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Original research

Impact of surveillance colonoscopy on colorectal cancer incidence and mortality in Lynch syndrome: a national observational cohort study of patients in the English NHS 2010–2022

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ABSTRACT

Background Lynch syndrome (LS) is a cancer susceptibility syndrome caused by germline pathogenic variants in DNA mismatch repair (MMR) genes. Due to increased risk of colorectal cancer (CRC), enhanced colonoscopic surveillance is recommended for heterozygote MMR carriers.

Objective Using a registry of English patients with LS linked to digital National Health Service records, we aimed to assess adherence of MMR carriers to national surveillance guidelines and to determine the impact of surveillance on CRC incidence and mortality.

Design We described the frequency of colonoscopies in 4732 MMR carriers and used logistic regression to determine predictors of surveillance adherence. For MMR carriers with a record of surveillance and those without, we estimated age-specific annual CRC incidence rates (AS-AIRs) and cumulative lifetime risks; assessed for stage shift by comparing CRC stage distributions and stage-specific AS-AIRs; and estimated risks of death from CRC and any cause using Kaplan-Meier methods and Cox proportional hazards regression.

Results Surveillance at a mean interval of ≤ 3 years ($n=3028$) was associated with a decrease in CRC-specific and all-cause mortality, without an associated change in total CRC incidence, even after multivariate adjustment. No strong evidence of stage shift was observed. Colonoscopic surveillance at a mean interval of ≤ 2 years ($n=1569$) was associated with an increase in total CRC incidence. Incidence of early-stage cancers was also higher, with no corresponding decrease in late-stage cancers, which may reflect the short follow-up period, spectrum bias, or the impact of overdiagnosis.

Conclusion The observed reduction in all-cause mortality among regularly surveilled MMR carriers may indicate an impact of surveillance on CRC-specific mortality, though in the context of a non-randomised study could also reflect the influence of selection bias.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Regular surveillance colonoscopy is recommended in Lynch syndrome (LS), though evidence to support this remains mixed. We searched PubMed for articles published from inception to 1 May 2024 using the terms 'Lynch syndrome', 'HNPCC', 'colonoscopy', 'sigmoidoscopy', 'surveillance' and 'screening'. We found one controlled trial and several small analytical studies dating from the early 2000s which compared surveilled and non-surveilled populations and found surveillance to be associated with reduced colorectal cancer (CRC) incidence and improved survival. More recent longitudinal observational studies, most without comparator groups, found a high incidence of CRC in LS populations despite being resident in countries where surveillance was recommended. A small number of studies directly assessed time since last colonoscopy against CRC incidence and stage with mixed findings. Finally, cross-sectional comparisons between countries of CRC incidence rates and surveillance interval recommendations found no relationship between the two.¹²

INTRODUCTION

Lynch syndrome (LS) is a cancer susceptibility syndrome caused by germline pathogenic variants (GPVs) in DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6* and *PMS2*). Heterozygote carriers of MMR gene GPVs (MMR carriers) have a high lifetime risk of colorectal cancer (CRC) compared with the general population, and thus may be offered additional preventative interventions, including regular surveillance colonoscopy with removal of polyps (adenomas). Surveillance in MMR carriers is theorised to prevent CRCs through disruption of the adenoma-carcinoma



