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Adenoma and colorectal cancer risks in Lynch syndrome, Lynch-like syndrome and familial colorectal cancer type X

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Abstract

Lynch syndrome (LS), Lynch-like syndrome (LLS) and familial colorectal cancer type X (FCCX) are different entities of familial cancer predisposition leading to an increased risk of colorectal cancer (CRC). The aim of this prospective study was to characterise and to compare the risks for adenoma and CRC in these three risk groups. Data was taken from the registry of the German Consortium for Familial Intestinal Cancer. Patients were prospectively followed up in an intensified colonoscopic surveillance programme that included annual examinations. Cumulative risks for adenoma and CRC were calculated separately for LS, LLS and FCCX, and then for males and females. Multivariate Cox regression was used to analyse the independent contributions of risk group, mismatch repair gene (within LS), sex and previous adenoma. The study population comprised 1448 individuals (103 FCCX, 481 LLS and 864 LS). The risks were similar for colorectal adenomas, but different for first and metachronous CRC between the three risk groups. CRC risk was highest in LS, followed by LLS and lowest in FCCX. Male sex and a prevalent adenoma in the index colonoscopy were associated with a higher risk for incident adenoma and CRC. In patients with LS, CRC risks were particularly higher in female *MSH2* than *MLH1* carriers. Our study may support the development of risk-adapted surveillance policies in LS, LLS and FCCX.

KEYWORDS

cancer risk, familial colorectal cancer type X, Lynch syndrome, Lynch-like syndrome, prospective study

Abbreviations: ACPGBI, Association of Coloproctology of Great Britain and Ireland; BSG, British Society of Gastroenterology; CI, confidence interval; CRC, colorectal cancer; dMMR, mismatch repair deficiency; FCCX, familial colorectal cancer type X; HR, hazard ratios; LLS, Lynch-like syndrome; LS, Lynch syndrome; MMR, mismatch repair; UKCGG, United Kingdom Cancer Genetics Group.

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What's new?

While associations between colorectal cancer (CRC) risk and Lynch syndrome (LS) are well-described, less is known about CRC risks linked to the closely related Lynch-like syndrome (LLS) and familial colorectal cancer type X (FCCX). In this prospective follow-up study of patients with LS, LLS, and FCCX, risks were similar for colorectal adenomas but considerably different for first and metachronous CRCs. In addition, LS females who carried *MSH2* mutations had notably higher CRC risks than female *MLH1* mutation carriers. The identification of variations in carcinogenic pathways between LS, LLS, and FCCX could enable risk-adapted CRC surveillance for these syndromes.

1 | INTRODUCTION

Lynch syndrome (LS) is the most common hereditary colorectal cancer (CRC) syndrome and responsible for about 2%-4% of all CRCs.[1] LS is caused by pathogenic germline variants in one of the DNA mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, *PMS2* or in the *EPCAM* gene.[2] Approximately one in 340 individuals in the general population carries a pathogenic MMR gene variant.[3] Besides CRC, individuals with LS face an increased risk of developing a broad spectrum of extracolonic cancers.[4,5]

MMR deficiency (dMMR) is an essential characteristic of LS associated tumours. However, not all patients with a MMR deficient tumour have a pathogenic MMR germline variant.[6] It has been suggested to classify these patients as having "Lynch-like syndrome" (LLS), if no *MLH1*-hypermethylation and germline mutation can be identified.[7,8] Several studies showed that double somatic pathogenic MMR gene variants are a likely cause for dMMR in this group.[9-11] Besides LS and LLS, there is a third distinct clinically defined group of patients, the so-called "familial colorectal cancer type X" (FCCTX or FCCX). This group comprises individuals from families showing clustering of LS specific tumours according to the clinical Amsterdam criteria without any signs of dMMR.[7,12] The different clinical aspects and molecular features of these three groups have been summarised elsewhere.[13] Recently, we compared the risks of different tumour types between LS, LLS and FCCX using prospective cohort data.[14]

It is assumed that LS associated CRC develop mainly via the classical adenoma-carcinoma sequence, although other pathways of CRC development have recently been proposed.[15,16] Therefore, and because of the highly elevated CRC risk, LS patients are advised to undergo frequent colonoscopies to detect and remove adenomas early, before they can develop into invasive cancer. The frequency of such surveillance measures is currently a matter of debate, particularly in LS. Since CRC risks are considerably different between MMR genes, gene-specific surveillance recommendations have been proposed, which consider adjusting the interval and the starting age.[17-21]

In order to develop appropriate surveillance programs not only for patients with LS, but also for LLS and FCCX, exact knowledge of adenoma and CRC risk is necessary. While such risks are described well in LS, fewer data are available in LLS and FCCX. Therefore, the aim of the present study was to describe and compare the risks for colorectal adenoma and CRC in individuals with LS, LLS and FCCX using prospective surveillance data of the German Consortium for Familial Intestinal Cancer.

2 | MATERIALS AND METHODS

2.1 | Study population

Data was taken from the prospective registry of the German Consortium for Familial Intestinal Cancer. All participants gave their written informed consent at registry inclusion, and the registry was approved by the Ethics Committees of all participating institutions. Six university centres collected information about families suspected of having Lynch syndrome based on the Amsterdam-II criteria and/or revised Bethesda guidelines.[22,23] A tissue sample (tumour or adenoma) of the index patient was examined for MMR deficiency (dMMR) using immunohistochemistry (IHC) and/or microsatellite analysis (MSA). In case of dMMR (or if no tissue sample was available), a germline mutation analysis of the MMR genes *MLH1*, *MSH2*, *MSH6* and *PMS2*, and the *EPCAM* gene was carried out. Details about the diagnostic procedure have been described elsewhere.[6] To ensure high data quality, a central data quality management process was implemented with automated checks for completeness,

plausibility and consistency of all data, which triggers queries in the event of errors.

