cancer Registry, • a bowel cancer specialist to plan appropriate surveillance and management.
USA	American Cancer Society, US Multi-Society Task Force on Colorectal Cancer, and American College of Radiology	*Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps (2008)*[8]	For people aged 50 or older: • High-sensitivity gFOBT every year • High-sensitivity FIT every year • High-sensitivity sDNA (interval uncertain) • Flexible sigmoidoscopy every 5 years • Colonoscopy every 10 years • Double contrast barium enema every 5 years • Computed tomography colonography every 5 years	• For people with one FDR with CRC or adenoma diagnosed before age 60, or two or more FDRs with CRC or adenoma diagnosed at any age: Colonoscopy every 10 years starting at age 40, or 10 years earlier than the youngest age at diagnosis of CRC or adenoma in the family, whichever comes first • For people with one FDR with CRC or adenoma diagnosed at age 60 or older or two or more SDRs with CRC: same strategy as for average-risk people, but starting at age 40.	• Genetic counselling • FAP: Flexible sigmoidoscopy every year, starting at age 10–12 • HNPCC: Colonoscopy every 1–2 years, starting at age 20–25, or 10 years earlier than the youngest diagnosis of CRC in the family, whichever occurs first. • Inflammatory bowel disease: Colonoscopy with biopsies for dysplasia every 1–2 years, starting at 8 years after onset of pancolitis, or 12–15 years after onset of left-sided colitis; refer to a centre for management of inflammatory bowel disease.

Country	Institution	Title	Recommendations by category of risk		
			Average risk	Moderate or increased risk	High risk
Canada	Canadian Task Force	*Recommendation statement from the Canadian Task Force on Preventive Health Care (2001)*[9]	• FOBT every 1–2 years starting at age 50	• Same strategy as for 'average risk' people	• Genetic counselling • FAP: Flexible sigmoidoscopy every 1–2 years, starting at puberty. • HNPCC: Colonoscopy (starting age and the interval were not specified).
	Canadian Association of Gastroenterology and Canadian Digestive Health Foundation	*Guidelines on colon cancer screening (2004)*[10]	Starting at age 50: • FOBT every 2 years • Flexible sigmoidoscopy every 5 years; or • Flexible sigmoidoscopy combined with FOBT every 5 years, or • Double contrast barium enema every 5 years, or • Colonoscopy every 10 years	• For people with one FDR with CRC or adenoma diagnosed after age 60, or two or more SDRs with CRC or adenoma: same strategy as for average-risk people, but starting at age 40. • For people with one FDR with CRC or adenoma diagnosed before age 60, or two or more FDRs with CRC or adenoma: Colonoscopy every 5 years starting at age 40, or 10 years earlier than the youngest diagnosis of CRC or polyp in the family, whichever comes first.	• HNPCC: Colonoscopy every 1–2 years from age 20 or 10 years earlier than the youngest diagnosis of CRC in the family, whichever occurs first. • FAP: Sigmoidoscopy every year, from age 10–12. • AAPC or AFAP: Colonoscopy every year, from age 16–18.
	Canadian Association of Gastroenterology	*Position statement on screening individuals at average risk for developing colorectal cancer (2010)*[11]	• FOBT (preferably FIT) every 2 years from age 50 to 75. • Flexible sigmoidoscopy every 10 years from age 50 to 75.	na	na
UK	British Society of Gastroenterology and Association of Coloproctology for Great Britain and Ireland	*Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (2010)12*	na	• For high-moderate risk people: Colonoscopy every 5 years from age 50 to 75. • For low-moderate risk people: Once-only colonoscopy at age 55; if normal—no follow-up.	Genetic counseling • At-risk HNPCC or MMR gene mutation carrier or people with FDR with MSI-H/IHC-MMR absent CRC: Colonoscopy every 1.5–2 years, starting at age 25 • At risk FAP: Colonoscopy or alternating colonoscopy and flexible sigmoidoscopy every year, starting from puberty to age 30; thereafter every 3–5 years until age 60. • MAP: Colonoscopy every 2 years, starting at age 25.

AFAP, attenuated familial adenomatous polyposis; CRC, colorectal cancer; FDR, first-degree relative; FIT, faecal immunochemical test; FOBT, Faecal occult blood test; gFOBT, guaiac-based faecal occult blood test; HNPCC, hereditary non-polyposis colorectal cancer; MMR, mismatch repair; SDR, second-degree relative; sDNA: stool DNA test; na, not available.

Ages at diagnosis are quoted in years.

