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Risk of Non-colorectal Malignancies in Sporadic *Versus* Lynch Syndrome–associated dMMR Colorectal Cancer

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Abstract

Background/Aim: Deficient mismatch repair (dMMR) colorectal cancer (CRC) arises from either sporadic epigenetic changes or hereditary Lynch syndrome. This retrospective multicenter cohort study is the first to evaluate the differences in risk for dMMR non-colorectal malignancy between patients with sporadic CRC and those with Lynch syndrome-associated CRC.

Patients and Methods: A cohort of 1,753 patients treated between 1996 and 2019 in Sweden, Finland, and the Czech Republic was evaluated for MMR status by immunohistochemistry and classified as either proficient (pMMR) or dMMR. The last one underwent *BRAF V600E* and *MLH1* methylation testing to classify sporadic *versus* Lynch-associated cases. Non-CRC malignancies occurring within ±20 years of CRC diagnosis were identified *via* national cancer registries and medical records. Incidence rate ratios (IRRs) were estimated using Poisson regression adjusted for age, sex, tumor site, and stage.

Results: Among 277 dMMR cases (186 sporadic, 91 Lynch), 101 patients (36%) developed at least one non-CRC malignancy. Sporadic dMMR was associated with significantly lower risk compared to Lynch-associated dMMR [multivariable IRR=0.82; 95% confidence interval (CI)=0.51-0.91; p=0.014]. The reduced risk was consistent for malignancies occurring both before (IRR=0.48; p=0.047) and after CRC diagnosis (IRR=0.37; p=0.026). Age was an independent predictor of risk.

Conclusion: Sporadic dMMR CRC confers a substantially lower risk of non-colorectal malignancy than Lynch syndrome-associated CRC. These findings underscore the importance of incorporating MMR etiology into personalized surveillance strategies.

Keywords: Colorectal cancer, sporadic deficient mismatch repair, Lynch syndrome, non-colorectal malignancy.

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Introduction

Colorectal cancer (CRC) ranks among the three most frequently diagnosed cancers worldwide, contributing roughly one in ten new cases each year (1-3). Established risk factors include obesity, dietary patterns, physical inactivity, tobacco use, and chronic inflammatory bowel disease (1). Approximately 5-10% of CRC cases are attributable to hereditary syndromes, most notably familial adenomatous polyposis (FAP) and Lynch syndrome, also referred to as hereditary non-polyposis colorectal cancer (HNPCC) (1).

CRC is a biologically heterogeneous disease, and evolving models of carcinogenesis continue to refine its pathogenesis. Two major pathways are recognized in the progression from normal colonic epithelium to adenomatous precursor lesions and invasive carcinoma (4). The chromosomal instability (CIN) pathway, present in approximately 85 % of sporadic CRCs, involves mutational inactivation of the *APC gene* (5). Approximately 15-20% of CRCs develop through loss of DNA mismatch repair, leading to microsatellite instability and an excess of replication errors. Hereditary dMMR cases (3-5% of all CRCs) are primarily due to germline mutations *in MLH1, MSH2, MSH6,* and *PMS2*, which underlie Lynch syndrome. Moreover, *EPCAM* exon deletions may induce epigenetic silencing of the adjacent *MSH2* gene, yielding a Lynch-like phenotype (6). Sporadic dMMR cases typically stem from epigenetic silencing of MLH1 *via* promoter hypermethylation, accounting for approximately 15% of sporadic CRCs (7-9).

Clinicopathological features, therapeutic response, and prognosis differ between sporadic and Lynch-associated CRCs (10). Lynch syndrome generally correlates with improved survival and enhanced chemosensitivity, although the molecular mechanisms remain incompletely elucidated (11, 12). Despite emerging from the same carcinogenic pathway, sporadic and Lynch-associated CRCs necessitate different screening and management protocols (13, 14). We previously investigated the relationship between sporadic dMMR and pMMR CRC in the context of non-colorectal malignancies (15). Findings indicated an elevated risk of non-CRCs among patients with sporadic dMMR, prompting further investigation.

The current study aimed to retrospectively assess the association between dMMR subtype (sporadic *vs*. Lynch syndrome–related) and the risk of non-colorectal malignancies in a large European multicenter cohort of patients with CRC.

