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ORIGINAL ARTICLE

Risk of multiple colorectal cancer development depends on age and subgroup in individuals with hereditary predisposition

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Abstract

Development of multiple colorectal cancers (CRCs), synchronously or metachronously, is associated with hereditary predisposition for cancer and accurate risk estimates of multiple tumour development are relevant to recommend rational surveillance programs. A cross-sectional study design was used to estimate the risks of synchronous CRC (SCRC) and metachronous CRC (MCRC) based on data from the National Danish Hereditary Nonpolyposis Register. In total, 7100 individuals from families within the subgroups Lynch syndrome, familial CRC (FCC) and moderate risk were used with estimates relative to a non-hereditary population control cohort. SCRC was diagnosed in 7.4% of the Lynch syndrome cases, in 4.2% of FCC cases and 2.5% of the moderate risk cases, which translated to relative risks of 1.9–5.6. The risk of MCRC was distinctively linked to Lynch syndrome with a life-time risk up to 70% and an incidence rate ratio of 5.0. The risk of SCRC was significantly increased in all subgroups of FCC and hereditary CRC, whereas the risk of MCRC was specifically linked to Lynch syndrome. These observations suggest that individuals with FCC or hereditary CRC should be carefully screened for second primary CRC at the time of diagnosis, whereas intensified surveillance for second primary CRC is motivated in Lynch syndrome with lower-intensity programs in families with yet unidentified genetic causes.

Keywords HNPCC · Lynch syndrome · Colonoscopy · Cross-sectional study · Metachronous neoplasms · Synchronous neoplasms · Multiple primary neoplasms

Introduction

Genetic factors are estimated to contribute to 20–25% of colorectal cancer (CRC) development [1]. The genetic landscape consists of high-penetrant germline genomic alterations that cause polyposis syndromes (e.g. *APC* and *MUTYH*) and genomic maintenance deficiency syndromes such as Lynch syndrome with mismatch repair (MMR) gene variants in *MLH1, MSH2, MSH6, PMS2* and the rarer variants in *POLE, POLD1* and *NTHL1* [2]. The genetically defined syndromes account for approximately 5% of the cases [3]. This implies that in the majority of cases with a pedigree suggestive of familial aggregation of CRC, no disease-predisposing variant can be identified and in this group unidentified major genes are estimated to cause one-third to half of the currently unexplained cases [4].

Multiple primary CRC can develop at the same time (synchronously) or over time (metachronously). Synchronous CRC (SCRC) is important to diagnose prior to surgery to define relevant resection margins, whereas the risk of metachronous CRC (MCRC) will influence recommendations for surveillance and may define populations suitable for prevention initiatives such as chemoprevention or extended primary surgery in addition to colonoscopy. Genetic predisposition, inflammatory bowel disease and environmental

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influences constitute the main causes of multiple primary CRC [5]. First-degree relatives of patients with CRC have been estimated to be at a 1.68–2.34 fold risk of CRC, which may suggest a familial predisposition beyond the rare hereditary cancer syndromes [6, 7]. Data on the risk of SCRC and MCRC in families without an identified genetic cause are scarce and recommendations for surveillance in these subgroups vary between centres. Based on the link between multiple CRC and familial predisposition and demonstration of multiple adenomas in 1.9% and high-risk adenomas in 8.7% of individuals with familial CRC (FCC), 5-yearly colonoscopies have been suggested to be relevant [5, 6, 8].

SCRC is diagnosed in 1–4% of patients with CRC, and development of synchronous colorectal neoplasia is a hallmark of inflammatory bowel disease and FCC and hereditary CRC [9–11]. SCRC has been associated with higher age, male sex, precursor adenomas, microsatellite instability and proximal location and also tend to be located in the same bowel segment [11–13]. Polyposis syndromes such as sessile serrated polyposis and familial adenomatous polyposis are characterized by synchronous neoplasia and among patients with SCRC 2–21% has been estimated to carry disease-predisposing genetic variants linked to familial adenomatous polyposis [9, 14].

