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a report from the Prospective Lynch Syndrome Database

Møller, Pål; Seppälä, Toni; Bernstein, Inge; Holinski-Feder, Elke; Sala, Paulo; Gareth Evans, D; Lindblom, Annika; Macrae, Finlay; Blanco, Ignacio; Sijmons, Rolf H; Jeffries, Jacqueline; Vasen, Hans F A; Burn, John; Nakken, Sigve; Hovig, Eivind; Rødland, Einar Andreas; Tharmaratnam, Kukatharmini; de Vos Tot Nederveen Cappel, Wouter H; Hill, James; Wijnen, Juul T; Jenkins, Mark A; Green, Kate; Laloo, Fiona; Sunde, Lone; Mints, Miriam; Bertario, Lucio; Pineda, Marta; Navarro, Matilde; Morak, Monika; Renkonen-Sinisalo, Laura; Valentin, Mev Dominguez; Frayling, Ian M; Plazzer, John-Paul; Pylvanainen, Kirsi; Genuardi, Maurizio; Mecklin, Jukka-Pekka; Möslin, Gabriela; Sampson, Julian R; Capellá, Gabriel; Mallorca Group

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Cancer risk and survival in *path_MMR* carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database

Pål Møller,^{1,2,3} Toni T Seppälä,⁴ Inge Bernstein,^{5,6} Elke Holinski-Feder,^{7,8} Paulo Sala,⁹ D Gareth Evans,^{10,11} Annika Lindblom,¹² Finlay Macrae,^{13,14} Ignacio Blanco,¹⁵ Rolf H Sijmons,¹⁶ Jacqueline Jeffries,¹⁷ Hans F A Vasen,¹⁸ John Burn,¹⁹ Sigve Nakken,² Eivind Hovig,^{2,20,21} Einar Andreas Rødland,² Kukatharmini Tharmaratnam,²² Wouter H de Vos tot Nederveen Cappel,²³ James Hill,²⁴ Juul T Wijnen,²⁵ Mark A Jenkins,²⁶ Kate Green,^{10,11} Fiona Lalloo,^{10,11} Lone Sunde,^{6,27,28} Miriam Mints,²⁹ Lucio Bertario,⁹ Marta Pineda,¹⁵ Matilde Navarro,¹⁵ Monika Morak,^{7,8} Laura Renkonen-Sinisalo,^{4,30} Mev Dominguez Valentin,^{1,2} Ian M Frayling, John-Paul Plazzer,¹³ Kirsi Pylvanainen,³¹ Maurizio Genuardi,³² Jukka-Pekka Mecklin,³³ Gabriela Moeslein, Julian R Sampson,¹⁷ Gabriel Capella,^{15,34} in collaboration with The Mallorca Group

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For numbered affiliations see end of article.

Correspondence to

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ABSTRACT

Background Most patients with *path_MMR* gene variants (Lynch syndrome (LS)) now survive both their first and subsequent cancers, resulting in a growing number of older patients with LS for whom limited information exists with respect to cancer risk and survival.

Objective and design This observational, international, multicentre study aimed to determine prospectively observed incidences of cancers and survival in *path_MMR* carriers up to 75 years of age.

Results 3119 patients were followed for a total of 24 475 years. Cumulative incidences at 75 years (risks) for colorectal cancer were 46%, 43% and 15% in *path_MLH1*, *path_MSH2* and *path_MSH6* carriers; for endometrial cancer 43%, 57% and 46%; for ovarian cancer 10%, 17% and 13%; for upper gastrointestinal (gastric, duodenal, bile duct or pancreatic) cancers 21%, 10% and 7%; for urinary tract cancers 8%, 25% and 11%; for prostate cancer 17%, 32% and 18%; and for brain tumours 1%, 5% and 1%, respectively. Ovarian cancer occurred mainly premenopausally. By contrast, upper gastrointestinal, urinary tract and prostate cancers occurred predominantly at older ages. Overall 5-year survival for prostate cancer was 100%, urinary bladder 93%, ureter 85%, duodenum 67%, stomach 61%, bile duct 29%, brain 22% and pancreas 0%. *Path_PMS2* carriers had lower risk for cancer.

Conclusion Carriers of different *path_MMR* variants exhibit distinct patterns of cancer risk and survival as they age. Risk estimates for counselling and planning of surveillance and treatment should be tailored to each patient's age, gender and *path_MMR* variant. We have updated our open-access website www.lscarsk.org to facilitate this.

INTRODUCTION

Lynch syndrome (LS) is associated with a high probability of gastrointestinal, gynaecological and other cancers.^{1,2} It is caused by germline pathogenic variants in any of four DNA MMR genes referred to here as *path_MSH2*, *path_MLH1*, *path_PMS2* or *path_MSH6* and collectively as *path_MMR*. Deletions in the *EPCAM* gene, which lead to inherited methylation of the adjacent *MSH2* promoter, are also referred to as *path_MSH2*. To date, most patients with LS have been identified following investigation because of their family or personal history of multiple and/or early onset cancers.

Carriers of *path_MMR* variants require reliable information about their future cancer risks so that they can be offered appropriately targeted surveillance. However, a paucity of prospectively obtained information has led current clinical guidelines to rely heavily upon retrospective data from patient cohorts whose selection for molecular testing has been subject to bias. The efficacy of effects of interventions to prevent cancers in *path_MMR* carriers is debated.¹⁻⁴

Most patients with LS receiving surveillance for LS-associated tumours develop colorectal, gynaecological or other cancers and now survive both their first and subsequent cancers.^{1,2} The consequence is a growing and ageing population of patients with LS. There is limited information on their cancer risks and survivals. One reason for this is that in former generations most patients with LS died from their first cancer, and the risks for survivors are therefore difficult to determine from retrospective family studies.⁵ A second reason is that measures to prevent or cure early onset cancers in LS are recent developments that have benefited mainly younger patients with LS. A third reason is the



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Significance of this study

What is already known on this subject?

- ▶ Inherited predisposition to colorectal, gynaecological, urinary tract, upper gastrointestinal and other cancers may be caused by pathogenic variants of mismatch repair (*path_MMR*) genes and is then commonly referred to as Lynch syndrome (LS).
- ▶ Most patients with LS undergoing surveillance nonetheless develop colorectal and/or other cancers but often survive both their first cancer and their subsequent cancers.
- ▶ Penetrance and expressions of the different *path_MMR* genes in older age are uncertain.

What are the new findings?

- ▶ Prostate, urinary tract, gastric, duodenal, bile duct and pancreatic cancers occurred frequently in older patients with LS.
- ▶ Prostate and urinary tract cancers predominantly occurred in *path_MSH2* carriers.
- ▶ Upper gastrointestinal tract cancers predominantly occurred in *path_MLH1* carriers.
- ▶ Ovarian cancer occurred predominantly in younger women, which is in contrast to ovarian cancers in *path_BRCA1/2* carriers and in the general population.
- ▶ Survival was very poor for bile duct and pancreatic cancers, intermediate for gastric, duodenal and urinary tract cancers and good for prostate cancer.
- ▶ Except for endometrial and prostate cancer, typical LS cancers were not diagnosed in *path_PMS2* carriers.

How might it impact on clinical practice in the foreseeable future?