Patients and Methods

Study setting and participants. We assembled three European cohorts: (i) 1,116 patients with CRC treated in Västerbotten County, Sweden (October 17, 1996 and March 31, 2009); (ii) 577 patients with CRC treated at Helsinki University Hospital, Finland (September 1, 1998 to December 31, 2005); and (iii) 414 patients with colon cancer treated at University Hospital of Pilsen, Czech Republic (January 1, 2018 to December 31, 2019). Inclusion criteria were histologically confirmed CRC, staging per AJCC TNM, and availability of clinical/demographic data (16). Exclusion criteria were age <18 years and appendiceal cancer.

MMR determination and molecular assays. Cohort ascertainment, MMR status determination, *BRAF V600E* mutation testing, and *MLH1* promoter hypermethylation analysis followed the previously described protocol with the present study extending follow-up and focusing on non-colonic malignancy risk stratified by dMMR etiology (15).

Loss of *MSH2* or *MSH6*, or isolated *PMS2* loss, indicated Lynch screening positivity. Tumors with *MLH1* loss underwent *BRAF V600E* mutation analysis; *MLH1* loss with *BRAF V600E* classified as sporadic dMMR. In *MLH1*-loss with BRAF wild type, *MLH1* promoter hypermethylation testing was performed; positive hypermethylation confirmed sporadic dMMR, whereas absence supported Lynch-associated dMMR.

Non-colorectal malignancies cases. Non-CRC malignancies were identified *via* linkage to national cancer registries

for Swedish and Finnish patients and by thorough medical-record review for Czech patients. The observation period spanned 20 years before CRC diagnosis until death or end of follow-up, and 20 years after CRC diagnosis for incident events.

Statistical analysis. Analyses were conducted using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were categorized for interpretability; proportions were compared using Pearson's χ^2 or Fisher's exact test when expected counts were <5. Poisson regression was used to estimate IRRs for non-colorectal malignancies with covariates age, sex, dMMR etiology (sporadic *vs*. Lynch), tumor site (right colon, left colon, rectum), and stage (I-IV). Two-sided α=0.05 was used for statistical significance.

Ethics approvals. Approvals were granted by the Regional Ethics Review Board Umeå (registration number 2014/371-31,), Masaryk Memorial Cancer Institute (2015/838/MOU), Helsinki University Hospital Surgical Ethics Committee, and the Finnish National Institute for Health and Welfare Dnro (THL/2137/5.05/00/2017 HUS 226/E6/06, additional petition TMK02 § 66/2013 and HUS/1223/2021).

Results

Baseline characteristics. A total of 277 patients with CRC were identified as having either sporadic or Lynch syndrome–associated dMMR tumors. Of these, 161 patients (58%) were female. Tumor location was predominantly in the right colon (n=180; 65%), while 36 patients (13%) presented with rectal tumors. The median age at diagnosis was 69 years [interquartile range (IQR)=63-75], and patients were dichotomized at 70 years. Lynch-associated dMMR was observed in 91 patients (33%).

Non-colorectal malignancies. Overall, 101 patients (36%) were diagnosed with at least one non-colorectal malignancy within 20 years before or after the index CRC diagnosis. Among these, Lynch-associated dMMR was present in 41 cases (40%), compared to 60 cases (60%) with sporadic dMMR (p=0.061) (Table I). A detailed distribution of non-colorectal malignancies by site and frequency is presented in Table II.

IRRs for non-colorectal malignancies. IRRs for the occurrence of non-colorectal malignancy within 20 years before or after CRC diagnosis (until death or end of follow-up) was significantly lower in patients with sporadic dMMR tumors compared to those with Lynch-associated dMMR tumors. In univariable analysis, the IRR was 0.44 (95%CI=0.22-0.87; p=0.018), and in multivariable analysis, the IRR was 0.82 (95%CI=0.51-0.91; p=0.014) (Table III). Age was identified as an independent predictor for non-colorectal malignancy in both univariable (IRR=1.03; 95%CI=1.01-1.07; p<0.001) and multivariable (IRR=1.09; 95%CI=1.03-1.26; p<0.001) models. No other variable demonstrated a statistically significant association (Table III).

IRRs for non-colorectal malignancy within 20 years before CRC diagnosis was significantly lower in patients with sporadic CRC compared to those with Lynch-associated dMMR CRC. In univariable analysis, the IRR was 0.48 (95%CI=0.28-0.98; p=0.035), and in multivariable analysis, the IRR remained significant at 0.48 (95%CI=0.24-0.99; p=0.047) (Table IV). Age was the only independent predictor of non-colorectal malignancy, with an IRR of 1.18 (95%CI=1.14-1.24; p=0.001) in univariable analysis and 1.29 (95%CI=1.13-1.32; p<0.001) in multivariable analysis. No other variable demonstrated a statistically significant association (Table IV).

