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Original Article

Evaluation of a population-based approach to familial colorectal cancer

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As Newfoundland has the highest rate of familial colorectal cancer (CRC) in the world, we started a population-based clinic to provide colonoscopic and Lynch syndrome (LS) screening recommendations to families of CRC patients based on family risk. Of 1091 incident patients 51% provided a family history. Seventy-two percent of families were at low or intermediate–low risk of CRC and colonoscopic screening recommendations were provided by letter. Twenty-eight percent were at high and intermediate–high risk and were referred to the genetic counsellor, but only 30% ($N = 48$) were interviewed by study end. Colonoscopy was recommended more frequently than every 5 years in 35% of families. Lower family risk was associated with older age of proband but the frequency of screening colonoscopy recommendations varied across all age groups, driven by variability in family history. Twenty-four percent had a high MMR predict score for a Lynch syndrome mutation, and 23% fulfilled the Provincial Program criteria for LS screening. A population-based approach in the provision of colonoscopic screening recommendations to families at risk of CRC was limited by the relatively low response rate. A family history first approach to the identification of LS families was inefficient.

Conflict of interest

Nothing to declare.

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Key words: colonoscopic screening – familial colorectal cancer – Lynch syndrome screening – population-based

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Newfoundland and Labrador (NL) has the highest incidence of colorectal cancer (CRC) in Canada and the highest CRC mortality rate (1). Age standardized CRC mortality rates per 100,000 population in 2015 for NL were 38 in males and 21 in females, and in Ontario they were 20 in males and 13 in females (1). The increased CRC mortality in NL is likely the result of increased CRC incidence, rather than higher prevalence of adverse prognostic factors at diagnosis, or diminished survival by stage after diagnosis (Appendix, Tables S1 and S2, Supporting information).

In collaboration with the Ontario Familial Colorectal Cancer Registry (OFCCR) we established the Newfoundland Familial Colorectal Cancer Registry (NFCCR) in 2001 and, using similar methodology, we enrolled 750 consecutive, consented, patients < 75 years from the population-based Newfoundland Cancer Registry (2). In all categories used to define family risk of CRC, the incidence was significantly higher in NL compared to Ontario, and NL had the highest rate of familial CRC worldwide when compared to other population-based studies (2).

Primary screening for CRC includes population-based testing for faecal occult blood or colonoscopic screening in high-risk individuals, particularly when defined by family history of CRC (3). A strong family history of CRC requires careful evaluation to determine the appropriate type of screening and the need for genetic

counselling (4). The term 'familial CRC' is used for individuals with a clinically important increased risk, based on their family history, which justifies screening using colonoscopy (5). The lifetime risk of developing CRC for these individuals is higher than 10% and depends on the number of relatives with CRC and the age at diagnosis (6).

The Amsterdam criteria were designed to identify hereditary non-polyposis colorectal cancer families with high specificity of a gene mutation (7). Among this group, there are two primary categories: Lynch syndrome in which mutations of genes involved in DNA mismatch repair (MMR) pathway cause CRC and extra colonic cancer susceptibility; and (2) familial CRC type X (FCCTX) in which tumours are proficient in DNA MMR proteins and there is no extra colonic cancer susceptibility (8, 9). In the NFCCR, only 2.8% of patients had mutations in MMR genes causing Lynch syndrome, and 2.3% were classified as FCCTX (7). A further 25% of incident cases had at least one first-degree relative with CRC, did not have a CRC predisposing mutation, and did not fulfil Amsterdam criteria (10). Thus, the greater burden of familial CRC occurs in families without a known mutation predisposing to CRC.

In 2010, we decided to start a Familial CRC clinic in two regions of NL to provide screening recommendations to families of incident CRC patients based on family risk of CRC. This was done because recommendations recognize family members of CRC patients as a high-risk group who require screening colonoscopies (3), because the incidence of familial CRC in NL is high (2), and because identification of hereditary and familial CRC is currently not optimal (11). In view of the benefits that accrued to LS mutation carriers as a result of colonoscopic screening and specific disease management issues in families with LS (12–14), we initiated a family history first approach in the Familial CRC clinic for the identification of selected patients who required tumour/DNA cascade testing for the diagnosis of LS (10).

The purpose of this report was (i) to assess the effectiveness with which the population-based familial CRC clinic provided colonoscopic screening recommendations to families at different degrees of risk of CRC; (ii) to examine the colonoscopic screening recommendations made, and the effect of age of the index patient on various measures of family risk of CRC and on recommendations; and (iii) to assess the characteristics of patients referred to see a genetic counsellor, and the effectiveness of a family history first approach in the identification of families at risk of Lynch syndrome.

Methods

Familial CRC clinic

Incident, pathologically confirmed, CRC patients, from the Newfoundland Cancer Registry, who presented from 2008–2010 in two NL health regions (Eastern and Central) were contacted by letter signed by the lead oncologist at the NL Cancer Centre and invited to attend clinic. Subsequently the Familial CRC clinic staff contacted the patient to confirm their response. Their physician was not notified. Patients with familial polyposis coli were excluded following review of pathology, and patients with other monogenic CRC syndromes did not present during the study period.

Patients were asked to provide a family history, including cancer occurrence and age at cancer diagnosis in first and second-degree relations. This was initially collected by mail, following which missing information was obtained and verification undertaken by phone. Where relevant, consent for release of information was obtained from family members and medical records requested to confirm cancer type. A family pedigree was reviewed by a medical geneticist (JSG) and a genetic counsellor, and family risk for Lynch syndrome and for CRC was determined. The clinical decision on risk was made by the geneticist (J. G.) using her educated, expert opinion, and incorporated age of onset of CRCs in the family, number of first and second-degree family members with CRC, family size, Amsterdam criteria, age and cancer modified Amsterdam criteria (ACMAC) and Bethesda criteria (7, 15) (definitions in Table S3), presence of multiple adenomatous polyps in a first-degree family member.

Definitions of family risk were:

(1) Low: No criteria of increased family risk of CRC.
(2) Intermediate–low: Increased family risk of CRC but not necessary to see a genetic counsellor.
(3) Intermediate–high: Increased family risk of CRC such as to make it necessary to see a genetic counsellor.
(4) High: Fulfilled Amsterdam or ACMAC criteria, necessary to see a genetic councillor.

Patients with family at high or intermediate–high risk of CRC were referred to the genetic counsellor to provide colonoscopy and other screening recommendations to families and to obtain consent, if necessary, for tumour/genomic DNA cascade testing to diagnose LS. Table S4 outlines the criteria used by the Provincial Medical Genetics Program (PMG) for the cascade testing protocol for MMR mutation identification. These criteria were developed by local expert opinion following review of the literature. Patients in a family at intermediate–low or low risk were sent a letter summarizing the family history and providing screening recommendations.