Index patients were classified as having LS, LLS or FCCX according to the results of the tissue examination and subsequent germline DNA analysis. LS index patients were defined by having a proven class 4/5 germline variant.[24] Relatives of LS index patients with the same class 4/5 variant found in the index patient were also considered as LS patients. LLS index patients were defined by not having a class 4/5 germline variant despite signs of dMMR, and FCCX index patients had no signs of dMMR while fulfilling the Amsterdam criteria. Relatives of LLS and FCCX index patients were considered as LLS and FCCX patients, respectively. Individuals from families with dMMR due to *MLH1* methylation were not regarded as LLS patients.

In total, 1998 individuals with LS, LLS and FCCX (index patients and relatives) were invited to participate in an intensified surveillance programme comprising annual colonoscopies, esophagogastroduodenoscopies and gynaecological examinations. Individuals were included in the present analysis if they had LS, LLS or FCCX according to the above definitions. In the LS group, only *MLH1*, *MSH2* and *MSH6* carriers were included. *EPCAM* and *PMS2* carriers were excluded due to low sample sizes. Only individuals with an index colonoscopy, that is, the first colonoscopy after registry inclusion, and at least one follow-up colonoscopy were included. According to these criteria, 1448 individuals were included in the analysis set. Each single surveillance examination was recorded in the registry. Individuals in the analysis set were younger compared to individuals who were excluded (median age [IQR] at index colonoscopy: 43 [36-50] vs 51 [42-60] years), and the proportion of women was higher (53% vs 44%).

2.2 | Statistical analysis

From the above study population, colorectal adenoma and cancer risks (invasive cancer only) were determined. The study population was divided into two subgroups.

The first subgroup comprised only individuals without any CRC before study inclusion. Prospective observation started at the index colonoscopy or at age 25, whichever occurred last.

For CRC as the event of interest, observation ended at the first incident CRC, or observation was censored at 80 years of age, last documented contact before 12 May 2019, or death, whichever came first. For adenoma as the event of interest, observation ended at the first incident adenoma (or CRC), or observation was censored at 80 years of age, last documented contact before 12 May 2019, or death, whichever came first.

The second subgroup included individuals who already had a CRC before registry inclusion. The time difference between the first and second CRC as well as between the first CRC and incident colorectal adenoma was analysed. Individuals had to have a prospective observation time of more than half a year, otherwise adenomas and CRCs were considered as prevalent. Censoring occurred at the last documented contact before 12 May 2019, or death, whichever came first.

Cumulative risks were determined separately for men and women stratified by the three risk groups LS, LLS and FCCX, and by dividing the LS group into *MLH1*, *MSH2* and *MSH6* carriers. Risk was estimated using the Kaplan-Meier product limit estimator accounting for the age at index colonoscopy (left-truncation).[25] For comparisons between groups, the log-rank test was used. The proportional hazards assumption was tested using scaled Schoenfeld residuals.[26,27] We also tested for nonlinearity of the continuous covariate "age at first CRC" within the Cox model. We found no significant deviations in the assumptions. In addition, the log-minus-log-transformed 95% confidence intervals of the product limit estimator were determined.[25,28]

Cox regression was used to examine whether and to what extent different risk factors are associated with adenoma and CRC risk. Hazard ratios (HR) were determined using Firth's Penalized Likelihood as proposed by Heinze and Schemper.[29,30] This method allows the estimation of HR even if no event has occurred in a risk group. The risk groups LS, LLS and FCCX as well as sex and the presence of adenoma at the index colonoscopy were considered as risk factors in the model. For the analysis of the LS group, gene, sex and presence of adenoma at index colonoscopy, and the interaction between gene and sex were included. In patients with previous CRC, age at first CRC was used as an additional risk factor.

To investigate whether multiple occurrences of adenomas instead of just considering the first incident occurrence would lead to different results in the time-to-event analyses, we used a specific modelling approach suggested by Andersen and Gill.[31]

All group comparisons were two-sided, and *P*-values lower than .05 were considered statistically significant. Due to the exploratory nature of the study, no correction for multiple testing was performed. Statistical analyses were carried out with R 3.6.1 for Windows (R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL: https://www.R-project.org). We used the R packages: base, coxphf, forestplot, graphics, grDevices, grid, gridBase, stringr, survival, survminer and utils.

3 | RESULTS

The study population comprised 1448 individuals (767 women) in total (103 FCCX, 481 LLS and 864 LS). Patient characteristics are shown in Table 1. A total of 897 individuals (61.9%) had had a CRC prior to the index colonoscopy. There were no major differences in the distribution of colonoscopy intervals among the three risk groups (Figure S4).

3.1 | Adenoma risks

The cumulative adenoma risks were similar in all three risk groups (Figure 1), except in men without previous CRC in the FCCX group,

who had lower adenoma risks (53.1% at 50 years of age, 95%CI 21.2-91.0%) compared to the LS (84.1%, 95%CI 74.7-91.5%) and LLS (82.1%, 95%CI 61.8-95.4%) group. However, this difference was not statistically significant. Adenoma risks were significantly higher in men compared to women (without previous CRC: HR 1.44, 95%CI 1.08-1.91, with previous CRC: HR 1.26, 95%CI 1.01-1.58) and were also significantly higher if an adenoma was found in the index colonoscopy (without previous CRC: HR 2.00, 95%CI 1.42-2.76, with previous CRC: HR 2.48, 95%CI 1.84-3.29). Individuals with previous CRC had significantly higher adenoma risks with increasing age at first CRC (HR 1.30 per 10-year increase, 95%CI 1.16-1.46). Patients diagnosed with first CRC at age 60 or older had a 2.44-fold elevated risk for incident adenomas compared to patients diagnosed with first CRC at age 29 or younger (see Figure S3A).

Within the LS group, adenoma risks were similar across the *MLH1*, *MSH2* and *MSH6* groups (Figure 2). The risk to develop an incident adenoma was significantly increased if an adenoma was found at the index colonoscopy both in LS patients with (HR 1.79, 95%CI 1.18-2.62) and those without previous CRC (HR 1.96, 95%CI 1.27-2.92). In LS patients with previous CRC, increasing age at first CRC was significantly associated with an increased adenoma risk (HR 1.34, 95%CI 1.14-1.56).

