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Risk of colorectal and endometrial cancers in *EPCAM* deletion-positive Lynch syndrome: a cohort study

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Summary

Background Lynch syndrome is caused by germline mutations in *MSH2*, *MLH1*, *MSH6*, and *PMS2* mismatch-repair genes and leads to a high risk of colorectal and endometrial cancer. We previously showed that constitutional 3′ end deletions of *EPCAM* can cause Lynch syndrome through epigenetic silencing of *MSH2* in *EPCAM*-expressing tissues, resulting in tissue-specific MSH2 deficiency. We aim to establish the risk of cancer associated with such *EPCAM* deletions.

Methods We obtained clinical data for 194 carriers of a 3′ end *EPCAM* deletion from 41 families known to us at the Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands and compared cancer risk with data from a previously described cohort of 473 carriers from 91 families with mutations in *MLH1*, *MSH2*, *MSH6*, or a combined *EPCAM–MSH2* deletion.

Findings 93 of the 194 *EPCAM* deletion carriers were diagnosed with colorectal cancer; three of the 92 women with *EPCAM* deletions were diagnosed with endometrial cancer. Carriers of an *EPCAM* deletion had a 75% (95% CI 65–85) cumulative risk of colorectal cancer before the age of 70 years (mean age at diagnosis 43 years [SD 12]), which did not differ significantly from that of carriers of combined *EPCAM–MSH2* deletion (69% [95% CI 47–91], p=0·8609) or mutations in *MSH2* (77% [64–90], p=0·5892) or *MLH1* (79% [68–90], p=0·5492), but was higher than noted for carriers of *MSH6* mutation (50% [38–62], p<0·0001). By contrast, women with *EPCAM* deletions had a 12% [0–27] cumulative risk of endometrial cancer, which was lower than was that noted for carriers of a combined *EPCAM–MSH2* deletion (55% [20–90], p<0·0001) or of a mutation in *MSH2* (51% [33–69], p=0·0006) or *MSH6* (34% [20–48], p=0·0309), but did not differ significantly from that noted for *MLH1* (33% [15–51], p=0·1193) mutation carriers. This risk seems to be restricted to deletions that extend close to the *MSH2* gene promoter. Of 194 carriers of an *EPCAM* deletion, three had duodenal cancer and four had pancreatic cancer.

Interpretation *EPCAM* deletion carriers have a high risk of colorectal cancer; only those with deletions extending close to the *MSH2* promoter have an increased risk of endometrial cancer. These results underscore the effect of mosaic MSH2 deficiency, leading to variable cancer risks, and could form the basis of an optimised protocol for the recognition and targeted prevention of cancer in *EPCAM* deletion carriers.

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Introduction

Lynch syndrome, or hereditary non-polyposis colorectal cancer, is caused by pathogenic germline mutations in one of the DNA mismatch-repair genes *MLH1, MSH2, MSH6,* or *PMS2*. This syndrome is characterised by a high risk of early onset colorectal cancer and several other extracolonic malignant tumours, especially endometrial cancer.[1] People who are carriers of mutations in *MLH1, MSH2,* or *MSH6* have a 30–80% risk of colorectal carcinoma by the age of 70 years.[2,3] Women with Lynch syndrome have an additional 27–71% risk of development of endometrial cancer by this age.[2–4]

Surveillance for colorectal cancer, starting at an early age, is recommended to improve survival for asymptomatic mutation carriers in families with Lynch syndrome. Equally, surveillance and prophylactic surgery for endometrial cancer are widely undertaken.[3] So far, the benefit of surveillance for other extracolonic malignancies is not known, but based on the occurrence of such diseases associated with Lynch syndrome within a specific family, additional surveillance is often considered.[4,5]

We previously identified germline deletions in the *EPCAM* gene (formerly known as *TACSTD1*) as a novel cause of Lynch syndrome.[6,7] Such deletions disrupt the 3′ end of *EPCAM*, leading to transcriptional read-through

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into, and subsequent epigenetic silencing of, its neighbouring gene, *MSH2*, causing Lynch syndrome.[6] Because this silencing event is restricted to cells expressing *EPCAM*, carriers of *EPCAM* deletions show mosaic patterns of *MSH2* inactivation that, compared with carriers of a mutation in *MSH2*, may lead to differences in tumour occurrence or spectrum. A comparatively high expression of *EPCAM* in colorectal-cancer stem cells[8,9] explains why carriers with an *EPCAM* deletion have a substantially increased risk of colorectal cancer. Since very little is known about expression of *EPCAM* in stem cells of extracolonic tumours, the risk of development of other tumours associated with Lynch syndrome in carriers of a 3′ end *EPCAM* deletion is unknown. Furthermore, because EPCAM can modulate both cell adhesion and proliferation,[10,11] inactivation of *EPCAM* itself might affect tumour risk.

