# Metachronous colorectal cancer risk according to Lynch syndrome pathogenic variant after extensive versus partial colectomy in the Netherlands: a retrospective cohort study

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# Metachronous colorectal cancer risk according to Lynch syndrome pathogenic variant after extensive versus partial colectomy in the Netherlands: a retrospective cohort study

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See Online for appendix

## Summary

**Background** Extensive colectomy (subtotal or total colectomy) is often advised for carriers of Lynch syndrome with colorectal cancer. However, the risk of metachronous colorectal cancer might differ by Lynch syndrome variant, meaning that partial colectomy, which has better functional outcomes, might be adequate for some patients with low-risk variants. We aimed to assess the risk of metachronous colorectal cancer after partial colectomy and extensive colectomy in carriers of Lynch syndrome with different pathogenic variants.

**Methods** For this retrospective cohort study, carriers of Lynch syndrome with colorectal cancer in the Netherlands were identified by linkage of the Dutch Foundation for the Detection of Hereditary Tumors (StOET) database and the Dutch Nationwide Network and Registry of Histopathology and Cytopathology (PALGA) database. Data on demographics, Lynch syndrome variants, colorectal cancers, surgery types, mortality, and surveillance colonoscopies were extracted. Data on colorectal cancer and surveillance colonoscopies were updated until Feb 28, 2022. Data on survival status was updated until Feb 7, 2022. *MLH1, MSH2,* and *EPCAM* were classified as high-risk variants and *MSH6* and *PMS2* as low-risk variants. Patients for whom the type of surgery was unknown were excluded. Cox regression time-to-event analyses were done to assess the risk of metachronous colorectal cancer in four subgroups based on pathogenic variant (high-risk *vs* low-risk variants) and the extent of surgery (extensive colectomy *vs* partial colectomy). Sex, age at the time of primary colorectal cancer, primary colorectal cancer stage, performance of surveillance colonoscopies, adherence to the surveillance guidelines, and time period of primary colorectal cancer diagnosis were added to the model as possible confounders. Metachronous colorectal cancer was defined as colorectal cancer diagnosed more than 6 months after the primary colorectal cancer. Patients were censored at time of death or assembly of the database.

**Findings** Of 1908 carriers of Lynch syndrome registered in StOET, 532 with a history of colorectal cancer were identified after linkage with PALGA. Five carriers were excluded because of an unknown surgery type, leaving 527 in our sample (mean age at primary colorectal cancer 48·7 years [SD 12·1]; 274 [52%] male and 253 [48%] female). 121 (23%) patients developed metachronous colorectal cancer (median time from primary colorectal cancer to metachronous colorectal cancer 11·0 years [IQR 2·1–17·8]). Metachronous colorectal cancer occurred in 12 (12%) of 97 patients with high-risk variants and extensive colectomy, in 85 (32%) of 267 patients with high-risk variants and partial colectomy, in zero (0%) of 11 patients with low-risk variants and extensive colectomy, and in 24 (16%) of 152 patients with low-risk variants and partial colectomy. Partial colectomy was associated with a higher risk of metachronous colorectal cancer than extensive colectomy in the high-risk variant group (hazard ratio 1·97, 95% CI 1·04–3·73; p=0·039). The risk of metachronous colorectal cancer did not differ between carriers of low-risk variants who had partial colectomy and those of high-risk variants who had extensive colectomy (1·14, 0·55–2·36; p=0·72).

**Interpretation** The risk of metachronous colorectal cancer after partial colectomy in carriers of low-risk variants is similar to the risk after extensive colectomy in carriers of high-risk variants. This finding suggests that partial colectomy followed by endoscopic surveillance is an appropriate management approach to treat colorectal cancer in carriers of low-risk Lynch syndrome variants.

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## Introduction

Colorectal cancer accounts for approximately 10% of cancer incidence worldwide.[1] The most common hereditary predisposition for colorectal cancer is Lynch syndrome.[2] Lynch syndrome is caused by a pathogenic germline variant in one of the DNA mismatch repair genes *MLH1, MSH2, MSH6,* and *PMS2,* or in the 3′ end of the *EPCAM* gene. Colorectal cancer risk differs depending on the specific gene involved. In particular, carriers of *MLH1* and *MSH2* mutations are prone to

## Research in context

### Evidence before this study

We did a systematic literature search in PubMed on Sept 19, 2019, searching since database inception, for studies in English reporting on the risk of metachronous colorectal cancer in carriers of Lynch syndrome in whom extensive or partial colectomy was done for primary colorectal cancer. The search was repeatedly updated, with the last search on April 4, 2023. Search terms were "Colectomy", "Resection", "Hemicolectomy", "Surgery", "Treatment", "Colorectal Neoplasms", "Hereditary Nonpolyposis", "Colorectal Cancer", "Lynch", "HNPCC", "*MLH1*", "*MSH2*", "*MSH6*", "*PMS2*", and "Metachronous". Knowing the risk of developing metachronous colorectal cancer is very important in choosing the optimal treatment, but studies comparing the risk of metachronous colorectal cancer following subtotal or total colectomy or partial colectomy in carriers of Lynch syndrome are scarce. Although improved survival has not been proven for extensive colectomy, previous research has shown that extensive colectomy was associated with a lower risk of metachronous colorectal cancer and a reduced need for additional surgery compared with partial colectomy, justifying the use of extensive colectomy in carriers of Lynch syndrome when this benefit outweighs other factors. However, most studies include low numbers of carriers of Lynch syndrome and do not incorporate assessment of the different mismatch repair genes involved. The scarce literature distinguishing between the different Lynch syndrome pathogenic variants mainly included carriers with high-risk variants. Previous studies have found no clear differences in the risk of metachronous colorectal cancer between different variant groups, but the numbers of included carriers of low-risk *MSH6* and *PMS2* variants were low.

### Added value of this study

This nationwide, retrospective cohort study provides robust data on the risk of metachronous colorectal cancer in carriers of Lynch syndrome with different pathogenic variants and types of surgery. The results suggest that carriers of low-risk Lynch syndrome variants (*MSH6* and *PMS2*) could have an acceptable risk of metachronous colorectal cancer with partial colectomy followed by regular endoscopic surveillance. Additionally, sensitivity analyses in carriers of Lynch syndrome with a primary colorectal cancer diagnosis in or after the year 2000 suggest an acceptable metachronous colorectal cancer risk for carriers with high-risk Lynch syndrome variants (*MLH1*, *MSH2*, and *EPCAM*) after partial colectomy. This finding suggests that improvements over time with regards to surveillance colonoscopies and colorectal cancer treatment might have made partial colectomy a sufficient treatment for carriers of high-risk variants as well.