Age at which screening should start and frequency of colonoscopy were provided to families. For the purposes of this paper frequency was classified into four groups: (i) 1, 1–2 or 2 years; (ii) 2–3, 3 years; (iii) 3–5, 4 years; (iv) ≥ 5 years. Colonoscopy recommendations were made by an expert, experienced CRC geneticist (J. G.) following clinical evaluation of the pedigree and of family risk of CRC. The recommendations were provided in writing to the patient to forward to family members.

Because of prior problems with immunohistochemistry testing at the regional health authority, Eastern Health (16), tumours and DNA were sent to Toronto for cascade testing to diagnose LS in selected patients.

At Eastern Health, staffing for the clinic included a subject matter expert research assistant, a genetic counsellor, a clerk and an information technology/data management research assistant. At Central Health staffing included a nurse and a clerk. From 2008–2010, 784 incident CRC cases were identified presenting to Eastern Health and 307 presenting to Central Health. Enrollment started in 2010 and the genetic counsellor left the region at the end of 2013. Subsequently all patients received recommendations for colonoscopy screening in family members pending work-up for LS. Incident endometrial and ovarian cancer patients from 2008–2011 were also contacted but data from this group are not presented in this report. Reasons for refusal to attend the clinic were recorded.

The study was approved by the Health Research Ethics Board of Newfoundland and Labrador.

Statistical analysis

Familial CRC was defined as having at least one first-degree relative (FDR) with CRC. Family history was classified according to Amsterdam, ACMAC and Bethesda criteria (Table S3). Family history score (FHS) was calculated to assess the risk of CRC in FDRs (17), and the MMR predict score was calculated to measure the risk of being a LS mutation carrier (18). Risk was also classified by the five criteria used in the PMG (Table S4).

Briefly, the FHS compares each member of a family to age and sex-matched population controls in terms of probability of disease (17, 19). This involves comparing the observed number of cases for a family over a specific time period to the expected number of cases, calculated based on family member covariates (age, sex, and race) and overall family structure. The proband was included in the score. The expected CRC incidences were calculated using the Surveillance, Epidemiology, and End Results (SEER) program from the National Cancer Institute.

MMR predict was the best performing model in the NFCCR for identifying CRC patients who had a DNA mismatch repair mutation and thus a high score identified patients who should be screened for LS (18). Variables in the model include age at diagnosis of CRC, sex, location of tumour, multiple CRCs, occurrence of, and age at, diagnosis of CRC in first-degree relatives, and occurrence of endometrial cancer in any first-degree relative.

In responders who provided a family history, proband and family characteristics were compared according to family risk classification determined by the medical geneticist. As geneticists use the history of the proband in making screening recommendations, the FHS included data from the proband. As both FHS and MMR predict were not normally distributed, these scores are presented as medians with interquartile range. Percentage >1.66 for MMR predict (corrected for family size) is presented as this was the cut-off criterion for optimal sensitivity and specificity in diagnosing MMR mutation carriers (20). Screening recommendations to family members are presented as age recommended for first colonoscopy, frequency of subsequent colonoscopies, and referral for tumour/DNA cascade testing for LS.

Results

Figure 1 is the flow chart on patients provided colonoscopic screening recommendations at the familial CRC clinic. Of 1091 CRC patients eligible to attend clinic, contact was made with 99.5%, 63.7% agreed to participate and 51.4 % provided a completed Family History Questionnaire.

Comparison of responders and non-responders

In patients who provided a family history, 166 (29.7%) were >75 years old, 319 (57.2%) were male, and 375 (67.2%) were from the Eastern Health Region. Comparable results in non-responding group were 141 (35.7%) >75 years, 227 (57.8%) male and 303 (77.1%) from the Eastern Health region.

Reasons for declining to attend the clinic

Of 267 patients who provided a reason for declining, 52.4% ($N = 140$) stated they had no interest, 19.4% ($N = 52$) stated they had no family history of CRC, 17.6% ($N = 47$) were too old or too sick, 15 (6%) said family members were already in a screening program, and the remaining 4.9% ($N = 13$) had miscellaneous reasons. A further 134 (12.3%) agreed to provide a family history but never did so.

Release of information

Of 256 patients who were asked to complete a release of information form to confirm tumour pathology, 146 (57%) completed this task, comprising 292 tumours. Table S5 provides the pathology results.

Family risk

Twenty percent of probands had familial CRC defined as at least one FDR with CRC. Only nine (1.7%) families fulfilled Amsterdam 1 or 2 criteria, 18.7% ($N = 99$) fulfilled ACMAC criteria, and 36.7% ($N = 194$) fulfilled at least one Bethesda criterion. The medical geneticist classified 57% ($N = 300$) of families at low risk for CRC, 15.5% ($N = 82$) at intermediate–low, 23.1% ($N = 122$) at intermediate–high, and 4.0% ($N = 21$) at high risk for CRC (Table 1). The latter two groups were referred to the genetic counsellor.

The distribution of FHS is shown in Table 2. The median score was 2.2 (interquartile range 1.6–3.8).

Twenty-three percent fulfilled at least one of the criteria required by the Provincial Medical Genetics Program for Lynch syndrome testing. Twenty-four percent had a MMR score >1.66. Distribution of MMR predict scores is provided in Fig. 2b.

The clinical and family characteristics of the patients by family risk of CRC, as defined by the medical

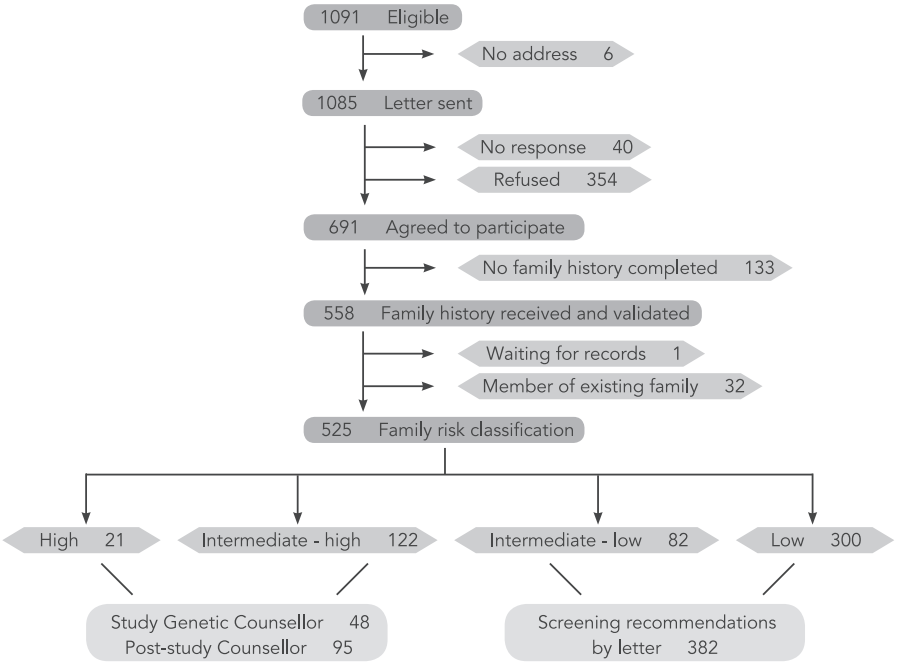

Fig. 1. Flow chart in the familial colorectal cancer (CRC) clinic for incident CRC patients provided colonoscopic screening recommendations.

