Received: 6 March 2020 | Revised: 12 June 2020 | Accepted: 24 June 2020

DOI: 10.1002/ijc.33224

IJC International Journal of Cancer

INVITED REVIEW

The "unnatural" history of colorectal cancer in Lynch syndrome: Lessons from colonoscopy surveillance

Aysel Ahadova[1,2,3] | Toni T. Seppälä[4,5,6] | Christoph Engel[7] | Richard Gallon[8] | John Burn[9] | Elke Holinski-Feder[10,11] | Verena Steinke-Lange[10,11] | Gabriela Möslein[12] | Maartje Nielsen[13] | Sanne W. ten Broeke[14] | Luigi Laghi[15,16] | Mev Dominguez-Valentin[17] | Gabriel Capella[18] | Finlay Macrae[19] | Rodney Scott[20] | Robert Hüneburg[21,22] | Jacob Nattermann[21,22] | Michael Hoffmeister[23] | Hermann Brenner[24,25] | Hendrik Bläker[26] | Magnus von Knebel Doeberitz[1] | Julian R. Sampson[27] | Hans Vasen[28] | Jukka-Pekka Mecklin[29,30] | Pål Møller[17] | Matthias Kloor[1]

[1]Department of Applied Tumour Biology, Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany

[2]Cooperation Unit Applied Tumour Biology, German Cancer Research Centre (DKFZ), Heidelberg, Germany

[3]Molecular Medicine Partnership Unit (MMPU), European Molecular Biology Laboratory (EMBL), Heidelberg, Germany

[4]Department of Surgery, Helsinki University Central Hospital, Helsinki, Finland

[5]Faculty of Medicine, University of Helsinki, Helsinki, Finland

[6]Surgical Oncology, Johns Hopkins Hospital, Baltimore, Maryland

[7]Department of Statistics and Epidemiology, Institute for Medical Informatics, University of Leipzig, Leipzig, Germany

[8]Translational and Clinical Research Institute, Faculty of Medical Sciences, Newcastle University, Newcastle, UK

[9]International Centre for Life, Central Parkway, Newcastle upon, Tyne, UK

[10]Medizinische Klinik und Poliklinik IV, Campus Innenstadt, Klinikum der Universität München, Munich, Germany

[11]Centre of Medical Genetics, Munich, Germany

[12]Centre for Hereditary Tumors, HELIOS Klinikum Wuppertal, University Witten-Herdecke, Wuppertal, Germany

[13]Department of Clinical Genetics, Leiden University Medical Centre, Leiden, the Netherlands

[14]Department of Clinical Genetics, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands

[15]Molecular Gastroenterology and Department of Gastroenterology, Humanitas Clinical and Research Center, Milan, Italy

[16]Department of Medicine and Surgery, University of Parma, Parma, Italy

[17]Department of Tumor Biology, Institute of Cancer Research, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway

[18]Hereditary Cancer Program, Institut Catala d'Oncologia-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain

[19]Colorectal Medicine and Genetics, The Royal Melbourne Hospital, Melbourne, Australia

[20]University of Newcastle and the Hunter Medical Research Institute, Callaghan, Australia

[21]Department of Internal Medicine I, University Hospital Bonn, Bonn, Germany

[22]National Centre for Hereditary Tumor Syndromes, University Hospital Bonn, Bonn, Germany

[23]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center (DKFZ), Heidelberg, Germany

Abbreviations: ADR, adenoma detection rate; CI, confidence interval; CRC, colorectal cancer; FSP, frameshift peptide; HNPCC, hereditary nonpolyposis colorectal cancer; IBD, inflammatory bowel disease; InSiGHT, International Society for Inherited Gastrointestinal Tumors; LS, Lynch syndrome; MMR, mismatch repair; MMR-DCF, mismatch repair-deficient crypt foci; MSI, microsatellite instability; PLSD, Prospective Lynch Syndrome Database.

[24]Division of Preventive Oncology, German Cancer Research Center (DKFZ) and National Center for Tumor Diseases (NCT), Heidelberg, Germany

[25]German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany

[26]Institute of Pathology, University Hospital Leipzig, Leipzig, Germany

[27]Institute of Medical Genetics, Division of Cancer and Genetics, Cardiff University School of Medicine, Cardiff, UK

[28]Department of Gastroenterology & Hepatology, Leiden University Medical Centre, Leiden, The Netherlands

[29]Department of Surgery, Central Finland Central Hospital, Jyväskylä, Finland

[30]Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

Correspondence
Aysel Ahadova, Department of Applied Tumor Biology, Institute of Pathology, University Hospital Heidelberg, Im Neuenheimer Feld 224, 69120 Heidelberg, Germany.
Email: aysel.ahadova@med.uni-heidelberg.de

Funding information
Open access funding enabled and organized by Projekt DEAL.

Abstract

Individuals with Lynch syndrome (LS), one of the most common inherited cancer syndromes, are at increased risk of developing malignancies, in particular colorectal cancer (CRC). Regular colonoscopy with polypectomy is recommended to reduce CRC risk in LS individuals. However, recent independent studies demonstrated that a substantial proportion of LS individuals develop CRC despite regular colonoscopy. The reasons for this surprising observation confirmed by large prospective studies are a matter of debate. In this review, we collect existing evidence from clinical, epidemiological and molecular studies and interpret them with regard to the origins and progression of LS-associated CRC. Alongside with hypotheses addressing colonoscopy quality and pace of progression from adenoma to cancer, we discuss the role of alternative precursors and immune system in LS-associated CRC. We also identify gaps in current knowledge and make suggestions for future studies aiming at improved CRC prevention for LS individuals.

KEYWORDS

colonoscopy surveillance, colorectal cancer, incident cancer risk, Lynch syndrome, microsatellite instability, mismatch repair deficiency

1 | NATURAL HISTORY OF LYNCH SYNDROME-ASSOCIATED COLORECTAL CANCER

The most common inherited colorectal cancer syndrome, Lynch syndrome (LS), is caused by inherited pathogenic germline variants of DNA mismatch repair (MMR) genes responsible for correction of mismatches during DNA replication: *MLH1*, *MSH2*, *MSH6* and *PMS2*.[1] In addition, deletions involving the *EPCAM* gene may silence the adjacent *MSH2* gene. The prevalence of pathogenic MMR gene variants predisposing to LS in the general population is estimated to be 1:250 or even higher.[2-5] LS is inherited as an autosomal-dominant trait, meaning that carriers of a monoallelic pathogenic germline variant (insight-database.org[6]), hereafter referred to as "carriers" or "*MLH1/MSH2/MSH6/PMS2* carriers", have an increased lifetime cancer risk. However, for LS-associated cancers to develop, somatic second hits that inactivate the remaining functional MMR allele are required (consistent with Knudson's two-hit hypothesis).[7,8] As a consequence of MMR deficiency, mismatch mutations can accumulate resulting in hypermutated tumors with >10point mutations per megabase.[9] MMR deficiency also leads to the accumulation of insertion/deletion of mutations at short repetitive sequences (microsatellites), as polymeraseslippage-induced insertion/deletion loops are not repaired during DNA replication, and the mutation is passed on to subsequent cell generations.[10] Insertion/deletion of mutations alter the length of microsatellites, resulting in the genetic phenotype of microsatellite instability (MSI).

Microsatellite mutations residing in protein-encoding regions of the genome can lead to loss of function of tumor suppressor genes, thereby contributing to cancer development and also to the generation of frameshift peptide (FSP) *neo*antigens. Certain MSI-related FSP *neo*antigens can encompass *neo*epitopes completely unknown to the host's immune system. This mechanism is commonly considered to be responsible for the high immunogenicity of MSI tumors[11] that has been demonstrated by several studies showing dense local immune infiltration[12-14] and reactivity of these immune cells to FSPs.[15,16] The immunogenicity of MSI tumors is also a likely reason for the observed favorable prognosis of MSI cancers and their response to immune checkpoint blockade therapy.[14,17-19]

The most common clinical manifestations of LS are colorectal cancer (CRC) and endometrial cancer. Prior to the discovery of LS-causing MMR gene variants in the early 1990s, namely those affecting *MSH2*

and *MLH1*, [20-22] the syndrome had been termed hereditary non-polyposis colorectal cancer (HNPCC) syndrome.[23] HNPCC defined the high CRC risk and underlined the major phenotypic difference between the syndrome and familial adenomatous polyposis (FAP): FAP presents with hundreds to thousands of colonic adenomatous polyps, while the number of polyps in LS patients is not substantially changed in comparison to the general population.[24-26] Even though polyposis is not part of the LS phenotype, benign polyp precursor lesions of LS CRC have been detected.[27,28] This suggested that polyp removal may be an effective measure for CRC prevention in LS and led to international clinical guidelines recommending regular colonoscopy in LS patients.