Several investigators have reported families with *EPCAM* deletions.[6,7,12–15] Determination of the possibly specific tumour spectrum and age-specific cancer risk in families carrying *EPCAM* deletions is needed to generate optimal recognition and surveillance strategies. Here, we employed deletion scanning with clinical inventories to establish cancer risks associated with *EPCAM* deletions and compared these risks with those for Lynch syndrome carriers of either a mutation in *MLH1*, *MSH2*, or *MSH6*, or a deletion affecting both *EPCAM* and its neighbouring gene *MSH2* (*EPCAM–MSH2*).

Methods

Study population and procedures

We included all 41 families with a 3′ end *EPCAM* deletion who were known to us at the Department of Human Genetics of the Radboud University Nijmegen Medical Centre (Nijmegen, Netherlands) by Nov 30, 2009. For all families, the deletion did not include the defined promoter region and open reading frame of the *MSH2* gene (Kuiper RP, unpublished data). The deletion has previously been reported for 14 of the 41 families.[6,7,12,14,16] Collection of the remaining families was based on the occurrence of as yet unexplained *MSH2*-deficient tumours in the Netherlands and Germany, and by analysis of germline DNA samples of patients with unexplained *MSH2*-deficient tumours that were referred to the Radboud University Nijmegen Medical Centre. We only included carriers who tested positive for a deletion and obligate carriers in our study. Genetic counsellors obtained data for carriers' sex, year of birth, year of death, and year of tumour diagnosis, and clinicopathological and molecular data such as location of the tumour, microsatellite instability status, immunohistochemical status of mismatch-repair proteins, and methylation status of the *MSH2* gene promoter.

We collected clinical data for deletion carriers at the Radboud University Nijmegen Medical Centre until Feb 1, 2010. Overall, we included data for 16 families harbouring 105 carriers of a Dutch founder deletion,[6] two families harbouring 42 carriers from Switzerland with an identical Swiss deletion,[14] and 23 families harbouring 47 carriers with various different deletions from Germany (nine families), Hungary (five), USA (four), Hong Kong (two), Canada (one), UK (one), and the Netherlands (one). Overall, we obtained information about 194 *EPCAM* deletion carriers representing 16 different deletions. The Committee on Research Involving Human Subjects (region Arnhem-Nijmegen, Netherlands) gave ethical

	EPCAM	*EPCAM–MSH2**	*MSH2*	*MSH6*	*MLH1*
Families	41	7	32	26	26
Mutation carriers	194	42	143	160	128
Colorectal cancer					
Carriers affected	93 (48%)	18 (43%)	60 (42%)	45 (28%)	68 (53%)
Mean age at diagnosis (years)	43 (12; 18–79)†	41 (10; 21–58)	44 (11; 19–65)	54 (11; 32–79)	44 (11; 22–78)
Cumulative risk	75% (65–85)‡	69% (47–91)	77% (64–90)	50% (38–62)	79% (68–90)
Excess risk§	73%	67%	75%	48%	77%
Endometrial cancer					
Female carriers	92	15	78	87	67
Carriers affected	3 (3%)	5 (33%)	20 (26%)	20 (23%)	11 (16%)
Mean age at diagnosis (years)	49 (7; 43–56)	42 (6; 33–51)	47 (7; 33–61)	50 (12; 28–72)	52 (6; 46–64)
Cumulative risk	12% (0–27)¶	55% (20–90)	51% (33–69)	34% (20–48)	33% (15–51)
Excess risk§	11%	54%	50%	33%	32%
Ratio of colorectal cancer in women to endometrial cancer	12·3	0·8	1·6	1·1	2·9