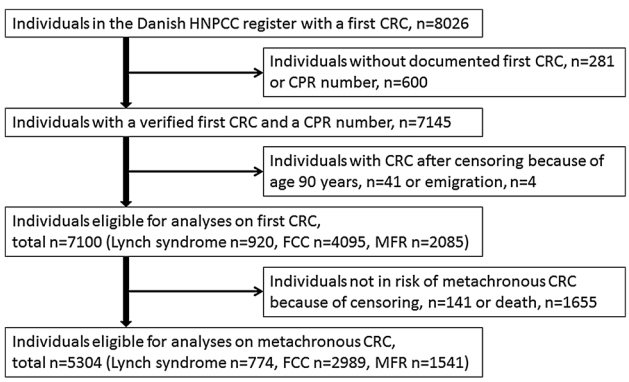
MCRC has been described to develop in 1.5-9% of patients with CRC with estimates around 3% after 10 years of follow-up [6, 10, 15, 16]. A high frequency of MCRC has been documented in Lynch syndrome with cumulative risks of 15–20% after 5–10 years of follow-up and up to 69% at 30 years of follow-up [17, 18]. The risk of MCRC depends on current age with an estimated cumulative risk of 36% from age 40 to 70 years, 31% from age 50 to 70 years, and 19% from age 60 to 70 years [19]. In individuals with Lynch syndrome, subtotal colectomy at the first CRC has been reported to be associated with significantly decreased risk of MCRC at 0–10% after 8–25 years of follow-up [18, 20, 21].

The Danish Hereditary Nonpolyposis Cancer (HNPCC) Register has collected data on more than 7000 families with a suspected inherited increased risk of CRC and thus allows for robust estimates in various subgroups of FCC and hereditary CRC. Based on these data, we determined the frequencies and risks of SCRC and MCRC in various FCC and hereditary CRC subgroups with comparison to a sporadic control cohort from the general population.

Patients and methods

The Danish national HNPCC Register was established in 1991. Clinicians and laboratories report data on family history, diagnosis (adenomas and cancers), surgical procedures and genetic test results. Based on these data, the families are classified as Lynch syndrome (disease-predisposing MMR gene variants), FCC or moderate familial risk of CRC (MFR). FCC fulfils the Amsterdam I or II criteria [22] with or without defined modifications as previously described [23]. MFR are defined either by one individual in the family diagnosed with CRC before age 50 years or by two first-degree relatives diagnosed with CRC after age 50. Detailed data by family subgroup are available in Supplementary Table 1 and Supplementary Fig. 1. The data are based on reports from hospitals, general practitioners, private clinics, specialized care and pathologic and genetic diagnostic laboratories.

Based on unique individual Central Population Registry (CPR) numbers, available since 1968, data from various national registers can be linked to ensure completeness and information on e.g. death and emigration. In Denmark, surveillance for individuals with Lynch syndrome follows international guidelines with biennial colonoscopies. During the study period, biennial colonoscopies were recommended also to individuals in the FCC subgroup, whereas individuals in MFR families were recommended colonoscopy with 5-year intervals. Data were extracted from the HNPCC Register on 2nd June 2016 and merged with data on CRC diagnosed 1943–2014 from the Danish National Cancer Register and with data on surgical procedures since 1977 from the Danish National Patient Register. Eligible cancers were verified based on pathology reports and/or clinical records (Fig. 1). Data on birth, death and emigration were retrieved from the CPR (Fig. 1). Follow-up was censored at the time of emigration, proctocolectomy, age 90 years or end of study, whichever came first; and for the analyses regarding MCRC a follow-up time of minimum 1 year was required (Fig. 1). Extra-colonic cancer development was not considered in the analyses.



HNPCC, hereditary non-polyposis colorectal cancer; FCC, familial colorectal cancer; MFR, moderate familial risk; CPR, Central Population Registry; CRC, colorectal cancer

Fig. 1 Flow chart summarizing eligibility, inclusion and exclusion criteria in the study

A sporadic cohort was generated for comparison of the frequencies and the risks of multiple CRCs. We retrieved data on all individuals in the Danish population in 2008–2012 from Statistics Denmark, stratified on sex and 1-year age intervals. All CRCs were collected from the Danish National Cancer Register. Individuals with inherited risk of CRC, which was defined as individuals registered in the Danish national HNPCC Register or in the Danish National Familial Adenomatous Polyposis Register and all individuals diagnosed with CRC before age 50, were subtracted to generate a population-based sporadic cohort that excluded familial and hereditary cases as far as possible.