- ▶ Knowledge of *path_MMR* gene-specific incidence and survival of cancers affecting different organs will inform genetic counselling and clinical management in the ageing LS population.
- ▶ Risk assessment and surveillance in LS should be based on age, gender and the *path_MMR* gene involved.
- ▶ Subgroups of patients with LS defined by age and *path_MMR* gene have high risks for different cancers, some with serious prognoses in older age.
- ▶ Prevention and cure of these late onset cancers is a growing clinical challenge in LS.

possibility that patients with LS affected by cancer at younger ages might have *path_MMR* variants of higher penetrance (as in *path_BRCA1*⁶) and/or carry genetic modifiers that increase penetrance⁷ and/or were exposed to a more carcinogenic environment (as for *path_RB*⁸).

Indeed, it was unknown whether LS patients with and without early onset cancer had similar risks for cancer later in life. If the risks differed substantially, these groups could not be pooled when assessing risks in older patients. The first report from the Prospective Lynch Syndrome Database (PLSD) described LS patients without cancer before their inclusion and showed that the different *path_MMR* genes had different penetrance and/or expression.¹ Few previous prospective reports had stratified results this way and the question of whether LS patients with early onset cancer have an increased risk for subsequent cancer could be confounded by differences related to which *path_MMR* gene the patients carried. We examined this issue further in a second report from PLSD and found similar future cancer incidence in

patients with LS who had a previous cancer compared with those who did not, when stratifying by *path_MMR* gene.² These findings allowed us to combine the two groups in the present report.

No single centre has sufficient patient numbers to estimate risks in older individuals and international multicentre collaboration is needed to obtain results within a reasonable timeframe. The PLSD provides sufficient numbers for calculation of cumulative incidences of cancer by organ, *path_MMR* variant and gender up to 75 years of age with reasonable precision. For some groups, we also present some figures for cumulative incidences up to 80 years of age.

In our two former reports^{1,2}, we demonstrated differences in the penetrance and/or expression between pathogenic variants of the four *MMR* genes *MLH1*, *MSH2*, *MSH6* and *PMS2*, and we demonstrated that within each group of *path_MMR* carriers, the annual incidences of cancers were age dependent. We also demonstrated that for carriers of pathogenic variants of a given *MMR* gene, annual incidence rates of cancers were similar in those who had a previous (early) cancer and those who did not. That is, cancers appeared to be age-dependent stochastic events and any putative differences in penetrance between carriers who had or did not have an early cancer, including influences of inherited genetic modifiers and environmental factors could be ignored when compiling the current report based on the combined series of both sets of patients. We emphasise that while such factors may be important determinants of penetrance, it is nonetheless legitimate to combine the data from the previous reports and calculate results for the current report without them being subject to major confounders because of these factors.

This report together with the two former reports now provide information relevant to personalised medical care for patients with LS of any age, gender, with or without previous cancer and with any *path_MMR* variant.

METHODS**Recruitment and follow-up**

PLSD database design and inclusion criteria have been described previously.^{1,2} This study is an open observational study without a control group. *Path_MMR* carriers aged 25 years or older on the day of their first prospectively planned and completed surveillance colonoscopy were included whether they had previous cancer. We have reported previously time to first cancer¹ and time to any subsequent cancer² up to 70 years in these patients. Any cancers that were diagnosed before or at the same age as the first prospectively planned and completed colonoscopy were scored as previous cancers, and all incident cancers reported here were detected at an older age than the age at inclusion. All patients received follow-up surveillance as reported previously (1-2, see online Supplementary table S1) until the last update of information when they were scored as alive or dead. All patients were followed up according to local clinical guidelines. Follow-up times were censored if a patient was lost to follow-up. Intervals between colonoscopies were not considered. Each patient was censored at the age at which the last information was available, which might have been a colonoscopy, any other clinical examination, a report from an examination done by others, or information that the patient had died, whichever came last. In this report, we consider only incidences and survival of cancers in patients with LS undergoing surveillance. As we found that cancers continued to occur, we are planning future studies to investigate the relationships between factors such as colonoscopy interval, adenoma detection and removal and the incidence and stage at diagnoses of colorectal cancer.

All patients were demonstrated to be carriers of *path_MMR* variants (as determined by reporting centres) by gene testing or were obligate carriers of familial *path_MMR* variants by pedigree structure. All reported *path_MMR* variants were checked against the Leiden Open Variation Database (LOVD) for LS (http://chromium.lovd.nl/LOVD2/colon_cancer/) in October 2015. Deletions in the *EPCAM* gene that silence *MSH2* were scored as *path_MSH2*. In sum 1865 (59.7%) of the patients had pathogenic (class 5) variants, 42 (1.3%) patients had probably pathogenic (class 4) variants and the remaining 1212 (38.9%) patients had variants that were not found in LOVD.

The following information was used for analyses: gender, *path_MMR* variant, age at inclusion, age at last update, age at any cancer, cancers scored by the first three positions in the International Classification of Diseases version 9 (ICD9) diagnostic system and age at death. Cancer stage at diagnosis was not included.

Some centres have reported prospective findings independently^{9–11} and their previously reported cases are included in the present series.

Statistical methods

The statistical methods were described in detail previously.^{1 2} In short, annual incidence rates (AIRs) by age were calculated in 5-year cohorts from 25 to 75 years of age. Cumulative incidence, denoted by Q, was computed starting at age 25, assuming zero incidence before age 25, using the formula $Q(\text{age}) = Q(\text{age}-1) + [1 - Q(\text{age}-1)] \cdot \text{AIR}(\text{age})$ where $\text{AIR}(\text{age})$ is the annual incidence rate as estimated from the corresponding 5-year interval. The 95% CIs were estimated as appropriate.

When calculating the AIR for a given cancer, only patients without previous cancer in that organ were included, and observation time was censored at first cancer in the organ, while cancers in other organs were ignored. This was considered appropriate based on our reported findings that LS patients with previous cancer have approximately the same incidence of subsequent cancers as those with no previous cancer.^{1 2} This way of calculating organ-specific cumulative incidences is in line with the established method for reporting cumulative incidence of breast and ovarian cancer separately in carriers of *path_BRCA1/2*.^{6 12}

Lifetime cumulative incidence of cancer was calculated as cumulative incidence from 25 to 75 years of age and compared with the population average from the reporting countries as extracted from <http://globocan.iarc.fr> in December 2015. Specific lifetime cumulative incidences for duodenal, colon and rectal cancers were extracted from <http://www-dep.iarc.fr/NORDCAN/NO/frame.asp> in December 2015 for the year 2013. Relative cumulative lifetime risk was calculated as observed cumulative lifetime incidence divided by population cumulative incidence at 75 years. Crude 5-year and 10-year survival following cancer was assessed by the Kaplan-Meier survivor function for patients aged 65 years or less at diagnoses.

Ethics

All reporting centres exported only deidentified data to the joint database used for this report. All genetic tests were performed with appropriate informed consent according to local and national requirements for health care and/or research. No named data was exported from participating centres.