2 | PERFORMANCE OF COLONOSCOPY FOR CRC PREVENTION IN THE GENERAL POPULATION AND IN LS

In the general population, colonoscopy with polypectomy has been associated with a reduction in CRC risk and improved survival through early detection of CRC.[29-32] In an observational re-analysis of the National Polyp Study (US) undertaken in the general population, screening colonoscopy with polypectomy reduced the risk of CRC death by 53% in 15 years of follow-up,[33] and the incidence of CRC was reduced by at least 66%. [34] A more recent population-based study (Germany) by Brenner et al[31] reported a 77% risk reduction for CRC in individuals who had a screening colonoscopy in the 10 years prior to assessment. Interestingly, and similar to other studies,[30,32,35] the risk reduction by colonoscopy was higher for left-sided CRC (84%) compared to right-sided CRC (56%). The preventive effect of colonoscopy on right-sided CRC was particularly limited in the younger age group, with only a 26% risk reduction in patients aged between 50 and 59 years. Although this study did not identify a difference in risk reduction between patients with and without a family history of CRC, the limited efficacy of colonoscopy particularly in young patients and for the right-sided colon is intriguing.[36,37] It may in part relate to more limited efficacy of colonoscopy to prevent CRC in LS, a disease predisposition known to be associated with an increased proportion of right-sided CRCs and earlier onset compared to the general population.[38]

In LS, CRC risk and its reduction by colonoscopy surveillance have been analyzed by several studies with different designs. Retrospective studies largely covering the time period before the introduction of regular colonoscopy reported up to 78% "natural" (without surveillance) risk of developing CRC in individuals with HNPCC.[39,40] A landmark non-randomized controlled study by Jarvinen et al[41] reported halving of CRC risk by 3-yearly colonoscopy in HNPCC, including a group of proven MMR carriers. However, LS patients under regular colonoscopy still had up to 15% risk of developing CRC in 10 years.[41-49] A summary of studies assessing CRC risk in LS carriers under surveillance independent of the affected MMR gene is presented in Table 1. Differences in the CRC risk observed between the studies can be explained by the variations in study design (retrospective vs prospective), colonoscopy protocols, eligibility criteria and censoring strategies.

In line with these observations, the Prospective Lynch Syndrome Database (PLSD, plsd.eu), the largest prospective database of known MMR carriers, demonstrated the development of a substantial number of CRCs despite colonoscopy with polypectomy.[50] Even in LS patients undergoing regular colonoscopy surveillance, CRC was the most frequent first cancer observed,[51] becoming clinically manifest as "incident cancers" (ie, diagnosed after the beginning of surveillance period). These findings were confirmed in an independent large series of MMR carriers.[52] In between-country comparisons, point estimates of the incidence of CRC in *MLH1* carriers who underwent colonoscopy every 1 or 2 years were insignificantly higher[53] or similar[54] to those receiving colonoscopy only every 3 to 3.5 years. Neither stage of CRC[54,55] nor survival[56] after diagnosis of CRC were associated with time since last colonoscopy. Notably, adjusting for country of origin to minimize a potential influence of country-specific factors did not change the results.[54] Previous studies also did not detect a significant variant-specific influence on penetrance of LS,[57] indicating that a potential effect of founder mutations[58] on the observed correlations is minor at most.[53] These observations support the concept that

TABLE 1 CRC risk under surveillance in LS variant carriers independent of the affected MMR gene

Study	Setting	Colonoscopy interval (years)	Observation time	CRC incidence
Jarvinen et al [41]	Prospective	3	15 years	18%
De vos tot Nederveen Cappel et al [44]	Retrospective	2 to 3	10 years	10.5% (95% CI: 3.8-17.2)
Mecklin et al [42]	Prospective	2 to 3	Age 60	Men: 35% (95% CI: 16%-49%) Women: 22% (95% CI: 7%-34%)
Järvinen et al [45]	Prospective	2 to 3	11.5 years	12.4%
Stupart et al [46]	Prospective	1 to 2	5 years	11%
Engel et al [47]	Prospective	1 to 2	Age 60	23% (95% CI: 14.8%-31.2%)
Vasen et al [48]	Retrospective	1 to 2	10 years	6% (95% CI: 2.7%-8.7%)
Newton et al [49]	Retrospective	2	Age 70	25% (95% CI: 17-32%)
Engel et al [54]	Prospective	1 to 3	10 years	8.4% (95% CI: 7.1%-10.2%)

TABLE 2 Cumulative CRC risk in confirmed LS variant carriers depending on the affected MMR gene reported by the largest studies published in the last decade

			Cumulative colorectal cancer risk at the age of 70[b] (95% CI)			
Study	Surveillance[a]	Gender	MLH1	MSH2	MSH6	PMS2
Bonadona et al [66]	No	Both	41% (25%-70%)	48% (30%-77%)	12% (8%-22%)	n.a.
Dowty et al [57]	No	Male	34% (25%-50%)	47% (36%-60%)	n.a.	n.a.
		Female	36% (25%-51%)	37% (27%-50%)		
Broeke et al [67]	No	Male	n.a.[c]	n.a.	n.a.	13% (8%-22%)
		Female				12% (7%-21%)
Dominguez-Valentin et al [52]	Yes	Male	53% (45%-62%)	46% (37%-59%)	12% (5%-35%)	3% (1%-35%)
		Female	44% (37%-52%)	42% (35%-50%]	20% (12%-41%)	

[a]Surveillance here refers to studies that included data only from patients undergoing regular colonoscopy with polypectomy. Note that the first three studies are based on often not fully documented retrospective cohorts including patients with differing colonoscopy exposures and censoring at the time of first colonoscopy or first polypectomy.
[b]All studies reported the cumulative CRC risk at the age of 70 years, except for Broeke et al that reported the cumulative CRC risk at the age of 80.
[c]n.a. not analyzed.

reducing colonoscopy intervals below 2 years is generally not associated with a clinical benefit in LS.

Moreover, LS carriers with a history of previous CRC and hemicolectomy, or with a history of previous extracolonic cancer, present with a similarly high CRC risk as LS carriers without previous history of cancer.[59] Therefore, the option of more radical surgery at first CRC should be discussed with patients; alternatively, stringent surveillance measures for controlling CRC risk in LS patients have to be maintained also after first cancer diagnosis.[60-64]

Importantly, CRC risk and colonoscopy efficacy depend on the affected MMR gene: *MLH1* and *MSH2* carriers had a lifetime CRC risk of up to 50%,[57,65,66] which remained high despite regular colonoscopy surveillance.[52,57] On the other hand, *MSH6* [65,66] and *PMS2* [67] carriers had a substantially lower lifetime CRC risk, which might be further reduced by colonoscopy surveillance in *MSH6* carriers or even become unmeasurably low in *PMS2* carriers[52,57,68] (Table 2, Figure 1).

Difference in the protection against CRC afforded by colonoscopy in the general population compared to LS suggests that any biological differences between LS and sporadic CRC in the general population maybe important determinants of the success of colonoscopy in cancer prevention in these two settings. In recent years, several hypotheses have been proposed to explain the observed epidemiologic data.[55,69] We discuss current hypotheses and consider the most likely explanations for the reported observations.