Register-based studies in Denmark are not subject to ethical review, but the study database and the register linkage were approved by the Danish Data Protection Agency (AHH-2014-008).

Definitions

The study encompassed the time period 1968–2014 to allow for linkage between the HNPCC Register and other relevant Danish national registers, but data from the Danish Cancer Register was used from 1943 to classify CRCs in the study period as first or subsequent CRCs and to account for resected bowel segments. Cases where information on surgical procedures was missing were assigned as segmentally resected, motivated by this being the standard procedure. SCRC was defined as more than one CRC diagnosed within 1 year of a primary CRC. MCRC was defined as a new primary CRC diagnosed more than 1 year after a CRC. Segmental resection was defined as right hemicolectomy, transverse resection, left hemicolectomy, sigmoid resection or rectum resection. Extended surgery was defined as subtotal or total colectomy. Proximal and distal tumour localizations were defined in relation to the splenic flexure. Absolute risk of MCRC was defined as the risk of being diagnosed with MCRC before the age of 90 with death as competing risk and conditioned on the individual not dying from a previous CRC.

Statistical analysis

Age at diagnosis was compared with the general linear model procedure in SAS 9.4. Distribution of all other demography variables was compared by the Pearson chi-squared test excluding unknowns. The proportion of SCRC at the first and subsequent CRC events was compared between subsets by the Pearson chi-squared test and exact confidence limits calculated. The proportion of SCRC per CRC event within a subset was analysed by the Cochran–Armitage trend test in SAS 9.4. Relative risk (RR) of SCRC was calculated by dividing the proportion of SCRC in this study with the proportion found in the sporadic cohort. Person years at risk of MCRC were calculated from 1 year after the first CRC or April 1968 whichever came last. IRs of MCRC were calculated in age intervals by sex and family subgroup. Incidence rate ratios (IRRs) adjusted for age and sex were calculated per family subset using Poisson regression and including time at risk for each stratum as an offset by comparison with the age- and sex-specific IRs of MCRC in the sporadic cohort. Absolute risk of MCRC up to age 90 was estimated by sex and attained age with death as a competing risk. Age specific mortality rates for the general population in 2008–2012 were retrieved from Statistics Denmark and probabilities for each of the three outcomes death, MCRC or entering the next age group without an event were calculated for each age group from 25 to 89 years of age. Probabilities were calculated from incidence and mortality rates using standard formulas for the Poisson distribution. The absolute risks for attained ages were calculated backwards through age using actuarial principles to estimate the risk of MCRC before age 90 or death, and cumulative incidence of MCRC at age 70 was calculated as time from first CRC to first MCRC with death as a competing event. These statistical analyses were performed in *R*-3.3.3 [24]. The level of statistical significance was set at $p < 0.05$.

Results

In the study population, 7100 individuals from 3174 families developed at least one primary CRC (Table 1; Supplementary Table 1). The median age at onset of the first CRC was significantly lower in Lynch syndrome (median age 50.5 years) than in the other subgroups (65.3 in FCC and 61.3 in MFR, $p < 0.0001$). Tumour location was more often in the proximal colon in the Lynch syndrome subset (50.1%) compared to FCC and MFR (25.1 and 26.8%, $p < 0.0001$). Extended colonic resection was more often performed in cases with Lynch syndrome (13.3%) than in the other subgroups (2.8–3.3%, $p < 0.0001$). Also the 1-year overall survival rate was more favourable in the Lynch syndrome subgroup (87.0%) compared to FCC (74.6%) and MFR cases (76.4%) though these figures were not adjusted for stage ($p < 0.0001$; Table 1; Supplementary Table 1).