### Implications of all the available evidence

In regards to oncological benefit, there was already insufficient evidence for extended colectomy over segmental resection for colorectal cancer in carriers of low-risk Lynch syndrome variants. Therefore, by contrast to earlier guidelines, 2020 guidelines state that the decision to perform partial colectomy or extensive colectomy in carriers of Lynch syndrome should balance the risk of metachronous colorectal cancer, the functional consequences of surgery, and the patient's age and wishes. Our study supplies the data needed to correctly interpret the risk of metachronous colorectal cancer for different Lynch syndrome variants. The results suggest that partial colectomy followed by endoscopic surveillance is sufficient for carriers of low-risk Lynch syndrome variants with colorectal cancer and might even be adequate for carriers of high-risk Lynch syndrome variants with colorectal cancer. The long follow-up data and robust number of carriers of both high-risk and low-risk variants in this study could be helpful in making a shared decision regarding the appropriate type of surgery for individual patients. For future research, we believe that these promising results should be substantiated in a prospective setting and complemented with additional data on factors that could potentially influence the risk of metachronous colorectal cancer, such as the quality of colonoscopy surveillance.

develop colorectal cancer (lifetime risk at 70 years of 34–41% for *MLH1* and 37–48% for *MSH2*).[3,4] Carriers of *MSH6* and *PMS2* mutations also have an increased risk for colorectal cancer development, albeit lower than that for *MLH1* and *MSH2* (lifetime risk at 70 years of 10–22% for *MSH6* and 11–19% for *PMS2*).[3,5] Additionally, carriers of *MSH6* mutations have a statistically significant lower risk and longer time to develop advanced neoplasia (advanced adenoma or colorectal cancer) than carriers of mutations in other mismatch repair genes.[6] *EPCAM* is associated with similar risk as *MSH2*, since *EPCAM* variants cause silencing of *MSH2* probably resulting in a similar effect.[7]

High-quality surveillance colonoscopy is of the utmost importance for colorectal cancer prevention in carriers of Lynch syndrome.[8] However, when colorectal cancer occurs, the risk of metachronous colorectal cancer is highly dependent on the extent of surgical treatment. A 2020 guideline, composed by the British Society of Gastroenterology, the Association of Coloproctology of Great Britain and Ireland, and the UK Cancer Genetics Group, suggests that the decision to perform partial colectomy or subtotal or total colectomy in carriers of Lynch syndrome with colorectal cancer should balance the risk of metachronous colorectal cancer, the functional consequences of surgery, and the patient's age and wishes.[9] This guideline also mentions that for carriers at low risk there is insufficient evidence for oncological benefit of extended colectomy over segmental resection. Extensive colectomy results in worse functional outcomes

than does partial colectomy, including higher stool frequency and other defecatory disorders.[10] Knowing the risk of developing metachronous colorectal cancer is important in choosing the optimal treatment, but studies comparing the risk of metachronous colorectal cancer following subtotal or total colectomy or partial colectomy in carriers of Lynch syndrome are scarce. Although improved survival has not been proven for extensive colectomy, previous research has shown that extensive colectomy was associated with a lower risk of metachronous colorectal cancer and the need for additional surgery, justifying the use of extensive colectomy in carriers of Lynch syndrome when this benefit outweighs other factors.[11,12] However, these studies included low numbers of carriers of Lynch syndrome and did not incorporate assessment of the different mismatch repair genes involved.

Considering that colorectal cancer risk differs between Lynch syndrome carrier groups, the risk of metachronous colorectal cancer could differ correspondingly, which might change decision making for the optimal surgical strategy. However, up until now, despite the known differences in colorectal cancer risk between the different variants, the risk of metachronous colorectal cancer after extensive colectomy versus partial colectomy has mostly been studied without subcategorising carriers with Lynch syndrome according to the pathogenic variant involved. The scarce literature distinguishing between the different mismatch repair groups mainly included carriers with high-risk variants.[13,14] In two of these studies, there were no clear differences in the risk of metachronous colorectal cancer between the different mismatch repair groups, but the numbers of included carriers of low-risk *MSH6* and *PMS2* variants were low.[13,14] One study did observe a lower risk of metachronous colorectal cancer after partial colectomy in patients with *MSH6* and *PMS2* versus *MLH1* and *MSH2* variants, but carriers of Lynch syndrome who had extensive colectomy were excluded from the analyses, making it difficult to determine whether this lower risk justifies partial colectomy in this subgroup of patients with low-risk variants.[15] It can be concluded that the risk of metachronous colorectal cancer is highest in carriers of high-risk *MLH1* and *MSH2* variants undergoing partial colectomy. Therefore, even when considering other factors (eg, age), extensive colectomy is still often recommended in this patient group, resulting in a risk of metachronous colorectal cancer that is deemed acceptable.[9] We hypothesise that the risk of metachronous colorectal cancer in carriers of *MSH6* and *PMS2* variants after partial colectomy is not significantly higher than this accepted risk in carriers of *MLH1* and *MSH2* variants after extensive colectomy. If this hypothesis is correct, it would provide evidence that partial colectomy is sufficient for the treatment of colorectal cancer in carriers of *MSH6* and *PMS2* variants. We therefore aimed to assess the risk of metachronous colorectal cancer after partial colectomy and extensive colectomy in carriers of Lynch syndrome with high-risk (*MLH1, MSH2,* and *EPCAM*) and low-risk (*MSH6* and *PMS2*) gene variants.

## Methods

### Study design and dataset

In this retrospective cohort study, individuals with a proven germline pathogenic variant of one of the Lynch syndrome genes registered in The Netherlands Foundation for the Detection of Hereditary Tumors (StOET) database were identified and linked to the Dutch Nationwide Network and Registry of Histopathology and Cytopathology (PALGA) database to identify carriers of Lynch syndrome with a history of colorectal cancer. The StOET database is a national prospective database with data from individuals with a proven germline variant of one of the Lynch syndrome genes in the Netherlands, including information on the involved mismatch repair gene (including *EPCAM*), diagnosed cancers, provided treatment, and date and cause of death. Clinical variables are registered by trained data managers. The registry started in 1985 and registered carriers of Lynch syndrome are prospectively followed up. Carriers of Lynch syndrome registered in the StOET database have granted written informed consent to retrieve their medical data and to use these data for research purposes, including consent to link their data with other databases. The PALGA database is an automated, nationwide prospective registry of pathology reports conducted in the Netherlands; it was started in 1971, and national coverage was reached from 1991 onwards. The database contains, among other information, pathology reports from biopsies taken during colonoscopy or during surgery.

Data from both StOET and PALGA were combined by staff from these databases to retrieve as much information as possible on colorectal cancers and metachronous colorectal cancers in Dutch carriers of Lynch syndrome. Through linking StOET with PALGA, we could correct for any missing data in StOET and check all additional pathology reports for additional colorectal cancers not registered in StOET. Demographic data and data on surveillance colonoscopies were also retrieved from the StOET database. Data from both databases were extracted from their inception and data on colorectal cancer and surveillance colonoscopies were updated until Feb 28, 2022, and survival status until Feb 7, 2022. The inclusion criteria were people who were confirmed carriers of Lynch syndrome and who had colorectal cancer. We excluded individuals for whom the type of surgery or mismatch repair gene was not specified in the database. The study design was approved by the Institutional Review Board of Erasmus MC (registration number MEC-2022-0431) and the scientific committee of StOET.