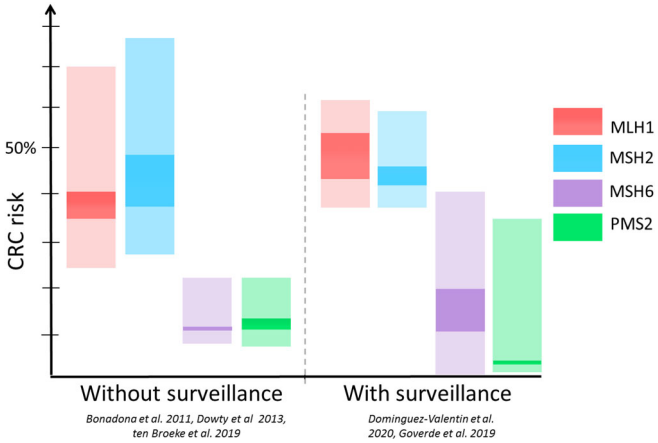

FIGURE 1 Schematic illustration of the effect of surveillance on CRC risk for different MMR gene variant carriers (based on the data summarized in Table 2). The CRC incidence is reduced by colonoscopy in *PMS2* carriers, and might be reduced by colonoscopy in *MSH6* carriers, whereas in *MLH1* and *MSH2* carriers CRC incidence seems not to be substantially influenced by colonoscopy surveillance. The darker shades represent the range of average risks reported by different studies for males and females, whereas the brighter shades represent the range of reported confidence intervals. Note: Influence of different penetrance in carriers of variant in different MMR genes on the colonoscopy efficacy cannot be formally excluded

3 | HYPOTHESES EXPLAINING CRC DESPITE SURVEILLANCE IN LS

3.1 | "Missed" lesions

One hypothesis to explain the occurrence of incident CRC in LS patients under colonoscopic surveillance is failure to identify or successfully remove adenomas. According to this hypothesis, improving the quality of colonoscopy would lead to improved detection and removal of adenomas and reduce incident cancers (Figure 2, "missed lesions"). The claim is that if colonoscopy is of high quality, all/most CRC in LS may be prevented.

Several factors impacting colonoscopy quality should be considered, including time-trends in techniques used, knowledge of what to look for, and inter-observer and intra-observer reproducibility. An incomplete colonoscopy that does not reach the caecum, inadequate bowel preparation, an inexperienced examiner, short withdrawal time

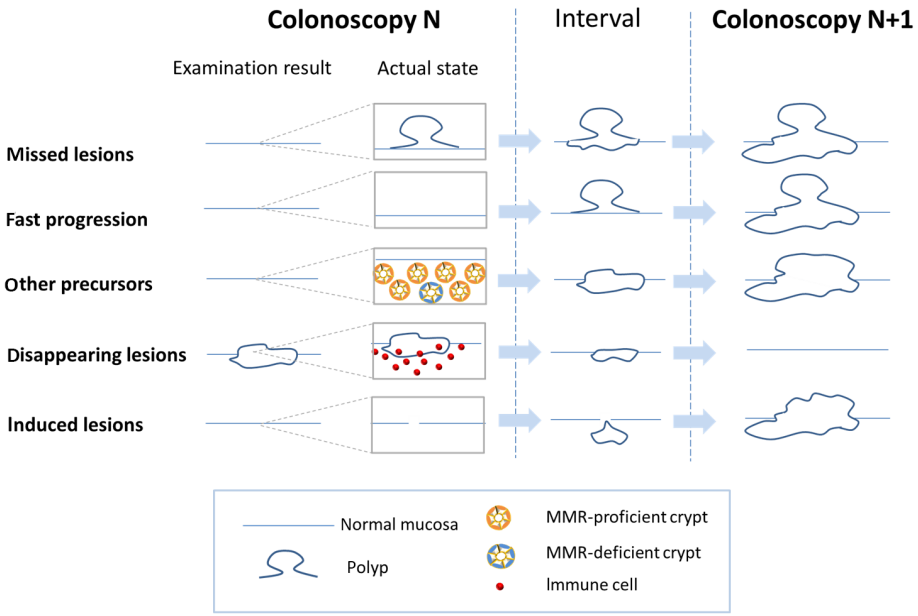

FIGURE 2 Summary of discussed hypotheses for CRC incidence in LS despite regular colonoscopy. The figure schematically summarizes the discussed hypotheses, including missed lesions, fast progression, alternative precursors, disappearing lesions and induced lesions, showing the hypothetical snapshots of colon during colonoscopy examination, of CRC progression/regression in the time intervals between colonoscopy examinations and of colon during the next examination

and the use of chromoendoscopy represent factors that may affect the likelihood of detecting polyps. In particular, small polyps or non-pedunculated flat lesions characteristic for LS may be overlooked.[70,71] A recent systematic review and meta-analysis demonstrated an adenoma miss rate as high as 33% in patients at increased CRC risk.[71] However, the majority of the studies conducted have not reported detailed quality measures for colonoscopy.[71,72]

Due to the wide acceptance of the adenoma-carcinoma model, adenomas removed have been often used as surrogate marker for CRCs prevented. One attempt to standardize colonoscopy quality across centers is the definition of the "adenoma detection rate" (ADR), describing the proportion of colonoscopies that result in the detection of an adenoma. In fact, ADR has been shown to inversely correlate with the risk of incident cancer.[73,74] However, using ADR for assessing surveillance quality in LS setting with regular examinations evidently has limitations, as population characteristics, namely the growth dynamics of adenomas in a given population, directly affect ADR. Accordingly, the highest possible and the lowest recommendable ADR for current LS surveillance colonoscopies are unknown and may depend on the distribution of pathogenic variants in the cohort, the extent of previous colectomies and the frequency of carriers ascertained without previous CRC. ADRs so far reported by independent studies vary: one large study that pooled prospective surveillance data from three different countries showed an average ADR of 16% per examination,[54] but ADR values as low as 10.6% and as high as 52.5% have been reported both before and after the implementation of a quality-improvement program.[73,75-79] A universal ADR cannot be determined due to geographical differences in adenoma risk as well as different target populations used to determine the ADR. Another important limitation of the ADR as a marker for high-quality colonoscopy is lack of information on the completeness of adenoma resection, as detected adenomas, when not completely resected, may also lead to incident cancer development.[80]

There is evidence that more sophisticated endoscopic modalities could lead to more efficient detection of adenomatous lesions during LS surveillance colonoscopy.[72,78,81-83] For example, it has been shown that chromoendoscopy, virtual chromoendoscopy (I-SCAN) and narrow-band imaging approaches allow detection of significantly more adenomas compared to standard colonoscopy.[78,81-83] A recent study reporting an optimized colonoscopy surveillance program suggested improvements in the cancer detection rate in LS without altering the ADR.[75] Another randomized controlled study analyzing neoplasia detection rates in LS at baseline and follow-up colonoscopy did not find a significant added value for chromoendoscopy over high-definition white-light endoscopy for the proximal colon,[77] nor did a randomized non-inferiority study comparing these two techniques for LS surveillance.[84] However, a clear time-trend toward higher ADR after the introduction of high-definition endoscopy has been observed by a recent study, also reporting development of incident cancers after the high-quality penultimate colonoscopy.[85]

Currently, it is not known how much optimization of colonoscopy—relating to all of the factors affecting colonoscopy quality discussed earlier—would reduce the occurrence of CRC in LS. Randomized controlled trials analyzing the impact of novel sensitive endoscopy techniques, including those using artificial intelligence-based approaches, on the ADR and on cancer incidence in LS are needed to clarify and quantify the contribution of "missed" lesions to incident cancers.

The surveillance colonoscopies currently reported in prospective studies have largely been conducted at highly specialized centers in different parts of the world. Given their expertise, and their ability to very effectively prevent CRC in the general population, it seems unlikely that inter-observer differences or technical limitations could be the only explanations for the high proportion of LS patients developing incident cancer while under regular colonoscopy surveillance. Although optimization of colonoscopy may reduce occurrence of CRC in LS, the extent of cancer prevention needs to be quantified in

prospective, ideally randomized international multicenter studies. To this end, time-trends will now be analyzed in the PLSD.