Data are n, n (%), mean (SD; range), or % (95% CI). *Combined deletion. †Mean age at diagnosis of first colorectal cancer in carriers of an *EPCAM* deletion was based on data for 91 affected carriers because age at onset was unknown for two carriers. ‡Cumulative risk of colorectal cancer was based on data for 186 carriers of an *EPCAM* deletion (eight *EPCAM* deletion carriers were excluded from the Kaplan-Meier curves for colorectal cancer because ages were unknown at colorectal cancer diagnosis [two carriers] or follow-up [six carriers]). §In the Netherlands, cumulative risk at age 70 years (both sexes) of development of colorectal cancer was 2·5% and was 1·6% for endometrial cancer.[17,18] For white people in the USA, the risk was 1·9% for colorectal cancer and 1·6% for endometrial cancer.[19] ¶Cumulative risk of endometrial cancer was based on data for 87 carriers of an *EPCAM* deletion (exact age at last follow-up was not known for five other carriers).

Table 1: **Mean age at diagnosis and cumulative risk by age 70 years of colorectal and endometrial cancers in carriers of a mutation associated with Lynch syndrome**

approval for the study (project approval 2009/167). Carriers had given written informed consent for analysis of Lynch syndrome associated genes during previous counselling. Therefore, for this study, we only checked medical records that were acquired during these counselling procedures, and no explicit informed consent was needed for this study.

To compare risk in *EPCAM* deletion carriers with carriers of other mutations associated with Lynch syndrome, we obtained clinical data for 95 families with Lynch syndrome from a previously described cohort.[5] Four families with an *EPCAM* deletion in this cohort were excluded as they were already incorporated as *EPCAM*-deletion families, and seven families with a deletion involving both *EPCAM* and the 5′ part of *MSH2* (which we report as *EPCAM–MSH2*) were assessed separately. We only included data for carriers who tested positive for a given mutation and obligate carriers in our analyses, resulting in seven families (42 carriers) with *EPCAM–MSH2* mutation, 32 (143) with *MSH2*, 26 (160) with *MSH6*, and 26 (128) with *MLH1* (91 families and 473 carriers in total).

We did immunohistochemistry analysis on formalin fixed, paraffin-embedded tissues with the antibody Ep-CAM Ab-1 (clone VU-ID9; Thermo Fisher Scientific, Fremont, CA, USA) with standard procedures.

Statistical analysis

We analysed differences in mean age of cancer occurrence between the five mutation groups with one-way ANOVAs. We calculated follow-up time for every carrier as time between date of birth and date of first occurrence of cancer diagnosis, last contact, or death, whichever came first. We used Kaplan-Meier survival analyses to calculate the risk (95% CI) of cancer until specific ages. Analyses were censored at age 70 years. We used the log-rank test for comparisons of risks. All analyses were done with SPSS version 16.0.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data and had final responsibility for the decision to submit for publication.

Results

We obtained clinical data for 667 mutation carriers from 132 independent families with Lynch syndrome. 41 of these families encompassed 194 *EPCAM* deletion carriers (table 1). During follow-up, 93 *EPCAM* deletion carriers were diagnosed with colorectal cancer at a mean age at first diagnosis of 43 years (SD 12, range 18–79); mean age was 43 years (SD 14, range 18–79) for men and 42 years (SD 11, range 22–69) for women. Mean age at diagnosis for *EPCAM* deletion carriers did not differ from that of carriers of *EPCAM–MSH2*, *MSH2*, or *MLH1* mutation, but was younger than for *MSH6* mutation carriers (p<0·0001; table 1). The cumulative risk of colorectal cancer in carriers of an *EPCAM* deletion by age 70 years was much the same as for carriers of *EPCAM–MSH2*, *MSH2*, or *MLH1* mutations, but was higher than for *MSH6* mutation carriers (p<0·0001; table 1, figure 1). The cumulative risk