SCRC was diagnosed in 7.4% of the Lynch syndrome cases, in 4.2% of FCC and in 2.5% of MFR families, which implies a significantly higher rate in the former subgroup ($p < 0.0001$). Compared to the sporadic cohort, all three hereditary and familial subgroups showed significantly increased risks for SCRC with RRs of 5.6, 3.2 and 1.9 respectively (Table 2). The frequencies of SCRC increased with the number of MCRC events and was observed in 4.1% at the first CRC, 8.3% at the second primary CRC and 20.4% at the third/fourth primary CRC ($p < 0.0001$, Table 2).

Table 1 Summary of clinical characteristics in the different study cohorts

	Total study	Lynch syndrome	Familial colorectal cancer	Moderate familial risk	p-values
Families, n (%)	3174 (100.0)	347 (10.9)	1462 (46.1)	1365 (43.0)	–
Individuals with CRC, n (%)	7100 (100.0)	920 (13.0)	4095 (57.7)	2085 (29.4)	–
Sex, men, n (%)	3584 (50.5)	523 (56.9)	2035 (49.7)	1026 (49.2)	0.0002
Median age at first CRC (1Q–3Q)	62.4 (50.7–72.2)	50.5 (39.7–61.3)	65.3 (55.2–74.0)	61.3 (49.3–71.5)	< 0.0001
Localization of first CRC					
Proximal colon, n (%)	2049 (28.9)	461 (50.1)	1029 (25.1)	559 (26.8)	< 0.0001
Distal colon/rectum, n (%)	4581 (64.5)	363 (39.5)	2772 (67.7)	1446 (69.4)	
Unspecified, n (%)	470 (6.6)	96 (10.4)	294 (7.2)	80 (3.8)	
Surgery at first CRC					
Extended resection[a], n (%)	315 (4.4)	122 (13.3)	134 (3.3)	59 (2.8)	< 0.0001
Segmental resection, n (%)	4838 (68.1)	599 (65.1)	2811 (68.6)	1428 (68.5)	
No resection/unspecified, n (%)	1947 (27.4)	199 (21.6)	1150 (28.1)	598 (28.7)	

CRC colorectal cancer, *1Q* first quartile, *3Q* third quartile

[a]Proctocolectomy or (sub)total colectomy

Table 2 Synchronous CRC in the different study cohorts in relation to metachronous CRC

	Total study	Lynch syndrome	Familial colorectal cancer	Moderate familial risk	p-values
Fraction of patients with SCRC at first CRC, n (%)	293/7100 (4.1)	68/920 (7.4)	172/4095 (4.2)	53/2085 (2.5)	< 0.0001
RR compared to background population (95% CI)	3.1 (2.7–3.7)	5.6 (4.3–7.3)	3.2 (2.6–3.9)	1.9 (1.4–2.6)	
Fraction of patients with SCRC at first MCRC, n (%)	31/372 (8.3)	15/181 (8.3)	9/134 (6.7)	7/57 (12.3)	0.44
RR compared to background population (95% CI)	2.3 (1.4–3.9)	2.3 (1.2–4.3)	1.9 (0.9–3.9)	3.4 (1.5–7.6)	
Fraction of patients with SCRC at subsequent MCRC, n (%)	10/48 (20.4)	9/44 (20.5)	1/4 (25)	0 (–)	1
Cochran–Armitage trend test (p-value)	< 0.0001	0.015	0.052	< 0.0001	

CRC colorectal cancer, *MCRC* metachronous colorectal cancer, *RR* relative risk, *SCRC* synchronous colorectal cancer