3.2 | Fast progression of newly formed adenomas

Another possible explanation for occurrence of CRC in LS carriers despite colonoscopy surveillance is provided by the hypothesis of accelerated progression from adenoma to carcinoma. This proposes that CRCs in LS develop from adenomas, but progression is so fast that there is often no time to detect and remove the lesion at pre-cancerous adenoma phase (Figure 2, "fast progression"). Several observations support this concept. In the general population, CRC formation usually involves a benign polypoid precursor stage and the transformation to invasive cancer appears to take 10 years or more.[86] This is why 10-yearly colonoscopy intervals are considered sufficient to successfully lower the incidence of CRC in the general population.[87,88] In LS, however, the progression to CRC has been suggested to be accelerated compared to the general population.[89-92] The different progression times indicate that there are biological differences between CRC development in LS carriers and the general population.

A study estimating the polyp dwell time has demonstrated a time period of approximately 3 years being required for the development of an advanced lesion, with an equal dwell time to adenoma as to cancer formation.[93] Calculations of longitudinal parameters, such as progression time, based on cross-sectional observations have to be interpreted with caution. However, equal dwell times of adenomas and cancers could have two possible reasons: either the progression from adenoma to carcinoma is very fast, or dwell time to adenoma and dwell time to carcinoma are not always connected by one linear progression, but rather represent two distinct branches of progression with different end points.

The hypothesis of accelerated progression is also consistent with the minor differences in adenoma incidence in LS compared to the general population.[25,26] This finding has been interpreted as supporting evidence for the hypothesis that elevated CRC risk in LS patients does not result from an increased likelihood of adenoma initiation as in FAP, but rather from accelerated progression of pre-existing adenomas into cancer due to acquisition of MMR deficiency and an increased mutation rate.[89,91,94,95] The hypothesis of faster progression was further supported by the correlation of MMR deficiency with larger size and higher grade of adenomas in LS,[25,96-100] though some studies reported high-grade dysplasia and MSI phenotype in lesions smaller than 5 mm.[25]

Although it seems highly likely that a subset of LS CRCs follow the tumorigenesis model proposed by the hypothesis of accelerated progression, other evidence suggests that many CRCs in LS, perhaps even the majority, do not. As discussed earlier, application of colonoscopy surveillance every 3 years has led to halving of the CRC risk and a reduction in CRC-related mortality; however, further improvement was not achieved by shortening colonoscopy intervals from 3 years down to 1 year, as shown by a PLSD study.[53] This was also confirmed by a large prospective observational study of three European LS registries comparing the outcomes of different surveillance protocols in three countries and showing no difference in the incidence of CRC between the three different colonoscopy intervals (annual, 2- and 3-yearly colonoscopy).[54] There was also no difference in the stage of CRCs detected, a finding which was later confirmed by studies of the PLSD.[55] A recent study in the PLSD reported no difference in CRC survival associated with the time since last colonoscopy prior to CRC diagnosis.[56] In summary, these reports question the assumptions underlying current clinical guidelines for colonoscopy in carriers: AGA: 1-2-year interval (GRADE low-quality evidence)[101]; ACG: at least 2-year interval (moderate quality and very low-quality evidence for annual interval)[102]; ASCO & ESMO: 1-2 year interval[103]; ESGE: 2-year interval (moderate-quality evidence)[104]; updated guidelines of EHTG are currently in preparation.

Interestingly, the success of colonoscopic surveillance could depend on which MMR gene is involved. For example, *PMS2* carriers undergoing regular colonoscopy have negligible CRC risk, especially at young ages,[52,105] and low CRC risks have also been shown for *MSH6* carriers under surveillance.[52,57] Such observations, further corroborated by distinct molecular characteristics of tumors from different MMR carriers,[106] could point to biological differences between colorectal tumorigenesis in different genetic backgrounds: the apparently hard-to-detect cancer precursors present in *MLH1* and *MSH2* carriers seem to be absent or very rare in *PMS2 or MSH6* carriers and the general population. These differences should be considered when formulating guidelines for management of LS.

3.3 | Not all CRCS in LS develop in a macroscopically visible adenoma, and not all adenomas are precursors

In recent years, evidence for colonoscopically invisible precursor lesions, or alternative, "adenoma-free" progression routes to cancer, has accumulated. Such routes could start from mismatch repair-deficient crypt foci (MMR-DCF) that are found in the normal-looking colonic mucosa of LS carriers but not in sporadic MSI CRC patients (Figure 2, "other precursors").[107,108] These lesions are not only undetectable by colonoscopy, but also microscopically unidentifiable, unless MMR protein staining is performed.[107,108] MMR-DCF exhibit MSI and carry mutations in microsatellite-bearing genes, also found in advanced lesions[109], suggesting their potential as cancer precursors.

Molecular analysis of LS CRC in fact indicates that MMR deficiency is often an early or even initiating event,[110,111] which frequently precedes canonical mutations affecting the genes *APC* and *KRAS*.[112] Moreover, it has been demonstrated that a substantial proportion of LS-associated CRC may develop without an adenomatous phase: LS CRCs that did not display features of cancer-adjacent adenoma cells were associated with specific molecular alterations, mainly *CTNNB1* and *TP53* mutations.[96,99] This observation indicates the

possibility that alternative molecular progression events, similar to inflammatory bowel disease (IBD)-associated colorectal neoplasia that are commonly initiated by APC-independent events,[113,114] are associated with the lack of polypoid precursor lesions.[115] This pathway of progression seems to be less common in *PMS2*-associated CRC, an observation that may reflect the minimal risk of cancers in *PMS2* carriers under surveillance.[116]

Thus, existing data strongly suggest that the assumption of a sequential model of colorectal carcinogenesis in LS where CRC is always preceded by an adenoma is wrong or, at least, a considerable oversimplification.[117,118] Thus, accounting for the diversity of colorectal carcinogenesis suggested by Jeremy Jass,[117,118] it is important to acknowledge the heterogeneity of LS CRCs. Instead of seeking one model for all cases, at least three pathways should be considered: (a) progression from an adenoma with secondary inactivation of the MMR system, (b) progression from an initially MMR-deficient adenoma and (c) progression from MMR-DCF directly to invasive cancer without adenoma formation.[110]

If there is more than one pathway to CRC in LS, what is the relative contribution of each? This question is difficult to answer precisely. Importantly, LS carcinogenesis might be influenced by the "observation" itself having an effect on the observed data. Here, the process of observation, that is, colonoscopy, may affect the disease status, either because the relative contributions of the three pathways are changed by removing adenomas, or because of the colonoscopy-mediated effects influencing carcinogenesis (as discussed later). The results reported by PLSD, in which cancers continued to develop despite colonoscopy, may reflect the effect of colonoscopy blocking progression from adenomas as precursors, and thereby increasing the proportion of CRCs progressing through a different molecular pathway, potentially similar to nonpolypoid CRCs in IBD patients,[115] via direct invasive growth without a polypoid precursor. Notably, molecular evidence from CRCs suggest that the proportion of cancers progressing through the second and the third, MMR deficiency-initiated pathways outweigh the proportion of cancers progressing through the first, adenoma-initiated pathway in LS.[110]

This conclusion has wide-ranging implications. First, it explains why even high-quality, short-interval colonoscopy with meticulous inspection of the intestinal mucosa and removal of all polyps cannot completely prevent LS-associated CRC, as CRC may develop without ever passing through a detectable non-invasive phase. Second, it predicts that any approach targeting MMR-deficient cells should be very effective in preventing the majority of LS-associated CRCs, particularly non-polypous cancers. Third, studies assessing CRC development in LS need to account for colonoscopy surveillance as a factor in the populations studied. Fourth, a better understanding of non-adenoma precursors is needed to define suitable end points for prevention trials and improve prevention and surveillance strategies. This is underlined by the observation of the CAPP2 study that, similar to observations in the general population,[119] reported a significant reduction in incidence of CRC, but not of colorectal adenomas, upon regular aspirin use.[120]

Conceptually, the hypothesis of invisible lesions is very similar to the hypothesis of missed lesions, with one very important difference: the hypothesis of missed lesions assumes that an improvement of colonoscopy techniques, shorter surveillance intervals or better training of gastroenterologists will make the invisible visible, at a phase of pre-invasive tumor development. Whether this is true and to what extent, remains to be demonstrated in prospective studies.