RESULTS

A total of 3119 patients including 1723 females, and 1396 males met the inclusion criteria. The total number of observation years

was 24 475. The numbers of patients and observation years were 1473 and 13 846 for *path_MLH1* carriers; 1060 and 7492 for *path_MSH2* carriers; 462 and 2613 for *path_MSH6* carriers; and 124 and 524 for *path_PMS2* carriers. Mean age at inclusion by gene and gender varied from 41.5 to 53.3; carriers of *path_MSH6* and *path_PMS2* were significantly older than carriers of *path_MLH1* and *path_MSH2* (table 1). Results for *path_PMS2* carriers are given, although numbers are generally insufficient to draw firm conclusions. In all, 813 cancers were diagnosed during follow-up. They affected 618 patients (20% of all patients with a mean of 1.3 cancers per affected patient) (details are given in online supplementary table S2). The observed incidences and cumulative incidences may be considered as risks of developing cancers and are discussed as such. Time from last colonoscopy to colorectal cancer in patients without prior cancer is given in our first report,¹ and time from last colonoscopy to colorectal cancer in patients having had a prior cancer is given in our second report²

Cumulative incidences of cancer by organ and age

The cumulative incidences of cancers in individual organs or groups of organs from 25 years of age are shown in tables 2 and 3. Cumulative incidence at 75 years for any cancer was 76% (95% CI 68.5% to 83.2%), 80% (95% CI 69.8% to 90.9%) and 61% (95% CI 42.7% to 79.0%) for *path_MLH1*, *path_MSH2* and *path_MSH6* carriers, respectively (table 2). A higher lifetime incidence for colorectal cancer was seen in *path_MLH1* and *path_MSH2* carriers compared with *path_MSH6* carriers (46% (95% CI 37.8% to 53.9%), 43% (95% CI 33.2% to 52.8%) and 15% (95% CI 3.3% to 26.6%), respectively). Colorectal cancer was not observed in the small number of *path_PMS2* carriers studied. Most colorectal cancer affected the colon rather than the sigmoid or rectum (table 3). Lifetime incidences for endometrial cancer were 43% (95% CI 33.1% to 52.3%); 57% (95% CI 41.8% to 71.6%) and 46% (95% CI 27.3% to 65.0%) for *path_MLH1*, *path_MSH2* and *path_MSH6* carriers, respectively. The corresponding incidences for ovarian cancer were: 10% (95% CI 4.8% to 15.4%), 17% (95% CI 5.7% to 28.0%) and 13% (95% CI 0.1% to 31.2%), respectively. Most gynaecological cancers occurred before the age of 60 years (tables 2 and 3). There was a significantly higher incidence of colon cancer in middle-aged *path_MLH1* males compared with females, but no significant gender differences were observed for colon cancer in *path_MSH2* and *path_MSH6* carriers (table 4).

Upper gastrointestinal cancers including those affecting the stomach, duodenum, bile duct, gall bladder or pancreas were diagnosed predominantly in old age. The cumulative lifetime incidence of upper gastrointestinal tumours was particularly high for *path_MLH1* carriers (21% (95% CI 15.6% to 27.1%)) compared with *path_MSH2* carriers (10% (95% CI 4.1% to 16.3%)) and *path_MSH6* carriers (7% (95% CI 0% to 14.8%)) (table 2). Among upper gastrointestinal cancers, the cumulative risk for stomach cancer was greatest: 7% (95% CI 3.5% to 10.8%) and 8% (95% CI 1.9% to 13.6%) for *path_MLH1* and *path_MSH2* carriers, respectively. Urinary tract cancers also occurred predominantly in older age. Their incidence was elevated particularly in *path_MSH2* carriers: 25% (95% CI 16.6% to 33.2%) compared with *path_MLH1* carriers (8% (95% CI 4.3% to 11.7%)) and *path_MSH6* carriers (11% (95% CI 1.7% to 20.3%)). Ureteric cancer was most prevalent. Cumulative incidences up to 75 years of age by *path_MMR* category for any cancer, upper gastrointestinal cancer and urinary tract cancer are shown in figure 1.

Table 1 Patients included, follow-up years and age at inclusion stratified on country, gender and *path_MMR* variants

Group	Sex	Cases	Follow-up years					Age at inclusion				
			Number	Mean	Min	Max	95% CI	Mean	Min	Max	95% CI	
All		3119	24 475	7.8	1	33	43.8	25	79	±0.46		
	F	1723	13 534	7.9	1	33	44.6	25	79	±0.62		
	M	1396	10 941	7.8	1	30	42.9	25	79	±0.67		
Country of origin												
Finland		952	9212	9.7	1	30	43.2	25	79	±0.88		
Denmark		515	3084	6.0	1	17	44.4	25	77	±1.09		
UK		386	2229	5.8	1	17	45.7	25	79	±1.29		
Norway		294	2217	7.5	1	22	44.7	25	79	±1.47		
Spain		202	1167	5.8	1	14	47.6	25	75	±1.75		
Germany		179	1276	7.1	1	29	43.5	25	72	±1.61		
Holland		165	898	5.4	1	28	45.5	25	78	±2.00		
Italy		163	1773	10.9	1	33	35.9	25	65	±1.42		
Sweden		159	1568	9.9	1	27	44.7	25	77	±2.07		
Australia		104	1051	10.1	1	30	39.2	25	70	±1.99		
Gene												
<i>MLH1</i>	F	781	7365	9.4	1	33	42.9	25	79	±0.93		
	M	692	6481	9.4	1	30	41.5	25	79	±0.96		
<i>MSH2</i>	F	599	4233	7.1	1	30	44.6	25	77	±1.02		
	M	461	3259	7.1	1	27	42.2	25	73	±1.05		
<i>MSH6</i>	F	276	1633	5.9	1	21	48.7	25	79	±1.60		
	M	186	980	5.3	1	28	46.8	25	79	±1.85		
<i>PMS2</i>	F	67	303	4.5	1	20	47.7	25	78	±2.73		
	M	57	221	3.9	1	22	53.3	26	77	±3.59		

Table 2 Cumulative incidence of cancers in groups of organs from 25 years of age up to the age indicated in the column Age, stratified on carriers of *path_MMR* variants in the different genes and 95% CIs in parentheses. Gynaecological cancer include endometrial and ovarian cancer. Upper gastrointestinal cancer include stomach, duodenum, bile duct, gall bladder or pancreas cancer. Genitourinary tract cancer include urinary bladder, ureter or kidney