The Andersen-Gill model, which accounts for multiple occurrences of adenomas during prospective observation, revealed the same significant associations as the Cox model, which considered only the first incident adenoma event (Figures S1 and S2).

3.2 | CRC risks

Cumulative CRC risks were significantly lower in FCCX compared to LS (without previous CRC: HR 0.13, 95%CI <0.01-0.94, with previous CRC: HR 0.19, 95%CI 0.02-0.69) (Figure 3). No incident CRC was observed in the FCCX group with previous CRC. Individuals with a previous CRC in the LLS group had a significantly lower CRC risk compared to the LS group (HR 0.54, 95%CI 0.30-0.92). Men had higher risks for first (HR 1.70, 95%CI 0.88-3.28) and second CRC (HR 2.24, 95%CI 1.37-3.79) than women. Higher age at first CRC was significantly associated with a higher risk for a second CRC (HR 1.38 per 10-year increase, 95%CI 1.07-1.77). This is consistent with an alternative Cox model using age at first CRC in groups instead of a continuous variable, showing that the subgroup with the highest age at first CRC (≥60 years) had the highest risks for incident CRC and adenoma (Figure S3B).

Women with LS had a higher CRC risk if they had a pathogenic variant in *MSH2* compared to women with a pathogenic *MLH1* variant (Figure 4). Cumulative risks for first CRC at age 50 were 24.2% (95% CI 9.6-53.4%) in *MSH2*, and 5.9% (95%CI 0.9-35.0%) in *MLH1*. Cumulative risks of a second CRC 25 years after the first CRC were 30.0% (95%CI 15.5-53.2%) in *MSH2*, and 14.1% (95%CI 2.6-58.0%) in *MLH1*. This difference was statistically significant (HR 4.91, 95%CI 1.46-25.23). In contrast to female carriers, cumulative first and second CRC risks in males were similar. This interaction between gene (*MSH2* vs *MLH1*) and sex was statistically significant in the multivariate regression analysis.

TABLE 1 Patient characteristics

			LS			
	FCCX	LLS	*MLH1*	*MSH2*	*MSH6*	Total
Individuals, n (number of women)	103 (55)	481 (268)	334 (177)	423 (214)	107 (53)	1448 (767)
CRC before index colonoscopy, number of individuals (number of women)	65 (34)	352 (183)	203 (94)	226 (97)	51 (19)	897 (427)
Incident adenoma, number of individuals (number of women)	38 (20)	149 (66)	121 (64)	176 (83)	41 (23)	525 (256)
Incident CRC, number of individuals (number of women)	1 (0)	24 (9)	28 (4)	51 (25)	6 (2)	110 (40)
Number of colonoscopies, median (interquartile range)	6 (4-10)	6 (4-10)	7.5 (5-11)	8 (5-12)	6 (4-9)	7 (5-11)
Colonoscopies, cumulative number	775	3514	2819	3813	757	11 678
Age at index colonoscopy, years, median (interquartile range)	48 (40-55)	43 (37-49)	41 (33-49)	43 (35-50)	43 (36-54)	43 (36-50)
Prospective observation time, years, median (interquartile range)	6.5 (3.2-9.7)	6.1 (3.5-9.3)	6.5 (3.2-9.9)	7.1 (4.0-10.5)	5.8 (2.7-10.0)	6.4 (3.5-9.8)
Age at index colonoscopy, number of individuals (number of women)						
≤29	4 (3)	43 (27)	46 (26)	51 (26)	5 (1)	149 (83)
30-39	18 (8)	116 (58)	94 (52)	119 (57)	37 (19)	384 (194)
40-49	39 (19)	205 (116)	117 (53)	145 (72)	29 (16)	535 (276)
50-59	24 (16)	72 (37)	52 (31)	72 (40)	21 (11)	241 (135)
60-69	10 (4)	34 (23)	17 (8)	34 (19)	10 (3)	105 (57)
70-79	8 (5)	11 (7)	8 (7)	2 (0)	5 (3)	34 (22)