IRRs for non-colorectal malignancy occurring after CRC diagnosis was significantly lower in patients with sporadic tumors compared to those with Lynch-associated dMMR tumors. In univariable analysis, the IRR was 0.38 (95%CI=0.17-0.85; p=0.019), and in multivariable analysis, the IRR remained significant at 0.37 (95%CI=0.16-0.89; p=0.026) (Table V). Age was identified as a significant independent predictor of non-colorectal malignancy in

Table I. *Clinical characteristics and tumor pathology of deficient mismatch repair (dMMR) cases with and without other non-colorectal cancer malignancies.*

Co-variable	Total (n=277)	Other cancer (n=101)	No other cancer (n=176)	*p*-Value
Age				NA
Years, median	69	70	68	
Range	28-89	41-85	28-89	
IQR	63-75	63-76	62-75	
Dichotomized at 70 years				0.126
<70	141 (51%)	56 (55%)	85 (48%)	
≥70	136 (49%)	45 (45%)	91 (52%)	
Sex ratio				0.247
Male	116 (42%)	45 (45%)	71 (40%)	
Female	161 (58%)	56 (55%)	105 (60%)	
Deficient MMR status				0.061
Sporadic	186 (67%)	60 (60%)	126 (72%)	
Lynch	91 (33%)	41 (40%)	50 (28%)	
Tumor site				0.609
Right colon	180 (65%)	71 (71%)	113 (64%)	
Left colon	61 (22%)	18 (17%)	40 (23%)	
Rectum	36 (13%)	12 (12%)	23 (13%)	
Tumor stage				0.125
I	19 (7%)	10 (10%)	9 (5%)	
II	116 (42%)	47 (47%)	70 (40%)	
III	100 (36%)	36 (36%)	63 (36%)	
IV	42 (15%)	8 (7%)	34 (19%)	

IQR: Interquartile range; NA: not applicable.

both univariable (IRR=1.14; 95%CI=1.12-1.17; $p<0.001$) and multivariable (IRR=1.20; 95%CI=1.06-1.38; $p<0.002$) analyses. No other variable demonstrated a statistically significant association (Table V).

Discussion

In this multicenter study involving a large cohort from three European medical centers, Lynch-associated dMMR cases demonstrated a significantly stronger association with non-colorectal malignancies within 20 years before and after CRC diagnosis compared to sporadic dMMR cases. This association remained significant in both univariable and multivariable analyses when estimating the incidence rate ratio for non-colorectal malignancies.

Our findings suggest that the impaired DNA mismatch repair mechanism in CRC contributes to the development of non-CRCs, particularly in hereditary cases, and to a lesser extent in sporadic dMMR CRC. This association was consistent across both 20-year periods preceding and following CRC diagnosis. To our knowledge, this is the first study to examine the relationship between Lynch syndrome and sporadic dMMR CRC in relation to the risk of non-colorectal malignancies. These results underscore the need for further research to evaluate surveillance strategies not only for hereditary cases but also for sporadic ones.

The primary objective of this study was to determine whether similar carcinogenic mechanisms – stemming from defective DNA replication error correction – apply to both hereditary and sporadic dMMR cases. While our previous work indicated a higher incidence of non-CRC malignancies in sporadic dMMR compared to pMMR cases, this relationship may involve mechanisms distinct from those underlying Lynch syndrome (15, 16). Moreover, prior research on the same population highlighted a synergistic interaction between age and defective mismatch repair in carcinogenesis. This aligns with other studies showing that increasing age correlates

Table II. *Non-colorectal malignancy in patients with colorectal cancer with sporadic deficient mismatch repair (dMMR) and Lynch syndrome.*