ICD9	Organ	Age	Cumulative incidence at age (% (95% CI))			
			<i>path_MLH1</i>	<i>path_MSH2</i>	<i>path_MSH6</i>	<i>path_PMS2</i>
153, 154	Any cancer	40	16.8 (12.2 to 21.3)	14.3 (8.0 to 20.3)	0	0
		50	40.2 (34.7 to 45.7)	37.2 (29.4 to 45.1)	18.1 (8.0 to 28.3)	0
		60	58.7 (52.8 to 64.6)	57.6 (49.3 to 65.9)	39.0 (25.8 to 52.2)	18.2 (0.0 to 41.0)
		70	71.7 (64.7 to 78.7)	71.6 (61.9 to 81.2)	53.6 (38.6 to 68.6)	18.2 (0.0 to 41.0)
		75	75.8 (68.5 to 83.2)	80.4 (69.8 to 90.9)	60.9 (42.7 to 79.0)	52.1 (0.1 to 100.0)
153, 154	Colorectal cancer	40	12.7 (8.6 to 16.9)	8.9 (4.0 to 13.7)	0	0
		50	25.0 (20.0 to 30.0)	19.4 (13.0 to 25.8)	1.8 (0.0 to 5.4)	0
		60	34.6 (28.9 to 40.3)	27.1 (19.9 to 34.3)	5.6 (0.0 to 11.9)	0
		70	40.1 (33.5 to 46.7)	40.8 (31.6 to 50.1)	15.0% (3.3 to 26.6)	0
		75	45.8 (37.8 to 53.9)	43.0 (33.2 to 52.8)	15.0 (3.3 to 26.6)	0
182, 183	Gynaecological cancer	40	5.7 (2.1 to 9.3)	5.2 (0.2 to 10.2)	4.2 (0.0 to 12.3)	0
		50	24.6 (18.2 to 30.9)	25.3 (16.1 to 34.5)	19.2 (6.2 to 32.1)	0
		60	41.4 (33.6 to 49.2)	49.2 (37.9 to 60.4)	36.1 (19.2 to 53.1)	26.4 (0.8 to 51.9)
		70	47.6 (38.9 to 56.4)	62.1 (49.1 to 75.0)	54.0 (34.6 to 73.4)	26.4 (0.8 to 51.9)
		75	49.8 (40.5 to 59.0)	65.7 (52.2 to 79.1)	54.0 (34.6 to 73.4)	26.4 (0.8 to 51.9)
151, 152, 156, 157	Upper gastrointestinal tract cancer	40	1.0 (0.0 to 2.1)	0	0	0
		50	3.3 (1.4 to 5.1)	1.5 (0.0 to 3.1)	0	0
		60	7.0 (4.3 to 9.7)	4.1 (1.3 to 6.9)	2.8 (0.0 to 6.7)	0
		70	17.1 (12.1 to 22.0)	6.7 (2.7 to 10.6)	2.8 (0.0 to 6.7)	0
		75	21.4 (15.6 to 27.1)	10.2 (4.1 to 16.3)	6.6 (0.0 to 14.8)	0
188, 189	Urinary tract	40	0.3 (0.0 to 0.9)	0	0	0
		50	1.3 (0.2 to 2.5)	3.4 (0.9 to 5.9)	3.0 (0.0 to 7.0)	0
		60	3.0 (1.1 to 4.8)	9.8 (5.6 to 14.0)	5.7 (0.3 to 11.1)	0
		70	7.2 (3.8 to 10.6)	14.2 (11.1 to 17.3)	7.2 (1.1 to 13.3)	0
		75	8.0 (4.3 to 11.7)	24.9 (16.6 to 33.2)	11.0 (1.7 to 20.3)	0

Table 3 Cumulative incidences of individual cancers in carriers of *path_MMR* variants in the different genes from 25 years of age up to the age of 75 are shown. Incidence of breast, endometrial and ovarian cancers were calculated in females and incidence of prostate cancers calculated in men; all others in both genders combined

ICD9	Organ	Age	Cumulative incidence by age (% (95% CI))			
			<i>path_MLH1</i>	<i>path_MSH2</i>	<i>path_MSH6</i>	<i>path_PMS2</i>
Colorectal cancer						
153	Colon	40	12.9 (8.8 to 17.1)	8.6 (3.9 to 13.3)	0	0
		50	25.7 (20.7 to 30.7)	20.2 (13.9 to 26.4)	1.8 (0.0 to 5.2)	0
		60	36.0 (30.4 to 41.6)	27.3 (20.3 to 34.3)	5.3 (0.0 to 11.2)	0
		70	41.6 (35.2 to 48.0)	40.2 (31.3 to 49.1)	14.2 (3.1 to 25.4)	0
		75	46.7 (39.2 to 54.3)	42.4 (32.9 to 51.9)	14.2 (3.1 to 25.4)	0
154	Sigmoid and rectum	40	1.6 (0.2 to 3.0)	0.6 (0.0 to 1.8)	0	0
		50	3.2 (1.3 to 5.0)	4.7 (1.7 to 7.7)	0	0
		60	6.3 (3.6 to 9.0)	9.8 (5.5 to 14.1)	3.0 (0.0 to 7.1)	0
		70	9.2 (5.6 to 12.9)	13.5 (8.0 to 19.0)	4.6 (0.0 to 9.7)	0
		75	11.8 (7.2 to 16.4)	18.3 (10.9 to 25.6)	4.6 (0.0 to 9.7)	0
Endometrial and ovarian cancer						
182	Endometrium	40	3.1 (0.4 to 5.8)	1.5 (0.0 to 4.4)	0	0
		50	18.7 (12.9 to 24.5)	15.9 (7.9 to 23.8)	15.4 (4.1 to 26.8)	0
		60	34.8 (27.1 to 42.5)	40.9 (29.2 to 52.6)	33.2 (16.5 to 49.9)	26.4 (0.8 to 51.9)
		70	40.3 (31.5 to 49.1)	52.7 (38.7 to 66.8)	46.2 (27.3 to 65.0)	26.4 (0.8 to 51.9)
		75	42.7 (33.1 to 52.3)	56.7 (41.8 to 71.6)	46.2 (27.3 to 65.0)	26.4 (0.8 to 51.9)
183	Ovaries	40	2.6 (0.1 to 5.2)	3.8 (0.0 to 8.0)	4.2 (0.0 to 12.3)	0
		50	6.8 (2.9 to 10.7)	10.7 (4.1 to 17.4)	4.2 (0.0 to 12.3)	0
		60	8.6 (4.0 to 13.2)	12.3 (5.1 to 19.5)	4.2 (0.0 to 12.3)	0
		70	10.1 (4.8 to 15.4)	16.9 (5.7 to 28.0)	13.1 (0.0 to 31.2)	0
		75	10.1 (4.8 to 15.4)	16.9 (5.7 to 28.0)	13.1 (0.0 to 31.2)	0
Upper gastrointestinal cancer						
151	Stomach	40	0.3 (0.0 to 0.9)	0	0	0
		50	0.8 (0.0 to 1.7)	0.5 (0.0 to 1.4)	0	0
		60	2.4 (0.7 to 4.0)	1.6 (0.0 to 3.4)	1.4 (0.0 to 4.2)	0
		70	6.3 (3.0 to 9.7)	4.1 (0.8 to 7.5)	1.4 (0.0 to 4.2)	0
		75	7.1 (3.5 to 10.8)	7.7 (1.9 to 13.6)	5.3 (0.0 to 13.1)	0
152	Duodenum	40	0.4 (0.0 to 1.1)	0	0	0
		50	1.1 (0.0 to 2.3)	1.0 (0.0 to 2.3)	0	0
		60	2.1 (0.5 to 3.7)	2.0 (0.1 to 4.0)	0	0
		70	4.1 (1.4 to 6.8)	2.0 (0.1 to 4.0)	0	0
		75	6.5 (2.7 to 10.2)	2.0 (0.1 to 4.0)	0	0
156	Bile duct and gall bladder	40	0	0	0	0
		50	0.3 (0.0 to 0.8)	0	0	0
		60	1.3 (0.0 to 2.5)	0	0	0
		70	3.7 (1.3 to 6.2)	0	0	0
		75	3.7 (1.3 to 6.2)	1.7 (0.0 to 5.1)	0	0
157	Pancreas	40	0.3 (0.0 to 0.9)	0	0	0
		50	1.1 (0.0 to 2.1)	0	0	0
		60	1.7 (0.3 to 3.1)	0.5 (0.0 to 1.5)	1.4 (0.0 to 4.2)	0
		70	3.9 (1.4 to 6.4)	0.5 (0.0 to 1.5)	1.4 (0.0 to 4.2)	0
		75	6.2 (2.6 to 9.8)	0.5 (0.0 to 1.5)	1.4 (0.0 to 4.2)	0
Urinary tract cancer						
188	Urinary bladder	40	0	0	0	0
		50	0.5 (0.0 to 1.2)	1.0 (0.0 to 2.3)	2.9 (0.0 to 7.0)	0
		60	1.9 (0.4 to 3.4)	3.6 (1.0 to 6.3)	4.3 (0.0 to 9.1)	0
		70	4.1 (1.5 to 6.7)	6.2 (2.3 to 10.2)	4.3 (0.0 to 9.1)	0
		75	4.1 (1.5 to 6.7)	8.1 (2.8 to 13.3)	8.2 (0.0 to 16.9)	0
189	Ureter and kidney	40	0.3 (0.0 to 0.9)	0	0	0
		50	0.8 (0.0 to 1.8)	2.4 (0.3 to 4.5)	0	0
		60	1.1 (0.0 to 2.2)	6.9 (3.3 to 10.5)	1.4 (0.0 to 4.2)	0
		70	3.8 (1.2 to 6.4)	16.0 (9.6 to 22.4)	3.0 (0.0 to 7.0)	0