4 | HYPOTHESES ADDRESSING THE HIGHER CRC INCIDENCE OBSERVED WITH MORE FREQUENT COLONOSCOPY SURVEILLANCE

4.1 | Overdiagnosis and disappearing lesions

The trend toward higher CRC incidence in groups of LS patients subjected to colonoscopy with shorter intervals[53] is surprising and could be explained by the spontaneous disappearance of colonic lesions. This is theoretically possible for precancerous lesions or even for invasive cancers (Figure 2, "disappearing lesions").[55] If true, longer colonoscopy intervals may tend to result in fewer identified lesions, because one has to look frequently to catch lesions destined to disappear between colonoscopies. Shortening of the colonoscopy interval could lead to detection of lesions that otherwise would have been eliminated by patient's immune system. Biological support for this hypothesis comes from data on MMR-DCF prevalence and LS penetrance: the number of MMR-DCF per LS patient is estimated to be 1000 times or more the numbers of manifest cancers.[107] On the one hand, such a low progression rate might be explained by acquisition of growth-repressing mutations leading to apoptosis or oncogenic mutations leading to oncogene-induced senescence of MMR-DCF; on the other hand, immune responses against these lesions could contribute to their elimination. It is known that LS-associated cancers are highly immunogenic, as shown by dense immune infiltration and Crohn's-like reactions observed in these tumors,[12,14] as well as their response to immune checkpoint blockade therapy.[16,19] LS-associated CRCs, as well as MMR-DCFs, have been shown to carry coding microsatellite mutations, resulting in the generation of FSPs that can elicit strong immune responses and cause *in vitro* killing of FSP-expressing cells by T cells.[121] Moreover, systemic cellular immune responses to FSP have been found in the blood of healthy LS carriers,[15] suggesting that FSP *neo*antigen-specific T cells may eliminate MMR-deficient lesions that might include both MMR-DCFs and more advanced lesions. Indeed, it has been shown that adenomas can regress,[122-124] and even cancers can be attacked by immune responses of the host and should be particularly vulnerable in LS due to a high tumor mutational burden and tumor-associated antigen load.[125-128] The low probability of lymph node and distant metastases and the good prognosis of LS-related CRC may also reflect the immune system's capability to restrain CRC.

It would be interesting to monitor the progression rate of adenomas in LS over time; however, due to ethical considerations such a study could not reasonably be conducted in humans. Recently developed organoid models may facilitate research into carcinogenetic

cascades in multiple organs. The favorable culture time and ability to retain genetic stability over time of such models may help to circumvent the complexity of *in vivo* studies of adenomas, carcinomas and immune response in humans.[129]

In short, the probability for developing a malignancy may be described as a balance between the carcinogenic mechanisms producing CRCs and the host's immune system removing them.

Alternatively, higher CRC incidence upon shorter colonoscopy intervals could be explained by the different penetrance of pathogenic variants in the same MMR gene (eg, strong founder mutation effect in the Finnish population[58]). Currently available data do not suggest a major influence of this factor,[53,57] though future studies are warranted.

4.2 | Induced lesions

The observation of a higher CRC incidence occurring in the context of shorter colonoscopy intervals is also consistent with colonoscopy itself playing a role in the pathogenesis of CRC (Figure 2, "induced lesions"). However, given the success story of colonoscopy in CRC prevention in the general population, this theoretical possibility seems unlikely in practice. Despite this, at least two colonoscopy-associated factors can be proposed that might favor tumor progression under certain circumstances. First, bowel preparation prior to colonoscopy affects the microbiome composition of the colon in a persisting way.[130] The impact of certain bacterial species in the development of CRC through modulation of the immune response has been extensively studied;[131-134] and it is conceivable that bowelpreparation-initiated microbiome changes may be related, positively or negatively, with CRC progression in the individual being examined. It is possible that such effects, even if minor at the individual level, may become detectable in a larger population. A second factor linked to the examination procedure itself is mechanical irritation. In theory, local pressure, distension and abrasion by the endoscope could lead to microinjuries of the mucosal surface, particularly if biopsies are taken, disturbing cell–cell contacts and damaging the mucosa. This could lead to the initiation or acceleration of a malignant process, particularly if MMR-deficient cells are in the vicinity. A recent study analyzing the impact of colonoscopy on the development of metachronous CRC has shown the possibility of tumor seeding during colonoscopy; the risk of such tumor cell spreading was estimated to be 0.3% to 0.6%.[135] However, the authors are not aware of any further experimental evidence supporting these theories so far. Therefore, colonoscopy will remain one central pillar of cancer prevention in LS with a reported risk of severe complications of, at most, 0.3%.[136,137]

5 | SUMMARY

CRC incidence in LS remains high despite regular colonoscopy. Although technical limitations may explain some incident cancers, strong evidence indicates that multiple CRC precursors in LS follow distinct fates of persistence, progression or regression depending on several factors. If we acknowledge these possibilities, we can better interrogate the biologic diversity and complexity of LS. By designing clinical trials that produce data analyzable for the distinct pathways separately, we will learn more about LS carcinogenesis. This knowledge will be essential to refine prevention and treatment strategies for LS patients.

ACKNOWLEDGMENTS

Work in the authors' lab (AA, MvKD, MK) was supported by Wilhelm Sander Foundation. TTS and JPM's work was supported by Finnish Cancer Foundation, Jane and Aatos Erkko Foundation, Emil Aaltonen Foundation, Finnish Medical Foundation, Sigrid Juselius Foundation, Instrumentarium Science Foundation. All contributors participating in the generation of the data discussed in this review article are gratefully acknowledged. Open access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

Potential financial conflict of interest outside the present work: Toni Seppälä is CEO and co-owner of Healthfund Finland. Potential personal conflict of interest: Finlay Macrae is practicing, publically funded colonoscopist; counselor of the International Society for Gastrointestinal Hereditary Tumors.

All other authors have no conflicts of interests to declare.

ORCID

Aysel Ahadova https://orcid.org/0000-0001-9890-0450
Christoph Engel https://orcid.org/0000-0002-7247-282X
Verena Steinke-Lange https://orcid.org/0000-0001-8491-3234
Mev Dominguez-Valentin https://orcid.org/0000-0001-7856-0057

REFERENCES

1. de la Chapelle A. Microsatellite instability. *N Engl J Med*. 2003;349:209-210.
2. de la Chapelle A. The incidence of Lynch syndrome. *Fam Cancer*. 2005;4:233-237.
3. Seth S, Ager A, Arends MJ, Frayling IM. Lynch syndrome—cancer pathways, heterogeneity and immune escape. *J Pathol*. 2018;246:129-133.
4. World Health Organization. *WHO Classification of Tumours: Digestive System Tumors*. 5th ed. Geneva, Switzerland: World Health Organization; 2019.
5. Win AK, Jenkins MA, Dowty JG, et al. Prevalence and penetrance of major genes and polygenes for colorectal cancer. *Cancer Epidemiol Biomarkers Prev*. 2017;26:404-412.
6. Plazzer JP, Sijmons RH, Woods MO, et al. The InSiGHT database: utilizing 100 years of insights into Lynch syndrome. *Fam Cancer*. 2013;12:175-180.
7. Knudson AG Jr. Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci U S A*. 1971;68:820-823.
8. Hampel H, Frankel WL, Martin E, et al. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. *J Clin Oncol*. 2008;26:5783-5788.
9. Chalmers ZR, Connelly CF, Fabrizio D, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. *Genome Med*. 2017;9(34):34.