### Procedures and definitions

Population characteristics were assessed for all carriers of Lynch syndrome and separately for the different

subgroups. Variables extracted were biological sex (as recorded in the StOET database, with the options of male or female), age at time of primary colorectal cancer diagnosis, date of primary colorectal cancer diagnosis, type of surgery for primary colorectal cancer, pathogenic Lynch syndrome variant involved, primary colorectal cancer location, type of primary colorectal cancer (adenocarcinoma, mucinous carcinoma, signet ring cell carcinoma, and unknown), primary colorectal cancer stage, synchronous colorectal cancer, metachronous colorectal cancer characteristics (date, location, and stage), and mortality (date and cause of death). Subtotal and total colectomy were categorised as extensive colectomy and all other types of surgery as partial colectomy. Colorectal cancer location was categorised as right-sided colon, left-sided colon, or rectum. The right-sided colon was defined as the caecum, ascending colon, hepatic flexure, and transverse colon. The left-sided colon was defined as the splenic flexure, descending colon, and rectosigmoid colon. The rectum was defined as the rectum or anus. Pathological TNM staging was done according to the eighth edition. If colorectal cancer was diagnosed before the eighth edition was published, we adjusted staging to the eighth edition on the basis of colorectal cancer characteristics. Multiple colorectal cancers were considered synchronous when diagnosed at the same time or within 6 months (inclusive of 6 months) after the primary colorectal cancer. When synchronous colorectal cancers were present, the colorectal cancer with the most advanced stage was described as the primary colorectal cancer. Metachronous colorectal cancer was defined as colorectal cancer diagnosed more than 6 months after the primary colorectal cancer. The location of metachronous colorectal cancer was divided into location on the anastomosis and location elsewhere in the colon.

Performance of surveillance colonoscopy was assessed and subsequently adequate adherence to the surveillance guidelines[16] for carriers of Lynch syndrome after colorectal cancer was evaluated. Performance of surveillance colonoscopy was marked as present when at least one surveillance colonoscopy was done after surgery. Guidelines recommend surveillance colonoscopy 1 year after primary colorectal cancer and, after that, surveillance every 2 years. Carriers of Lynch syndrome were classified as being adherent when more than 90% of surveillance colonoscopies were done when indicated, with an allowed deviation of 6 months.

### Statistical analysis

Descriptive statistics are used to summarise characteristics for the entire study population and the separate subgroups. Population characteristics are presented as mean with SD or median with IQR for numerical data or as count with percentage for categorical data.

We assessed the risk of metachronous colorectal cancer following partial colectomy or extensive colectomy for colorectal cancer in carriers of Lynch syndrome at high risk (*MLH1*, *MSH2*, and *EPCAM*) and low risk (*MSH6* and *PMS2*). Cox regression time-to-event analyses were done to compare the risk of metachronous colorectal cancer among four subgroups of carriers of Lynch syndrome: those at high risk who underwent extensive colectomy (reference group); those at high risk who underwent partial colectomy; those at low risk who underwent extensive colectomy; and those at low risk who underwent partial colectomy. Metachronous colorectal cancer occurrence in carriers of Lynch syndrome was assessed starting from the date of their primary colorectal cancer diagnosis (time of origin) to the date of the first diagnosis of metachronous colorectal cancer, death, or final assembly of the database, whichever came first. Sex, age at the time of primary colorectal cancer, primary colorectal cancer stage, performance of surveillance colonoscopies, adherence to the surveillance guidelines, and time period of primary colorectal cancer diagnosis were added to the model as possible confounders. The time period of primary colorectal cancer diagnosis was divided into two groups: colorectal cancer diagnosed before 2000 and colorectal cancer diagnosed in or after 2000. The year 2000 was chosen to provide information on metachronous colorectal cancer after primary colorectal cancer diagnosis in more modern times. All confounders were identified from our study database with a causal directed acyclic graph (appendix p 2). Patients were censored at time of death or assembly of the database. To assess potential bias from censoring patients at time of death, additional analyses on the cause-specific hazards and the cause-specific cumulative incidence curves were done, considering death as a competing risk.[17] The competing risk analyses were not performed for the secondary analyses that are explained next.

Cox regression time-to-event analyses were also done to assess the effect of multiple possible influencing factors on the risk of metachronous colorectal cancer and to assess the effect of multiple possible influencing factors (including the occurrence of metachronous colorectal cancer) on mortality risk in all included carriers of Lynch syndrome with colorectal cancer. The occurrence of metachronous colorectal cancer in carriers of Lynch syndrome was assessed starting from the date of their primary colorectal cancer diagnosis (time of origin) to the date of the first diagnosis metachronous colorectal cancer, death, or final assembly of the database, whichever came first. In these analyses, patients were also censored at time of death or assembly of the database. Possible factors influencing the risk of metachronous colorectal cancer that we examined were sex, age at primary colorectal cancer diagnosis, high-risk pathogenic variant, performance of extensive colectomy, advanced stage (stage III or stage IV) of primary colorectal cancer, performance of surveillance colonoscopy, adherence to surveillance colonoscopies, and primary colorectal cancer before the year 2000. Mortality in carriers of Lynch syndrome was assessed

starting from the date of their primary colorectal cancer diagnosis (time of origin) to the date of death or final assembly of the database, whichever came first. In these analyses, patients were censored at the time of assembly of the database. Possible influencing factors on mortality risk examined were sex, age at primary colorectal cancer diagnosis, high-risk pathogenic variant, performance of extensive colectomy, advanced stage of primary colorectal cancer, metachronous colorectal cancer occurrence, and primary colorectal cancer before the year 2000.

In sensitivity analyses in carriers of Lynch syndrome with a primary colorectal cancer diagnosis in or after