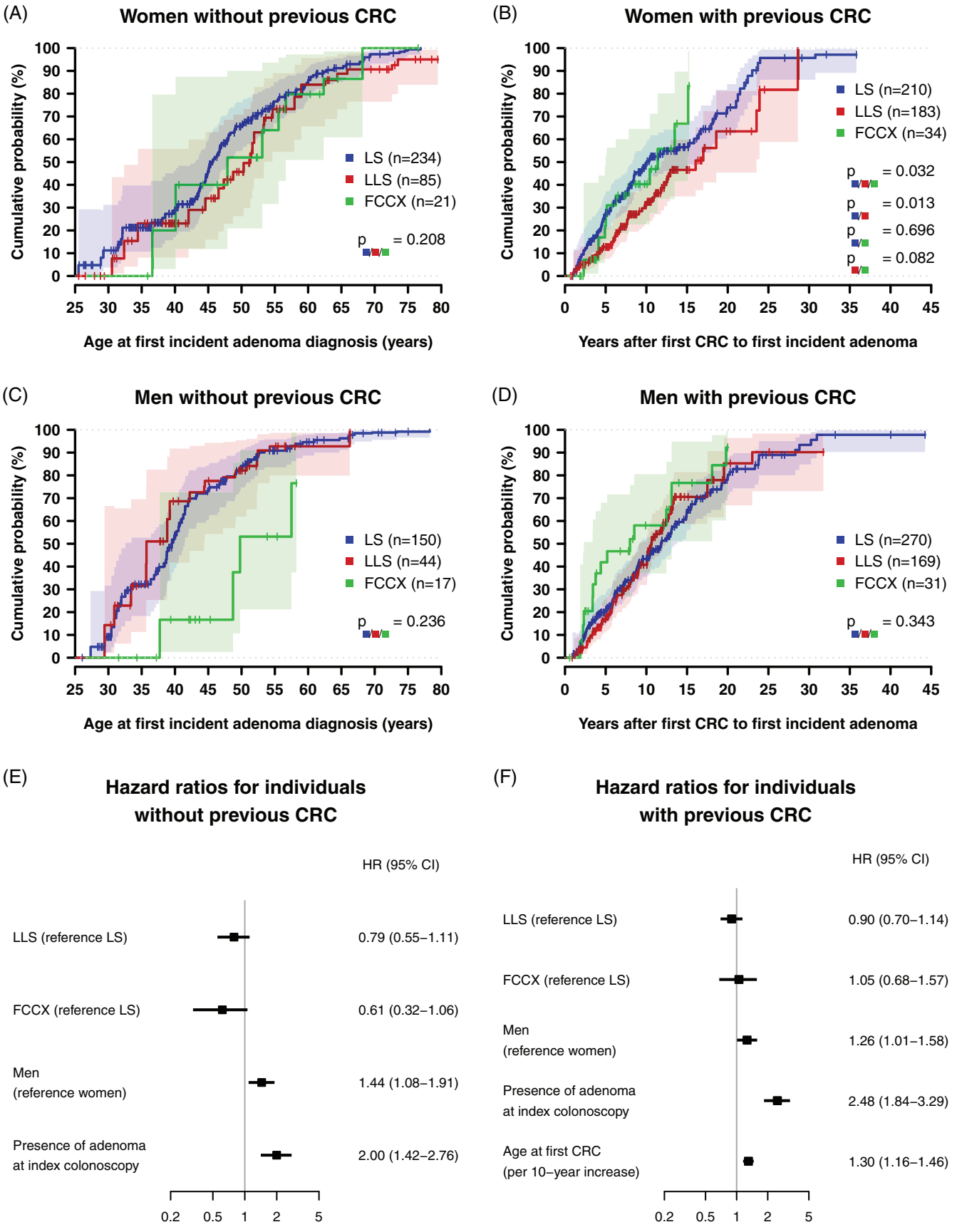

FIGURE 1 Cumulative adenoma risks and results of multivariate Cox regression analysis

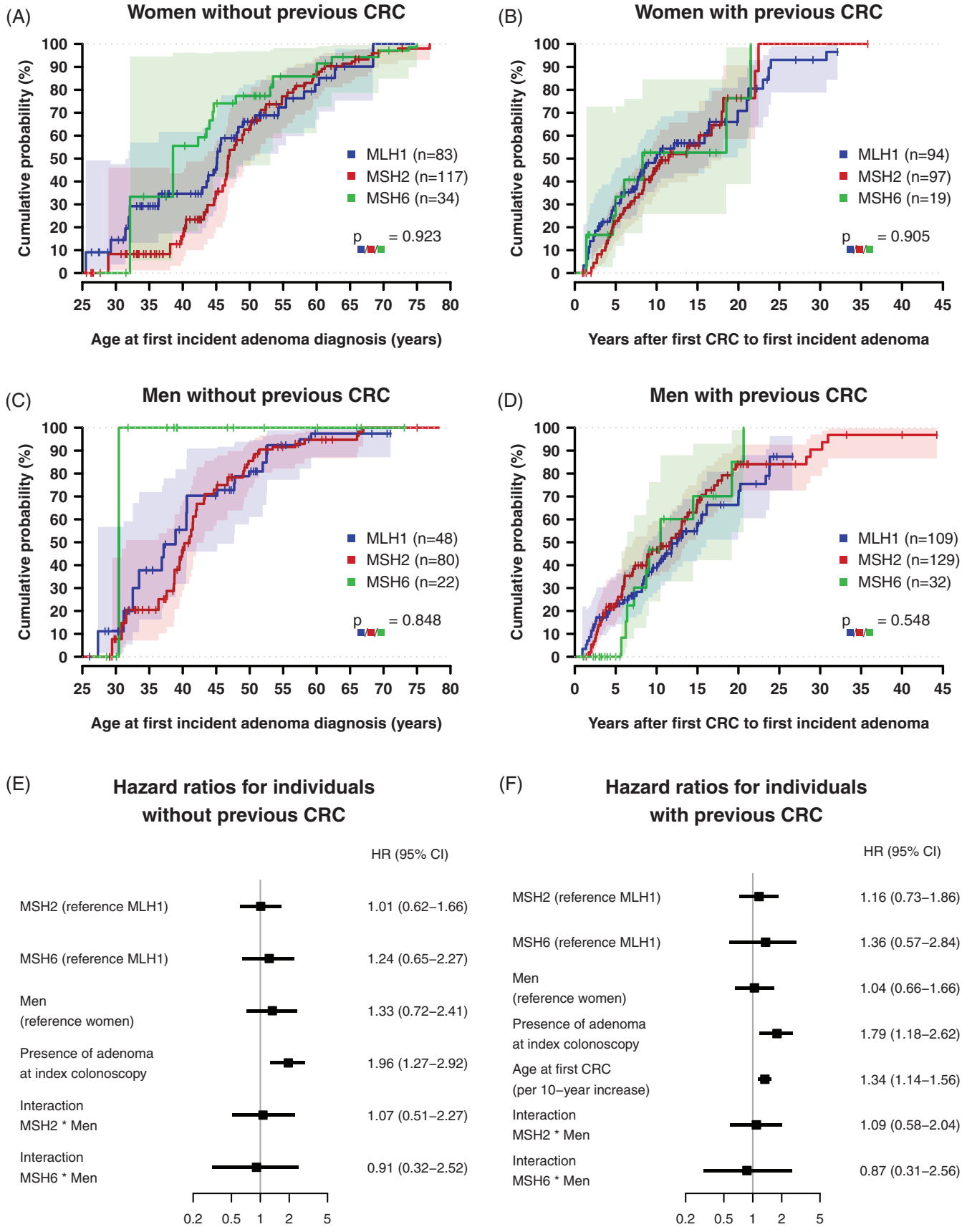

FIGURE 2 Cumulative adenoma risks and results of multivariate Cox regression analysis (LS subgroup only)