Malignancy type	Total n (%) (N=101)	Sporadic dMMR n (%) (N=60)	Lynch n (%) (N=41)	*p*-Value
Prostate	21 (21%)	18 (30%)	3 (7%)	0.005
Breast	11 (11%)	9 (15%)	2 (5%)	0.109
Endometrial	13 (13%)	4 (6.6%)	9 (22%)	0.024
Hematologic	10 (10%)	9 (15%)	2 (5%)	0.109
Urinary tract	11 (11%)	7 (11.7%)	4 (10%)	0.764
Melanoma	4 (4%)	1 (1.6%)	3 (7%)	0.152
Endocrine	5 (5%)	3 (5%)	2 (5%)	0.976
Ovarian	5 (5%)	1 (1.6%)	4 (10%)	0.065
Stomach/Esophagus	6 (6%)	2 (3.3%)	4 (10%)	0.180
Hepatobiliary	2 (2%)	1 (1.8%)	1 (2%)	0.787
Lung	3 (3%)	2 (3.3%)	1 (2%)	0.794
Brain	4 (4%)	2 (3.3%)	2 (5%)	0.696
Pancreas	3 (3%)	1 (1.8%)	1 (2%)	0.787
Head & neck	1 (1%)	0 (0%)	1 (2%)	NA
Unspecified	0 (0%)	0 (0%)	0 (0%)	NA
Small bowel	1 (1%)	0 (0%)	1 (2%)	NA
Skeletal	1 (1%)	0 (0%)	1 (2%)	NA

NA: Not applicable.

with a higher risk of *MLH1* promoter hypermethylation, a key contributor to sporadic dMMR carcinogenesis (17). This association could explain the divergent pattern in the distribution of non-colorectal malignancies between sporadic and Lynch-associated dMMR cases in our study. Prostate cancer was significantly more common among patients with sporadic dMMR CRC (p=0.005), whereas endometrial cancer was more frequent in Lynch syndrome cases (p=0.024). Sporadic dMMR tumors, driven by *MLH1* promoter hypermethylation, are associated with age-related epigenetic alterations, which may predispose to prostate cancer – a malignancy strongly linked to aging and methylation changes in CpG islands. Although both sporadic and hereditary dMMR cases originate from the same mismatch repair pathway, they differ primarily in the absence of specific MMR proteins and in *BRAF* mutation status. The role of *BRAF V600E* mutation in carcinogenesis is well established, being implicated in melanoma, colorectal cancer, and multiple myeloma (18). Interestingly, Lynch syndrome cases – which exhibit a higher incidence of non-colorectal tumors – predominantly harbor wild-type BRAF (19, 20).

To date, no study has examined the association between non-colorectal malignancies and cases arising from exon deletions at the 3′ end of the *EPCAM* gene. Theoretically, these cases should exhibit a similar carcinogenic profile due to *MSH2* gene silencing, resulting in a clinical phenotype comparable to Lynch syndrome (6). Furthermore, differences in carcinogenic potential linked to the loss of specific MMR proteins remain largely unexplored, although some evidence suggests a stronger association between *MSH2* loss and endometrial cancer (21). The interplay between loss of specific MMR proteins, *BRAF* mutation status, and the phenotypic differences between Lynch-associated and sporadic dMMR cases appears even more complex. Lynch-associated cases tend to demonstrate a more robust immune response, characterized by a higher mutational burden and an increased number of neoantigens compared to sporadic cases. This immunogenic distinction may have implications for tumor biology and therapeutic strategies, especially in relationship to tumors revealing increased inflammatory profile (22-25).

These complex phenotypic differences were evident in our study, where Lynch-associated cases showed a statistically significant association with non-colorectal malignancies – such as endometrial and ovarian cancer – compared to sporadic cases. This finding contrasts

Table III. *Incidence rate ratio (IRR) for the occurrence of non-colorectal malignancies within 20 years before and after a colorectal cancer diagnosis (univariable and multivariable analyses).*

Variable	IRR (Univariate)	95%CI	*p*-Value	IRR (Multivariate)	95%CI	*p*-Value
Age (per year)	1.03	1.01-1.07	0.001	1.09	1.03-1.26	0.001
Female *vs.* Male	1.39	0.82-2.33	0.218	1.20	0.71-1.34	0.513
Sporadic *vs.* Lynch	0.44	0.22-0.87	0.018	0.82	0.51-0.91	0.014
Right colon *vs.* rectum	0.84	0.39-1.79	0.652	1.51	0.68-3.31	0.318
Left colon *vs.* rectum	0.74	0.33-1.64	0.457	0.97	0.35-2.70	0.956
Stage I *vs.* IV	0.57	0.16-2.32	0.390	1.64	0.47-6.02	0.457
Stage II *vs.* IV	0.85	0.34-2.01	0.719	1.53	0.53-4.41	0.431
Stage III *vs.* IV	0.95	0.39-2.34	0.906	1.48	0.50-4.01	0.476

CI: Confidence interval.