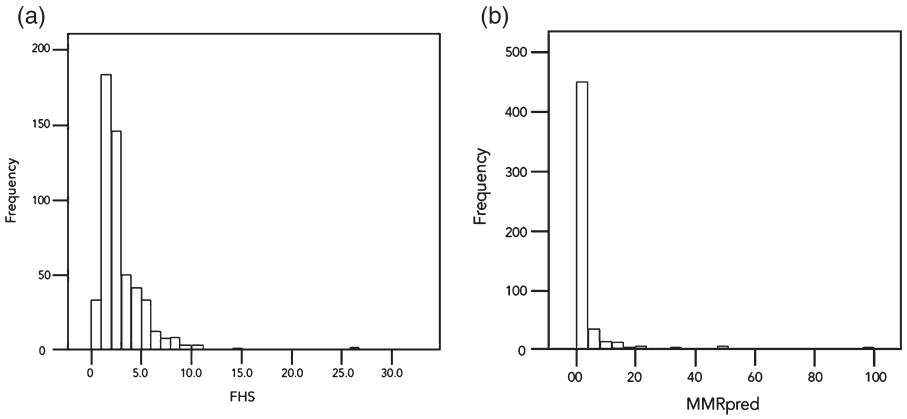

Fig. 2. Distribution of family history score (FHS) for colorectal cancer (a) and of MMR predict score for risk of Lynch syndrome in consecutive incident CRC patients (b).

geneticist, are outlined in Table 1. Higher family risk was associated with lower proband age and female gender. There was little difference in family history score, MMR predict score, or in the proportion fulfilling Bethesda criteria when comparing intermediate–high to intermediate–low, but there was a difference in the rate of ACMAC (49% *vs* 34%, respectively) and in the frequency at which colonoscopy was recommended, in these groups.

Colonoscopy screening recommendations

Three percent of the families were recommended to have screening colonoscopy every 1, 2, or 1–2 years, 11% 2–3 or 3 years, 21% 3–5 or 4 years and the remaining 65% ≥5 years. A recommendation of higher frequency of colonoscopy screening was associated with higher FHS and MMR predict scores, proportions who fulfilled Amsterdam and ACMAC criteria, or had ≥2 of the five Bethesda criteria or polyps in a first-degree relative. The recommendations provided, analysed by proband and family risk characteristics, are outlined in Table 2.

The clinical and family risk characteristics, and family screening colonoscopy recommendations by proband age, are outlined in Table 3. The rate of familial CRC differed little by age but there was a difference in the degree of family risk. Twenty-seven percent of patients were ≥75 years of age, of whom 20.9% had families at high or intermediate–high risk of CRC, compared to 36.6% of patients <75 years with similar risks. Nonetheless in the group ≥75 years 11.8% fulfilled ACMAC criteria 31.3% fulfilled Bethesda criteria, and 19.4 % had familial CRC. Screening recommendations

Table 1. The clinical and family risk characteristics by family risk of CRC defined by geneticist

	Family risk of CRC					
	High (21)	Int–High (122)	Int–Low(82)	Low (300)	Total (529)	p value
Mean age ± SD	56.2 ± 15.0	65.1 ± 11.0	68.0 ± 11.5	68.9 ± 9.9	67.3 ± 11.0	0.000
≥75 years *N* (%)	3 (14.3)	27 (22.1)	22 (26.8)	92 (30.7)	144 (27.2)	NS
Male *N* (%)	9 (42.9)	65 (53.3)	48 (58.5)	179 (59.7)	305 (57.7)	NS
Location *N* (%)						0.011
Eastern	15 (71.4)	96 (78.7)	53 (64.6)	190 (63.3)	355 (67.1)	
Central	6 (28.6)	26 (21.3)	29 (35.4)	110 (36.7)	174 (32.9)	
FHS proband median	7.8	3.1	2.6	1.9	2.2	0.000
Interquartile range	5.1–9.8	1.9–4.9	1.8–4.1	1.4–2.5	1.6–3.8	
Upper decile %	72.2	16.5	8.9	2.7	9.4	
MMRPred median (*N*)	7.8	1.1	0.7	0.2	0.4	0.000
Interquartile range	2.5–34.2	0.3–3.2	0.2–2.8	0.1–0.6	0.1–1.6	
% > 1.66	83.3	34.7	38.0	11.4	23.7	
Amsterdam *N* (%)	9 (42.9)	0 (0.0)	0 (0.0)	0 (0.0)	9 (1.7)	0.000
Am1	8 (38.1)	0 (0.0)	0 (0.0)	0 (0.0)	8 (1.5)	0.000
Am2	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0.000
Bethesda *N* (%)	12 (57.1)	107 (87.7)	75(91.5)	0 (0.0)	194 (36.7)	0.000
Beth1 CRC < 50 years	2 (9.5)	10 (8.2)	8 (9.8)	0 (0.0)	20 (3.8)	0.000
Beth2 synchronous/metachronous	2 (9.5)	21 (17.2)	19 (23.2)	0 (0.0)	42 (7.9)	0.000
Beth3 MSI histology	2 (9.5)	10 (8.2)	3 (3.7)	0 (0.0)	15 (2.8)	0.000
Beth4 1° rel with Ca < 50 years	5 (23.8)	13 (10.7)	7 (8.5)	0 (0.0)	25 (4.7)	0.000
Beth5 two 1° rel or 2° rel with Ca	6 (28.6)	73 (59.8)	48 (58.5)	0 (0.0)	127 (24.0)	0.000
1° rel Polyps *N* (%)	0 (0.0)	11 (9.0)	5 (6.1)	1 (0.3)	17 (3.2)	0.000
2+ Bethesda or polyps	4 (19.0)	21 (17.2)	10 (12.2)	0 (0.0)	35 (6.6)	0.000
3+ Bethesda or polyps	1 (4.8)	4 (3.3)	3 (23.7)	0 (0.0)	8 (1.5)	0.024
FamCRC *N* (%)	18 (85.7)	55 (45.1)	32 (39.0)	0 (0.0)	105 (19.8)	0.000
PMG criteria *N* (%)	12 (57.0)	74 (60.7)	37 (45.1)	0 (0.0)	123 (23.3)	0.000
PMG1 ACMAC	11 (52.4)	60 (49.2)	28 (34.1)	0 (0.0)	99 (18.7)	0.000
PMG2 CRC before 40 years	1 (4.8)	6 (4.9)	2 (2.4)	0 (0.0)	9 (1.7)	0.007
PMG3 endo before 45 years	1 (4.8)	1 (0.8)	1 (1.2)	0 (0.0)	3 (0.6)	0.060
PMG4 sebaceous/multiple	2 (9.5)	9 (7.4)	11 (13.4)	0 (0.0)	22 (4.2)	0.000
PMG5 multiple HNPCC Ca	0 (0.0)	8 (6.6)	2 (2.4)	0 (0.0)	10 (1.9)	0.000
Colon screening age *N*(%)						0.000
<30	7 (33.3)	4 (3.3)	1 (1.2)	0 (0.0)	12 (2.3)	
30–34	3 (14.3)	4 (3.3)	1 (1.2)	1 (0.3)	9 (1.7)	
35–39	3 (14.3)	8 (6.6)	2 (2.4)	0 (0.0)	13 (2.5)	
40–44	5 (23.8)	21 (17.2)	4 (4.9)	10 (3.3)	40 (7.6)	
45–49	0 (0.0)	27 (22.1)	11 (13.4)	29 (9.7)	67 (12.7)	
50	0 (0.0)	51 (41.8)	55 (67.1)	244 (81.3)	350 (66.2)	
Missing	3 (14.3)	7 (5.7)	8 (9.8)	16 (5.3)	38 (7.2)	
Colon screening frequency *N* (%)						0.000
1–2 years	12 (57.1)	2 (1.6)	0 (0.0)	0 (0.0)	14 (2.6)	
2–3 years	5 (23.8)	46 (37.7)	4 (4.9)	1 (0.3)	56 (10.6)	
3–5 years	0 (0.0)	53 (43.4)	32 (39.0)	19 (6.3)	106 (20.0)	
5 years	0 (0.0)	16 (13.1)	42 (51.2)	272 (90.7)	330 (62.4)	
Missing	2 (9.5)	5 (4.1)	4 (4.9)	8 (2.7)	23 (4.3)	