Rare predisposing genetic mutations

In the last two decades, there have been great advances in the discovery of genetic causes of familial risk of CRC, beginning with the identification of the adenomatous polyposis coli (APC) gene, which when mutated, causes familial adenomatous polyposis.[13] The human homologs of the DNA mismatch repair genes (MLH1, MSH2, MSH6, PMS2) were discovered in the 1990s to be implicated in what is now referred to as Lynch Syndrome.[14] Since then, mutations in the genes MUTYH,[15] STK11,[16] BMPR1A,[17] SMAD4 and PTEN,[18] have also been found to be genetic causes of CRC.

Approximately 5% of all CRC can be attributed to germline mutations in the CRC predisposing genes listed above, but this percentage is highly dependent on age. For example, 2-4% of all CRCs are attributable to Lynch Syndrome, but 10-15% of CRCs diagnosed before age 50 are attributable to Lynch Syndrome.[19-27] Approximately 1% of all CRC cases are due to familial adenomatous polyposis, and similarly, around 1% are due to MUTYH-associated polyposis and other polyposis syndromes (table 3).[28]

Table 3: *Colorectal cancer syndromes and their predisposing germline mutations.*

Syndrome	Phenotype OMIM ID	Genes	Genotype OMIM ID
Non-polyposis syndromes			
Lynch Syndrome (Hereditary non-polyposis colorectal cancer)	120435	MLH1 MSH2 MHS6 PMS2 EPCAM	120436 609309 600678 600259 185535
Adenomatous polyposis syndromes			
Familial adenomatous polyposis MUTYH-associated polyposis	175100 608456	APC MUTYH	611731 604933
Hamartomatous polyposis syndromes			
Juvenile polypsis syndrome	174900	SMAD4 BMPR1A	600993 601299
Peutz-Jeghers syndrome	175200	STK11	602216
Cowden disease (multiple hamartoma syndrome)	158350	PTEN	601728
Bannayan-Riley-Ruvalcaba syndrome	153480	PTEN	601728
Other syndromes			
Hereditary Mixed Polyposis syndrome	601228	GREM1	603054
Gorlin syndrome (Basal cell nevus syndrome)	109400	PTCH1	601309
Neurofibromatosis 1	162200	NF1	613113
Multiple endocrine neoplasia syndrome 2B	162300	RET	164761
Oligodontia-colorectal cancer syndrome	608615	AXIN2	604025
Other germline mutations for colorectal cancer		GALNT12 SMAD7 POLD1 POLE	610290 602932 174761 174762

OMIM, Online Mendelian Inheritance in Man (http://omim.org).

Familial adenomatous polyposis is an autosomal dominantly inherited disorder caused by germline mutations in APC (chromosome 5q21).[13] Prevalence of germline APC mutations in caucasian populations is estimated to be one in 13,000.[29] APC mutation carriers are almost certain to develop hundreds to thousands of adenomatous polyps throughout the bowel before age 40 years. If prophylactic colectomy is not performed, CRC will occur by the sixth

decade of life in nearly all APC mutation carriers.[30] These mutation carriers also have an elevated risk of gastric, duodenal, thyroid and brain cancers.[31]

Lynch Syndrome, previously termed Hereditary Non-Polyposis Colorectal Cancer,[32] is an autosomal dominantly inherited disorder of cancer predisposition caused by germline mutations in one of the DNA mismatch repair genes: MLH1 (chromosome 3p21.3);[33] MSH2 (chromosome 2p22-21);[34] MSH6 (chromosome 2p16);[35,36] and PMS2 (chromosome 7p22.2);[37,38] or constitutional 3´ end deletions of EPCAM (chromosome 2p21).[39,40] Estimates of prevalence of germline mutations of these genes in the population vary widely (depending on the assumptions used) from approximately one in 370 to one in 3100 people.[41,42] Risk of CRC to age 70 years for mismatch repair gene mutation carriers is estimated to be from 10% to 50%, depending on their sex and the gene that is mutated. Mutation carriers also have a substantial risk of subsequent primary (metachronous) CRC following colon, rectal, or endometrial cancer (table 4). Compared with the general population, mutation carriers are at increased risk of cancers of the colon, rectum, endometrium, stomach, ovary, ureter, renal pelvis, brain, small bowel and hepatobiliary tract, and the diagnoses of these cancers generally occur at younger ages than for the general population.[43] In addition, mutation carriers may also be at increased risk of cancer of the pancreas,[44,45] prostate,[46-49] breast,[45,50-52] and cervix,[53] although to a lesser extent than the cancers above. For people with Lynch Syndrome, colonoscopy is usually recommended every one–two years, starting at age 20–25 years or 10 years earlier than the youngest age at diagnosis of CRC in the family, whichever comes first (table 2).[54]