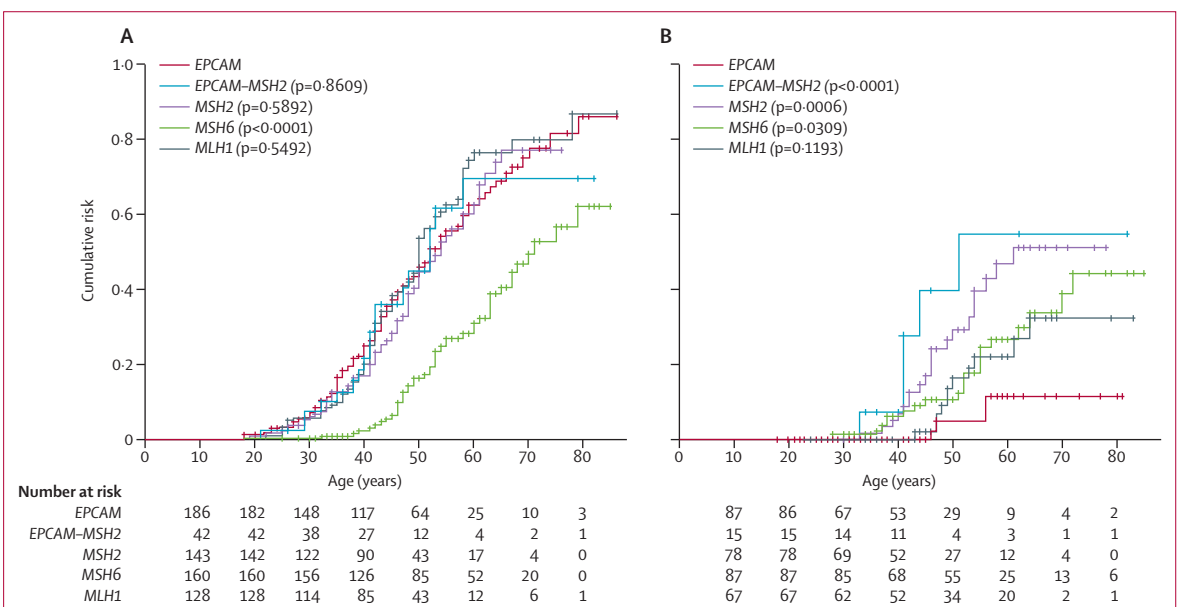

Figure 1: **Kaplan-Meier estimates of cumulative risk of colorectal cancer (A) and endometrial cancer (B) in carriers of an *EPCAM* deletion**
Log-rank p values are comparisons with carriers of an *EPCAM* deletion. Numbers at risk are numbers of mutation carriers who are at risk of a first colorectal cancer (A) or endometrial cancer (B). Eight *EPCAM* deletion carriers were excluded from the Kaplan-Meier curves for colorectal cancer because ages were unknown at colorectal cancer diagnosis (two carriers) or follow-up (six carriers). Five female *EPCAM* deletion carriers were excluded from the Kaplan-Meier curves for endometrial cancer because data for follow-up were incomplete.