| | Total of all carriers of Lynch syndrome with colorectal cancer (n=527) | Carriers with high-risk variants and extensive colectomy (n=97) | Carriers with high-risk variants and partial colectomy (n=267) | Carriers with low-risk variants and extensive colectomy (n=11) | Carriers with low-risk variants and partial colectomy (n=152) |
|---|---|---|---|---|---|
| Sex | | | | | |
| Male | 274 (52%) | 47 (48%) | 136 (51%) | 9 (82%) | 82 (54%) |
| Female | 253 (48%) | 50 (52%) | 131 (49%) | 2 (18%) | 70 (46%) |
| Age at time of primary colorectal cancer, years | 48·7 (12·1) | 48·5 (9·9) | 46·0 (12·2) | 52·6 (11·9) | 53·4 (12·0) |
| Pathogenic Lynch syndrome variant | | | | | |
| *MLH1* | 164 (31%) | 47 (48%) | 117 (44%) | NA | NA |
| *MSH2* | 192 (36%) | 48 (49%) | 144 (54%) | NA | NA |
| *MSH6* | 126 (24%) | NA | NA | 10 (91%) | 116 (76%) |
| *PMS2* | 37 (7%) | NA | NA | 1 (9%) | 36 (24%) |
| *EPCAM* | 8 (2%) | 2 (2%) | 6 (2%) | NA | NA |
| Primary colorectal cancer location | | | | | |
| Right-sided colon | 340 (65%) | 78 (80%) | 175 (66%) | 7 (64%) | 80 (53%) |
| Left-sided colon | 127 (24%) | 17 (18%) | 62 (23%) | 3 (27%) | 45 (30%) |
| Rectum | 53 (10%) | 1 (1%) | 26 (10%) | 1 (9%) | 25 (16%) |
| Unknown | 7 (1%) | 1 (1%) | 4 (1%) | 0 (0%) | 2 (1%) |
| Type of primary colorectal cancer | | | | | |
| Adenocarcinoma | 507 (96%) | 92 (95%) | 256 (96%) | 11 (100%) | 148 (97%) |
| Mucinous carcinoma | 14 (3%) | 4 (4%) | 6 (2%) | 0 (0%) | 4 (3%) |
| Signet ring cell carcinoma | 1 (<1%) | 0 (0%) | 1 (<1%) | 0 (0%) | 0 (0%) |
| Unknown | 5 (1%) | 1 (1%) | 4 (1%) | 0 (0%) | 0 (0%) |
| Primary colorectal cancer stage | | | | | |
| Stage I | 174 (33%) | 46 (47%) | 82 (31%) | 4 (36%) | 42 (28%) |
| Stage II | 224 (43%) | 24 (25%) | 119 (45%) | 5 (45%) | 76 (50%) |
| Stage I or II, not specified | 14 (3%) | 5 (5%) | 7 (3%) | 0 (0%) | 2 (1%) |
| Stage III | 93 (18%) | 17 (18%) | 48 (18%) | 2 (18%) | 26 (17%) |
| Stage IV | 10 (2%) | 2 (2%) | 6 (2%) | 0 (0%) | 2 (1%) |
| Unknown | 12 (2%) | 3 (3%) | 5 (2%) | 0 (0%) | 4 (3%) |
| Synchronous metastases | | | | | |
| None | 505 (96%) | 96 (99%) | 255 (96%) | 11 (100%) | 143 (94%) |
| Liver | 6 (1%) | 1 (1%) | 3 (1%) | 0 (0%) | 2 (1%) |
| Abdominal wall | 2 (<1%) | 0 (0%) | 2 (1%) | 0 (0%) | 0 (0%) |
| Abdominal fluid | 1 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) |
| Unknown location | 1 (<1%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) |
| Unknown stage | 12 (2%) | 0 (0%) | 7 (3%) | 0 (0%) | 5 (3%) |
| Synchronous colorectal cancer at time of primary colorectal cancer | 42 (8%) | 10 (10%) | 18 (7%) | 3 (27%) | 11 (7%) |
| Type of surgery in primary colorectal cancer | | | | | |
| Extensive colectomy | 108 (20%) | NA | NA | NA | NA |
| Partial colectomy | 419 (80%) | NA | NA | NA | NA |
| Primary colorectal cancer occurrence before the year 2000 | 182 (35%) | 29 (30%) | 114 (43%) | 0 (0%) | 39 (26%) |

Data are n (%) or mean (SD). NA=not applicable.

***Table 1:*** **Baseline characteristics of carriers of Lynch syndrome with colorectal cancer**

the year 2000, we compared the risk of metachronous colorectal cancer between the same four subgroups using Cox regression time-to-event analyses, including sex, age at time of primary colorectal cancer, primary colorectal cancer stage, surveillance colonoscopy performance, and adherence to surveillance guidelines as possible confounders.

For all tests, a statistical significance level of 0·05 was used. Analyses were run in SPSS (version 25). Competing risk analyses were run in R (version 4.1.3).

### Role of the funding source

There was no funding source for this study.

## Results

1908 molecularly confirmed carriers of Lynch syndrome were identified from the StOET database. After linkage between StOET and PALGA, 532 carriers of Lynch syndrome with a history of one or more colorectal cancers were identified. Five carriers of Lynch syndrome were excluded because the type of surgery done was unknown. Therefore, a total of 527 confirmed carriers of Lynch syndrome with a history of colorectal cancer (mean age 48·7 years [SD 12·1] at the time of primary colorectal cancer diagnosis; 274 [52%] men and 253 [48%] women) were included in the current analyses. Baseline characteristics are presented in table 1. The involved

| | Total of all carriers of Lynch syndrome with colorectal cancer (n=527) | Carriers with high-risk variants and extensive colectomy (n=97) | Carriers with high-risk variants and partial colectomy (n=267) | Carriers with low-risk variants and extensive colectomy (n=11) | Carriers with low-risk variants and partial colectomy (n=152) |
|---|---|---|---|---|---|
| Surveillance colonoscopies performed after colorectal cancer | 413 (78%) | 88 (91%) | 199 (75%) | 10 (91%) | 116 (76%) |
| Time to first surveillance colonoscopy after colorectal cancer, months | 22·0 (11·0–55·3) | 15·5 (8·3–33·8) | 24·0 (11·0–58·0) | 11·5 (8·0–15·3) | 25·0 (12·0–84·5) |
| Adherence to surveillance guidelines after colorectal cancer | 158 (30%) | 48 (49%) | 64 (24%) | 7 (64%) | 39 (26%) |
| Metachronous colorectal cancer | 121 (23%) | 12 (12%) | 85 (32%) | 0 (0%) | 24 (16%) |
| Time from primary colorectal cancer to metachronous colorectal cancer, years | 11·0 (2·1–17·8) | 11·5 (9·0–23·1) | 11·0 (5·4–17·7) | NA | 9·3 (2·4–16·8) |
| Metachronous colorectal cancer within 10 years | 60 (11%) | 5 (5%) | 42 (16%) | 0 (0%) | 13 (9%) |
| In case of metachronous colorectal cancer, primary colorectal cancer location | | | | | |
| Right-sided colon | 68/121 (56%) | 11/12 (92%) | 48/85 (56%) | NA | 9/24 (38%) |
| Left-sided colon | 33/121 (27%) | 1/12 (8%) | 25/85 (29%) | NA | 7/24 (29%) |
| Rectum | 17/121 (14%) | 0/12 (0%) | 10/85 (12%) | NA | 7/24 (29%) |
| Unknown | 3/121 (2%) | 0/12 (0%) | 2/85 (2%) | NA | 1/24 (4%) |
| First metachronous colorectal cancer location* | | | | | |
| Anastomosis | 23/121 (19%) | 4/12 (33%) | 12/85 (14%) | NA | 7/24 (29%) |
| Elsewhere | 88/121 (73%) | 8/12 (67%) | 65/85 (76%) | NA | 17/24 (71%) |
| Unknown | 10/121 (8%) | 0/12 (0%) | 8/85 (9%) | NA | 0/24 (0%) |
| First metachronous colorectal cancer stage | | | | | |
| Stage I | 54/121 (45%) | 5/12 (42%) | 40/85 (47%) | NA | 9/24 (38%) |
| Stage II | 43/121 (36%) | 4/12 (33%) | 32/85 (38%) | NA | 7/24 (29%) |
| Stage I or II, not specified | 2/121 (2%) | 0/12 (0%) | 2/85 (2%) | NA | 0/24 (0%) |
| Stage III | 13/121 (11%) | 1/12 (8%) | 6/85 (7%) | NA | 6/24 (25%) |
| Stage IV | 2/121 (2%) | 1/12 (8%) | 0/85 (0%) | NA | 1/24 (4%) |
| Unknown | 7/121 (6%) | 1/12 (8%) | 5/85 (6%) | NA | 1/24 (4%) |
| Mortality | 91 (17%) | 18 (19%) | 58 (22%) | 2 (18%) | 13 (9%) |
| Time from primary colorectal cancer to death, years | 13·8 (7·4–19·8) | 14·3 (6·5–20·7) | 14·5 (7·6–22·2) | 9·0 (6·6–11·3) | 12 (7·6–16·1) |
| Mortality related to colorectal cancer | 22/91 (24%) | 3/18 (17%) | 16/58 (28%) | 0/2 (0%) | 3/13 (23%) |