Table 4: *Risks of colorectal cancer for people with germline mutations in mismatch repair genes or MUTYH.*

Specific gene mutation	Hazard ratio (95% confidence interval)		Cumulative risk % to age 70 years* (95% confidence interval)	
	Male	Female	Male	Female
Lynch Syndrome				
Risk of first colorectal cancer				
MLH1[53]	Age ≤40: 183 (102–328) Age 50: 84.3 (30.9–230) Age ≥60: 7.8 (1.5–41.5)	Age ≤40: 45.4 (19.4–106) Age 50: 74.1 (29.3–187) Age ≥60: 37.0 (12.7–108)	34 (25–50)	36 (25–51)
MSH2[53]	Age ≤40: 139 (82.3–236) Age 50: 134 (66.1–274) Age ≥60: 34.6 (11.7–103)	Age ≤40: 120 (64.3–223) Age 50: 152 (67.5–344) Age ≥60: 18.3 (5.6–59.6)	47(36–60)	37 (27–50)
MSH6[90]	8.6 (5.5–13.4)	6.4 (3.6–11.4)	22 (14-32)	10 (5–17)
PMS2[91]	5.2 (2.8–9.7)	5.2 (2.8–9.7)	20 (11–34)	15 (8–26)
EPCAM[92]	not available	not available	75 (63–87)	74 (56–92)
Risk of metachronous colorectal cancer following segmental resection for colon cancer				
All genes combined[93]	not available	not available	10 years: 16 (10–25) 20 years: 41 (30–52) 30 years: 62 (50–77)	
Risk of metachronous colon cancer following rectal cancer				
All genes combined[94]	not available	not available	10 years: 19 (9–31) 20 years: 47 (31–68) 30 years: 69 (45–89)	
Risk of colorectal cancer following endometrial cancer				
All genes combined[52]	39.9 (27.2–58.3)		10 years: 20 (13–28) 20 years: 48 (35–62)	
MUTYH mutation				
Risk of first colorectal cancer				
biallelic[61]	108 (25.9–454)	129 (43.7–380)	75.4 (41.2–96.6)	71.7 (44.5–92.1)
monoallelic[61]	2.46 (1.54–3.93)	2.67 (1.67–4.26)	7.2 (4.5–11.2)	5.6 (3.5–8.7)

*Cumulative risk of colorectal cancer to age 70 years for the Australian general population is estimated to be approximately 3.6% for males and 2.5% for females.

MUTYH-associated polyposis is an autosomal recessively inherited disorder caused by germline mutations in both alleles of MUTYH (biallelic mutation), whether they are homozygotes or compound heterozygotes.[15] Germline mutations in one allele of MUTYH (monoallelic mutation; heterozygote) are also associated with development of colorectal adenoma and cancer.[55] In the general population, the prevalence of monoallelic and biallelic MUTYH mutations in caucasians is estimated to be 1.7%, and 0.01% respectively.[56] In individuals with attenuated colorectal polyposis syndrome, the prevalence of monoallelic and biallelic MUTYH mutations is between 0-2% and 2-7% respectively.[57] Biallelic mutation carriers have a very high risk of CRC with 70% risk to age 70 years.[58-60] Monoallelic mutation carriers have approximately 6-7% risk of colorectal cancer to age 70 years.[61] Further, biallelic mutation carriers might also be at increased risk of duodenal, ovarian, bladder and skin cancers;[62] and monoallelic mutation carriers might also be at increased risk of gastric, endometrial and liver cancer.[63,64]

Given there is almost complete penetrance of CRC for biallelic MUTYH mutation carriers,[58-60] we recommend that biallelic MUTYH mutation carriers should consider colonoscopy screening every one-two years starting at age 20 years,[65,66] and consider prophylactic total colectomy with ileorectal anastomosis depending on the individual, age of presentation and number and size of polyps present.[65,67,68] Based on our recent estimates of CRC risk for monoallelic MUTYH mutation carriers,[61] we recommend that monoallelic MUTYH mutation carriers should consider colonoscopy beginning at age 40 years, with follow-up at intervals dependent on the presence or absence of polyps, but no less often than every five years if they have a first-degree relative diagnosed with CRC.

Recently, germline mutations in other genes have been identified as risk factors for the development of CRC including POLE and POLD1.[69] However, no study has been conducted to date to estimate risk of CRC for these mutation carriers. Until these age and sex-specific penetrance studies have been conducted, it will not be possible to make clinical recommendations including cancer screening.