1° rel, first-degree relative; 2° rel, second-degree relative; ACMAC, age and cancer modified Amsterdam criteria; Ca, HNPCC cancer; endo, endometrial cancer; HNPCC, hereditary nonpolyposis colorectal cancer; PMG, provincial medical genetics.

were provided to family members for a colonoscopy, more frequently than once every 5 years, in 22.8% of these families.

Referrals to the genetic counsellor

Twenty-seven percent ($N = 143/525$) of probands were referred to the genetic counsellor, 21 (15%) of whom had high family risk, and 122 (85%) who had intermediate–high risk. During the study only 48 (34%) were actually interviewed by the genetic counsellor (Fig. 1), and 24 (50%) of these consented to tumour/DNA cascade testing. The remaining 95 patients were seen by a genetic counsellor after the study was completed, provided with colonoscopy recommendations for family members based on the data available from the pedigree, and evaluated for LS cascade testing.

Table 2. The clinical and family risk characteristics by frequency of colonoscopy screening recommendations

	Annual screening frequency						
Colonoscopy frequency N	1–2 years 14	2–3 years 56	3–5 years 106	5 years 330	Missing 23	Total 529	p value
Mean age ± SD	59.0 ± 14.6	61.4 ± 13.1	64.3 ± 11.3	69.5 ± 9.3	68.8 ± 12.9	67.3 ± 11.0	0.000
≥ 75 years *N* (%)	2 (14.3)	9 (16.1)	21 (19.8)	102 (30.9)	10 (43.5)	144 (27.2)	0.011
Family Male *N* (%)	8 (57.1)	31 (55.4)	59 (55.7)	196 (59.4)	11 (47.8)	305 (57.7)	NS
Risk							0.000
High	12 (85.7)	5 (8.9)	2(1.9)	0 (0.0)	2 (8.7)	21 (4.0)	
Intermediate–high	2 (14.3)	46 (82.1)	53 (50.0)	16 (4.8)	5 (21.7)	122 (23.1)	
Intermediate–low	0 (0.0)	4 (7.1)	32 (30.2)	42 (12.7)	4 (17.4)	82 (15.5)	
Low	0 (0.0)	1 (1.8)	19 (17.9)	272 (82.4)	8 (34.8)	300 (56.7)	
Location *N* (%)							0.137
Eastern	12 (85.7)	37 (66.1)	78 (73.6)	216 (65.5)	12 (52.2)	355 (67.1)	
Central	2 (14.3)	19 (33.9)	28 (26.4)	114 (34.5)	11 (47.8)	174 (32.9)	
FHS median (*N*)	6.8	3.7	2.7	2.0	2.4	2.2	0.000
Interquartile range	4.6–9.5	2.1–5.3	1.9–4.4	1.4–2.6	1.0–5.7	1.6–3.8	
% Upper quintile (above 4.1)	71.4 (10)	42.9 (24)	29.2 (31)	8.8 (29)	34.8 (8)	19.3 (102)	
MMRPred median (*N*)	7.8	2.0	0.6	0.2	0.7	0.4	0.000
Interquartile range	1.7–83.6	0.5–5.5	0.2–2.3	0.1–0.7	0.1–1.9	0.1–1.6	
Percentage >1.66	75.0	51.8	30.8	14.6	25.0	23.7	
Amsterdam *N* (%)	5 (35.7)	2 (3.6)	0 (0.0)	0 (0.0)	2 (8.7)	9 (1.7)	0.000
Am1	4 (28.6)	2 (3.6)	0 (0.0)	0 (0.0)	2 (8.7)	8 (1.5)	0.000
Am2	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0.000
Bethesda *N* (%)	10 (71.4)	48 (85.7)	79 (74.5)	51 (15.5)	8 (34.8)	196 (37.1)	0.000
Beth1 CRC <50 years	2 (14.3)	7 (12.5)	11 (10.4)	0 (0.0)	0 (0.0)	20 (3.8)	0.000
Beth2 syn-chronous/metachronous	2 (14.3)	6 (10.7)	12 (11.3)	18 (5.4)	4 (17.3)	42 (7.9)	0.071
Beth3 MSI histology	1 (7.1)	7 (12.5)	5 (4.7)	1 (0.3)	0 (0.0)	14 (2.6)	0.000
Beth4 1° rel with Ca <50 years	3 (21.4)	9 (16.1)	8 (7.5)	4 (1.2)	1 (4.3)	25 (4.7)	0.000
Beth5 two 1° rel or 2° rel with Ca	6 (42.9)	28 (50.0)	56 (52.8)	33 (10.0)	3 (13.0)	126 (23.8)	0.000
1° rel polyps *N* (%)	0 (0.0)	7 (12.5)	4 (3.8)	6 (1.8)	0 (0.0)	17 (3.2)	0.001
2+ Bethesda or polyps	4 (28.5)	9 (16.1)	12 (11.3)	9 (2.7)	0 (0.0)	34 (6.4)	0.000
3+ Bethesda or polyps	0 (0.0)	3 (5.4)	3 (2.8)	1 (0.3)	0 (0.0)	7 (1.3)	0.011
Familial CRC *N* (%)	13 (92.9)	28 (50.0)	41 (38.7)	17 (5.2)	6 (26.1)	105 (19.8)	0.000
PMG criteria *N* (%)	9 (64.3)	31 (55.4)	47 (44.3)	30 (9.1)	6 (23.1)	123 (23.3)	0.000
PMG1 ACMAC	8 (57.1)	25 (44.6)	40 (37.7)	21 (6.4)	5 (21.7)	99 (18.7)	0.000
PMG2 CRC <40 years	0 (0.0)	3 (5.4)	2 (1.9)	3 (0.9)	1 (4.3)	9 (1.7)	NS
PMG3 endo <45 years	0 (0.0)	1 (1.8)	1 (0.9)	1 (0.3)	0 (0.0)	3 (0.6)	NS
PMG4 sebaceous/multiple	2 (14.3)	2 (3.6)	6 (5.7)	11 (3.3)	1 (4.3)	22 (4.2)	NS
PMG5 multiple HNPCC Ca	1 (7.1)	3 (5.4)	3 (2.8)	1 (0.3)	2 (8.7)	10 (1.9)	0.002
Colon screening age *N* (%)							0.000
<30	8 (57.1)	2 (3.6)	2 (1.9)	0 (0.0)	0 (0.0)	12 (2.3)	