10. Jiricny J. Postreplicative mismatch repair. *Cold Spring Harb Perspect Biol*. 2013;5:a012633.
11. Kloor M, von Knebel Doeberitz M. The immune biology of microsatellite-unstable cancer. *Trend Cancer*. 2016;2:121-133.
12. Dolcetti R, Viel A, Doglioni C, et al. High prevalence of activated intraepithelial cytotoxic T lymphocytes and increased neoplastic cell apoptosis in colorectal carcinomas with microsatellite instability. *Am J Pathol*. 1999;154:1805-1813.
13. Smyrk TC, Watson P, Kaul K, Lynch HT. Tumor-infiltrating lymphocytes are a marker for microsatellite instability in colorectal carcinoma. *Cancer*. 2001;91:2417-2422.
14. Buckowitz A, Knaebel HP, Benner A, et al. Microsatellite instability in colorectal cancer is associated with local lymphocyte infiltration and low frequency of distant metastases. *Br J Cancer*. 2005;92:1746-1753.
15. Schwitalle Y, Kloor M, Eiermann S, et al. Immune response against frameshift-induced neopeptides in HNPCC patients and healthy HNPCC mutation carriers. *Gastroenterology*. 2008;134:988-997.
16. Le DT, Durham JN, Smith KN, et al. Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. *Science*. 2017;357:409-413.
17. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. *J Clin Oncol*. 2005;23:609-618.
18. Mlecnik B, Bindea G, Angell HK, et al. Integrative analyses of colorectal cancer show immunoscore is a stronger predictor of patient survival than microsatellite instability. *Immunity*. 2016;44:698-711.
19. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med*. 2015;372:2509-2520.
20. Peltomaki P, Aaltonen LA, Sistonen P, et al. Genetic mapping of a locus predisposing to human colorectal cancer. *Science*. 1993;260:810-812.
21. Thibodeau SN, Bren G, Schaid D. Microsatellite instability in cancer of the proximal colon. *Science*. 1993;260:816-819.
22. Lindblom A, Tannergard P, Werelius B, et al. Genetic mapping of a second locus predisposing to hereditary non-polyposis colon cancer. *Nat Genet*. 1993;5:279-282.
23. Boland CR, Lynch HT. The history of Lynch syndrome. *Fam Cancer*. 2013;12:145-157.
24. Boland CR. Evolution of the nomenclature for the hereditary colorectal cancer syndromes. *Fam Cancer*. 2005;4:211-218.
25. De Jong AE, Morreau H, Van Puijenbroek M, et al. The role of mismatch repair gene defects in the development of adenomas in patients with HNPCC. *Gastroenterology*. 2004;126:42-48.
26. Lynch HT, Snyder CL, Shaw TG, Heinen CD, Hitchins MP. Milestones of Lynch syndrome: 1895-2015. *Nat Rev Cancer*. 2015;15:181-194.
27. Love RR. Adenomas are precursor lesions for malignant growth in nonpolyposis hereditary carcinoma of the colon and rectum. *Surg Gynecol Obstet*. 1986;162:8-12.
28. Jass JR, Stewart SM. Evolution of hereditary non-polyposis colorectal cancer. *Gut*. 1992;33:783-786.
29. Gupta N, Kupfer SS, Davis AM. Colorectal cancer screening. *JAMA*. 2019;321:2022-2023.
30. Samadder NJ, Curtin K, Pappas L, et al. Risk of incident colorectal cancer and death after colonoscopy: a population-based study in Utah. *Clin Gastroenterol Hepatol*. 2016;14:279-286 e1-2.
31. Brenner H, Chang-Claude J, Seiler CM, Rickert A, Hoffmeister M. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. *Ann Intern Med*. 2011;154:22-30.
32. Brenner H, Stock C, Hoffmeister M. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. *BMJ*. 2014;348:g2467.
33. Bretthauer M, Kalager M. Colonoscopy as a triage screening test. *N Engl J Med*. 2012;366:759-760.
34. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med*. 1993;329:1977-1981.
35. Doubeni CA, Corley DA, Quinn VP, et al. Effectiveness of screening colonoscopy in reducing the risk of death from right and left colon cancer: a large community-based study. *Gut*. 2018;67:291-298.
36. Brenner H, Hoffmeister M, Arndt V, Stegmaier C, Altenhofen L, Haug U. Protection from right- and left-sided colorectal neoplasms after colonoscopy: population-based study. *J Natl Cancer Inst*. 2010;102:89-95.
37. Brenner H, Chang-Claude J, Seiler CM, Hoffmeister M. Interval cancers after negative colonoscopy: population-based case-control study. *Gut*. 2012;61:1576-1582.
38. Fitzgibbons RJ Jr, Lynch HT, Stanislav GV, et al. Recognition and treatment of patients with hereditary nonpolyposis colon cancer (Lynch syndromes I and II). *Ann Surg*. 1987;206:289-295.
39. Aarnio M, Mecklin JP, Aaltonen LA, Nyström-Lahti M, Järvinen HJ. Life-time risk of different cancers in hereditary non-polyposis colorectal cancer (HNPCC) syndrome. *Int J Cancer*. 1995;64:430-433.
40. Barrow E, Hill J, Evans DG. Cancer risk in Lynch syndrome. *Fam Cancer*. 2013;12:229-240.
41. Jarvinen HJ, Aarnio M, Mustonen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology*. 2000;118:829-834.
42. Mecklin JP, Aarnio M, Laara E, et al. Development of colorectal tumors in colonoscopic surveillance in Lynch syndrome. *Gastroenterology*. 2007;133:1093-1098.
43. Vasen HF, Nagengast FM, Khan PM. Interval cancers in hereditary non-polyposis colorectal cancer (Lynch syndrome). *Lancet*. 1995;345:1183-1184.
44. de Vos tot Nederveen Cappel WH, Nagengast FM, Griffioen G, et al. Surveillance for hereditary nonpolyposis colorectal cancer: a long-term study on 114 families. *Dis Colon Rectum*. 2002;45:1588-1594.
45. Jarvinen HJ, Renkonen-Sinisalo L, Aktan-Collan K, et al. Ten years after mutation testing for Lynch syndrome: cancer incidence and outcome in mutation-positive and mutation-negative family members. *J Clin Oncol*. 2009;27:4793-4797.
46. Stupart DA, Goldberg PA, Algar U, Ramesar R. Surveillance colonoscopy improves survival in a cohort of subjects with a single mismatch repair gene mutation. *Colorectal Dis*. 2009;11:126-130.
47. Engel C, Rahner N, Schulmann K, et al. Efficacy of annual colonoscopic surveillance in individuals with hereditary nonpolyposis colorectal cancer. *Clin Gastroenterol Hepatol*. 2010;8:174-182.
48. Vasen HF, Abdirahman M, Brohet R, et al. One to 2-year surveillance intervals reduce risk of colorectal cancer in families with Lynch syndrome. *Gastroenterology*. 2010;138:2300-2306.
49. Newton K, Green K, Lalloo F, Evans DG, Hill J. Colonoscopy screening compliance and outcomes in patients with Lynch syndrome. *Colorectal Dis*. 2015;17:38-46.
50. Moller P. The prospective Lynch syndrome database reports enable evidence-based personal precision health care. *Hered Cancer Clin Pract*. 2020;18:6.
51. Moller P, Seppala T, Bernstein I, et al. Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. *Gut*. 2017;66:464-472.
52. Dominguez-Valentin M, Sampson JR, Seppala TT, 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(1):15–25.
53. Seppala T, Pylvanainen K, Evans DG, et al. Colorectal cancer incidence in path_MLH1 carriers subjected to different follow-up