Data are n (%), median (IQR), or n/N (%). NA=not applicable. *First metachronous colorectal cancer location is subdivided into location on the anastomosis and location elsewhere in the colon. For all carriers of Lynch syndrome with metachronous colorectal cancer, the following applies: of those located on the anastomosis (23 of 121), one occurred after total colectomy, three after subtotal colectomy, two after ileocaecal resection, seven after right hemicolectomy, two after partial resection of the transverse colon, two after left hemicolectomy, two after partial resection of the sigmoid colon, one after left hemicolectomy combined with low anterior resection, two after low anterior resection alone, and one after rectal resection with unspecified strategy. For metachronous colorectal cancers on anastomosis, it was not known for all of them where exactly this anastomosis was located. Of the metachronous colorectal cancers located elsewhere in the colon (88 of 121), 40 were located in the right-sided colon, 31 in the left-sided colon, 16 in the rectum, and for one the exact location in the colon was unknown (but was not on the anastomosis). Of the metachronous colorectal cancers for which location on the anastomosis or not was unknown (ten of 121), four were located in the right-sided colon, two were located in the rectum, and the exact location was unknown for four.

*Table 2:* **Surveillance, metachronous colorectal cancer, and mortality in carriers of Lynch syndrome**

| | Carriers of Lynch syndrome with metachronous colorectal cancer (n=121) | Carriers of Lynch syndrome without metachronous colorectal cancer (n=406) | Hazard ratio (95% CI) | p value |
|---|---|---|---|---|
| People with high-risk variants and extensive colectomy | 12 (10%) | 85 (21%) | 1 (ref) | 1 (ref) |
| People with high-risk variants and partial colectomy | 85 (70%) | 182 (45%) | 1·97 (1·04–3·73) | 0·039 |
| People with low-risk variants and extensive colectomy | 0 (0%) | 11 (3%) | NA* | NA* |
| People with low-risk variants and partial colectomy | 24 (20%) | 128 (32%) | 1·14 (0·55–2·36) | 0·72 |
| Included confounders | | | | |
| Male sex | 68 (56%) | 206 (51%) | 1·26 (0·87–1·82) | 0·22 |
| Age at time of primary colorectal cancer | NA | NA | 1·01 (0·99–1·03) | 0·37 |
| Advanced stage of primary colorectal cancer† | 25 (21%) | 78 (19%) | 1·32 (0·84–2·08) | 0·23 |
| Surveillance colonoscopy performed | 79 (65%) | 334 (82%) | 0·35 (0·24–0·53) | <0·001 |
| Adherence to surveillance | 19 (16%) | 139 (34%) | 1·09 (0·63–1·87) | 0·77 |
| Primary colorectal cancer before the year 2000 | 82 (68%) | 100 (25%) | 1·80 (1·16–2·80) | 0·009 |

Data are n (%), unless otherwise specified. Cox regression time-to-event analysis was done to determine the metachronous colorectal cancer risk. The reference group was people with high-risk variants and extensive colectomy. NA=not applicable. *Analyses for the low-risk extensive colectomy subgroup were not reliable because this subgroup consisted of only 11 people. †Advanced stage of primary colorectal cancer was defined as stage III or IV.

***Table 3:*** **Metachronous colorectal cancer risk in different variant and colectomy subgroups**

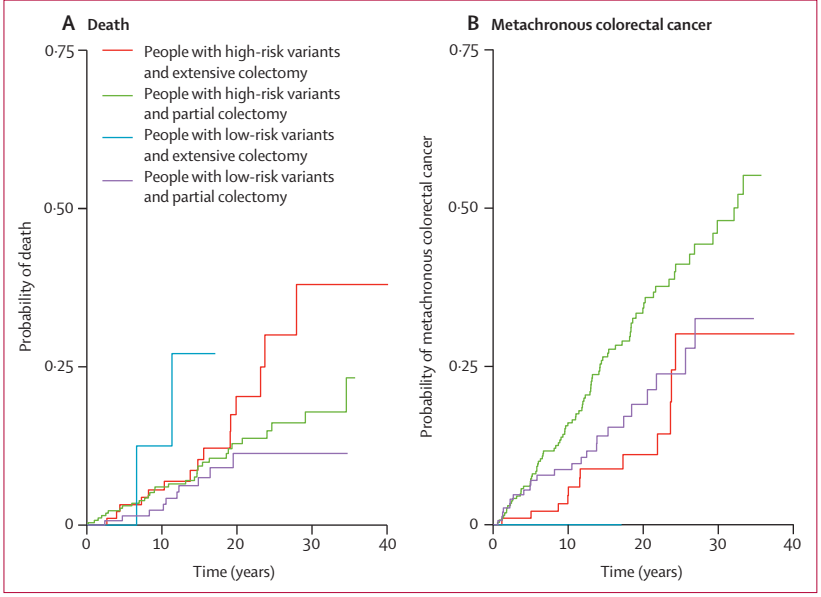


***Figure:*** **Competing risk analyses**
Competing risk analyses of the risk of death when considering metachronous colorectal cancer as a competing risk (A) and of the risk of metachronous colorectal cancer when considering death as a competing risk (B) for subgroups according to Lynch syndrome pathogenic variants and type of colectomy.

pathogenic variant was *MLH1* in 164 (31%) of 527 carriers of Lynch syndrome, *MSH2* in 192 (36%) carriers, *MSH6* in 126 (24%) carriers, *PMS2* in 37 (7%) carriers, and *EPCAM* in eight (2%) carriers. Primary colorectal cancers were predominantly located in the right-sided colon, were mostly adenocarcinomas, and were predominantly stage I or II (table 1). Extensive colectomy was done in 108 (20%) of 527 patients and partial colectomy in 419 (80%). Synchronous colorectal cancer occurred in 42 (8%) carriers, of whom 13 received extensive colectomy and 29 received partial colectomy.