30–34	2 (14.3)	6 (10.7)	0 (0.0)	1 (0.3)	0 (0.0)	9 (1.7)	
35–39	1 (7.1)	6 (10.7)	6 (5.7)	0 (0.0)	0 (0.0)	13 (2.5)	
40–44	2 (14.3)	15 (26.8)	17 (16.0)	6 (1.8)	0 (0.0)	40 (7.6)	
45–49	0 (0.0)	14 (25.0)	26 (24.5)	27 (8.2)	0 (0.0)	67 (12.7)	
50	0 (0.0)	11 (19.6)	54 (50.9)	285 (86.4)	0 (0.0)	350 (66.2)	
Missing	1 (7.1)	2 (3.6)	1 (0.9)	11 (3.3)	23 (100.0)	38 (7.2)	

1° rel, first-degree relative; 2° rel, second-degree relative; ACMAC, age and cancer modified Amsterdam criteria; Ca, HNPCC cancer; endo, endometrial cancer; HNPCC, hereditary nonpolyposis colorectal cancer; PMG, provincial medical genetics.

Discussion

This study supports four main conclusions: (i) experience with a population-based familial CRC clinic in NL revealed a response rate (provision of a completed family history questionnaire) of 51%, and the efficiency of genetic counsellor services was poor; (ii) rate of referral to a genetic counsellor was high (27%); (iii) although the degree of family risk varied by age of the proband, risk-specific colonoscopic screening recommendations for family members were necessary even with older probands; (iv) a family history first

Table 3. The clinical and family risk characteristics by age of CRC patient together with the colonoscopy screening recommendations.

	Age group				
	≥75 years	74–65 years	<65 years	Total	
N	144	175	210	529	p value
Family risk *N* (%)					0.001
High	3 (2.1)	2 (1.1)	16 (7.6)	21 (4.0)	
Intermediate–high	27 (18.8)	34 (19.4)	61 (29.0)	122 (23.1)	
Intermediate–low	22 (15.3)	36 (20.6)	24 (11.4)	82 (15.5)	
Low	92 (63.9)	102 (58.3)	106 (50.5)	300 (56.7)	
Male	81 (56.3)	102 (58.3)	122 (58.1)	305 (57.7)	NS
Location *N* (%)					0.034
Eastern	86 (59.7)	116 (66.3)	153 (72.9)	355 (67.1)	
Central	58 (40.3)	59 (33.7)	57 (27.1)	174 (32.9)	
FHS Median (*N*)	1.7	2.1	2.6	2.2	0.000
Interquartile range	1.1–2.8	1.5–3.3	2.0–4.5	1.6–3.8	
Upper quintile *N* (%)	18 (12.5)	24 (13.7)	60 (28.6)	102 (19.3)	
MMRPred median (*N*)	0.1	0.3	0.7	0.4	0.000
Interquartile range	0.0–0.3	0.1–1.3	0.3–3.2	0.1–1.6	
Percentage >1.66	8.6	20.6	36.4	23.7	
Amsterdam *N* (%)	2 (1.4)	0 (0.0)	7 (3.3)	9 (1.7)	0.040
Am1	2 (1.4)	0 (0.0)	6 (2.9)	8 (1.5)	0.072
Am2	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.2)	NS
Bethesda *N* (%)	45 (31.3)	65 (37.1)	84 (40.0)	194 (36.7)	0.242
Beth1 CRC <50 years	0 (0.0)	1 (0.6)	19 (9.0)	20 (3.8)	0.000
Beth2 synchronous/metachronous	16 (11.1)	14 (8.0)	12 (5.7)	42 (7.9)	NS
Beth3 MSI histology	3 (2.1)	0 (0.0)	12 (5.7)	15 (2.8)	0.003
Beth4 1° rel with Ca <50 years	3 (2.1)	14 (8.0)	8 (3.8)	25 (4.7)	0.034
Beth5 Two 1° rel or 2° rel with Ca	30 (20.8)	44 (25.1)	53 (25.2)	127 (24.0)	NS
1° rel polyps *N* (%)	6 (4.2)	3 (1.7)	8 (3.8)	17 (3.2)	NS
2+ Bethesda or polyps	8 (5.6)	8 (4.6)	19 (9.0)	35 (6.6)	NS
3+ Bethesda or polyps	2 (1.4)	1 (0.6)	5 (2.4)	8 (1.5)	NS
FamCRC *N* (%)	28 (19.4)	39 (22.3)	38 (18.1)	105 (19.8)	NS
PMG criteria *N* (%)	25 (17.4)	38 (21.7)	60 (28.6)	123 (23.3)	0.042
PMG1 ACMAC	17 (11.8)	31 (17.7)	51 (24.3)	99 (18.7)	0.012
PMG2 CRC before 40 years	3 (2.1)	5 (2.9)	1 (0.5)	9 (1.7)	NS
PMG3 endo before 45 years	0 (0.0)	2 (1.1)	1 (0.5)	3 (0.6)	NS
PMG4 sebaceous/multiple	7 (4.9)	7 (4.0)	8 (3.8)	22 (4.2)	NS
PMG5 multiple HNPCC Ca	2 (1.4)	3 (1.7)	5 (2.4)	10 (1.9)	NS
Colon screening age *N* (%)					0.00
<30	1 (0.7)	2 (1.1)	9 (4.3)	12 (2.3)	
30–34	3 (2.1)	2 (1.1)	4 (1.9)	9 (1.7)	
35–39	1 (0.7)	4 (2.3)	8 (3.8)	13 (2.5)	
40–44	3 (2.1)	3 (1.7)	34 (16.2)	40 (7.6)	
45–49	5 (3.5)	9 (5.1)	53 (25.2)	67 (12.7)	
50	114 (79.2)	146 (83.4)	90 (42.9)	350 (66.2)	
Now/null	17 (11.8)	9 (5.1)	12 (5.7)	38 (7.2)	
Colon screening frequency *N* (%)					0.00
1–2 years	2 (1.4)	3 (1.7)	9 (4.3)	14 (2.6)	
2–3 years	9 (6.3)	13 (7.4)	34 (16.2)	56 (10.6)	
3–5 years	21 (14.6)	29 (16.6)	56 (26.7)	106 (20.0)	
5 years	102 (70.8)	125 (71.4)	103 (49.0)	330 (62.4)	
Missing	10 (6.9)	5 (2.9)	8 (3.8)	23 (4.3)	