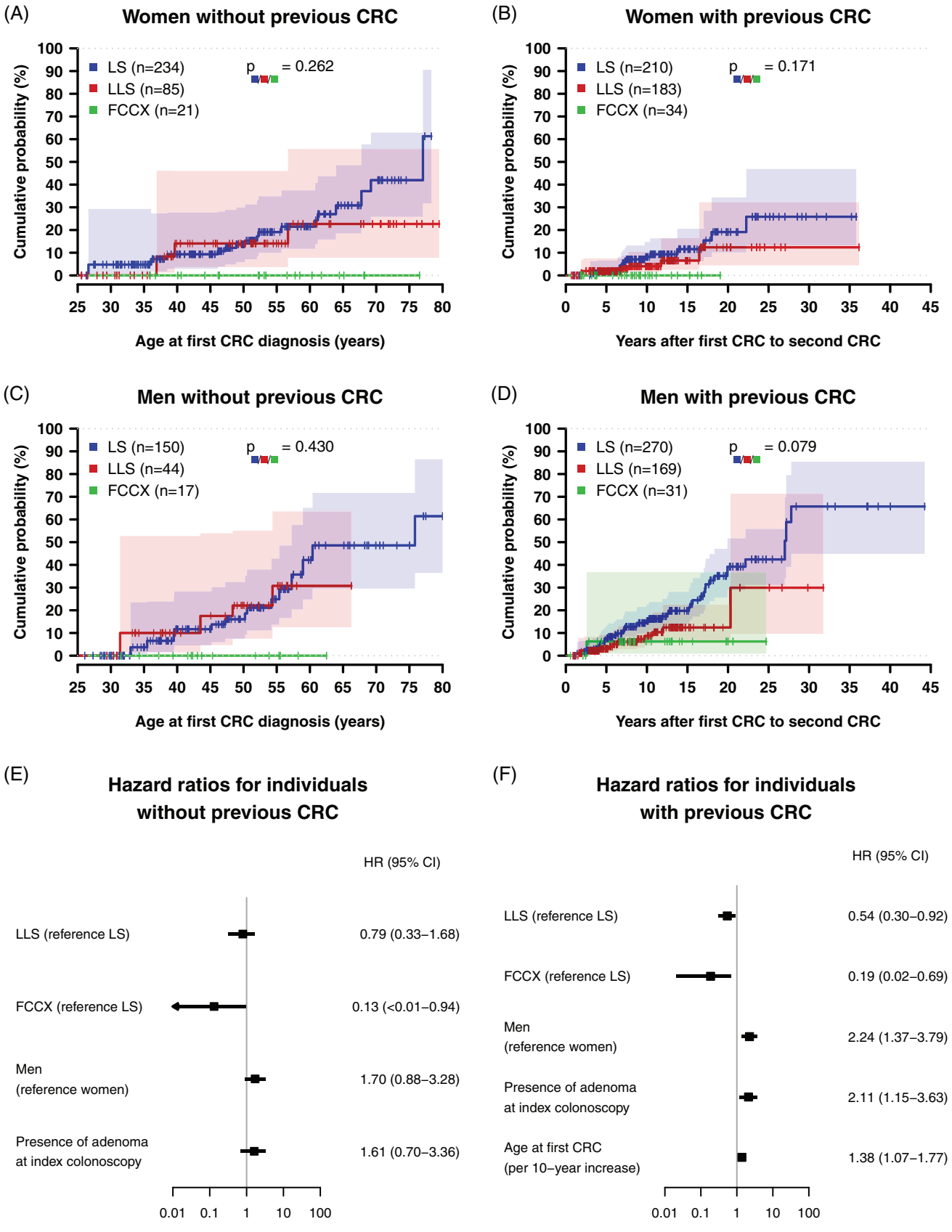

FIGURE 3 Cumulative CRC risks and results of multivariate Cox regression analysis