Median follow-up from the time of primary colorectal cancer diagnosis to assembly and analysis of our data was 17·3 years (IQR 11·0–25·7). Surveillance colonoscopies after primary colorectal cancer were done in 413 (78%) patients, with a median duration until first surveillance colonoscopy of 22·0 months (IQR 11·0–55·3; table 2). Median duration until first surveillance colonoscopy was longer for carriers of Lynch syndrome with metachronous colorectal cancer (29·0 months, IQR 14·0–86·0) than for those without metachronous colorectal cancer (19·0 months, 11·0–51·5). Adequate adherence according to surveillance guidelines was found for 158 (30%) of 527 carriers of Lynch syndrome. Metachronous colorectal cancer occurred in 121 (23%) carriers in our sample, with a median duration until metachronous colorectal cancer of 11·0 years (IQR 2·1–17·8), of whom 99 (82%) had stage I or II first tumours. Of all patients with metachronous colorectal cancer, 95 (79%) had only one metachronous colorectal cancer and 26 (21%) had more than one reoccurrence. In people who developed metachronous colorectal cancer, 68 (56%) of the primary colorectal cancers were located in the right-sided colon. First metachronous colorectal cancer was located on the anastomosis in 23 (19%) of 121 patients. Location was a rectal anastomosis in eight of these patients. When location was elsewhere in the colon or when it was unknown whether the cancer was located on the anastomosis, first metachronous colorectal cancer was located in the rectum in 18 patients, resulting in a large proportion of first metachronous colorectal cancers located on the rectal anastomosis or in the rectum (26 [21%] of 121). Metachronous colorectal cancer occurred in 44 (27%) of 164 carriers of *MLH1* variants, 50 (26%) of 192 carriers of *MSH2* variants, 18 (14%) of 126 carriers of *MSH6* variants, six (16%) of 37 carriers of *PMS2* variants, and three (38%) of eight carriers of *EPCAM* variants. Metachronous colorectal cancer within 10 years occurred in 60 (11%) of 527 carriers of Lynch syndrome. 91 (17%) carriers died during follow-up (median time from primary colorectal cancer to death 13·8 years, IQR 7·4–19·8), of whom 22 (24%) had colorectal cancer-related death. Other causes of death were another cancer in 44 (48%) patients and heart or vascular disease (or both) in three (3%) patients. Cause of death was unknown for 22 (24%) patients.

97 carriers of Lynch syndrome were classified as high risk and had extensive colectomy, 267 were classified as high risk and had partial colectomy, 11 were classified as low risk and had extensive colectomy, and 152 were classified as low risk and had partial colectomy.

Metachronous colorectal cancer occurred in 12 (12%) patients with high-risk variants and extensive colectomy, in 85 (32%) patients with high-risk variants and partial colectomy, in zero patients with low-risk variants and extensive colectomy, and in 24 (16%) patients with low-risk variants and partial colectomy. Differences in the risk of metachronous colorectal cancer between the subgroups are presented in table 3. Within the group with high-risk variants, partial colectomy was associated with a significantly higher risk of metachronous colorectal cancer compared with extensive colectomy (hazard ratio [HR] 1·97, 95% CI 1·04–3·73; p=0·039). The risk of metachronous colorectal cancer was similar between carriers of low-risk variants who had partial colectomy and carriers of high-risk variants who had extensive colectomy (HR 1·14, 0·55–2·36; p=0·72). Competing risk analyses showed that the risk of metachronous colorectal cancer between the subgroups significantly differed when considering death as a competing risk (p=0·0009), whereas the risk of death between the subgroups did not differ when considering metachronous colorectal cancer as a competing risk (p=0·081; figure).

Assessment of possible factors influencing the risk of metachronous colorectal cancer is shown in table 4. Having a high-risk Lynch syndrome variant or a primary colorectal cancer diagnosis before the year 2000 significantly increased the risk of metachronous colorectal cancer occurrence. Extensive colectomy and performance of surveillance colonoscopy were associated with a lower risk of metachronous colorectal cancer than partial colectomy and no surveillance colonoscopies, respectively. Male sex, age at primary colorectal cancer diagnosis, advanced stage of primary colorectal cancer, and adequate adherence to surveillance colonoscopy guidelines showed no effect on metachronous colorectal cancer risk.

Because primary colorectal cancer diagnosis before the year 2000 was associated with a significantly higher risk of metachronous colorectal cancer, sensitivity analyses were done selecting only carriers of Lynch syndrome with a primary colorectal cancer diagnosis in or after the year 2000 (n=345; appendix p 3). These analyses also showed that the risk of metachronous colorectal cancer was similar between people with low-risk variants after partial colectomy and people with high-risk variants after extensive colectomy (HR 1·05, 95% CI 0·37–2·95; p=0·93). However, for patients with high-risk variants, there was no difference in the risk of metachronous colorectal cancer after partial versus extensive colectomy (HR 1·68, 0·67–4·24; p=0·27).

Assessment of possible influencing factors for mortality risk is shown in table 5. Older age at primary colorectal cancer diagnosis and a high-risk Lynch syndrome variant were associated with significantly higher mortality. The risk of death was not associated with male sex, performance of extensive colectomy, advanced tumour stage of the primary colorectal cancer, primary colorectal cancer diagnosis before the year 2000, or occurrence of metachronous colorectal cancer.

| | Carriers of Lynch syndrome with metachronous colorectal cancer (n=121) | Carriers of Lynch syndrome without metachronous colorectal cancer (n=406) | Hazard ratio (95% CI) | p value |
|---|---|---|---|---|
| Male sex | 68 (56%) | 206 (51%) | 1·25 (0·87–1·81) | 0·23 |
| Age at time of primary colorectal cancer | NA | NA | 1·01 (0·99–1·03) | 0·36 |
| High-risk Lynch syndrome variant | 97 (80%) | 267 (66%) | 1·76 (1·09–2·84) | 0·020 |
| Extensive colectomy performed | 12 (10%) | 96 (24%) | 0·49 (0·26–0·92) | 0·027 |
| Advanced stage of primary colorectal cancer | 25 (21%) | 78 (19%) | 1·33 (0·84–2·08) | 0·22 |
| Surveillance colonoscopy performed | 79 (65%) | 334 (82%) | 0·36 (0·24–0·53) | <0·001 |
| Adherence to surveillance | 19 (16%) | 139 (34%) | 1·09 (0·63–1·87) | 0·77 |
| Primary colorectal cancer before the year 2000 | 82 (68%) | 100 (25%) | 1·82 (1·17–2·82) | 0·008 |

Data are n (%), unless otherwise specified. Cox regression time-to-event analysis was done to determine the influence of sex (male=1), age at time of primary colorectal cancer, Lynch syndrome gene variant (high-risk variant=1), surgery performed (extensive colectomy=1), primary colorectal cancer stage (advanced stage [ie, stage III or IV]=1), surveillance colonoscopy performed after primary colorectal cancer (surveillance performed=1), adherence to surveillance guidelines (adherence=1), and primary colorectal cancer diagnosis before the year 2000 (primary colorectal cancer before the year 2000=1) on the risk of metachronous colorectal cancer. NA=not applicable.

