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Metachronous Colorectal Cancer in Icelandic *MSH6* and *PMS2* Lynch Syndrome Carriers in 1955–2017: A Population-based Study

Lynch syndrome is an autosomal dominant inherited disorder caused by a pathogenic germline mutation in 1 of 4 mismatch repair genes: *MLH1, MSH2* (or *EPCAM*), *MSH6*, or *PMS2*. Lynch syndrome accounts for 2%–3% of all colorectal cancer cases[1] and causes a significant risk of metachronous colorectal cancer (a new malignancy occurring ≥12 months after the first diagnosis).[2] Colonoscopy screening and removal of adenomas are recommended for prevention as well as consideration of extended surgery with ileosigmoidal/ileorectal anastomosis at cancer diagnosis. Because the lifetime risk varies depending on the mismatch repair gene involved, screening guidelines are evolving to become gene-specific.[3] The reported incidence of metachronous colorectal cancer is up to 20%–30% at 10 years in patients with Lynch syndrome who undergo a segmental resection.[2] These data on metachronous colorectal cancer reflect mainly on *MLH1* and *MSH2* carriers and are not as well described in *MSH6* and *PMS2* carriers.

Lynch syndrome was not known in the Icelandic population until 2017 when 3 founder mutations, 1 in *MSH6* (p.Leu585Pro) and 2 in *PMS2* (p.Met1? and p.Pro246Cysfs*3), were identified as the most common causes of Lynch syndrome with the highest population prevalence described so far (1/226). Colorectal cancer risk by age 75 is 36% (95% confidence interval [CI], 5.1–20.1) for men and 25% (95% CI, 5.1–20.1) for women with the *MSH6* p.Leu585Pro mutation, 8% (95% CI, 0.94–5.3) for men and 6% (95% CI, 0.94–5.3) for women with the *PMS2* p.Met1? mutation, and 13% (95% CI, 2.2–5.9) for men and 9% (95% CI, 2.2–5.9) for women with *PMS2* p.Pro246Cysfs*3 mutation.[4] DeCODE Genetics has performed whole-genome sequencing on 49,708 individuals and genotyping on 116,573 individuals, and using genealogic information, genotype probabilities for 290,482 untyped relatives of the genotyped individuals have been calculated. This allows an accurate assessment of the prevalence of Lynch syndrome in the country.[5] Furthermore, around 99% of all cancer diagnoses have been captured in the Icelandic Cancer Registry since 1955.[6]

The purpose of this study was to describe the metachronous colorectal cancer incidence by including all individuals with variants in *MLH1*, *MSH2*, *MSH6*, and *PMS2* extracted from deCODE's database and cross-referencing with colorectal cancer diagnoses and colon polyp diagnoses from the Icelandic Cancer Registry from 1955 to 2017. The Icelandic National Bioethics Committee approved this study (VSNb201810023/03.03).

One minus the Kaplan-Meier estimates were used to graph the cumulative incidence of metachronous colorectal cancer. The Pearson χ^2 test was used to compare the difference of advanced adenomas in *MSH6* and *PMS2* carriers (defined as adenomas ≥1 cm, having villous or tubulovillous histology, and/or having high-grade dysplasia or intramucosal adenocarcinoma).

During the study period, 65 Lynch syndrome carriers were diagnosed with colorectal cancer. Consistent with the known founder mutations, most carriers had *MSH6* (39%) or *PMS2* (52%) pathogenic variants (Supplementary Table 1). The cumulative incidence of metachronous colorectal cancer was 1 case (in a *MSH2* carrier, 23 months after the initial diagnosis) with a median follow-up time of 58 months (interquartile range [IQR], 8–167; range, 0–365), as shown in Figure 1. No metachronous colorectal cancer cases were diagnosed in *MSH6* or *PMS2* carriers. Three patients (5%) had synchronous colorectal cancers: 1 *MLH1* carrier, 1 *MSH2* carrier, and 1 *MSH6* carrier. The *MSH6* carrier was diagnosed with a synchronous colorectal cancer 10 months after the primary colorectal cancer diagnosis. The median age at colorectal cancer diagnosis was 60.0 years (IQR, 55–72; range, 41–90) in *MSH6* carriers and 64 years (IQR, 54–73; range, 40–94) in *PMS2* carriers. Sixty-three individuals (97%) underwent a colonic resection with only 2 individuals (3%), 1 with *MSH2* and 1 with *MSH6* pathogenic variants, undergoing total colectomy. Significantly more *MSH6* carriers had a history of advanced adenomas as compared with *PMS2* carriers (44% vs 12%, $P = .005$).

This study represents the largest study performed on metachronous colorectal cancer risk in unscreened *MSH6* and *PMS2* carriers. None of the *MSH6* or *PMS2* carriers had a metachronous colorectal cancer diagnosis from 1955 to 2017. This period was chosen because Lynch syndrome was not at all known to clinicians in Iceland until 2017 and these patients were therefore not undergoing Lynch syndrome surveillance. Therefore, this can be considered real-world data in undiagnosed *MSH6* and *PMS2* Lynch syndrome carriers. Most carriers had the same *MSH6* and *PMS2* founder pathogenic variants, and therefore this information is most relevant for Lynch syndrome carriers with these specific pathogenic variants.