Continued

Table 3 Continued

ICD9	Organ	Age	Cumulative incidence by age (% (95% CI))			
			<i>path_MLH1</i>	<i>path_MSH2</i>	<i>path_MSH6</i>	<i>path_PMS2</i>
		75	4.6 (1.6 to 7.6)	17.8 (10.6 to 25.0)	3.0 (0.0 to 7.0)	0
Other LS or possible LS cancers						
174	Breast	40	0	2.6 (0.0 to 6.2)	0	0
		50	2.9 (0.6 to 5.2)	5.2 (0.7 to 9.8)	0	0
		60	8.3 (4.2 to 12.4)	6.1 (1.3 to 11.0)	4.7 (0.0 to 11.0)	8.6 (0.0 to 24.8)
		70	12.0 (6.7 to 17.3)	11.5 (4.6 to 18.4)	13.3 (2.2 to 24.4)	8.6 (0.0 to 24.8)
		75	12.0 (6.7 to 17.3)	11.5 (4.6 to 18.4)	13.3 (2.2 to 24.4)	55.9 (0.0 to 100.0)
185	Prostate	40	0	0	0	0
		50	0.6 (0.0 to 1.6)	0	0	37.9 (0.0 to 95.9)
		60	5.3 (1.4 to 9.1)	4.2 (0.0 to 8.8)	0	37.9 (0.0 to 95.9)
		70	13.3 (6.1 to 20.4)	13.2 (3.7 to 6.1)	4.4 (0.0 to 12.9)	37.9 (0.0 to 95.9)
		75	16.9 (8.5 to 25.3)	31.6 (11.7 to 51.5)	18.3 (0.0 to 44.4)	37.9 (0.0 to 95.9)
191	Brain	40	0.3 (0.0 to 0.9)	0	0	0
		50	0.3 (0.0 to 0.9)	0	0	0
		60	0.3 (0.0 to 0.9)	1.1 (0.0 to 2.6)	1.4 (0.0 to 4.2)	0
		70	1.0 (0.0 to 2.4)	1.9 (0.0 to 4.0)	1.4 (0.0 to 4.2)	0
		75	1.0 (0.0 to 2.4)	5.3 (0.2 to 10.3)	1.4 (0.0 to 4.2)	0

LS, Lynch syndrome

The cumulative incidences at 75 years of age for prostate cancer were 17% (95% CI 8.5% to 25.3%), 32% (95% CI 11.7% to 51.5%) and 18% (95% CI 0% to 44.4%) for *path_MLH1*, *path_MSH2* and *path_MSH6* carriers, respectively. For detailed description of all observation years and incident cancer cases in each 5-year age group, see online supplementary table S3.

Relative cumulative incidences

Cumulative incidences at 75 years of age were compared with population incidences to arrive at cumulative relative risk (RR) (see table 5). *Path_MLH1*, *path_MSH2* and *path_MSH6* carriers showed an RR of any cancer of 3.1 (95% CI 2.8 to 3.4), 3.3 (95% CI 2.9 to 3.7) and 2.5 (95% CI 1.7 to 3.2), respectively. By genotype, *path_MLH1* carriers had the highest RR for duodenal (RR 64.7), colon (RR 22.3), bile duct/gall bladder (RR 18.7) and pancreatic cancers (RR 7.8); *path_MSH2* carriers had the highest RR for endometrial (RR 35.5), ovarian (RR 16.9), urinary tract (RR 10.8) and prostate cancers (RR 3.2).

Path_MSH6 carriers had similar RR for endometrial and ovarian cancer as *path_MLH1* and *path_MSH2* carriers (RR 28.8 and 13.0, respectively) but less frequent cancer in other organs. The few *path_PMS2* carriers included had endometrial prostate and breast cancers, but none of the other cancers typically seen in LS were diagnosed (table 5).

Survival following cancer

Five-year and 10-year crude survival by affected organ for all cases diagnosed with cancer before 65 years of age are shown in table 6. Five-year survival was 96% for colon cancer and 75% for recto-sigmoid cancer. Corresponding 10-year survival was 88% and 70%, respectively. Five-year survival for endometrial cancer was 93% and for ovarian cancer 83%, and corresponding 10-year survival was 93% and 74%, respectively. Among other extracolonic cancers, 5-year survival was also very good for prostate (100%), urine bladder (93%) and ureter and kidney (85%) cancers and remained good at 10 years. Five-year survival

Table 4 Cumulative incidence colon and sigmoidal-rectal cancer stratified by age, *path_MMR* variant and gender. There was no observed colon or sigmoid-rectal cancer in *path_PMS2* carriers in any age group (see table 3)

	Age	Cumulative incidence by age (% (95% CI))					
		<i>path_MLH1</i>		<i>path_MSH2</i>		<i>path_MSH6</i>	
		Females	Males	Females	Males	Females	Males
Colon cancer (ICD9=153)	40	10.4 (5.2 to 15.6)	15.4 (9.0 to 21.9)	10.1 (2.9 to 17.3)	7.4 (1.2 to 13.6)	0	0
	50	18.8 (12.6 to 25.0)	33.3 (25.5 to 41.1)	23.8 (14.8 to 32.8)	15.8 (7.2 to 24.3)		0
	60	28.1 (20.9 to 35.2)	45.2 (36.6 to 53.8)*	31.4 (21.9 to 41.0)	21.5 (11.3 to 31.6)		
	70	37.3 (28.5 to 46.1)	45.2 (36.6 to 53.8)	44.7 (33.7 to 55.7)	32.4 (17.7 to 47.2)		
	75	42.1 (31.8 to 52.5)	50.8 (40.1 to 61.5)	44.7 (33.7 to 55.7)	42.6 (20.4 to 64.9)		
Sigmoid-rectal cancer (ICD9=154)	40	1.4 (0.0 to 3.3)	1.9 (0.0 to 4.1)	0	1.3 (0.0 to 3.8)	0	0
	50	2.9 (0.3 to 5.4)	3.6 (0.8 to 6.4)	1.0 (0.0 to 3.0)	8.9 (3.0 to 14.7)	0	0
	60	6.1 (2.4 to 9.8)	6.5 (2.6 to 10.5)	4.0 (0.2 to 7.8)	17.9 (9.2 to 26.5)	4.6 (0.0 to 10.7)	0
	70	10.2 (4.9 to 15.6)	7.6 (3.2 to 12.1)	8.2 (2.2 to 14.3)	20.7 (10.7 to 30.7)	7.0 (0.0 to 14.6)	0
	75	11.7 (5.7 to 17.7)	11.7 (4.7 to 18.7)	12.9 (4.4 to 21.3)	26.0 (12.3 to 39.7)	7.0 (0.0 to 14.6)	0

*Increased ($p < 0.05$) compared with same-aged females.