*Table 4:* **Impact of factors on risk of metachronous colorectal cancer in carriers of Lynch syndrome**

| | People who died during follow-up (n=91) | People who survived during follow-up (n=436) | Hazard ratio (95% CI) | p value |
|---|---|---|---|---|
| Male sex | 47 (52%) | 227 (52%) | 0·99 (0·64–1·52) | 0·94 |
| Age at time of primary colorectal cancer | NA | NA | 1·08 (1·06–1·10) | <0·001 |
| High-risk Lynch syndrome variant | 76 (84%) | 288 (66%) | 3·55 (1·86–6·78) | <0·001 |
| Extensive colectomy performed | 20 (22%) | 88 (20%) | 1·05 (0·61–1·81) | 0·85 |
| Advanced stage of primary colorectal cancer | 20 (22%) | 83 (19%) | 1·14 (0·66–1·96) | 0·63 |
| Metachronous colorectal cancer occurrence | 33 (36%) | 88 (20%) | 1·22 (0·73–2·02) | 0·45 |
| Primary colorectal cancer before the year 2000 | 51 (56%) | 131 (30%) | 1·01 (0·58–1·77) | 0·96 |

Data are n (%), unless otherwise specified. Cox regression time-to-event analysis was done to determine the influence of sex (male=1), age at time of primary colorectal cancer, Lynch syndrome gene variant (high-risk variant=1), surgery performed (extensive colectomy=1), primary colorectal cancer stage (advanced stage[ie, stage III or IV]=1), primary colorectal cancer diagnosis before the year 2000 (primary colorectal cancer before the year 2000=1), and metachronous colorectal cancer occurrence (metachronous colorectal cancer occurrence=1) on mortality risk. NA=not applicable.

*Table 5:* **Impact of factors on risk of mortality in carriers of Lynch syndrome with colorectal cancer**

## Discussion

In this retrospective cohort study, we showed that the risk of developing metachronous colorectal cancer did not differ after partial colectomy in carriers of low-risk Lynch syndrome variants versus after extensive colectomy in carriers of high-risk Lynch syndrome variants. Previous studies, including two meta-analyses, investigating the risk of metachronous colorectal cancer in carriers of Lynch syndrome either did not subcategorise patients by variant, did not focus on differences between high-risk and low-risk variants, or did not include many carriers of *MSH6* or *PMS2*.[11,13,14,18–25] Our study provides important information

for clinicians in deciding the best surgical treatment option for carriers of Lynch syndrome with colorectal cancer. In carriers of high-risk Lynch syndrome variants with colorectal cancer undergoing extensive colectomy, the risk of metachronous colorectal cancer is inherent to the underlying disease. Even so, the number of metachronous colorectal cancers in this population is deemed acceptable. Therefore, especially when also considering the benefit of an improved functional outcome, our results suggest that partial colectomy, followed by regular endoscopic surveillance, can be considered for the treatment of primary colorectal cancer in patients with low-risk Lynch syndrome variants. A guideline from 2020 already states that there is insufficient evidence for the oncological benefit of extended colectomy over segmental resection in carriers of low-risk variants.[9] We believe that our study provides evidence to support this statement.

In our study, most colorectal cancers (both primary and metachronous) were diagnosed at an early stage, probably at least partly due to the advised colonoscopy surveillance every 2 years in carriers of Lynch syndrome. Even so, metachronous colorectal cancer was diagnosed in almost a quarter of participants. Although additional analyses showed that the occurence of metachronous colorectal cancer did not affect mortality risk, metachronous colorectal cancer and the need for additional surgery can still be a high burden for patients. Within carriers of high-risk Lynch syndrome variants, partial colectomy was associated with a higher risk of metachronous colorectal cancer than extensive colectomy. This finding suggests that the advantages and disadvantages of partial colectomy in these carriers should be clearly discussed with patients, especially with those who might be unlikely to be compliant with surveillance colonoscopies, weighing the high risk of metachronous colorectal cancer after partial colectomy against other factors, such as age, patient's wishes, and functional outcomes. However, sensitivity analyses of carriers of Lynch syndrome diagnosed with primary colorectal cancer in or after the year 2000 showed no difference in the risk of metachronous colorectal cancer after partial versus extensive colectomy for people with high-risk gene variants. Therefore, changes in surveillance colonoscopy guidelines and novel treatments could have made partial colectomy a sufficient treatment for carriers of high-risk Lynch syndrome variants with colorectal cancer. By performing partial colectomy, worse functional outcomes and social effects from extensive colectomy can be prevented. For example, one study found that carriers of Lynch syndrome who had a total colectomy for colorectal cancer had a longer surgery time, more blood loss, worse bowel function, and lower bowel-related quality of life than did people who underwent a hemicolectomy.[26] Nonetheless, carriers of Lynch syndrome are still at risk of developing metachronous colorectal cancer after partial colectomy, so continuance of strict colorectal surveillance is still indicated.

Stage III and IV metachronous colorectal cancer was uncommon, even in patients with high-risk variants after partial colectomy, limiting the impact of the cancer, especially with the current availability of immunotherapy for Lynch syndrome-associated colorectal cancer. Even so, subsequent treatment is then still needed.

When choosing to perform extensive colectomy to reduce the risk of metachronous colorectal cancer and subsequent treatment, rectal-sparing surgery could be preferred: functional outcome is especially better versus rectal surgery and the rectum is an easy location for surveillance.[27] When looking at the locations of metachronous colorectal cancers in this study, the cancer was located on the rectal anastomosis in eight patients and, when not located on the anastomosis or when it was unknown whether the cancer was located on the anastomosis, the cancer was located in the rectum in 18 people, resulting in a large proportion of first metachronous colorectal cancers being located on the rectal anastomosis or in the rectum. Therefore, when choosing rectal-sparing surgery, surveillance endoscopy is still of utmost importance.

At least one surveillance colonoscopy was done in 78% of all carriers of Lynch syndrome and was associated with a lower risk of metachronous colorectal cancer, emphasising the necessity of colorectal surveillance. Median duration until first surveillance colonoscopy was also longer for carriers of Lynch syndrome with metachronous colorectal cancer than for carriers without metachronous colorectal cancer. Adherence to the current surveillance guidelines was found in only 30% of people and was not associated with the risk of metachronous colorectal cancer. Within the participants who developed metachronous colorectal cancer, only 19 of 121 adhered to surveillance guidelines, indicating that metachronous colorectal cancer occurrence was low in the adherent group. The reason why this finding was not statistically significant can possibly be explained by the low number of patients in the adherent group and by the fact that colonoscopies were done that were not in line with the intervals recommended by the guidelines. Reasons for non-adherence are unknown but could be due to the wide time range of the study; because mismatch repair genes were found to be causative for Lynch syndrome only in the 1990s, carriers who developed colorectal cancer before this time might have had less strict surveillance intervals.[28–31] Although newly favoured strict adherence was not associated with differences in the risk of metachronous colorectal cancer, the effect of time was still shown, with primary colorectal cancer diagnosis before 2000 being associated with a higher risk of metachronous colorectal cancer than diagnosis in or after 2000.