protocols: a prospective Lynch syndrome database report. *Hered Cancer Clin Pract*. 2017;15(18):18.
54. Engel C, Vasen HF, Seppala 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.e2-1409.e2.
55. Seppala TT, Ahadova A, Dominguez-Valentin M, et al. Lack of association between screening interval and cancer stage in Lynch syndrome may be accounted for by over-diagnosis; a prospective Lynch syndrome database report. *Hered Cancer Clin Pract*. 2019;17(8). https://doi.org/10.1186/s13053-019-0106-8.
56. Dominguez-Valentin M, Seppala TT, Sampson JR, et al. Survival by colon cancer stage and screening interval in Lynch syndrome: a prospective Lynch syndrome database report. *Hered Cancer Clin Pract*. 2019;17(28). https://doi.org/10.1186/s13053-019-0127-3.
57. Dowty JG, Win AK, Buchanan DD, et al. Cancer risks for MLH1 and MSH2 mutation carriers. *Hum Mutat*. 2013;34:490-497.
58. Nystrom-Lahti M, Kristo P, Nicolaides NC, et al. Founding mutations and Alu-mediated recombination in hereditary colon cancer. *Nat Med*. 1995;1:1203-1206.
59. Moller P, Seppala T, Bernstein I, et al. Incidence of and survival after subsequent cancers in carriers of pathogenic MMR variants with previous cancer: a report from the prospective Lynch syndrome database. *Gut*. 2017;66:1657-1664.
60. Anele CC, Adegbola SO, Askari A, et al. Risk of metachronous colorectal cancer following colectomy in Lynch syndrome: a systematic review and meta-analysis. *Colorectal Dis*. 2017;19:528-536.
61. Heneghan HM, Martin ST, Winter DC. Segmental vs extended colectomy in the management of hereditary nonpolyposis colorectal cancer: a systematic review and meta-analysis. *Colorectal Dis*. 2015;17:382-389.
62. Parry S, Win AK, Parry B, et al. Metachronous colorectal cancer risk for mismatch repair gene mutation carriers: the advantage of more extensive colon surgery. *Gut*. 2011;60:950-957.
63. Roh SJ, Hong YH, Kim BC, et al. Analysis of metachronous colorectal neoplasms and survival following segmental or extended resection in patients with hereditary non-polyposis colorectal cancer. *Int J Colorectal Dis*. 2020;35:1273-1282.
64. Quezada-Diaz FF, Hameed I, von Mueffling A, et al. Risk of metachronous colorectal neoplasm after a segmental colectomy in Lynch syndrome patients according to mismatch repair gene status. *J Am Coll Surg*. 2020;230:669-675.
65. Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-society Task Force on colorectal cancer. *Am J Gastroenterol*. 2014;109:1159-1179.
66. Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA*. 2011;305:2304-2310.
67. Ten Broeke SW, van der Klift HM, Tops CMJ, et al. Cancer risks for PMS2-associated Lynch syndrome. *J Clin Oncol*. 2018;36:2961-2968.
68. Goverde A, Eikenboom EL, Viskil EL, et al. Yield of Lynch syndrome surveillance for patients with pathogenic variants in DNA mismatch repair genes. *Clin Gastroenterol Hepatol*. 2020;18(5):1112–1120.
69. Boland PM, Yurgelun MB, Boland CR. Recent progress in Lynch syndrome and other familial colorectal cancer syndromes. *CA Cancer J Clin*. 2018;68:217-231.
70. Rondagh EJ, Gulikers S, Gomez-Garcia EB, et al. Nonpolypoid colorectal neoplasms: a challenge in endoscopic surveillance of patients with Lynch syndrome. *Endoscopy*. 2013;45:257-264.
71. Zhao S, Wang S, Pan P, et al. Magnitude, risk factors, and factors associated with adenoma miss rate of tandem colonoscopy: a systematic review and meta-analysis. *Gastroenterology*. 2019;156:1661.e11-1674.e11.
72. van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. *Am J Gastroenterol*. 2006;101:343-350.
73. Corley DA, Jensen CD, Marks AR, et al. Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med*. 2014;370:1298-1306.
74. Kaminski MF, Regula J, Kraszewska E, et al. Quality indicators for colonoscopy and the risk of interval cancer. *N Engl J Med*. 2010;362:1795-1803.
75. Perrod G, Samaha E, Rahmi G, et al. Impact of an optimized colonoscopic screening program for patients with Lynch syndrome: 6-year results of a specialized French network. *Therap Adv Gastroenterol*. 2018;11:1756284818775058.
76. Vleugels JLA, Sahin H, Hazewinkel Y, et al. Endoscopic detection rate of sessile serrated lesions in Lynch syndrome patients is comparable with an age- and gender-matched control population: case-control study with expert pathology review. *Gastrointest Endosc*. 2018;87:1289-1296.
77. Haanstra JF, Dekker E, Cats A, et al. Effect of chromoendoscopy in the proximal colon on colorectal neoplasia detection in Lynch syndrome: a multicenter randomized controlled trial. *Gastrointest Endosc*. 2019;90:624-632.
78. Rahmi G, Lecomte T, Malka D, et al. Impact of chromoscopy on adenoma detection in patients with Lynch syndrome: a prospective, multicenter, blinded, tandem colonoscopy study. *Am J Gastroenterol*. 2015;110:288-298.
79. Liljegren A, Barker G, Elliott F, et al. Prevalence of adenomas and hyperplastic polyps in mismatch repair mutation carriers among CAPP2 participants: report by the colorectal adenoma/carcinoma prevention programme 2. *J Clin Oncol*. 2008;26:3434-3439.
80. Lamba M, Ebel R, Hamilton SM, et al. What's my risk of cancer doctor? Interval colorectal cancer risk in Lynch syndrome: Results from the New Zealand National Registry. *Gastroenterology*. 2019;156(6):S-179.
81. East JE, Suzuki N, Stavrinidis M, Guenther T, Thomas HJ, Saunders BP. Narrow band imaging for colonoscopic surveillance in hereditary non-polyposis colorectal cancer. *Gut*. 2008;57:65-70.
82. Bisschops R, Tejpar S, Willekens H, de Hertogh G, van Cutsem E. Virtual chromoendoscopy (I-SCAN) detects more polyps in patients with Lynch syndrome: a randomized controlled crossover trial. *Endoscopy*. 2017;49:342-350.
83. Huneburg R, Lammert F, Rabe C, et al. Chromocolonoscopy detects more adenomas than white light colonoscopy or narrow band imaging colonoscopy in hereditary nonpolyposis colorectal cancer screening. *Endoscopy*. 2009;41:316-322.
84. Rivero-Sanchez L, Arnau-Collell C, Herrero J, et al. White-light endoscopy is adequate for Lynch syndrome surveillance in a randomized and non-inferiority study. *Gastroenterology*. 2020;158(4):895–904.
85. Lappalainen J, Holmstrom D, Lepisto A, et al. Incident colorectal cancer in Lynch syndrome is usually not preceded by compromised quality of colonoscopy. *Scand J Gastroenterol*. 2019;54:1473-1480.
86. Stryker SJ, Wolff BG, Culp CE, Libbe SD, Ilstrup DM, MacCarty RL. Natural history of untreated colonic polyps. *Gastroenterology*. 1987;93:1009-1013.
87. Stock D, Paszat LF, Rabeneck L. Colorectal cancer mortality reduction is associated with having at least 1 colonoscopy within the previous 10 years among a population-wide cohort of screening age. *Gastrointest Endosc*. 2016;84:133-141.
88. Chen C, Stock C, Hoffmeister M, Brenner H. How long does it take until the effects of endoscopic screening on colorectal cancer mortality are fully disclosed?: a Markov model study. *Int J Cancer*. 2018;143:2718-2724.