Among the 7100 patients with primary CRC, 5304 patients were eligible for analyses of the risk of MCRC. No patients were lost to follow-up, but 2 (0.04%) patients were censored at the date of emigration. In total, 471 MCRCs developed in 383 individuals. The proportion of patients with MCRC was 24.1% in Lynch syndrome, 5.0% in FCC and 4.3% in MFR. The age- and sex-adjusted IRRs compared to the sporadic cohort were 5.0 in Lynch syndrome, 1.1 in FCC and 1.2 in MFR. The IRR was only significantly increased in the Lynch syndrome subgroup (Table 3). In Lynch syndrome, the risk was further analysed in relation to disease-predisposing genes with IRRs of 5.0 for *MLH1*, 5.8 for *MSH2* and 2.5 for *MSH6* mutation carriers (Table 3). We did also analyse the risk in relation to surgical treatment of the first CRC and found an IRR of 5.5 after segmental resection and 0.9 after total/subtotal colectomy, corresponding to an IRR between the two treatments of 5.9 (2.5–19.1) (Table 3). In order to estimate the absolute risk of MCRC in the age span 25–90 years with death as competing risk, IRs and mortality rates were summarized within each age interval (Fig. 2; Supplementary Table 2). The IRs of MCRC relative to the sporadic cohort was significantly increased only in the Lynch syndrome subgroup and applied for both sexes and below age 80 (Supplementary Table 2). The absolute risk up to age 90 or death was 67.7% for men and 70.5% for women who developed their first primary CRC before age 29. With increasing age the absolute risk of MCRC decreases due to less time left until age 90 or death, leaving a risk of MCRC at 41.0% for men and 46.5% for women with Lynch syndrome and a first CRC at or before age 60. Increased absolute risks applied to all MMR genes except for *PMS2*. The risk was lower for carriers of disease predisposing variants in *MSH6* than in *MLH1* and *MSH2* before age 60–70, but after that age the risks were at similar level (Fig. 3). Extended surgical

Table 3 Metachronous CRC in the different study cohorts

	Total	Lynch syndrome	Familial colorectal cancer	Moderate familial risk
Individuals at risk of MCRC, n (% of patients with first CRC)	5304 (74.7)	774 (84.1)	2989 (73.0)	1541 (73.9)
PYRS, years (%)	38,021 (100.0)	8054 (21.2)	21,490 (56.5)	8478 (22.3)
Events of MCRC, n (%)	471 (100.0)	254 (53.9)	153 (32.5)	64 (13.6)
IRR[a] for MCRC relative to sporadic MCRC (95% CI)	1.7 (1.5–1.9)	5.0 (4.2–6.0)	1.1 (0.9–1.3)	1.2 (0.9–1.5)
IRR[a] for MCRC by gene in Lynch syndrome (95% CI)				
MLH1		5.0 (3.9–6.4)		
MSH2		5.8 (4.7–7.2)		
MSH6		2.5 (1.6–3.6)		
PMS2		1.0 (0.1–4.3)		
IRR[a] for MCRC by surgery in Lynch syndrome (95% CI)				
Segmental resection		5.5 (4.6–6.7)		
(Sub)total colectomy		0.9 (0.3–2.2)		

CRC colorectal cancer, *IRR* incidence rate ratio, *MCRC* metachronous colorectal cancer, *PYRS* person years at risk of metachronous CRC