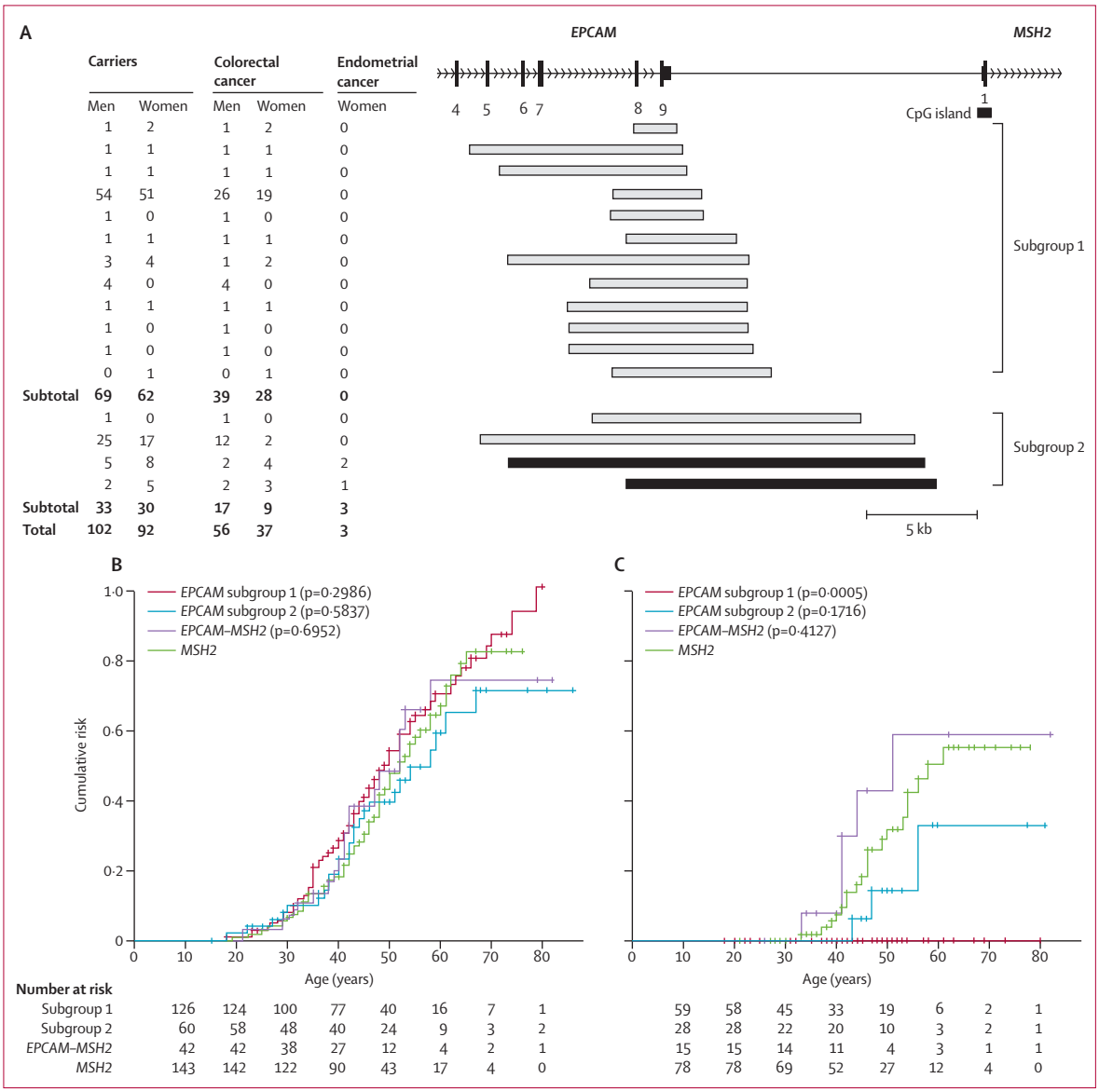

Figure 2: **Cancer risk in carriers of an *EPCAM* deletion in relation to deletion breakpoint and deletion size**
(A) Schematic representation of the size of every *EPCAM* deletion (bars) and position relative to the *MSH2* CpG island promoter. Black bars show deletions noted in carriers with endometrial cancer and grey bars depict deletions for which no patients with endometrial cancer were noted. The number of carriers of an *EPCAM* deletion and carriers with colorectal cancer or endometrial cancer are shown on the left. Kaplan-Meier estimates of cumulative colorectal cancer risk (B) and endometrial cancer risk (C) for the two subgroups (subgroup 1 were carriers with deletions located at least 10·0 kb upstream of *MSH2*; subgroup 2 were carriers with deletions extending to closer than 5·8 kb upstream of *MSH2*), *MSH2-EPCAM*, and *MSH2* are shown; log-rank p values are comparisons with carriers of the *MSH2* mutation. Numbers at risk are numbers of mutation carriers who are at risk of a first colorectal cancer (B) or endometrial cancer (C). Eight *EPCAM* deletion carriers were excluded from the Kaplan-Meier curves for colorectal cancer because ages were unknown at colorectal cancer diagnosis (two carriers) or follow-up (six carriers). Five female *EPCAM* deletion carriers were excluded from the Kaplan-Meier curves for endometrial cancer because data for follow-up were incomplete.

for colorectal cancer by age 70 years for *EPCAM* deletion carriers was 75% for men (95% CI 63–87) and 74% for women (56–92).

Three endometrial cancers were diagnosed in 92 women carrying an *EPCAM* deletion (table 1). Two of these endometrial cancers occurred in a family who were originally described by Chan and colleagues;[16] patient II-1 developed colorectal cancer at age 30 years and subsequently endometrial cancer at 56 years, and patient II-3 was diagnosed with endometrial cancer at age 43 years. Both patients were MSH2 deficient. The third case of endometrial cancer was reported by family history as the only tumour in an obligate carrier at age 47 years. Age at diagnosis of these three endometrial cancers was within the range reported for that of the other four mutation groups (table 1). However, the number of cases of endometrial cancer in women with an *EPCAM* deletion was found to be more than 12-times

lower than the number of such women with colorectal cancer, and this ratio is much lower than that reported for other mutation groups (table 1). Overall, on the basis of a Kaplan-Meier analysis, we calculated that *EPCAM* deletion carriers had a 12% (95% CI 0–27) cumulative risk of endometrial cancer by the age of 70 years, which was lower than was the risk for carriers of mutations of *EPCAM–MSH2*, *MSH2*, or *MSH6* (table 1 and figure 1).