89. Jass JR, Young J, Leggett BA. Evolution of colorectal cancer: change of pace and change of direction. *J Gastroenterol Hepatol*. 2002;17:17-26.
90. Dove-Edwin I, de Jong AE, Adams J, et al. Prospective results of surveillance colonoscopy in dominant familial colorectal cancer with and without Lynch syndrome. *Gastroenterology*. 2006;130: 1995-2000.
91. Fearon ER. Molecular genetics of colorectal cancer. *Annu Rev Pathol*. 2011;6:479-507.
92. Reitmair AH, Cai JC, Bjerknes M, et al. MSH2 deficiency contributes to accelerated APC-mediated intestinal tumorigenesis. *Cancer Res*. 1996;56:2922-2926.
93. Edelstein DL, Axilbund J, Baxter M, et al. Rapid development of colorectal neoplasia in patients with Lynch syndrome. *Clin Gastroenterol Hepatol*. 2011;9:340-343.
94. Goh HS, Jass JR. DNA content and the adenoma-carcinoma sequence in the colorectum. *J Clin Pathol*. 1986;39:387-392.
95. Lynch HT, Smyrk T, Jass JR. Hereditary nonpolyposis colorectal cancer and colonic adenomas: aggressive adenomas? *Semin Surg Oncol*. 1995;11:406-410.
96. Halvarsson B, Lindblom A, Johansson L, Lagerstedt K, Nilbert M. Loss of mismatch repair protein immunostaining in colorectal adenomas from patients with hereditary nonpolyposis colorectal cancer. *Mod Pathol*. 2005;18:1095-1101.
97. Meijer TW, Hoogerbrugge N, Nagengast FM, et al. In Lynch syndrome adenomas, loss of mismatch repair proteins is related to an enhanced lymphocytic response. *Histopathology*. 2009;55:414-422.
98. Rijcken FE, Hollema H, Kleibeuker JH. Proximal adenomas in hereditary non-polyposis colorectal cancer are prone to rapid malignant transformation. *Gut*. 2002;50:382-386.
99. Jacoby RF, Marshall DJ, Kailas S, et al. Genetic instability associated with adenoma to carcinoma progression in hereditary nonpolyposis colon cancer. *Gastroenterology*. 1995;109:73-82.
100. Iino H, Simms L, Young J, et al. DNA microsatellite instability and mismatch repair protein loss in adenomas presenting in hereditary non-polyposis colorectal cancer. *Gut*. 2000;47:37-42.
101. Rubenstein JH, Enns R, Heidelbaugh J, et al. American Gastroenterological Association Institute Guideline on the diagnosis and management of Lynch syndrome. *Gastroenterology*. 2015;149:777-782; quiz e16-7.
102. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol*. 2015;110:223-262; quiz 263.
103. Stoffel EM, Mangu PB, Gruber SB, et al. 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 Clin Oncol*. 2015;33:209-217.
104. 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.
105. Moller P, Seppala TT, 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.
106. Engel C, Ahadova A, Seppala T, et al. Associations of pathogenic variants in MLH1, MSH2, and MSH6 with risk of colorectal adenomas and tumors and with somatic mutations in patients with Lynch syndrome. *Gastroenterology*. 2020;158:1326-1333.
107. Kloor M, Huth C, Voigt AY, et al. Prevalence of mismatch repair-deficient crypt foci in Lynch syndrome: a pathological study. *Lancet Oncol*. 2012;13:598-606.
108. Pai RK, Dudley B, Karloski E, et al. DNA mismatch repair protein deficient non-neoplastic colonic crypts: a novel indicator of Lynch syndrome. *Mod Pathol*. 2018;31:1608-1618.
109. Staffa L, Echterdiek F, Nelius N, et al. Mismatch repair-deficient crypt foci in Lynch syndrome—molecular alterations and association with clinical parameters. *PLoS One*. 2015;10:e0121980.
110. Ahadova A, Gallon R, Gebert J, et al. Three molecular pathways model colorectal carcinogenesis in Lynch syndrome. *Int J Cancer*. 2018;143:139-150.
111. Sekine S, Mori T, Ogawa R, et al. Mismatch repair deficiency commonly precedes adenoma formation in Lynch syndrome-associated colorectal tumorigenesis. *Mod Pathol*. 2017;30:1144-1151.
112. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell*. 1990;61:759-767.
113. Galandiuk S, Rodriguez-Justo M, Jeffery R, et al. Field cancerization in the intestinal epithelium of patients with Crohn's ileocolitis. *Gastroenterology*. 2012;142:855.e8-864.e8.
114. Baker AM, Cross W, Curtius K, et al. Evolutionary history of human colitis-associated colorectal cancer. *Gut*. 2019;68:985-995.
115. Ullman TA, Itzkowitz SH. Intestinal inflammation and cancer. *Gastroenterology*. 2011;140:1807-1816.
116. Ten Broeke SW, van Bavel TC, Jansen AML, et al. Molecular background of colorectal tumors from patients with Lynch syndrome associated with germline variants in PMS2. *Gastroenterology*. 2018; 155:844-851.
117. Jass JR. Do all colorectal carcinomas arise in preexisting adenomas? *World J Surg*. 1989;13:45-51.
118. Jass JR. Pathogenesis of colorectal cancer. *Surg Clin North Am*. 2002; 82:891-904.
119. Amitay EL, Carr PR, Jansen L, et al. Association of aspirin and nonsteroidal anti-inflammatory drugs with colorectal cancer risk by molecular subtypes. *J Natl Cancer Inst*. 2019;111:475-483.
120. Burn J, Gerdes AM, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet*. 2011;378:2081-2087.
121. Linnebacher M, Gebert J, Rudy W, et al. Frameshift peptide-derived T-cell epitopes: a source of novel tumor-specific antigens. *Int J Cancer*. 2001;93:6-11.
122. Pickhardt PJ, Kim DH, Pooler BD, et al. Assessment of volumetric growth rates of small colorectal polyps with CT colonography: a longitudinal study of natural history. *Lancet Oncol*. 2013;14:711-720.
123. Sievers CK, Zou LS, Pickhardt PJ, et al. Subclonal diversity arises early even in small colorectal tumours and contributes to differential growth fates. *Gut*. 2017;66:2132-2140.
124. Basso G, Carnaghi CRD, Bossi P, et al. Spontaneous remission of metachronous neoplastic lesions in a lynch syndrome patient: efficient immune reaction deciphered by modern medicine? International society for gastrointestinal hereditary tumours-InSiGHT. *Fam Cancer*. 2017;16:1-134.
125. Erdman SE, Sohn JJ, Rao VP, et al. CD4+CD25+ regulatory lymphocytes induce regression of intestinal tumors in ApcMin/+ mice. *Cancer Res*. 2005;65:3998-4004.
126. Cavalleri T, Bianchi P, Basso G, et al. Combined low densities of FoxP3(+) and CD3(+) tumor-infiltrating lymphocytes identify stage II colorectal cancer at high risk of progression. *Cancer Immunol Res*. 2019;7:751-758.
127. Karakuchi N, Shimomura M, Toyota K, et al. Spontaneous regression of transverse colon cancer with high-frequency microsatellite instability: a case report and literature review. *World J Surg Oncol*. 2019;17:19.
128. Utsumi T, Miyamoto S, Shimizu T, et al. Spontaneous regression of mismatch repair deficient colorectal cancers: a case series. *Dig Endosc*. 2020. https://doi.org/10.1111/den.13723. [Epub ahead of print].
129. Tuveson D, Clevers H. Cancer modeling meets human organoid technology. *Science*. 2019;364:952-955.
130. Drago L, Toscano M, De Grandi R, et al. Persisting changes of intestinal microbiota after bowel lavage and colonoscopy. *Eur J Gastroenterol Hepatol*. 2016;28:532-537.

131. Tilg H, Adolph TE, Gerner RR, Moschen AR. The intestinal microbiota in colorectal cancer. *Cancer Cell*. 2018;33:954-964.
132. Smith PM, Howitt MR, Panikov N, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science*. 2013;341:569-573.
133. Iida N, Dzutsev A, Stewart CA, et al. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. *Science*. 2013;342:967-970.
134. Sivan A, Corrales L, Hubert N, et al. Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. *Science*. 2015;350:1084-1089.
135. Backes Y, Seerden TCJ, van Gestel R, et al. Tumor seeding during colonoscopy as a possible cause for metachronous colorectal cancer. *Gastroenterology*. 2019;157:1222-1232.e4.
136. Zwink N, Holleczek B, Stegmaier C, Hoffmeister M, Brenner H. Complication rates in colonoscopy screening for cancer. *Dtsch Arztebl Int*. 2017;114:321-327.
137. Niv Y, Bogolavski I, Ilani S, et al. Impact of colonoscopy on quality of life. *Eur J Gastroenterol Hepatol*. 2012;24:781-786.

How to cite this article: Ahadova A, Seppälä TT, Engel C, et al. The "unnatural" history of colorectal cancer in Lynch syndrome: Lessons from colonoscopy surveillance. *Int. J. Cancer*. 2020;1–12. https://doi.org/10.1002/ijc.33224