The *PMS2* founder frameshift pathogenic variant is very common outside of the Icelandic population and can be traced back to around 1630 years ago.[7] Most studies on metachronous colorectal cancer risk in Lynch syndrome are based on *MLH1* and *MSH2* carriers with the cumulative risk reported around 20% at 10 years and 40% at 20 years of follow-up.[8,9] In the largest published study to date, 3 of 22 *MSH6* carriers were diagnosed with metachronous colorectal cancer, whereas none of 19 *PMS2* carriers developed metachronous colorectal cancer with a mean follow-up of 9 years.[8] A more recent study included 20

Abbreviations used in this paper: **CI, confidence interval; IQR, interquartile range.**

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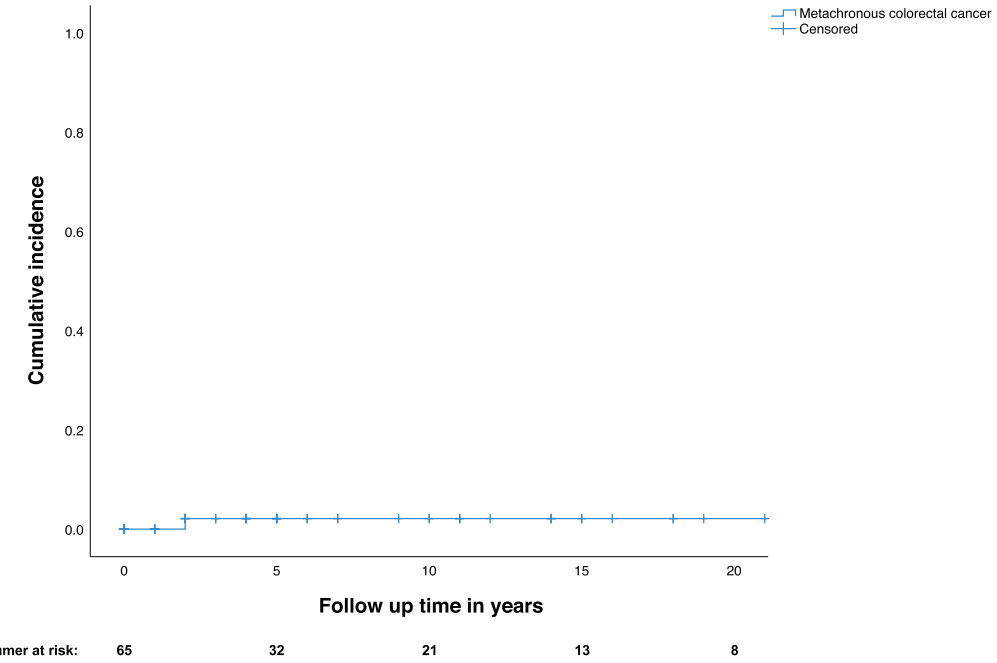

Figure 1. Cumulative incidence of metachronous colorectal cancer in 1955–2017 in Icelandic Lynch syndrome carriers.

MSH6 carriers, of which 1 developed metachronous colorectal cancer 46 years after the index cancer, and 13 *PMS2* carriers, of which 2 were diagnosed with metachronous cancer 20 and 37 years, respectively, after the first diagnosis.[10] With those results and the results of our study, it seems evident that *MSH6* and *PMS2* carriers have a much lower risk of developing metachronous colorectal cancer than *MLH1* and *MSH2* carriers.

The results from our study support the recommendations from the European Hereditary Tumor Group and European Society of Coloproctology of standard or segmental colonic resection for *MSH6* or *PMS2* pathogenic variant carriers.[3] Furthermore, our results support initiating colonoscopy screening at age 35 for *MSH6* or *PMS2* carriers (unless family history compels earlier screening) and colonoscopy intervals of 2–3 years for *MSH6* carriers and 5 years for *PMS2* carriers as recommended by the European Hereditary Tumor Group and European Society of Coloproctology guidelines.[3]

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org and at https://doi.org/10.1053/j.gastro.2023.02.007.

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Conflicts of interest
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Supplementary Table 1. Patient Characteristics (n = 65)

Characteristics	Values
Median age at first colorectal cancer diagnosis, y (interquartile range)	63.0 (54.0–72.5)
Gender of patient	
Female	24 (36.9)
Male	41 (63.1)
Gene affected	
MLH1	3 (4.6)
MSH2	3 (4.6)
MSH6	25 (38.5)
PMS2	34 (52.3)
Location of tumor	
Right colon	35 (53.8)
Left colon	16 (24.6)
Rectum[a]	14 (21.5)
TNM stage at diagnosis	
Stage 1	7 (10.8)
Stage 2	35 (53.8)
Stage 3	14 (21.5)
Stage 4	3 (4.6)
No data	6 (9.2)
Type of colectomy	
Segmental	61 (93.8)
Total	2 (3.1)
No surgery	2 (3.1)
Other lifetime cancer	
No	42 (64.6)
Yes	23 (35.4)

Values are n (%) unless otherwise defined.
[a]Rectosigmoid included.