Common predisposing genetic variants

While much research capital has been spent on the search for new genes involved in CRC development in the last decade, there has been little success. However, genetic variants that are associated with the risk have been identified and have the potential to be used to identify people more likely to develop the disease. Genome wide association studies have identified single nucleotide polymorphisms (SNPs) associated with CRC risk at 15 genetic loci.[70,71] The minor alleles of each of these SNPs are carried by 5-50% of the population, and have been shown to be associated with small increases or decreases in CRC risk – the average effect size of the association (odds ratio) being approximately 1.2.[72-80] In total, these variants explain approximately 6% of the familial risk of CRC.[81] There is some support for the utility of genotyping for these SNPs to identify people at sufficiently high risk to justify more intensive CRC screening.[81] Clinical and population screening could change dramatically if the underlying causal variants that explain the SNP associations are discovered and the cost of targeted genotyping reduces.

Unexplained familial risks

All known genetic mutations and variants described above can only explain about 30% of the average two-fold familial risk of CRC.[82] The causes of the remainder of familial risk are presently unknown, but might consist of a combination of unmeasured minor genetic factors (often termed 'polygenic effect'), high-risk mutations in other CRC predisposing genes and environmental risk factors shared by relatives, that to date have either not been measured, or not been adequately measured.[83]

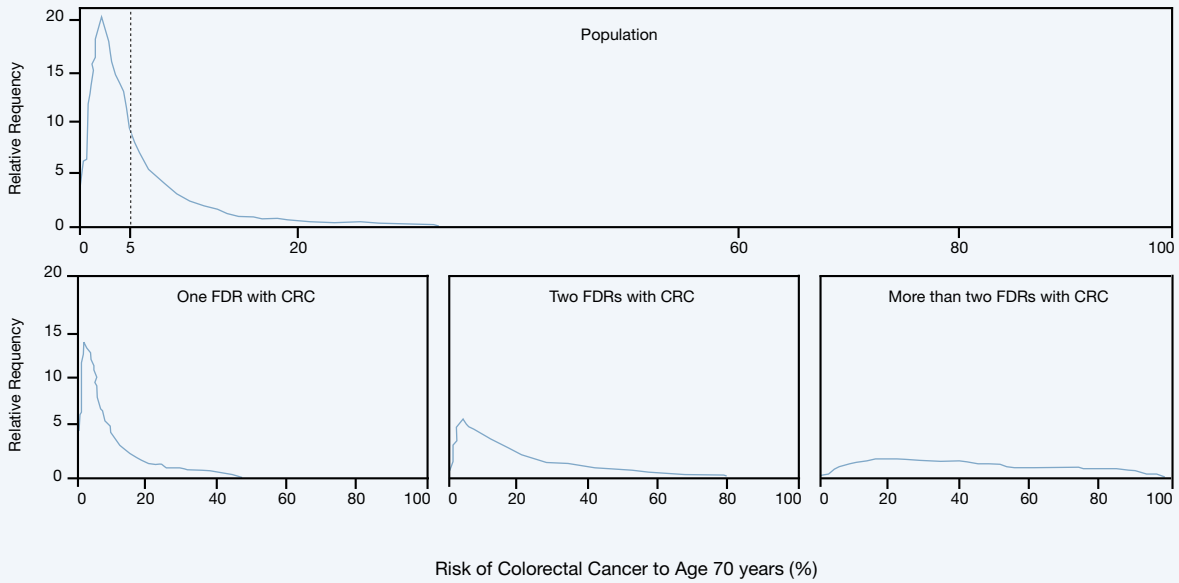
Variation in CRC risks

Given the personal differences in physical characteristics, family history of cancer, genetic factors and exposure to environmental risk factors, there is a wide spectrum of CRC risk across the population, ranging from almost zero to almost certainty. Even within a specific family history category, there is substantial heterogeneity of risk for CRC. Statistical modelling suggests that if all the familial/genetic risk factors act multiplicatively: (i) the risk of CRCs varies approximately 20-fold between the people in the lowest quartile for risk (average 1.25% lifetime risk) and the people in the highest quartile for risk (average 25% lifetime risk); and (ii) 90% of all CRCs occur in people who are above the median familial risk.[84,85]

Figure 1 shows the estimated distribution of lifetime risk (to age 70 years) of CRC for the overall population, and for three scenarios of having a family history of CRC. The shape of the distributions of risk are based on the fact that having an affected first-degree relative approximately doubles the risk, and presuming an underlying genetic risk model that involves multiple variants in multiple genes that have a multiplicative effect on risk.[85] It should be noted that: these distributions do not include the small proportion of people with inherited high-risk mutations in predisposing genes such as APC and the mismatch repair genes who have lifetime risks of approximately 100% and 50%, respectively.