[a]Age- and sex adjusted

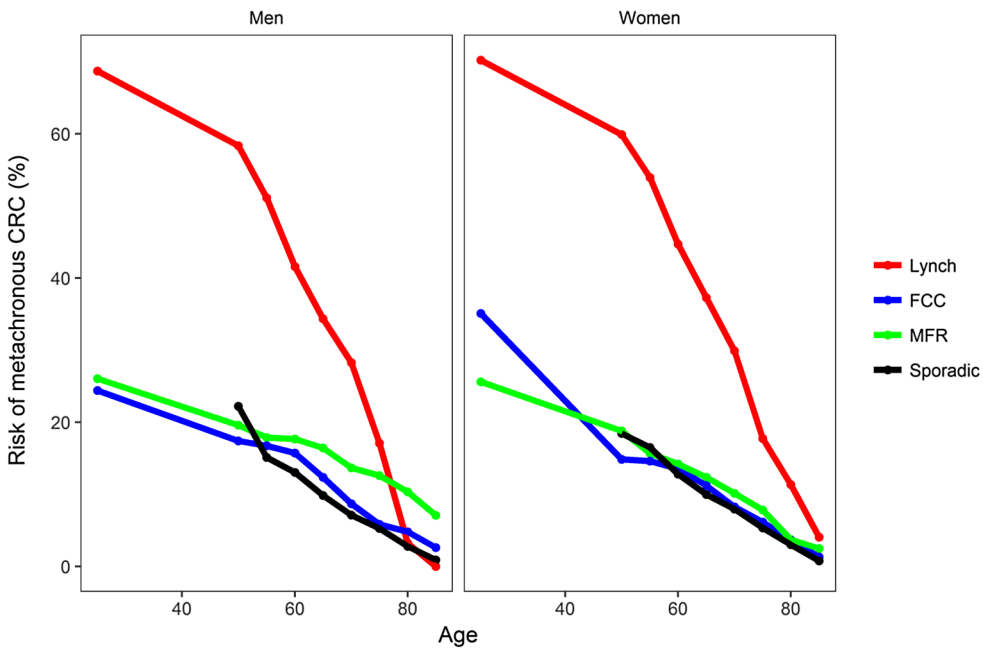


Fig. 2 Age-specific absolute risk estimates of MCRC up to age 90 for men and women with Lynch syndrome (Lynch), familial colorectal cancer (FCC), moderate risk (MFR) and for the sporadic population cohort (Sporadic). (Color figure online)

resection as treatment for the first CRC gave the largest absolute risk reduction in the youngest patients (from 74.7 to 11.2% in men and from 74.9 to 34.0% in women) with decreasing relative benefit at higher age (Fig. 3). Cumulative incidence of MCRC until age 70 was 43.0% (95% CI 9.6–76.5%) in Lynch syndrome, 5.2% (95% CI 3.2–11.5%) in FCC, and 4.1 (95% CI 2.3–8.6%) in MFR.

Discussion

Robust risk estimates provide a basis for development of precision medicine in FCC and hereditary CRC. Gene, age and gender-based surveillance programs would be beneficial to rationalize surveillance [25]. At genetic