1° rel, first-degree relative; 2° rel, second-degree relative; ACMAC, age and cancer modified Amsterdam criteria; Ca, HNPCC cancer; endo, endometrial cancer; HNPCC, hereditary nonpolyposis colorectal cancer; PMG, provincial medical genetics.

approach to identify the risk of Lynch syndrome was inefficient.

As indicated in the appendix it is unlikely that the higher CRC mortality rate in NL (1), compared to Ontario, is caused by diagnosis at a later stage, or the presence of a higher rate of adverse prognostic factors at baseline, or to diminished survival following diagnosis (Appendix). The implications of these results are that a focus on prevention of CRC is needed in NL. Population-based screening for CRC using faecal

immunohistochemistry (FIT) testing or flexible sigmoidoscopy is associated with reduced mortality (21, 22), but faecal occult blood testing has only just begun in some regions of NL, and is not appropriate for families at high risk. Colonoscopic surveillance in individuals with a family history of CRC has been associated with an 80% reduction of CRC (23). As the province has the highest reported rate of familial CRC in the world (2), CRC surveillance in family members of patients who present with CRC (3) may also decrease the incidence of CRC in NL.

Incident cases with CRC in the population were invited to attend the clinic but only 51% provided a family history sufficient to provide colonoscopic screening recommendations to families. This compares with 61% of incident cases who provided family histories to the NFCCR, a prior research project that required research consent (2). However these proportions contrast with the observation that in Australia only 1% of unaffected people at potentially high risk of CRC reported appropriate screening (24). In addition, the response to other requests (completion of family address and release of information forms) was similar to the family history response rate. The majority of non-responders just had no interest in the service being offered. A higher proportion of non-responders compared to responders were older than 75 years. Their decision may have been misguided since family risk was still quite high in the older age group.

The pedigree assessment by the medical geneticist engendered referrals for genetic counselling in 27% of incident cases. The decision to refer for counselling, or not, in those with intermediate–high *vs* intermediate–low risk family histories, was a clinical decision based on clinical interpretation of the family history. There was little difference in FHS, MMR predict or in the fulfilment of the Bethesda criteria, but there was a difference in the fulfilment of ACMAC criteria. Guidelines exist for the genetic/familial high-risk assessment of CRC but their application to specific families is not clear-cut (25). In particular in NL family size is large, family information is extensive, and clinical judgement is necessary in determining family risk and colonoscopic screening recommendations. Consequently, the classifications of the medical decisions made in this study was those made by an educated, experienced geneticist, incorporating multiple parameters of family risk.

Efficiency in provision of counselling was poor as only 34% of high and intermediate–high-risk families were seen by the genetic counsellor during the duration of the study. This was the result of delays in ensuring accuracy of the family history via communication with the family for release of information consent and in obtaining information from hospitals, plus creation of a large referral wait-list to the genetic counsellor, which also included patients presenting with gynaecological cancer with families at high risk of cancer. The decision not to refer intermediate–low risk patients to a genetic counsellor was driven by limited resources for genetic counselling and the likelihood of further increasing the wait-list. It is possible that this triage has missed some families with Lynch syndrome.

The prevalence of high-risk CRC families was higher in a previous population-based cohort study from Newfoundland (10). When comparing the previous study with the current one, the Amsterdam I or II criteria were fulfilled in 3.7% *vs* 1.7%, familial CRC was present in 31% *vs* 19.8%, and low risk families comprised 52.7% *vs* 57%, respectively. The lower prevalence of high-risk families identified could be the result of screening, as families with previously identified hereditary non-polyposis colorectal cancer have received intensive screening. In fact, both screened males and females with a Lynch syndrome *MSH2* mutations in Newfoundland had a 71% lower risk of colorectal cancer compared to the expected incidence derived from the non-screened control group (13). A study is underway to examine the impact of colonoscopic screening in FCCTX.

Age recommended for starting colonoscopic screening and frequency of colonoscopy is determined predominantly by the family history, and provision of screening recommendations to families at risk of CRC requires expertise. By anecdote, family doctors were pleased to receive letters outlining the recommendations, not only in high-risk families but particularly in families at lower risk. The limitation in financial resources for genetic counselling has suggested we examine predictive models of family risk and of various screening recommendations to determine whether electronic methods would safely improve the efficiency of the provision of recommendations.

We examined the capture of higher risk families by age of the proband. Although the rate of higher risk families, no matter how classified, decreased the older the proband, nonetheless the prevalence was quite high in probands $\geq$75 years: 19.4% had familial CRC, 31.3% fulfilled at least one Bethesda criterion, and screening colonoscopy frequency recommended to family members was greater than every 5 years in 23% of families.