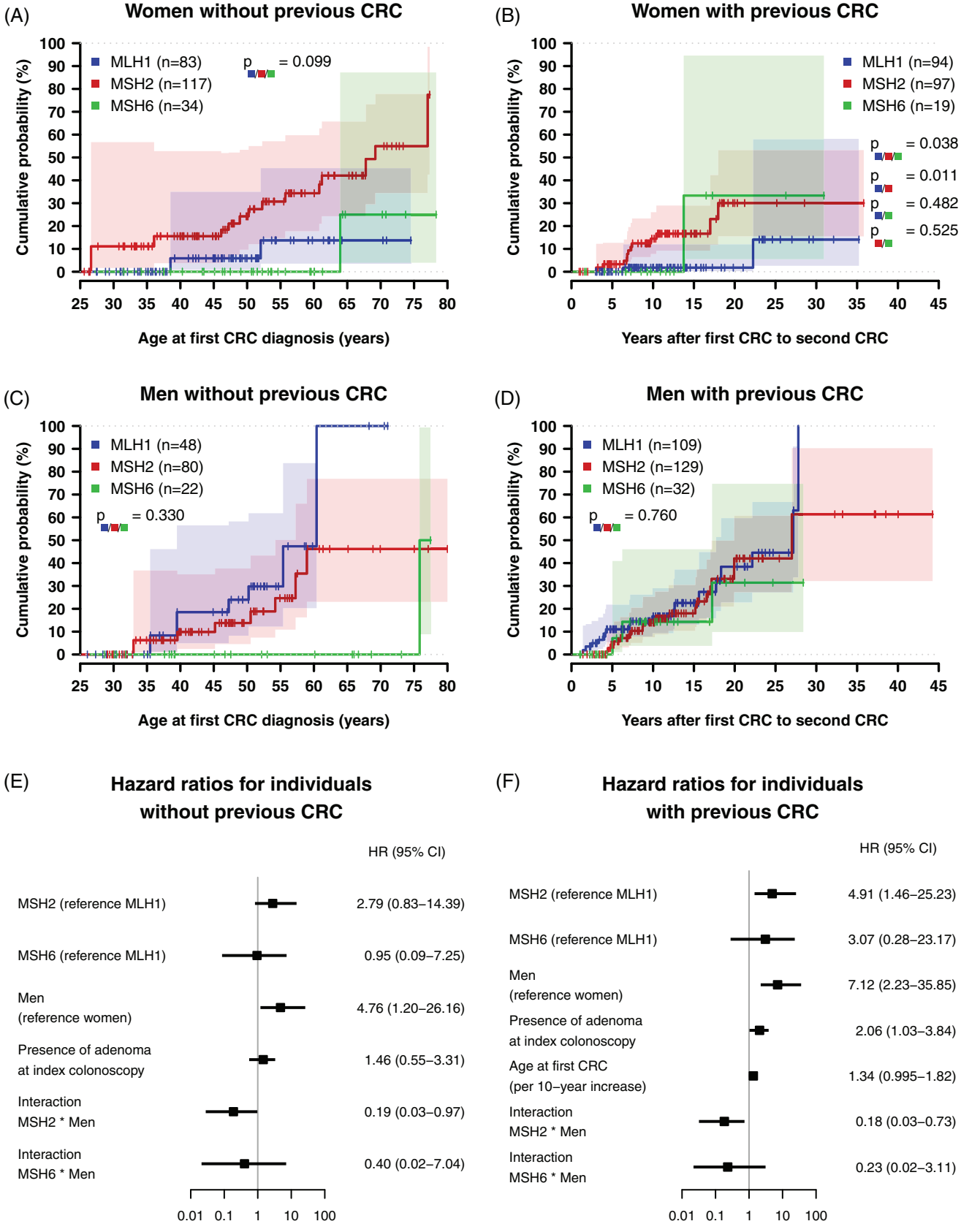

FIGURE 4 Cumulative CRC risks and results of multivariate Cox regression analysis (LS subgroup only)

4 | DISCUSSION

The aim of our study was to characterise the risks for CRC and colorectal adenoma development in individuals with LS, LLS and FCCX, as this is an important prerequisite for the development of appropriate risk-adapted surveillance policies.

We found that the risks for colorectal adenomas were similar between the three risk groups, both within the group of individuals without previous CRC and within the group of individuals who had a prior CRC diagnosis before start of surveillance. The adenoma risk was somewhat lower in men without previous CRC in the FCCX group compared to the LS and LLS groups, but the sample size in this specific group was very low (n = 17) and this difference was not statistically significant. Since there was no such trend in females, we assume that this observation is most likely attributable to chance. The Anderson and Gill model, a specific approach to consider multiple occurrences of adenomas during prospective observation, revealed very similar results compared to the Cox model considering only the first incident adenoma occurrence. A major reason for this is that most patients had only one (n = 299) or two (n = 113) positive colonoscopies during their follow-up, while only 113 patients had three or more metachronous occurrences of adenomas.

In contrast to the adenoma risks, CRC risks were different between the three risk groups (highest in LS followed by the LLS and lowest in the FCCX group). However, the difference of CRC risks between LS and LLS was statistically significant only in the group of patients who had had a CRC diagnosis prior to study entry. The lower CRC risk in LLS compared to LS is consistent with a study of Pico et al, who compared standardised incidence ratios of CRC in first-degree relatives of patients with LS and LLS.[32] They found elevated risks in both groups, whereby the risks were significantly higher in LS than in LLS.

With regard to sex, we observed higher risks for adenomas and CRCs in men than in women. Relative risks for men were 1.26/1.44 for adenoma, and 2.24/1.70 for CRC in individuals with/without previous CRC, respectively. Interestingly, however, in the LS group, the CRC risk difference between *MSH2* and *MLH1* seemed to be confined to female carriers, which was underpinned by a significant interaction between sex and the *MSH2-MLH1* contrast in the multivariate Cox regression analysis. The underlying pathogenetic mechanism for this sex-gene interaction, if this should be confirmed in independent and larger studies, remains unclear. Another risk factor, which was associated with higher adenoma and CRC risk, was the prevalence of an adenoma in the index colonoscopy (HR 2.48/2.00 for incident adenoma, and 2.11/1.61 for CRC in individuals with/without previous CRC, respectively).

Given the different CRC risks between LS, LLS and FCCX, but also within the LS group depending on the MMR gene, risk-adapted colonoscopic surveillance policies seem to be advisable, also to minimise patient burden, but they need to be appropriately defined and evaluated. Besides the question at which age surveillance should commence, appropriate examination intervals must be determined. With regard to LS, a comparative study analysing pooled prospective surveillance data in 2747 LS patients from Germany, The Netherlands and Finland showed that a strict annual surveillance policy, as was usual in the German LS Consortium until recently, was not associated with a lower CRC incidence or more favourable CRC stages.[33] This result led the German LS Consortium to revise its recommendation to 1-2 yearly intervals.[34] Current LS surveillance guidelines recommend colonoscopy intervals of 1-2 years,[19,35] 2 years[20,36] or 2-3 years.[21] None of these guidelines currently advise different intervals depending on sex, which was associated with adenoma and CRC risk in the present study.