Our study has several limitations. First, although we partly corrected for the effects of performance and adherence to surveillance colonoscopies in our analyses, the quality of these colonoscopies was unknown and could have affected the risk of metachronous colorectal

cancer. Additionally, our study included primary colorectal cancers from a wide time range in which surveillance recommendations and surgical management have changed over time. To partly correct for this influence, primary colorectal cancer diagnosis before the year 2000 was added as a confounder in our analyses. Sensitivity analyses were also done in carriers of Lynch syndrome with a primary colorectal cancer diagnosis in or after the year 2000.

Second, competing risk analyses showed that, when accounting for death as a competing risk, the risk of metachronous colorectal cancer might have been affected. To partly overcome this problem, we censored patients from the analyses at time of death, but patients who died could in theory have developed metachronous colorectal cancer. Even so, our study gives the best possible approximation of metachronous colorectal cancer risk in the different subgroups. Specifically, the possibility that there would have been more instances of metachronous colorectal cancer in the group with low-risk variants if individuals in that group had not died could have affected our main conclusion. However, this subgroup had fewer deaths (9%) than the subgroup with high-risk variants and extensive colectomy (19%), making this hypothetical situation very unlikely. It is important to note that the cause-specific hazards approach used for the statistical analysis of the competing events relies on specific assumptions to provide a valid causative estimate of the direct effect of exposure on the outcome, such as a well defined intervention and no unmeasured confounding.[32]

Third, loss to follow-up was unknown in our study. Known carriers of Lynch syndrome registered in the national Lynch syndrome database StOET are prospectively followed up, and the national pathology database PALGA has a nationwide collaboration with pathology laboratories, so the risk of missing a colorectal cancer report was minimised by combining these two databases. However, in theory, a colorectal cancer report could be missing, leading to an unknown loss to follow-up.

Fourth, we were hindered by the number of carriers of Lynch syndrome registered in the StOET database. One of our subgroups (ie, low-risk variants and extensive colectomy) consisted of only 11 people. This small sample size prevented us from drawing definitive conclusions about this subgroup. Nevertheless, this study focused mainly on comparing carriers with low-risk and high-risk Lynch syndrome variants who had partial colectomy with carriers with high-risk variants who had extensive colectomy.

Fifth, many carriers of Lynch syndrome with advanced stage colorectal cancers also receive neoadjuvant or adjuvant chemoradiotherapy alongside their surgery. Unfortunately, for many carriers, it was not known whether this treatment was given when indicated, which could have also affected the metachronous colorectal cancer risk. Of course, the effects of immunotherapy (eg, given in a neoadjuvant setting) could also reduce the risk of metachronous colorectal cancer. This effect should be evaluated when long-term follow-up data are available and could alter our current advice.[33,34]

Sixth, when partial colectomy was done, the reason for this type of surgery was unknown. Some patients might have had partial colectomy because it was not yet known that they were carriers of Lynch syndrome before their colorectal cancer pathology results. There could also be other reasons (eg, comorbidity) that could have led to a decreased life expectancy and thus smaller chance to find metachronous colorectal cancer in the partial colectomy group.

Finally, our study design was limited by the possibility of unmeasured confounding factors and possible changes in HR with time. Unmeasured confounding was limited by careful selection of confounders with a causal directed acyclic graph. However, not all possible confounders were available for inclusion in our analyses—eg, smoking status and alcohol consumption were unknown. Possible changes in HR with time were partly corrected by including primary colorectal cancer diagnosis before the year 2000 as a confounder in our analyses. Even so, HRs have a built-in selection bias that might have influenced our results.[35]

Nonetheless, our study included a relatively large cohort of carriers of Lynch syndrome, which enabled us to mutually compare carriers of high-risk and low-risk Lynch syndrome variants. Additionally, data were combined from two national prospective databases, giving the best representation of Dutch carriers of Lynch syndrome with colorectal cancer as possible. Despite the limitations, we therefore believe that we have reliably assessed the risk of metachronous colorectal cancer in carriers of different Lynch syndrome variants.

To conclude, we showed that the risk of metachronous colorectal cancer did not differ between carriers of low-risk Lynch syndrome variants who had partial colectomy and carriers of high-risk variants who had extensive colectomy. This finding suggests that carriers of low-risk *MSH6* and *PMS2* Lynch syndrome variants could be advised a partial colectomy in the case of colorectal cancer, consistent with the standard surgical approach for sporadic colorectal cancer. Additionally, the performance of at least one surveillance colonoscopy was associated with a reduced risk of metachronous colorectal cancer. This finding suggests that partial colectomy, followed by regular endoscopic surveillance, can be considered for the treatment of primary colorectal cancer in carriers of *MSH6* and *PMS2* Lynch syndrome variants. Sensitivity analyses in carriers of Lynch syndrome with a primary colorectal cancer diagnosis in or after the year 2000 showed no difference in the risk of metachronous colorectal cancer for people with high-risk variants having partial versus extensive colectomy. Changes in surveillance colonoscopy guidelines and novel treatments could have made partial colectomy a

sufficient treatment for carriers of high-risk Lynch syndrome variants as well, although sensitivity analyses should be interpreted with caution. This study endorses further research into more personalised management for carriers of Lynch syndrome, as has been suggested previously.[36] For future research, we believe that these promising results should be substantiated in a prospective setting and complemented with additional data on factors that could potentially influence the risk of metachronous colorectal cancer, such as the quality of colonoscopy surveillance.

#### Contributors

All authors conceptualised the paper. ELE and SM curated the data. ELE, SM, and GP analysed the data. ELE, SM, and MCWS oversaw the investigation. ELE, SM, GP, MEvL, AW, and MCWS were responsible for the methodology. MCWS was responsible for the project administration. MD, MEvL, ED, and MCWS were responsible for acquiring the resources. ELE, SM, and GP were responsible for the software. MCWS supervised the project. All authors validated the study. ELE, SM, MEvL, ED, PJT, and MCWS were responsible for the visualisations of data. ELE, SM, and MCWS wrote the original draft. All authors edited and reviewed the subsequent drafts. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. ELE and SM accessed and verified the data.

#### Declaration of interests

We declare no competing interests.

#### Data sharing

Data from this study are not publicly available. Deidentified participant data used in this study will be shared (via SURFfilesender) with researchers who submit a research proposal, upon approval of the proposal by the Erasmus MC and StOET Research Board, with publication. Additional related documents will not be made available.

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