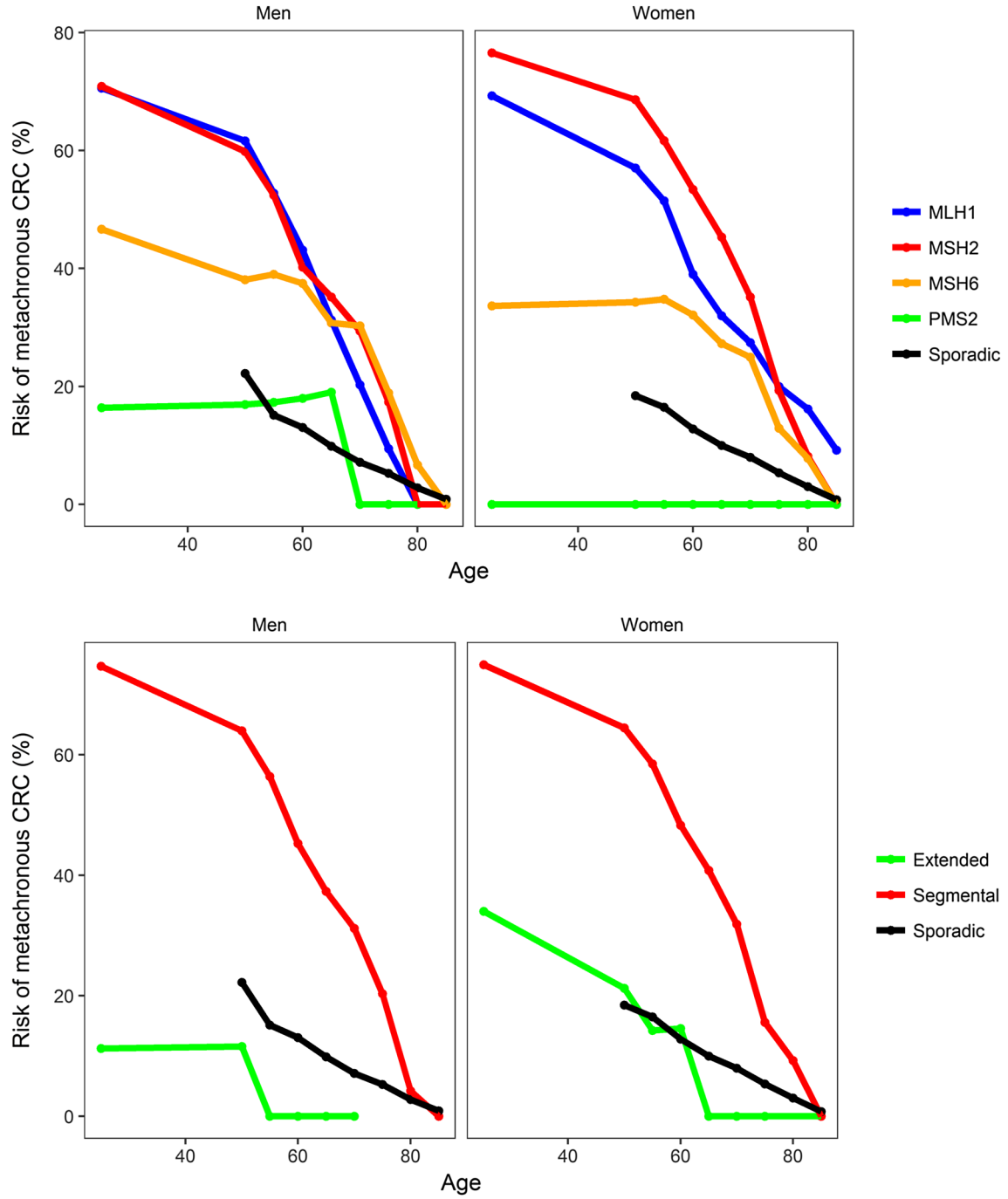


Fig. 3 Top: age-specific absolute risk estimates of MCRC up to age 90 for men and women with Lynch syndrome according to the 4 MMR genes *MLH1* (blue), *MSH2* (red), *MSH6* (orange) and *PMS2* (green) and the background population (black). Bottom: risk estimates in relation to type of surgical treatment for the first CRC with extended resection (green) and segmental resection (red). (Color figure online)

counselling, accurate risk estimates are especially challenging in individuals with a familial aggregation of CRC without an identified genetic variant. This led us to estimate the risks of SCRC and MCRC in the three major subgroups Lynch syndrome, FCC and MFR with comparison to a population-based sporadic cohort. Our data support the notion that a distinct risk profile with clearly increased risks for SCRC and MCRC apply to Lynch syndrome (Tables 2, 3) [26]. SCRC has been reported to occur in 5–25% of the first primary CRC in individuals with Lynch syndrome [27–29] and we support a risk in the lower range of this estimate with 7.1% SCRC diagnosed. The increased

risk of multiple CRCs in Lynch syndrome applies predominantly to MCRC, which in the Danish cohort were found to develop in 24.1% of the patients after a mean follow-up time of 10.4 years with a cumulative incidence of 43% up to age 70. Our observations in the Lynch syndrome cohort support previous results with cumulative risks ranging from 6 to 22% after 10 years, 41 to 47% at 20 years and 62 to 69% at 30 years and up to 36% from age 40 to 70 years [15, 17, 19, 21, 28, 30, 31]. The somewhat higher risk estimates identified in our cohort could be explained by differences in selection criteria, variable definitions of follow-up times and differences in the statistical approaches. The age- and sex-adjusted IRR for MCRC relative to the sporadic cohort was 5.0. The life-time risks of MCRC in Lynch syndrome was 67.7% for men and 70.1% for women with their first CRC below age 29, which compares well to the 30-year cumulative incidences of 69% reported by Win et al. [17].