We have previously shown a direct correlation between *EPCAM* expression and *MSH2* promoter methylation in carriers of a 3′ end *EPCAM* deletion.[9] The low frequency of new cases of endometrial cancer in this group might, therefore, be related to lower expression of the *EPCAM–MSH2* fusion transcript in tumour-initiating endometrial cells. In mature endometrial carcinomas, EPCAM was detectable by immunohistochemistry in 72 sporadic and 12 Lynch syndrome-related endometrial carcinomas (three with mutations affecting *MSH2-EPCAM*, two *MSH2*, five *MSH6*, and two *MLH1*). Moreover, we detected methylation of the *MSH2* promoter in the one endometrial carcinoma that was available for testing.

All three endometrial tumours occurred in patients from families with an *EPCAM* deletion extending close (<2·5 kb upstream) to the *MSH2* promoter region (figure 2, webappendix). Within these families, there were only 13 confirmed female deletion carriers. These findings suggest that *EPCAM* deletions extending close to *MSH2* might more efficiently inactivate *MSH2*. To explore this suggestion, we divided the *EPCAM* deletion families into two subgroups (figure 2). The first subgroup were carriers with deletions located at least 10·0 kb upstream of the *MSH2* gene (69 male and 62 female carriers), and the second subgroup were carriers with deletions extending to closer than 5·8 kb upstream of the *MSH2* gene (33 male and 30 female carriers). Cumulative risk of colorectal cancer before 70 years of age was 78% (95% CI 67–90) for subgroup 1 and 66% (46–85) for subgroup 2, and did not differ from that in carriers of an *EPCAM–MSH2* deletion or a *MSH2* mutation (figure 2). The risk of endometrial cancer in subgroup 2 was 31% (0–65), which seems lower than that for carriers of an *EPCAM–MSH2* deletion or a *MSH2* mutation (figure 2), suggesting that either not all carriers in subgroup 2 had an increased endometrial cancer risk or that the risk per individual was lower than that of carriers of an *EPCAM–MSH2* deletion or a *MSH2* mutation. These findings suggest that an increased risk of endometrial cancer is dependent on the location of the *EPCAM* deletion.

We identified 16 cases of malignant disease other than colorectal or endometrial cancer in carriers of an *EPCAM* deletion (table 2), two of which occurred in one patient. Three such carriers had duodenal cancer. Two of these cancers were available for analysis, and showed microsatellite instability (MSI-high), negative immunohistochemical staining for MSH2, and methylation of the *MSH2* promoter, which is indicative of a role of an *EPCAM* deletion in the development of the DNA mismatch-repair deficiency. Four carriers of an *EPCAM* deletion had pancreatic cancer, but no tumour specimens were available for further analysis. We did not detect duodenal cancer in 473 carriers of *EPCAM–MSH2*, *MSH2*, *MLH1*, or *MSH6* mutations, and noted only one pancreatic cancer in this group.

	Patients	Microsatellite instability status	Age at diagnosis (years)
Duodenum	3	Two high, one unknown*	52, 54, and unknown*
Pancreas	4	Unknown	46, 51, 65, and unknown
Breast	2	Unknown	57 and 59
Urothelial carcinoma	1	Stable	60
Kidney	1	Unknown	Unknown
Prostate	1	Unknown	71
Basal-cell carcinoma	1	Unknown	41
Brain	1	Unknown	Unknown
Gall bladder	1	Unknown	69
Myelodysplastic syndrome	1	Unknown	79

*Same patient.