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WHAT THIS STUDY ADDS

⇒ Here, we conduct an observational cohort study on a large national cohort of mismatch repair germline pathogenic variant carriers (MMR carriers) in England (n=4732), comparing CRC incidence and mortality in individuals with a record of regular surveillance to those without. Through linkage of the English National Lynch Syndrome Registry to Hospital Episodes Statistics data, we are uniquely able to study a comprehensive national population of MMR carriers and identify the dates on which colonoscopies were undertaken over time, allowing assessment of adherence to national surveillance guidelines and the impact this has on CRC outcomes. Notably, receipt of regular colonoscopy was strongly associated with deprivation as well as ethnicity. The results show that regular surveillance at an average interval of 3 years (or less) is not associated with a reduction in CRC incidence when compared with less frequent surveillance, but an apparent decrease in both CRC-specific and overall mortality is observed, even after adjustment for confounding variables. Conversely, regular surveillance at an average interval of 2 years (or less) is associated with an increase in CRC incidence when compared with less frequent surveillance, which may suggest increased diagnosis of early-stage cancers or, due to the absence of a reduction in late-stage cancers, overdiagnosis. The observed impact of surveillance on overall mortality may demonstrate the impact of surveillance on CRC-specific mortality or, in the context of an observational (non-randomised) study, indicate that the results are subject to selection bias.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Evidence for the benefit of surveillance colonoscopy remains mixed. While polypectomy would be anticipated to prevent CRC development (thus reducing CRC incidence), several studies have observed increased frequency of CRCs in MMR carriers undergoing frequent surveillance colonoscopy, which may reflect overdiagnosis. The selection bias inherent to observational studies of surveillance renders mortality outcomes challenging to interpret. Randomised controlled trials of colonoscopic surveillance in MMR carriers are required for effectiveness of this intervention to be accurately assessed. Given ethical and feasibility challenges, randomised controlled trials might be complemented by quasi-experimental designs using advanced observational methods for assessing effectiveness.

sequence, thus reducing CRC incidence, and to facilitate earlier detection, thus reducing CRC mortality.

In the UK, Europe and elsewhere, enhanced endoscopic surveillance has been recommended for MMR carriers since the early 2000s. In 2010, the British Society of Gastroenterology (BSG), the Association of Coloproctology of Great Britain and Ireland (ACPGBI) and the UK Cancer Genetics Group (UKCGG) updated their surveillance guidelines to specify 18-monthly colonoscopies from the ages of 25–75 for all MMR carriers, and again in 2020 to specify two-yearly colonoscopies from age 25 for *MLH1* carriers and *MSH2* carriers, and from age 35 for *MSH6* carriers and *PMS2* carriers.^{1,2}

These recommendations were introduced following the publication of, to this day, the only (non-randomised) controlled trial of colonoscopic surveillance in LS, in which a reduction

in CRC incidence and mortality was observed in LS individuals receiving regular surveillance compared with those who were not.^{3,4} These results were replicated in several small (likewise non-randomised) studies, which found a reduction in CRC incidence and mortality in surveilled MMR carriers.^{5–7} In the 2010s, the advent of large multicountry prospective registries of MMR carriers, such as the Prospective Lynch Syndrome Database (PLSD), ushered in a new era of international longitudinal studies of LS populations, which demonstrated MMR carriers to have persistently high CRC incidence rates despite regular surveillance.^{8–10} Comparisons of LS populations across countries with differing surveillance intervals report no reduction in CRC incidence with surveillance at an interval of 1–2 years compared with 3 years.^{11,12} Yet other studies have shown there both to be an association between surveillance interval and CRC development, and conversely, no association between surveillance interval and CRC stage.^{12–16}

The evidence for the impact on incidence and mortality of regular colonoscopic surveillance thus remains mixed. A series of explanations have been proffered for the continued high incidence of CRC in MMR carriers resident in countries where regular surveillance is recommended, including a rapid adenoma-carcinoma sequence, alternative pathways of tumour development, overdiagnosis and low-quality surveillance.¹⁷ However, without direct assessment of adherence and analysis of a relevant comparator group, the possibility of an even higher CRC incidence in non-surveilled populations of MMR carriers cannot be excluded. Thus, the generation of robust evidence to underpin surveillance recommendations has been hampered by a lack of large, comprehensive MMR carrier cohorts in which the adherence of participants to regular surveillance programmes is known.

The English National Lynch Syndrome Registry (ENLSR), a nationally comprehensive register of MMR carriers in England, affords an opportunity to address some of these challenges by providing a large cohort of LS individuals whose participation in surveillance can be determined through linkage to Hospital Episode Statistics (HES) data.¹⁸ In this analysis, we aimed to use the ENLSR cohort to assess adherence of MMR carriers to national surveillance guidelines and to determine the impact of regular surveillance on CRC incidence and mortality.