The cost-effectiveness of family history-based CRC screening in Australia was examined using a Markov model. It demonstrated that in people at increased risk due to a strong family history of CRC, five yearly colonoscopy cost Au$12,405 per year gained, with an average life expectancy of 16.1 years (26).

The family history first approach failed to assess 48% of incident cases for LS risk because no family history was provided. However, 36% of these non-responders were over 75 years and at lower risk of having a LS mutation. Of those who responded, 23% fulfilled the local criteria for tumour/genomic DNA cascade testing for LS mutations. If families at risk of LS, as defined by MMR predict, were referred to the genetic counsellor, the proportion of probands referred would have been 24%. The process whereby patients were identified as requiring a tumour/genomic DNA work-up for LS was cumbersome and inefficient: 66% of high/intermediate–high-risk families were waiting to see the genetic counsellor at the end of the study, so no decision on cascade testing could be made. Of the 48 patients seen by the genetic counsellor during the study, 50% were referred for LS testing. Of the 95 patients not seen by a genetic counsellor during the study all subsequently

received recommendations for colonoscopic screening based on the pedigree, but data on those who needed work-up for LS is not yet available. The results of the LS work-up may change screening recommendations. The inefficiency of the process was exacerbated by the further need to send tumour tissue and genomic DNA to Toronto for cascade testing. Efficiency would presumably be improved by narrowing the criteria for referral to a genetic counsellor and/or hiring another genetic counsellor.

An alternate process to the family history first approach for LS identification is the tumour first approach with universal immunohistochemistry testing for the four MMR proteins, and/or microsatellite stability testing, in CRCs at time of initial surgery (27).

Universal tumour MMR testing among CRC probands had a greater sensitivity for the identification of LS compared with multiple alternative strategies, although the increase in diagnostic yield was modest (28).The decision to undertake universal testing will be influenced by the utility of defining MMR deficiency for immunotherapies(29).

As a result of our conclusion that the high CRC mortality rate in NL is likely the result of high CRC incidence, and because the familial CRC rate is high in the province, we recommend development of population-based colonoscopic screening strategies to target families at risk of CRC. Assessment of an accurate pedigree is probably best provided by subject matter experts in a central location, but algorithmic approaches to defining risk should be investigated. The strategy examined in this paper had a response rate of 51% but an inefficient process in the management of high and intermediate risk families. The work-load of the genetic counsellor was too broad given the resources available, even though counselling was limited to high and intermediate–high-risk families. To identify families at high risk of LS a family history first approach in patients who presented with CRC was inefficient, although it may be the only option for screening unaffected persons. A tumour/genomic DNA testing first approach may be better with referral for counselling because of the presence of microsatellite instability and/or deficiency of a MMR protein in the tumour (not caused by methylation).

Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site.

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References

1. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2015. Toronto, ON: Canadian Cancer Society, 2015.
2. Green RC, Green JS, Buehler SK et al. Very high incidence of familial colorectal cancer in Newfoundland: a comparison with Ontario and 13 other population-based studies. Fam Cancer 2007: 6: 53–62.
3. Levin B, Lieberman DA, McFarland B et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology 2008: 134 (5): 1570–1595.
4. Doubem CA. Precision screening for colorectal cancer: promise and challenges. Ann Intern Med 2015: 163: 390–391.
5. Mesher D, Dove-Edwin I, Sasieni P et al. A pooled analysis of the outcome for prospective colonoscopic surveillance foe familial colorectal cancer. Int J Cancer 2014: 134: 939–947. DOI: 10.1002/ijc.28397.
6. Van der Meulen-de Jong AE, Morreau H, Becx MC et al. High detection rates of adenomas in familial colorectal cancer. Gut 2011: 60 (1): 73–76. DOI: 10.1136/ gut.2010.217091.
7. Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC). Gastroenterology 1999: 116 (6): 1453–1456.
8. Lindor NM, Rabe K, Petersen GM et al. Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. JAMA 2005: 293 (16): 1979–1985.
9. Warden G, Harnett D, Green J et al. A population-based study of hereditary non-polyposis colorectal cancer: evidence of pathologic and genetic heterogeneity. Clin Genet 2013: 84: 522–530.
10. Woods MO, Hyde AJ, Curtis FK et al. High frequency of hereditary colorectal cancer in Newfoundland likely involves novel susceptibility genes. Clin Cancer Res 2005: 11 (19): 6853–6861.
11. Vasen HF, Möslein G, Alonso A et al. Recommendations to improve identification of hereditary and familial colorectal cancer in Europe. Fam Cancer 2010: 9 (2): 109–115.
12. Stuckless S, Parfrey PS, Woods MO et al. The phenotypic expression of three MSH2 mutations in large Newfoundland families with lynch syndrome. Fam Cancer 2007: 6 (1): 1–12.
13. Stuckless S, Green J, Morgenstern M et al. Impact of colonoscopic screening in male and female Lynch syndrome carriers with an MSH2 mutation. Clin Genet 2012: 82 (5): 439–445.
14. Watkins KE, Way CY, Fiander JJ et al. Lynch syndrome: barriers to and facilitators of screening and disease management. Hered Cancer Clin Pract 2011: 9: 8. DOI: 10.1186/1897-4287-9-8.
15. Umar A, Boland CR, Terdiman JP et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004: 96 (4): 261–268.
16. Gregory DM, Parfrey PS. The breast cancer hormone receptor retesting controversy in Newfoundland and Labrador, Canada: lessons for the health system. Healthc Manage Forum 2010: 23 (3): 114–118.
17. Yang Q, Khoury MJ, Rodriguez C, Calle EE, Tatham LM, Flanders WD. Family history score as a predictor of breast cancer mortality: prospective data from the cancer prevention study II, United States 1982–1991. Am J Epidemiol 1998: 147 (7): 652–659.
18. MMR Predict Calculator. University of Edinburg and MRC Human Genetics Unit, Edinburgh, Scotland. http//hnpccpredict.hgu.mrc.ac.uk/ 2014.
19. Chakraborty R, Weiss KM, Majumder PP, Strong LC, Herson J. A method to detect excess risk of disease in structured data: cancer in relatives of retinoblastoma patients. Genet Epidemiol 1984: 1 (3): 229–244.
20. Green RC, Parfrey PS, Woods MO, Younghusband HB. Prediction of Lynch syndrome in consecutive patients with colorectal cancer. J Natl Cancer Inst 2009: 101: 331–340.
21. Health Quality Ontario. Fecal occult blood test for colorectal cancer screening: an evidence based analysis. Ont Health Technol Assess Ser 2009: 9 (10): 1–40.
22. Elmunzer BJ, Hayward RA, Schoenfeld PS et al. Effect of flexible sigmoidoscopy-based screening on incidence and mortality of colorectal cancer: a systematic review and meta-analysis of randomized controlled trials. PLoS Med 2012: 9: e1001352.
23. Dove-Edwin I, Sasieni P, Adams J, Thomas HJ. Prevention of colorectal cancer by colonoscopic surveillance in individuals with a family history