Table 2: **Extracolonic and extraendometrial cancers in carriers of an *EPCAM* deletion**

Discussion

To our knowledge, this is the first study describing the cancer profile and risk estimate in a large cohort of Lynch syndrome families with *EPCAM* deletions (panel). We noted a high risk of colorectal cancer in deletion carriers, which was much the same as that for carriers with a mutation in the *MSH2* gene or a deletion affecting both *EPCAM* and *MSH2* genes. Additionally, a relatively high risk of duodenal and pancreatic cancer was reported. By contrast, the overall cumulative risk by age 70 years of endometrial cancer was only 12%, and seemed to be consistently low in carriers with *EPCAM* deletions located further upstream of the *MSH2* gene, as all three endometrial cancers were reported in women with the two *EPCAM* deletions that extended closest to the *MSH2* gene. Together, these results suggest that carriers of *EPCAM* deletions in families with Lynch syndrome have a distinct cancer risk, and that this risk is dependent on the location of the deleted region.

In our study, the index patients are included in the risk estimates for all different types of mutations. Because of ascertainment bias, this will have led to an overestimation of the actual cancer risk for each of the mutations. In our cohort of families with Lynch syndrome and a *MSH2* mutation, the colorectal cancer risk seemed somewhat higher than was reported by others, whereas the endometrial cancer risk for *MSH2* mutation carriers and both the colorectal and endometrial cancer risks of *MLH1* and *MSH6* mutation carriers were much the same as that reported by others.[20–24] We reported several duodenal and pancreatic cancers in *EPCAM* deletion carriers, whereas no duodenal cancer and only one pancreatic cancer was noted in carriers with a mutation in one of the mismatch-repair genes. This finding is in line with

See Online for webappendix

the very low frequency of duodenal and pancreatic cancer reported in families harbouring a mismatch-repair gene mutation.[23,25,26] Whether the risk for these cancers is higher in individuals with an *EPCAM* deletion than it is in individuals with a mismatch-repair gene mutation remains to be established. Comparison of a larger cohort of families with an *EPCAM* deletion, a combined *EPCAM–MSH2* deletion, or a mutation in *MSH2* might unravel whether the inactivation of *EPCAM* is important for the apparently increased risk of these cancers.

Although the 12% cumulative risk of endometrial cancer at 70 years of age in *EPCAM* deletion carriers is higher than is the population risk of 1·6%,[17] this risk is much lower than that for *MSH2* mutation carriers (51%) or combined *MSH2–EPCAM* deletion carriers (55%). This finding probably relates to the mosaic tissue-specific pattern of *MSH2* inactivation in these carriers, which is dependent on the tissue-specific amount of *EPCAM* expression. As we previously reported,[6] transcriptional read-through of *EPCAM* results in in-*cis* epigenetic silencing of the *MSH2* gene, whereas in tissues that do not show *EPCAM* expression, *MSH2* remains active. We assume, therefore, that the low number of cases of endometrial cancer could be explained by an insufficient amount of *EPCAM* expression in endometrial cells during early stages of tumour development, resulting in a normal activity of *MSH2* and consequently a lower than expected risk of tumour development.

The low number of cases of endometrial cancer in *EPCAM* deletion carriers is unlikely to be attributable to a selection bias for families with colorectal cancer. All *EPCAM* deletion carriers included in our study were derived from cohorts of patients with clinical presentation suggestive of Lynch syndrome, which was very similar to that in the cohort from which the families with *MSH2, MLH1,* and *MSH6* mutations were selected. The low rate of endometrial cancer is also unlikely to have been affected by unintended selection of the tumour type carried by the index patients, as 74% of the women included in this study were either derived from one large Dutch family (55% of women) or two large Swiss families (19% of women), in which relatives up to the fifth degree of the original index patient have been tested for the presence of a mutation. Although we cannot exclude that a modifying genetic factor acts in *cis* with either the Dutch or Swiss founder deletion, this seems unlikely as an absence of endometrial cancers in families with specific *MSH2* mutations has not been reported before. Moreover, inactivation of the *EPCAM* gene is not a protective factor by itself, as the risk of endometrial cancer in individuals with a combined *EPCAM–MSH2* deletion is akin to that of individuals with a mutation affecting only *MSH2*.