**Lower ($p < 0.05$) than in *path_MLH1* or *path_MSH2* carrier with same gender and age.

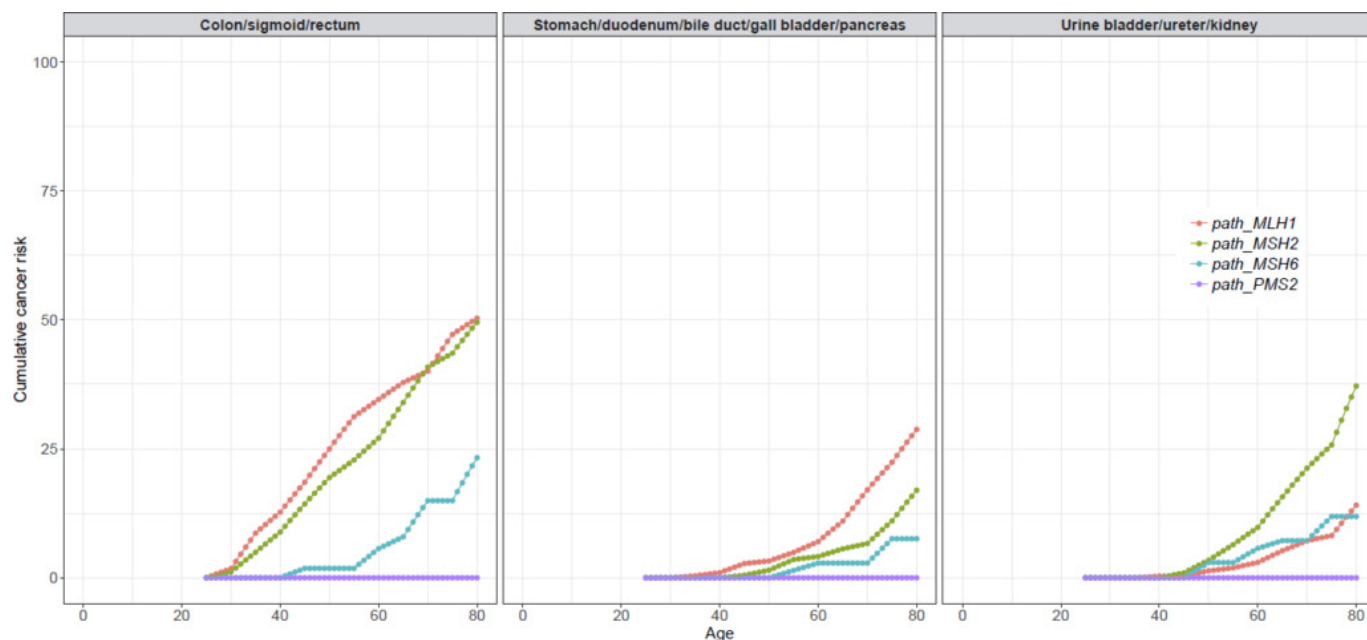


Figure 1 Cumulative incidences of colorectal cancer, upper gastrointestinal cancer (including stomach, duodenum, bile duct, gall bladder and pancreas) and urinary tract cancer (not including prostate).

for stomach and duodenal cancer was lower at 61% and 67%, respectively, while 5-year survival was poor following bile duct or gallbladder cancer (29%) or pancreatic cancer (0%).

Given the high mortality of some late-onset cancers and the probability that individuals affected by early-onset cancers with good prognoses might have developed and died from such cancers later, we recalculated survival after censoring patients as lost to follow-up when they developed a cancer with <70% 5-years survival. This did not result in any significant differences. The results of these calculations are illustrated in figure 2.

Combining risk for cancer and survival following cancer

Data on the risk of cancer affecting an organ and the chance of survival after that cancer occurs may be combined to calculate the risk of dying from a cancer in that organ. This combined risk may be calculated for a patient based on age, gender and *path_MMR* variant. As an example, the cumulative risk for colon cancer in a *path_MSH6* carrier at 60 years is 5%, 10-year survival is 88% and the risk of developing and dying of colorectal cancer before 70 years of age (subject to follow-up according to guidelines)

Table 5 Relative cumulative incidence (RR) cancer at 75 years in carriers of *path_MMR* genes stratified by gene. 95% CIs are shown in parentheses. Significantly increased ($p < 0.05$) RRs are highlighted in bold. Maximum RR by gene underlined

ICD9	Organ	Population incidence (%)	Relative cumulative incidence (95% CI)			
			<i>path_MLH1</i>	<i>path_MSH2</i>	<i>path_MSH6</i>	<i>path_PMS2</i>
Any cancer		24.4	3.1 (2.8 to 3.4)	3.3 (2.9 to 3.7)	2.5 (1.7 to 3.2)	2.1 (0 to 4.1)
In separate organs order by RR						
152	Duodenum	0.1	64.7 (27.4 to 102.1)	20.1 (0.6 to 39.6)	0	0
182	Endometrium	1.6	26.7 (20.7 to 32.7)	35.5 (26.1 to 44.8)	28.9 (17.1 to 40.6)	16.5 (0.5 to 32.4)
153	Colon	2.1	22.3 (18.7 to 25.9)	20.2 (15.6 to 24.7)	6.8 (1.5 to 12.1)	0
156	Bile duct and gall bladder	0.2	18.7 (6.3 to 31.1)	8.6 (0 to 25.4)	0	0
183	Ovary	1.0	10.1 (4.8 to 15.4)	16.9 (5.7 to 28.0)	13.1 (0 to 31.2)	0
189	Ureter and kidney	1.3	3.5 (1.2 to 5.9)	13.7 (8.2 to 19.2)	2.3 (0 to 5.4)	0
154	Sigmoid and rectum	1.4	8.4 (5.2 to 11.7)	13.0 (7.8 to 18.3)	3.3 (0 to 6.9)	0
191	Brain	0.5	1.9 (0 to 4.8)	10.5 (0.4 to 20.6)	2.9 (0 to 8.4)	0
151	Stomach	0.8	8.9 (4.4 to 13.4)	9.7 (2.3 to 17.0)	6.6 (0 to 16.4)	0
188	Urine bladder	1.0	4.1 (1.5 to 6.7)	8.1 (2.8 to 13.3)	6.2 (0 to 16.9)	0
157	Pancreas	0.8	7.8 (3.3 to 12.3)	0.6 (0 to 1.9)	1.8 (0 to 5.2)	0
185	Prostate	10	1.7 (0.9 to 2.7)	3.2 (1.2 to 5.1)	1.8 (0 to 4.4)	3.8 (0 to 9.6)
174	Breast	9.4	1.3 (0.7 to 1.8)	1.2 (0.5 to 2.0)	1.4 (0.2 to 2.6)	6.0 (0 to 10.6)
In anatomical regions ordered by RR						
Gynaecological		2.6	19.1 (15.6 to 22.7)	25.3 (20.1 to 30.4)	20.8 (13.3 to 28.2)	10.1 (0.3 to 20)
Colorectal		3.8	12.1 (10 to 14.2)	11.3 (8.7 to 13.9)	3.9 (0.9 to 7.0)	0
Upper gastrointestinal cancer		1.9	11.2 (8.2 to 14.3)	5.4 (2.1 to 8.6)	3.5 (0 to 7.8)	0
Urinary tract cancer		2.3	3.5 (1.9 to 5.1)	10.8 (7.2 to 14.4)	4.8 (0.7 to 8.8)	0