LLS is defined by the absence of a pathogenic germline MMR gene variant despite the presence of microsatellite instability in the tumours.[13]

LLS is thought to comprise a heterogeneous mixture of patients with undetected germline variants, with other hereditary cancer syndromes, and with sporadic CRC. Several studies have convincingly shown that pathogenic double somatic MMR gene variants can be detected in more than half of the patients with dMMR, who have neither a *MLH1* hypermethylation nor a pathogenic germline variant.[9-11] Xavier et al analysed next-generation sequencing data from 22 MMR genes in 274 LLS patients and found that genes associated with the DNA MMR process (mainly *MLH1*, *MSH2*, *MSH6*, *EXO1*, *POLD1*, *RFC1*, *RPA1* and *MLH3*) were most likely associated with LLS.[37] Xu et al found variants of unknown significance in mismatch repair genes and other mutated genes in 44 of 81 individuals with LLS, with the most frequent alterations in *MUTYH*, *POLE*, *BRCA2* and *GJB2*.[38] They recommend multigene panel testing for all dMMR patients to distinguish between LS and LLS, which has not yet been done in our present cohort. Besides, they found high risks of extracolonic cancers and a high frequency of metachronous CRC in individuals with LLS. They suggest tailored surveillance policies based on family history and confirmed pathogenic or likely pathogenic variants, for example, gastroduodenoscopy in *MUTYH* or gynaecological and breast examinations in *BRCA* variant carriers. The guideline of the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG) suggests biennial colonoscopies from the age of 25 to 75 years for individuals with LLS, if no evidence of biallelic somatic MMR gene inactivation has been found.[20]

CRC risks in FCCX are considerably lower compared to LS and LLS, which is reflected in less intensive surveillance recommendation in some guidelines. The BSG/ACPGBI/UKCGG guidelines recommend that individuals with a family history of CRC and a high risk (ie, three first-degree relatives with CRC for more than one generation) should undergo colonoscopies every 5 years from the age of 40 to 75 years. The ESMO Clinical Practice Guidelines for Hereditary Gastrointestinal Cancers recommend that individuals with FCCX should undergo colonoscopic surveillance at 3 to 5 year intervals, starting at the age of 40 or 10 years before earliest CRC in the family.[19]

Our general observation of different CRC risks among the three risk groups despite similar adenoma risks could possibly be the result of the different importance of alternative carcinogenic pathways, which have recently been proposed.[16] If this is the case, it is also

conceivable that surveillance measures are differently effective in the three risk groups. For instance, if the classical adenoma-carcinoma sequence would be the predominant pathway in LLS and FCCX, one may expect a better efficacy of early adenoma removal on CRC incidence compared to LS, in which direct CRC development from normal mucosa possibly plays a more important role.

A major strength of the present study was its prospective design, which mitigates the problem of risk overestimation due to ascertainment bias in clinic-based retrospective studies.[39] Moreover, the patients in the three risk groups took part in the same structured surveillance program with the same quality of data collection, which should minimise bias. However, some limitations should be noted. One was that observation times above the age of 60 years were relatively low. Second, the sample sizes of the LLS and especially the FCCX groups were comparably low, resulting in wide confidence intervals for the risk estimates even for adenomas. It therefore remains to be shown whether adenoma risks are lower in these groups compared to the LS group. Third, no multiplicity correction was performed, due to the exploratory nature of the study. Therefore, statistical significance should be interpreted with caution. Fourth, an important point to consider, albeit not being a specific methodological weakness of our study, is that all of the observed patients were under intensified colonoscopic surveillance, with possible colorectal cancer prevention (to an unknown extent) due to adenoma removal. Therefore, the CRC risks obtained in our study may not reflect the natural course of disease.[40] Furthermore, an analysis of the exact number of detected adenomas or polyps per colonoscopy would have been interesting. However, corresponding data were largely not available.

5 | CONCLUSIONS

Patients with LS, LLS and FCCX exhibit different CRC risks, while adenoma risks were similar. This may indicate a different significance of alternative carcinogenic pathways, which should be investigated in further studies. With regard to LLS and FCCX, larger prospective studies and ideally internationally pooled data are needed to obtain more precise risk estimates, to clarify the role of risk factors, and to compare the effectiveness of different surveillance policies.

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CONFLICT OF INTEREST

Deepak B. Vangala received Speakers honoraria from Falk Foundation and Roche, Travel support and congress registration fees from Celgene and Gilead, Advisory board BMS. All other authors declare not to have conflicts of interests.

DATA AVAILABILITY STATEMENT

The data used in our study will be made available upon reasonable request. Please contact the corresponding author (karolin.bucksch@imise.uni-leipzig.de).

ETHICS STATEMENT

Data was taken from the prospective registry of the German Consortium for Familial Intestinal Cancer. All participants gave their written informed consent at registry inclusion, and the registry was approved by the Ethics Committees of all participating institutions.

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REFERENCES

1. Yurgelun M, Kulke M, Fuchs C, et al. Cancer susceptibility gene mutations in individuals with colorectal cancer. *J Clin Oncol*. 2017;35:1086-1095.
2. Lynch HT, Snyder CL, Shaw TG, Heinen CD, Hitchins MP. Milestones of Lynch syndrome: 1895–2015. *Nat Rev Cancer*. 2015;15:181-194.
3. Grzymski JJ, Elhanan G, Morales Rosado JA, et al. Population genetic screening efficiently identifies carriers of autosomal dominant diseases. *Nat Med*. 2020;26:1235-1239.
4. Møller P, Seppälä T, Bernstein I, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age. A report from the prospective Lynch syndrome database. *Gut*. 2018;67:1306-1316.
5. Dominguez-Valentin M, Sampson J, Seppälä T, et al. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the prospective Lynch syndrome database. *Genet Med*. 2020;22:15-25.
6. Steinke V, Holzapfel S, Loeffler M, et al. Evaluating the performance of clinical criteria for predicting mismatch repair gene mutations in Lynch syndrome: a comprehensive analysis of 3,671 families. *Int J Cancer*. 2014;135:69-77.
7. Da Silva FC, Wernhoff P, Dominguez-Barrera C, Dominguez-Valentin M. Update on hereditary colorectal cancer. *Anticancer Res*. 2016;36:4399-4405.
8. Rodríguez-Soler M, Pérez-Carbonell L, Guarinos C, et al. Risk of cancer in cases of suspected lynch syndrome without germline mutation. *Gastroenterology*. 2013;144:926-932.
9. Mensenkamp AR, Vogelaar IP, van Zelst-Stams WA, et al. Somatic mutations in MLH1 and MSH2 are a frequent cause of mismatch-repair deficiency in Lynch syndrome-like tumors. *Gastroenterology*. 2014;146(3):643-646.
10. Haraldsdottir S, Hampel H, Tomsic J, et al. Colon and endometrial cancers with mismatch repair deficiency can arise from somatic, rather than germline, mutations. *Gastroenterology*. 2014;147(6):1308-1316.
11. Pearlman R, Haraldsdottir S, de la Chapelle A, et al. Clinical characteristics of patients with colorectal cancer with double somatic mismatch repair mutations compared with Lynch syndrome. *J Med Genet*. 2019;56(7):462-470.
12. Lindor N, Rabe K, Petersen G, et al. Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. *JAMA*. 2005;293:1979-1985.
13. Chen E, Xu X, Liu T. Hereditary nonpolyposis colorectal cancer and cancer syndromes: recent basic and clinical discoveries. *J Oncol*. 2018;2018:3979135.