The main diagram of figure 1 shows that while the average lifetime risk of CRC for the general population is approximately 5%, there is a wide spectrum of risk across the population, with the majority below 'average' risk. Lifetime risk of CRC for people with one affected first-degree relative (average two-fold increased risk) ranges from ~0% to ~40%. This overlaps substantially with lifetime risk of CRC for people with two affected first-degree relatives (average four-fold increased risk) whose risk ranges broadly from ~0% to ~80%, and for people with more than two affected first-degree relatives (average eight-fold increased risk) whose risk ranges from ~0% to ~100%. That is, simply counting affected relatives to define family history appears a rather naïve approach and an imprecise measure of actual familial risk of CRC, even more so if information on the ages of unaffected relatives, ages at diagnosis of affected relatives, and the genetic relationships between family members are not taken into account.[86]

Figure 1: *Under the polygenic multiplicative model, for colorectal cancer (CRC) with average lifetime risk of 5%, the distribution of lifetime risk for: the population; people with one affected first-degree relative (FDR); people with two affected FDRs; and people with more than two affected FDRs. Modified the Figure 2 of Hopper (2011).*[85]



Variation in CRC risks for people with predisposing genetic mutations

Even for people with Lynch Syndrome, there is substantial variation in CRC risks. For example, a large study of 166 MLH1 and 224 MSH2 mutation families showed that on average, 34% of male MLH1 carriers, 47% of male MSH2 carriers, 36% of female MLH1 carriers, and 37% of female MSH2 carriers would be diagnosed with CRC by age 70 years (table 4). However, this average risk belies a wide of range risk between mutation carriers (standard deviation 1.6); a not insubstantial proportion of carriers being almost certain to be diagnosed with CRC (e.g. 19% of male MSH2 carriers have a risk of 90% or higher) while an even greater proportion are at only moderately elevated risk (e.g. 17% of male MSH2 carriers have a risk of 10% or less (see detail in Dowty et al.[53]).

A recent study also showed that there is a substantial variation of CRC risks for monoallelic MUTYH mutation carriers (standard deviation of 1.1). This translates that monoallelic MUTYH mutation carriers with a first-degree relative diagnosed with CRC, have about 10-12% risk of CRC to age 70 years, while the risk for all monoallelic mutation carriers irrespective of family history is about 6-7% (see detail in Win et al.[61]).

Future paradigms

The implications of the variation of CRC risk for the general population, for people with a family history, and for mutation carriers are considerable. Family history of CRC is only one of the risk factors for the disease, and is a crude way of capturing a wide variation in familial risk. Current CRC screening guidelines addressing familial risk (including the Australian National Health and Medical Research Council (NHMRC) 2005 guidelines)[6] use only age and rudimentary metrics of family history after excluding those with a personal history of CRC, advanced adenoma, or inflammatory bowel disease, to stratify people in to different screening regimens. For a complex disease such as CRC, this binary concept is of limited relevance, particularly with regard to prevention and early treatment. Current CRC prevention policies fail to integrate and use: 1) critical information on the skewed distribution of CRC risk in the population; and 2) genetic and environmental risk factors that have been consistently shown to be associated with a higher risk of CRC. In such a context, risk prediction models appear to be a promising tool to incorporate and translate into practice a continuously growing body of knowledge on CRC risk and the genetic pathways of its development.

If it were possible to measure all the familial/genetic risk factors and accurately estimate personal risk of CRC, then those at high-risk could be identified and targeted for CRC screening by colonoscopy, leaving those at the lowest risk to be safely recommended faecal occult blood testing (FOBT), potentially at different ages or frequencies, thereby saving on screening costs. This would reduce the number of unwarranted invasive and expensive procedures for those who are at low-risk of developing CRC and are least likely to benefit from CRC screening, and result in fewer screening related injuries such as bowel perforation. As a consequence, effectiveness and cost-effectiveness for CRC screening could be increased.

Prediction tools for an individual's CRC risk can be designed based on their age, sex, personal and family history of cancer (including ages, ages at diagnoses,

and relationships across multiple generations), all known genetic factors (rare high-risk genetic mutations as well as common genetic variants), unmeasured genetic background, and environmental factors and personal characteristics.[83] These will be crucial developments to provide personalised risk of CRC and enable personalised screening, surveillance and genetic testing interventions beyond those currently available.

Recommendations

In this chapter, we have focused on the rationale for familial risk profiling of CRC (rather than screening). We suggest that an update of the Australian NHMRC 2005 Screening Guidelines needs to consider a more advanced utility of familial risk profile. However, we are not able to propose specific changes at this stage, given that a comprehensive tool for personalised risk prediction of CRC is not yet available to enable a personalised screening approach.

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