The choice of surgery for CRC in Lynch syndrome is debateable as there is no grade-1 evidence for performing extended resection versus segmental resection. Extended bowel resections have been linked to low (up to 10%) frequencies of MCRC [18–20, 27]. At the same time, total or subtotal colectomy has implications on functional outcome [19]. Current study data are not readily comparable since factors such as age at diagnosis and death as competing risk have been handled differently in the analyses. Our analyses have accounted for these factors and demonstrate decreased life-time risk of MCRC in both sexes to maximum 11.2 and 34.0% for men and women. The IRR of MCRC was 5.9 after segmental resection compared to extended resection, which corresponds well with reports of odds ratio at 4.0, hazard ratio at 5.0 and RR at 8.6 [18–20]. Patients with Lynch syndrome should thus be informed of a high risk of MCRC and the need for life-long surveillance.

The disease-predisposing MMR gene may also influence the risk of MCRC in Lynch syndrome and we demonstrate a two times higher life-time risk in patients with disease-predisposing variants in *MLH1* or *MSH2* compared to *MSH6* due to a higher risk before the age of 60–70 years (Fig. 3). Previous studies on the impact from the different genes on the risk of MCRC have reached partly different conclusions, though a lower risk has been documented in *MSH6*, which is compatible with a lower penetrance and a higher age at onset of CRC in this subgroup [28, 32].

In the FCC and MFR subgroups, SCRC occurred in 4.2 and 2.5% of patients with a first CRC compared to 1.3% in the sporadic cohort, which corresponds to RRs of 3.2 and 1.9, respectively. The significant difference between these groups and the general population, albeit limited in absolute numbers, may reflect the exclusion of familial and hereditary cases from the general population sample to which they contribute in most comparative studies. This is also reflected in general population estimates of SCRC that have generally been 3–4% [9–11, 33]. The higher frequency of SCRC linked to subsequent MCRC needs further investigation, but could reflect increased tendency for multiplicity with age, environmental exposure and influence from yet unidentified epigenetic/genetic defects. SCRC may also constitute a marker of MCRC development with a hazard rate of 2.7 and RR at 13.9 identified [10, 16]. Though an association between MCRC and SCRC exists, analyses of somatic alterations suggest that the tumorigenic pathways may differ with a strong concordance in MSI status and molecular alterations between SCRC, suggestive of a stronger influence from environmental factors herein [34–36]. In contrast, genetic factors may play a stronger role in MCRC, which is also supported by the high risk of MCRC in the Lynch syndrome subgroup in our study.

The risk of MCRC in FCC and MFR was not significantly different from the sporadic cohort with MCRC diagnosed in 5.0 and 4.3% of the patients, respectively. An overall lower cancer incidence has been documented in FCC families compared to Lynch syndrome [37]. The findings in the FCC and the MFR subgroups were similar; supporting that similar clinical guidelines can be applied in these groups. Similar frequencies of adenomas and outcome of colonoscopy in FCC Type X and in families with late onset CRC has previously been demonstrated, suggesting that these groups may benefit from common clinical guidelines [8].

Strengths of the study include use of population-based, complete, validated and enriched data, based on National Health Register linkage. The comparative general population cohort has been generated after exclusion of familial and hereditary cases, which is unique to our study. Herein, age-specific mortality rates from the same population were imported to provide unbiased and comparable estimates of the absolute risk of MCRC up to age 90 in the various subgroups. Long-term (47 years) follow-up also allow for robust risk estimates. Limitations include a retrospective study design and restricted sample sizes for the oldest age groups and for carriers of pathogenic *PMS2* variants. Lack of data on adherence to surveillance and outcome of colonoscopies may also influence outcome. In principle, colonoscopic surveillance has since the mid-1990s been recommended with 2-year intervals in Lynch syndrome and FCC and with 5-year intervals in moderate risk families. Following CRC, a standardized surveillance program is initiated regardless of family history of CRC, so systematic differences that influence SCRC and MCRC are not expected. Further, data on inflammatory bowel disease were not available, though unlikely to have different impact in the various subgroups.

In summary, we demonstrate an increased prevalence of SCRC in all three subsets of hereditary CRC, and an increased risk of MCRC only in the Lynch syndrome subset. The increased incidence of SCRC serves as a reminder of

careful evaluation of the entire colorectum prior to CRC surgery. The risk of MCRC was increased in Lynch syndrome, but not in the FCC and MFR subsets, which has implications for choice of surgery and follow-up strategies and intervals.

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