Table IV. *Incidence rate ratio (IRR) of non-colorectal malignancies within 20 years before a colorectal cancer diagnosis (univariable and multivariable).*

Variable	IRR (Univariate)	95%CI	*p*-Value	IRR (Multivariate)	95%CI	*p*-Value
Age (per year)	1.18	1.14-1.24	0.001	1.29	1.13-1.32	0.001
Female *vs.* Male	0.80	0.47-1.35	0.400	0.94	0.66-1.33	0.719
Sporadic *vs.* Lynch	0.48	0.28-0.98	0.035	0.48	0.24-0.99	0.047
Right colon *vs.* rectum	1.20	0.56-2.52	0.637	1.10	0.71-1.68	0.678
Left colon *vs.* rectum	0.85	0.32-2.41	0.797	0.86	0.52-1.42	0.563
Stage I *vs.* IV	2.60	0.74-9.31	0.135	0.93	0.42-2.03	0.855
Stage II *vs.* IV	2.18	0.76-6.23	0.146	1.26	0.72-2.20	0.425
Stage III *vs.* IV	1.91	0.65-5.56	0.238	0.86	0.47-1.58	0.636

CI: Confidence interval.

Table V. *Incidence rate ratios (IRRs) for non-colorectal malignancies occurring after a colorectal cancer diagnosis (univariable and multivariable).*

Variable	IRR (Univariate)	95%CI	*p*-Value	IRR (Multivariate)	95%CI	*p*-Value
Age (per year)	1.14	1.12-1.17	0.001	1.20	1.06-1.38	0.002
Female *vs.* Male	0.61	0.38-1.12	0.073	0.68	0.35-1.27	0.241
Sporadic *vs.* Lynch	0.38	0.17-0.85	0.019	0.37	0.16-0.89	0.026
Right colon *vs.* rectum	0.87	0.39-1.91	0.727	1.26	0.53-2.99	0.604
Left colon *vs.* rectum	0.86	0.30-2.50	0.784	1.08	0.36-3.20	0.892
Stage I *vs.* IV	1.08	0.22-5.34	0.927	0.62	0.12-3.21	0.568
Stage II *vs.* IV	0.89	0.20-3.80	0.862	0.56	0.12-2.59	0.454
Stage III *vs.* IV	0.96	0.22-4.12	0.959	0.69	0.15-2.98	0.627

IRR: Incidence rate ratio; CI: confidence interval.

with a previous analysis of the same population, which reported significant differences between sporadic dMMR cases and other non-CRC malignancies when compared to pMMR cases, theoretically due to the distinct underlying carcinogenic mechanisms (15).

Results regarding sex-specific cancer risk in Lynch syndrome remain controversial. Some studies suggest a stronger association between male sex and colorectal, gastric, bladder, and urothelial cancers, whereas others report a higher cumulative cancer incidence among females (26, 27). In our study, no significant relationship was observed between sex and non-colorectal malignancies within 20 years before or after the index CRC diagnosis. However, these findings should

be interpreted with caution given several limitations. First, the retrospective design introduces inherent bias, and potential heterogeneity may arise from differences in populations, medical centers, and study periods. Cases treated in the 1990s – when knowledge of Lynch syndrome and the MMR system was limited – are particularly susceptible to underestimation and misclassification. Additionally, this study lacks data on EPCAM-related cases and epigenetic silencing of the adjacent *MSH2* gene. A major strength of this study is the inclusion of patients from multiple medical centers and the unique opportunity to leverage national cancer registry data for the Scandinavian population, which enhances the reliability and generalizability of our findings.

Conclusion

Compared with Lynch-associated dMMR CRC, sporadic *MLH1*-driven dMMR CRC is associated with a lower risk of non-colorectal malignancies within ±20 years of the CRC diagnosis. These findings underscore the importance of incorporating MMR etiology into personalized surveillance strategies.

Conflicts of Interest

The Authors declare no competing interests in relation to this study.

Authors' Contributions

Conceptualization: IG, RP, CH; Methodology: IG, JN, TK, PF, CB, SE; Formal analysis: IG; Investigation: KS, TS, JH; Resources: PF, TS, JH; Data curation: IG, JN; Writing – original draft: IG; Writing – review & editing: all Authors; Supervision: RP, CH.

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Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model (ChatGPT, OpenAI) was used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning–based image enhancement tools.

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