The three early-onset endometrial cancers that we reported occurred in women with a deletion that extended close to the *MSH2* promoter region.[27,28] There are a number of possible scenarios that might contribute to this occurrence. First, the efficiency of *MSH2* inactivation could be associated with the distance of the *EPCAM* and *MSH2* promoters on the allele carrying the deletion. Large *EPCAM* deletions extending close to the *MSH2* gene would put the two promoters into closer proximity, thus enabling endometrial cells to drive *MSH2* methylation, despite the weaker *EPCAM* promoter activity in these cells. Second, in carriers with deletions that extend close to the *MSH2* gene, the inactivation of *MSH2* might be less dependent on high *EPCAM* expression because of loss of a regulatory element. The presence of such an element in this region has thus far not been reported, but we did notice that the region overlaps with a punctuate site of enriched dimethylation and trimethylation of histone H3 on lysine 4 (H3K4Me2 and H3K4Me3) in HepG2 cells,[29,30] which strongly correlate with active promoters or enhancers.[31,32]

Whatever the mechanism might be, our data suggest that the risk for endometrial cancer in carriers of *EPCAM* deletions is dependent on the size and location of the deletion. The exact criteria of deletions conferring a low risk of endometrial cancer remain to be defined by further assessments of endometrial cancer incidence in carriers of different *EPCAM* deletions and analyses of the *EPCAM–MSH2* intergenic region for transcription-mediating capacity.

Surveillance programmes for Lynch syndrome families are typically aimed at early detection of colorectal and endometrial tumours, and are sometimes supplemented with surveillance for other malignant diseases associated with Lynch syndrome that occur within the family.[24,33] For example, surveillance for urinary tract cancer in *MSH2* mutation carriers has been recommended.[5] However, for cases in which the predicted rate of cancer is low, a targeted cancer

***Panel:* Research in context**

Systematic review

To provide a complete overview of *EPCAM* 3′ end deletions and to compare the cumulative risks in our cohorts of different mismatch-repair gene mutations with those in the published work, we searched Medline and PubMed databases for articles in English published up to Sept 30, 2010 including the search terms "HNPCC", "Lynch syndrome", "*EPCAM*", "*TACSTD1*", "*MLH1*", "*MSH2*", "*MSH6*", and "mismatch repair gene". We checked reference lists iteratively for relevant articles. To provide estimates of lowest and highest cumulative risk of colorectal and endometrial cancer in mismatch-repair mutation carriers we included peer-reviewed meta-analyses, landmark studies, and high-quality cohort studies.

Interpretation

EPCAM 3′ end deletions are a newly identified genetic cause of Lynch syndrome that function through a mechanism of tissue-specific epigenetic silencing. To our knowledge, this is the first study that describes the cumulative cancer risks and cancer profile of *EPCAM* deletion carriers. We show a profound difference in frequency of cases of endometrial cancer in this group compared with other Lynch syndrome families with mismatch-repair gene mutations. Strikingly, endometrial cancer was observed only in carriers with large *EPCAM* deletions that extended close to the *MSH2* gene, suggesting that the risk for this tumour type depends on the characteristics of the deletion. Consequently, our data are indicative for an adapted guideline of recognition and surveillance of carriers of a 3′ end *EPCAM* deletion.

prevention programme is less likely to offer clinical benefit, especially when evidence for its efficacy is limited. Therefore, we suggest that surveillance and preventive surgery for endometrial cancer could be omitted for carriers of small *EPCAM* deletions extending a long way from the *MSH2* promoter.

In conclusion, we report that carriers of an *EPCAM* deletion that leads to tissue-specific inactivation of *MSH2* have a high risk of development of colorectal cancer, which is similar to that noted for carriers of *MLH1* or *MSH2* mismatch-repair gene mutations. However the risk of endometrial cancer is lower in this group than it is with other Lynch-syndrome associated mutations. Our study provides a basis for an optimised protocol for the recognition and targeted prevention of cancer in *EPCAM* deletion carriers.

Contributors

MJLL and NH designed the study. CWO, MJEK, and RSvdP set up the database and collected and analysed clinical data. RPK and MJLL characterised the different deletions. POC, PH, NR, HKS, VS, EH-F, MM, MK, RCN, RHS, IK, FBLH, EML, JJPG, CMA, EJWR, FJH, CMJT, BPMvN, MEvG, EBGG, DME, DJB, SS, EMS, JOC, MRP, TG, LV, JP, EO, TLC, and SYL were responsible for clinical or molecular data acquisition. EV did the bioinformatic analyses of the intergenic region. JHvK, IDN, MG, and RB collected and analysed pathological materials. LALMK and MJEK did the statistical analyses, and MJLL and NH supervised the work. CWO, MJEK, RPK, AGvK, NH, and MJLL wrote the manuscript, with assistance and final approval from all authors.

Conflicts of interest

The authors declared no conflicts of interest.

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