METHODS**Study design and participants**

This was an observational cohort study. Data originated from the ENLSR,¹⁸ Germline Genetic Testing Dataset (GGT),¹⁹ National Cancer Registration Dataset (NCRD),²⁰ HES Admitted Patient Care²¹ and HES Outpatients datasets. A cohort for analysis was constructed from an extract of the ENLSR censored on 28 November 2024, comprising the total known LS population in England on that date. All LS carriers included in the registry have a clinical diagnosis of LS and are known carriers of a GPV in an MMR gene. Demographic (date of birth, person stated gender (hereafter referred to as sex), National Health Service (NHS) number, ethnicity, postcode of residence, vital status, date of death) and genetic (MMR gene, date of clinical LS diagnosis) data were drawn from the ENLSR. Dates of molecular diagnosis for individuals (without a clinical date of LS diagnosis) were drawn from the GGT. Cancer (date of diagnosis, type of cancer, stage of cancer at diagnosis) and additional demographic (ethnicity, underlying cause of death) data were obtained from the NCRD. Colonoscopy (type of procedure, date of procedure) and further demographic (ethnicity, Index of Multiple Deprivation (IMD))

quintile (of residence)) data were obtained from HES. ENLSR data were cleaned and deduplicated using methods previously described.¹⁸ Datasets were linked using unique patient identifiers. Inclusion criteria were: (1) known demographic details (NHS number, date of birth, sex), (2) known genetic details (MMR gene and date of LS diagnosis), (3) diagnosed with LS prior to any CRC (date of LS diagnosis must precede date of first colorectal diagnosis by at least 60 days, no individuals with prior CRC are included) and (4) eligible for surveillance colonoscopy (according to 2020 guidelines) during the study period (1 January 2010 to 31 December 2022). Further details on data sources, linkage and cleaning are provided in the online supplemental methods.

Colonoscopy analyses

The outcome of interest was '3-year-adherent', defined as a mean surveillance interval (MSVI) of ≤ 3 years during the follow-up period. The follow-up period was defined as the time for which each individual was eligible for surveillance, beginning at the latest of study start (1 January 2010), date of (clinical or molecular) LS diagnosis or individual eligibility for surveillance (aged 25 for *MLH1/MSH2* carriers, aged 35 for *MSH6/PMS2* carriers), and ending at the earliest of study end (31 December 2022), date of first CRC diagnosis, date of death/embarcation or date that individual eligibility for surveillance ends (age 75). MSVI was calculated for each individual by dividing the total follow-up time by the number of surveillance colonoscopies during that period. Surveillance colonoscopies were identified by a list of predefined Office of Population Censuses and Surveys Classification of Interventions and Procedures, version 4 (OPCS-4) codes from which OPCS-4 procedure codes definitely not constituting surveillance events were removed a priori (online supplemental table 1). These were grouped into single events if occurring within 90 days of one another and assigned the date of the first procedure. Logistic regression was used to model the relationship between explanatory variables (MMR gene, sex, age at start of follow-up period, ethnicity and IMD quintile) and the binary outcome variable '3-year-adherent'. Univariable models were constructed for each explanatory variable in turn and associated variables carried through to the multivariable model. P values for linear trend were calculated for ordinal variables using linear polynomial contrasts.

CRC incidence analyses

The outcome of interest was a first diagnosis of invasive CRC (International Classification of Diseases, 10th Revision (ICD-10) codes C18, C19, C20), and the explanatory variable was '3-year-adherent' (MSVI ≤ 3 years). The follow-up period was the same as for the colonoscopy analyses. Age-specific annual CRC incidence rates (AS-AIRs) per 100 000 person-years for 5-year age bands were calculated in (1) all MMR carriers combined and (2) MMR carriers of each individual gene for '3-year-adherent' MMR carriers compared with non-'3-year-adherent' MMR carriers. The z-test was used to test for a statistically significant difference between analysis groups. Life table methods were used to estimate the cumulative risk of CRC from ages 25–74 for the same analysis groups. For all MMR carriers combined, the possibility of stage-shift between analysis groups ('3-year-adherent' vs non-'3-year-adherent') was investigated by comparing stage distributions using the χ^2 test and by calculating stage-specific and AS-AIRs in 5-year age bands for early-stage cancers (stages 1 and 2) and late-stage cancers (stages 3 and 4). The analysis was then repeated using '2-year-adherent' (MSVI