14. Bucksch K, Zachariae S, Aretz S, et al. Cancer risks in Lynch syndrome, Lynch-like syndrome, and familial colorectal cancer type X: a prospective cohort study. *BMC Cancer*. 2020;20:460.
15. Ahadova A, von Knebel Doeberitz M, Bläker H, Kloor M. CTNNB1-mutant colorectal carcinomas with immediate invasive growth: a model of interval cancers in Lynch syndrome. *Fam Cancer*. 2016;15:579-586.
16. Ahadova A, Gallon R, Gebert J, et al. Three molecular pathways model colorectal carcinogenesis in Lynch syndrome. *Int J Cancer*. 2018;143:139-150.
17. Vasen H, Blanco I, Aktan-Collan K, et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. *Gut*. 2013;62:812-823.
18. Stoffel EM, Mangu PB, Limburg PJ, American Society of Clinical Oncology, European Society for Medical Oncology. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology clinical practice guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology clinical practice guidelines. *J Oncol Pract*. 2015;11:e437-e441.
19. Stjepanovic N, Moreira L, Carneiro F, et al. Hereditary gastrointestinal cancers: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2019;30:1558-1571.
20. Monahan KJ, Bradshaw N, Dolwani S, et al. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). *Gut*. 2020;69:411-444.
21. Seppälä TT, Latchford A, Negoi I, et al. European guidelines from the EHTG and ESCP for Lynch syndrome: an updated third edition of the Mallorca guidelines based on gene and gender. *Br J Surg*. 2021;108(5):484-498.
22. Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the international collaborative group on HNPCC. *Gastroenterology*. 1999;116:1453-1456.
23. Umar A, Boland C, Terdiman J, et al. Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst*. 2004;96:261-268.
24. Plon SE, Eccles DM, Easton D, et al. Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results. *Hum Mutat*. 2008;29:1282-1291.
25. Klein J, Moeschberger M. *Survival Analysis. Techniques for Censored and Truncated Data*. New York: Springer; 1997.
26. Grambsch P, Therneau T. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81:512-526.
27. Therneau T. R documentation: Package survival version 3.1–12, function cox.zph: Test the Proportional Hazards Assumption of a Cox regression. https://stat.ethz.ch/R-manual/R-devel/library/survival/html/cox.zph.html. Accessed April 14, 2020.
28. Borgan Ø, Liestøl K. A note on confidence intervals and bands for the survival function based on transformations. *Scand J Stat*. 1990;17:35-41.
29. Heinze G, Schemper M. A solution to the problem of monotone likelihood in cox regression. *Biometrics*. 2001;57:114-119.
30. Firth D. Bias reduction of maximum likelihood estimates. *Biometrika*. 1993;80:27-38.
31. Andersen PK, Gill RD. Cox's regression model for counting processes: a large sample study. *Ann Stat*. 1982;10:1100-1120.
32. Picó MD, Sánchez-Heras AB, Castillejo A, et al. Risk of cancer in family members of patients with Lynch-like syndrome. *Cancer*. 2020;12:2225.
33. Engel C, Vasen HF, Seppälä T, et al. No difference in colorectal cancer incidence or stage at detection by colonoscopy among 3 countries with different Lynch syndrome surveillance policies. *Gastroenterology*. 2018;155:1400-1409.e2.
34. Hüneburg R, Aretz S, Büttner R, et al. Empfehlungen zur Früherkennung, Risikoreduktion, Überwachung und Therapie bei Patienten mit Lynch-Syndrom [Current recommendations for surveillance, risk reduction and therapy in Lynch syndrome patients]. *Z Gastroenterol*. 2019;57:1309-1320.
35. Provenzale D, Gupta S, Ahnen D, et al. Genetic/familial high-risk assessment: colorectal version 1.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2016;14:1010-1030.
36. van Leerdam ME, Roos VH, van Hooft JE, et al. Endoscopic management of Lynch syndrome and of familial risk of colorectal cancer: European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy*. 2019;51:1082-1093.
37. Xavier A, Olsen MF, Lavik LA, et al. Comprehensive mismatch repair gene panel identifies variants in patients with Lynch-like syndrome. *Mol Genet Genomic Med*. 2019;7:e850.
38. Xu Y, Huang Z, Li C, et al. Comparison of molecular, clinicopathological, and pedigree differences between Lynch-like and Lynch syndromes. *Front Genet*. 2020;11:991.
39. Carayol J, Khlat M, Maccario J, Bonaïti-Pellié C. Hereditary nonpolyposis colorectal cancer: current risks of colorectal cancer largely overestimated. *J Med Genet*. 2002;39:335-339.
40. Ahadova A, Seppälä TT, Engel C, et al. The 'unnatural' history of colorectal cancer in Lynch syndrome: lessons from colonoscopy surveillance. *Int J Cancer*. 2021;148:800-811.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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