Table 6 Five-year and 10-year overall survival calculated by the Kaplan-Meier algorithm stratified on diagnoses for patients prospectively diagnosed <65 years of age

ICD9 diagnosis	Organ	n	5-year survival		10-year survival	
			Survival (%)	95% CI	Survival (%)	95% CI
Colorectal cancer						
153	Colon	159	96	91% to 98%	88	77% to 94%
154	Sigmoid rectum	47	75	56% to 87%	70	49% to 84%
Gynaecological cancer						
182	Endometrium	104	93	85% to 97%	93	85% to 97%
183	Ovary	25	83	55% to 94%	74	44% to 90%
Upper gastrointestinal tract cancer						
151	Stomach	17	61	33% to 81%	61	33% to 81%
152	Duodenum	11	67	28% to 88%	67	28% to 88%
157	Pancreas	10	0			
156	Bile duct and gall bladder	8	29	04% to 61%	14	1% to 47%
Urinary tract cancer						
189	Ureter kidney	28	85	64% to 94%	71	34% to 89%
188	Urine bladder	20	93	59% to 99%	81	42% to 95%
Other						
185	Prostate	17	100		80	20% to 97%
174	Breast	31	95	70% to 99%	89	61% to 97%
191	Brain	9	22	3% to 51%	22	3% to 59%

is $(5\% \cdot 12\%) = 0.6\%$. Other examples may be: the combined risk for a *path_MSH6* carrier of developing and dying from an ovarian cancer before 70 years would be $(4\% \cdot 26\%) = 1\%$. The combined risk for a *path_MLH1* carrier of developing and dying from bile duct cancer before 80 years would be $(4\% \cdot 86\%) =$

3%. It follows from the CIs in tables 3 and 6 that such calculated combined risks for contracting and dying from specific cancers have wide confidence intervals.

Path_MSH2 carriers had a substantial risk of urinary tract and prostate cancers in older ages and most but not all survived these

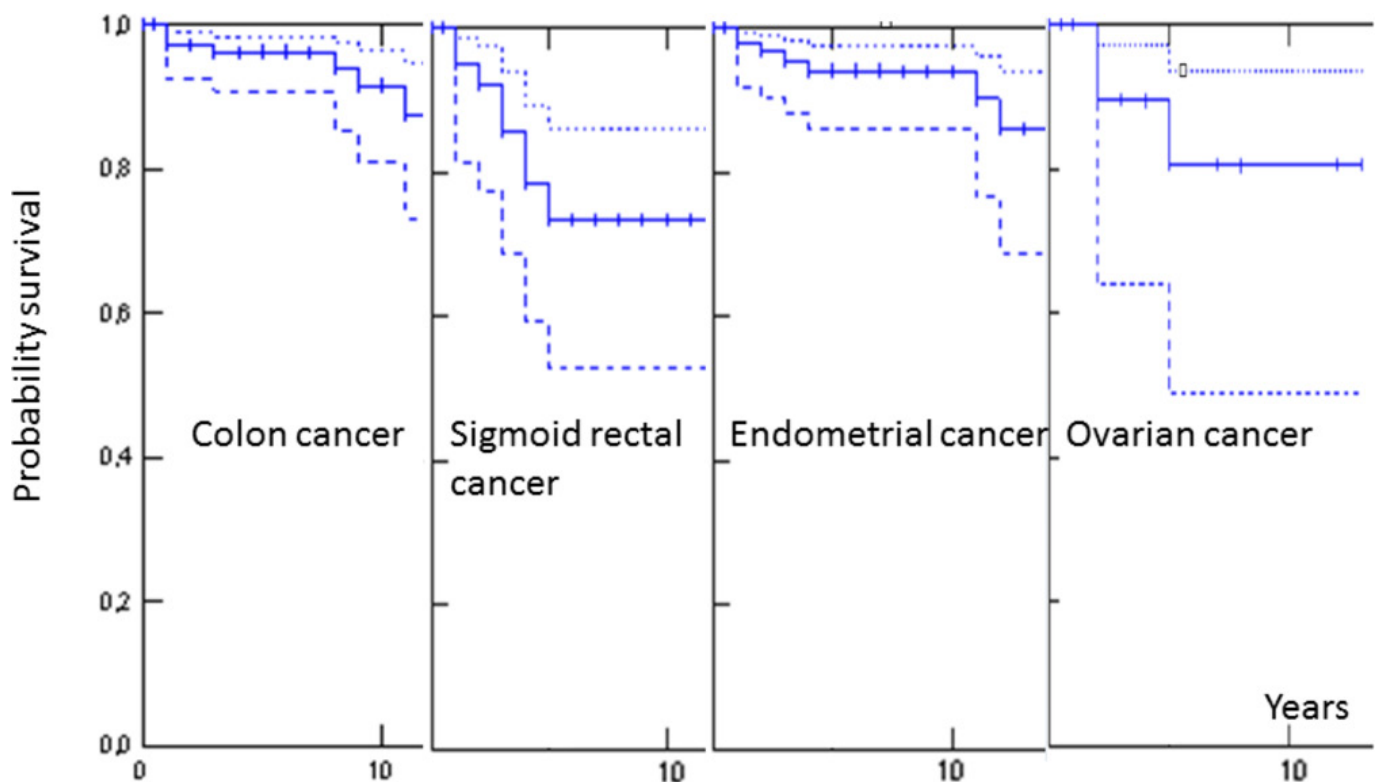


Figure 2 Kaplan-Meier estimates of 10-year crude survival following colon cancer, sigmoid-rectal cancer, endometrial cancer or ovarian cancer that was diagnosed before 65 years of age after censoring for upper gastrointestinal or brain tumours. Solid line indicates point values; dotted lines indicate 95% CIs.

cancers. In this report, the risk of cancer is presented for some ages only. Using our interactive website www.lscarisk.org, the risks of cancers may be calculated for patients with LS of any age.

DISCUSSION

This study included both LS patients without a previous cancer and patients with LS who had survived early cancer(s), thereby providing numbers that were sufficient to calculate cancer risks stratified by *path_MMR* variant for each organ involved up to 75 years of age. The majority of patients included in the study were *path_MLH1* or *path_MSH2* carriers, and the majority of older patients in these groups had survived previous cancer(s).¹² The tables describing cumulative cancer incidences are the results of the study and are discussed below. An interactive website (www.lscarisk.org) based on online supplementary table S3 allows cancer risks to be calculated for any patients with LS simply by providing the patient's age and gender and represents the applied outcome of the study.