with colorectal cancer: 16 years prospective follow-up study. BMJ 2005: 331 (7524): 1047.
24. Ouakrim A, Boussioutas A, Lockett T et al. Screening practices of unaffected people at familial risk of colorectal cancer. Cancer Prev Res (Phila) 2012: 5: 240–247.
25. National Comprehensive Cancer Network, NCCN. Clinical Practice Guidelines in Oncology. Genetic/Familial High-risk Assessment: Colorectal. Version 1, NCCN, Org, 2016.
26. Ouakrim DA, Boussioutas A, Lockett T, Hopper JL, Jenkins MA. Cost-effectiveness of family history-based colorectal cancer screening in Australia. BMC Cancer 2014: 14: 261. DOI: 10.1186/1471-2407-14-261.
27. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Genet Med 2009: 11: 35–41.
28. Moreira L, Balaguer F, Lindsor N et al. Identification of Lynch Syndrome among patients with colorectal cancer. JAMA 2012: 308: 1555–1565.
29. Westdorp H, Fennemann FL, Weren RD et al. Opportunities for immunotherapy in microsatellite instable colorectal cancer. Cancer Immunol Immunother 2016: 65: 1249–1259. DOI: 10.1007/s0022-016-1832-7.
30. Cotterchio M, McKeown-Eyssen G, Sutherland H et al. Ontario familial colon cancer registry: methods and first-year response rates. Chronic Dis Can 2000: 21: 81–86.
31. Easson AM, Cotterchio M, Crosby JA et al. A population – based study of the extent of surgical resection of potentially curable colon cancer. Ann Surg Oncol 2002: 9 (4): 380–387.

Appendix

Objective

To determine whether the increased mortality in NL was the result of poor survival after diagnosis (rather than increased CRC incidence) we compared adverse prognostic indicators at diagnosis and survival in incident CRC patients in NL and in Ontario.

Methods

Clinical and outcome data were obtained from the Newfoundland Familial Colorectal Cancer Registry NFCCR and Ontario Familial Colorectal Registry (OFCCR) that recruited population-based series of incident cases of colorectal cancer among adults between 20 and 74 years of age. NL identified patients who presented with CRC between 1 January 1999 and 31 December 2003, and Ontario did so for the period between 1 January 1997 and 31 December 2000. OFCCR included 20% of low familial risk cases whereas NFCCR included all low risk cases. Participant recruitment and details regarding data collection have been previously described (2, 30). Once consent was obtained, individuals provided demographic information, family history for CRC, and epidemiological data, and also consented to providing a DNA sample and access to tissue blocks. Prognostic indicators on each member of the NFCCR and OFCCR were obtained through a series of standardized chart reviews including pathology reports, operative records, oncology progress notes, and general medical records. Pathology reports were used to confirm patient diagnosis information.

From the NFCCR, 739 incidence cases were recruited, comprised of 510 colon and 229 rectal cancer patients. On behalf of decreased eligible participants, proxies provided consent, of whom, 232 were enrolled in this manner. OFCCR registrants included 1185 incident cases comprised of 906 colon and 279 rectal cancer patients. The OFCCR did not request proxies to consent, which resulted in systematic exclusion of many patients who died within 1–2 years of diagnosis. The proportion of stage IV disease was 8%, yet one would expect up to 25% (31). Therefore, survival analyses and multivariate modelling was undertaken for stage I–III cases only. We compared other baseline characteristics (age at diagnosis, sex, and MSI status) and survival in the NFCCR and OFCCR case series. A minimum 4-year follow-up was completed for all cases from both provinces.

NL cases included in this study were compared to 409 NL patients that declined study entry to determine if the study group was representative of the population. Variables available for inclusion of non-enrolled cases were colon or rectal cancer diagnosis, sex, and age at diagnosis. No significant difference was found between enrolled and non-enrolled cases.

All data were analysed using the Statistical Package for Social Sciences (SPSS) Version 18. Survival analysis was conducted, from the date of diagnosis to death, with censoring at the time of last follow-up. Overall survival comparing the two provinces, stratified by stage and anatomic location, was undertaken using the log rank test. The impact of province on survival was assessed using multivariate cox regression analysis to estimate hazard ratios (HR) and 95% confidence intervals (CI). Prognostic variables in this model included sex, stage of disease, age at diagnosis, and MSI status.

Results

In the NFCCR 24.3% of colon and 12.7% of rectal cancer patients had stage 4 disease at diagnosis (Table 1). Using stage I–III colon cancers as the denominator in NL 18.9% were diagnosed at stage I, 44.3% at stage II and 36.8% at stage III, whereas the respective proportions in OFCCR were 21.2%, 46.2% and 32.6%. For rectal cancer in NL 19.5% were diagnosed at stage I, 37.5% at stage II, and 43% at stage III, with the respective proportions in Ontario being 30.7%, 30.3% and 39.0% (Table 1). Age at diagnosis and proportion with MSI-high tumours were comparable in NFCCR and OFCCR cohorts.

Adjuvant treatment was administered to colon cancer patients diagnosed at stage III disease in 89% of NFCCR patients and in 96% of OFCCR patients. In rectal cancer patients diagnosed at stage II and III disease, 89% in NFCCR and 86% in OFCCR received adjuvant treatment. Survival by stage and anatomical location in NFCCR and OFCCR cases showed no significant differences in survival for stage I–III (Table 2) except for colon cancer patients diagnosed at stage II, who had significantly better survival in NL compared to Ontario (HR = 0.62, 95% CI, 0.44–0.87).

In a multivariate model of stage I–III patients, independent of prognostic factors at diagnosis the survival of both colon and of rectal cancer patients was

significantly better in NL, than in Ontario (for colon HR 0.79, 95% CI 0.63, 0.99; for rectum HR 0.66, 95% CI 0.48, 0.92).

Conclusion

Whether the increased CRC mortality in NL is the result of increased CRC incidence, rather than more adverse prognostic factors at diagnosis, or diminished survival by stage after diagnosis, is an important question, as it may determine whether increased resources should be allocated to screening.

We conclude that in NL the high CRC mortality rate is likely the result of the high CRC incidence, which together with the high rate of familial CRC, provides a rationale for a population-based approach to the provision of colonoscopic screening recommendations in families at risk of CRC.