Older *path_MSH2* carriers had a particularly high incidence of urinary tract and prostate cancers, while older *path_MLH1* carriers had the highest incidence of upper gastrointestinal cancers. Survival was very poor for bile duct and pancreatic cancer, intermediate for gastric and urinary tract cancers and good for prostate cancer. These findings demonstrate that genetic subgroups in LS are at risk for different cancers in old age and that these cancers have very different prognoses. Compared with *path_MLH1* and *path_MSH2* carriers, we show that *path_MSH6* carriers are at lower risk for early onset cancer and, except for an intermediate risk for urinary tract or prostate cancer, at lower risk for late onset cancers too.

The current study refines estimates of cancer risk for all patients with LS but in particular provides data that will better inform counselling and clinical management of older patients with LS. Previous reports^{9-11 13-17} did not include sufficient numbers of patients to stratify cancer risk in older age by *path_MMR* variant, as has been possible here.

Despite its international multicentre design, this study still identified too few *path_PMS2* carriers to draw firm conclusions about their cancer risks. Apart from endometrial and prostate cancer, however, none of the cancers considered to be part of LS were diagnosed in *path_PMS2* carriers.

We calculated the incidence of ovarian or endometrial cancer in female LS patients with censoring at prophylactic oophorectomy or hysterectomy that was undertaken in some patients. In contrast to *path_BRCA1/2* carriers¹² and the general population, most ovarian cancers in LS were diagnosed before the menopause, and their prognosis was good. This finding brings into question the practice of recommending prophylactic oophorectomy at the menopause in females with LS.⁴

Risks for breast cancer in patients with LS were not increased significantly, and therefore we could not confirm previous reports that have suggested that breast cancer is part of the LS cancer spectrum.¹⁷

The structure of the database (PLSD) established for our studies enables us to add any information of interest later for all patients. The results obtained so far raise further questions that we should now investigate, such as the relationships between colonoscopy interval, stage at prospectively detected CRC and its treatment and survival. We have a lot more to do, and we invite further centres to join PLSD so that we can answer these clinically important questions as quickly and as definitively as possible.

The novelty of this report is that we provide for the first time the empirical prospectively observed outcome of healthcare into old ages for patients with LS including stratification by *path_MMR* variant. Before management guidelines are revised to take account of this stratification, validation of the findings of this study should be achieved in at least one other similar but independent study. We are in collaboration with the European Hereditary Tumour Group (www.mallorca-group.org) and InSiGHT (www.insight-group.org) with the aim of establishing an independent series to validate the findings presented here. If our findings are confirmed, we may have a larger combined cohort to narrow the CIs of the observed point estimates before discussing conclusions with respect to clinical guidelines. To this end, we invite other centres with compatible cohorts of patients with LS to contribute. In particular, there is a need for much more data on *path_PMS2* and *path_MSH6* patients.

This is the first comprehensive study of cancer risk and prognosis in older LS patients stratified by *path_MMR* variant. We have updated our website www.lscarisk.org to include the results presented here. Using the website, the age, gender and *path_MMR* variant in any given patient may now be entered to calculate the remaining lifetime risk for cancer in individual organs. This is likely to be of interest both to patients with LS and their healthcare providers

For further information on the collaborating activities, please visit <http://insight-group.org/> and <http://mallorca-group.org/>.

Author affiliations

¹Department of Medical Genetics, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway

²Department of Tumor Biology, Institute of Cancer Research, The Norwegian Radium Hospital, part of Oslo University Hospital, Oslo, Norway

³Center for Hereditary Tumors, HELIOS-Klinikum Wuppertal, University of Witten-Herdecke, Wuppertal, Germany

⁴Department of Gastrointestinal Surgery, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland

⁵The Danish Hereditary Non-polyposis Colorectal Cancer Register, Clinical Research Centre, Copenhagen University Hospital, Hvidovre, Denmark

⁶Department of Surgical Gastroenterology, Aalborg University Hospital, Aalborg, Denmark

⁷Medizinische Klinik und Poliklinik IV, Campus Innenstadt, Klinikum der Universität München, Ziemssenstr, Germany

⁸MGZ – Medizinisch Genetisches Zentrum, Munich, Germany

⁹Unit of Hereditary Digestive Tract Tumors IRCCS Istituto Nazionale Tumori Milan, Milano, Italy

¹⁰Manchester Centre for Genomic Medicine, Central Manchester University Hospitals NHS Foundation Trust, London, UK

¹¹Manchester Centre for Genomic Medicine, University of Manchester, London, UK

¹²Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

¹³Colorectal Medicine and Genetics, The Royal Melbourne Hospital, Melbourne, Australia

¹⁴Department of Medicine, Melbourne University, Melbourne, Australia

¹⁵Hereditary Cancer Program, Institut Català d'Oncologia-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain

¹⁶Department of Genetics, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

¹⁷Division of Cancer and Genetics, Institute of Medical Genetics, Cardiff University School of Medicine, Heath Park, UK

¹⁸Department of Gastroenterology and Hepatology, Leiden University Medical Centre, Leiden, The Netherlands

¹⁹Institute of Genetic Medicine Newcastle University, Newcastle upon Tyne, UK

²⁰Institute of Cancer Genetics and Informatics, The Norwegian Radium Hospital, part of Oslo University Hospital, Oslo, Norway

²¹Department of Informatics, University of Oslo, Oslo, Norway

²²Department of Mathematics and Statistics, Lancaster University, Lancaster, UK

²³Department of Gastroenterology and Hepatology, Isala Clinics, Zwolle, The Netherlands

²⁴Department of Surgery, Central Manchester University Hospitals NHS Foundation Trust and University of Manchester, London, UK

²⁵Department of Clinical Genetics and Department of Human Genetics Leiden, University Medical Centre, Leiden, The Netherlands

- ²⁶Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Parkville, Victoria, Australia
- ²⁷Department of Clinical Genetics, Aarhus University Hospital, Aarhus, Denmark
- ²⁸Department of Biomedicine, Aarhus University, Aarhus, Denmark
- ²⁹Department of Women's and Children's health, Division of Obstetrics and Gynaecology, Karolinska Institutet, Karolinska University Hospital, Solna, Stockholm, Sweden
- ³⁰Genome-Scale Biology Research Program, University of Helsinki, Helsinki, Finland
- ³¹Department of Education and Science, Central Finland Health Care District, Yväskylä, Finland
- ³²Institute of Genomic Medicine, "A. Gemelli" Faculty of Medicine, Catholic University of the Sacred Heart, Rome, Italy
- ³³University of Eastern Finland, Kuopio, Finland
- ³⁴Center for Hereditary Tumors, HELIOS-Klinikum Wuppertal, University of Witten-Herdecke, Wuppertal, Germany

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Contributors Pål Mø: Designed the study, managed the database and computed the results. Pål Mø, Julian Sampson and GC wrote the manuscript. EH, SN, EARØ and KT calculated the confidence intervals to the cumulative incidences. EH and SN constructed the website calculating individual risks. All: Participated in study design, interpreting of results, commenting the manuscript and approved the final manuscript.

Competing interests John Burn has a patent for high speed low cost tumour profiling pending to John Burn and QuantuMDx.

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Data sharing statement The report is based on The Prospective Lynch Syndrome Database which is a joint venture by the contributors and endorsed by EHTG (mallorca-gropu.org) Group and InSiGTH (insight-group.org). Formal ownerships and development of the activities will be discussed at this year joint meeting for EHTG and InSiGTH in Florence July 5th-8th this year. All interested are welcomed to join.

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