≤ 2 years) as the explanatory variable to examine the impact of more frequent colonoscopies. MMR carriers with no recorded colonoscopies were defined as non-adherent; these individuals were therefore included in the non-'3-year-adherent' and non-'2-year-adherent' groups, respectively.

Mortality analyses

The follow-up period for the mortality analysis began at the latest of the study start date (1 January 2010), the date of (clinical or molecular) LS diagnosis or the date the individual became eligible for surveillance (aged 25 for *MLH1/MSH2* carriers or aged 35 for *MSH6/PMS2* carriers), and ended at the earliest of date of death, date of embarkation or study end date. The outcomes of interest were (a) death from any cause during the study period and (b) death from CRC during the study period. CRC-specific death was defined as any death where a CRC ICD-10 code (C18, C19, C20) appeared as a cause code in any section (1A, 1B, 1C or 2) of the death certificate. Kaplan-Meier methods were used to estimate the risk of death from (1) CRC only, (2) any cause and (3) any non-CRC cause for individuals with an MSVI ≤ 3 years ('3-year-adherent') compared with those with an MSVI > 3 years (non-'3-year-adherent'). Cox proportional hazards modelling was used to estimate hazard ratios (HRs) for associations between MSVI ≤ 3 years ('3-year-adherent'), MMR gene, sex, age at start of follow-up period, IMD quintile and risk of death from (1) CRC only and (2) any cause. For each variable, the proportional hazards assumption was tested using Schoenfeld residuals, and only variables meeting this assumption were included in the model.

Sensitivity analyses

To investigate the potential for skewing of the MSVI in individuals with short follow-up periods, a second cohort was constructed excluding all individuals from the primary cohort who had less than 1 year of follow-up. The CRC incidence analysis protocol described above was repeated. To investigate whether inclusion of 'prevalent' CRCs in our analyses affected CRC incidence results, we constructed a third cohort excluding all individuals from the primary cohort who had a cancer diagnosed within 90 days of their first colonoscopy. We selected this definition as a proxy for prevalent CRC, as we did not have access to colonoscopy results, and designated all other CRCs as incident. We then repeated the CRC incidence protocol as described above for all pathogenic variant carriers combined only.

Patient and public involvement

This work uses data that have been provided by patients and collected by the NHS as part of their care and support. The data are collated, maintained and quality assured by the National Disease Registration Service (NDRS), which is part of NHS England. NDRS is committed to patient and public involvement, including providing publicly downloadable reports, running public awareness campaigns and webinars and providing opportunities for public consultation and representation.²²

RESULTS

Cohort description

Following exclusions, the cohort consisted of 4732 MMR carriers (online supplemental figure 1). The cohort was majority white (n=3908, 82.6%) and female (n=2908, 61.5%), with representation from all 10-year age bands from ages 25–74 and all IMD quintiles. The MMR genes in which GPVs were most commonly identified were *MSH2* (n=1856 (including

Table 1 Description of Lynch syndrome cohort and analysis groups

		MSVI 2 years						MSVI 3 years			
		Total		≤2 years		>2 years		≤3 years		>3 years	
		n	%	n	%	n	%	n	%	n	%
Total		4732		1569	33.2	3163	66.8	3028	64.0	1704	36.0
MMR gene	<i>MLH1</i>	1315	27.8	410	26.1	905	28.6	837	27.6	478	28.1
	<i>MSH2</i>	1856	39.2	608	38.8	1248	39.5	1224	40.4	632	37.1
	<i>MSH6</i>	1011	21.4	371	23.6	640	20.2	655	21.6	356	20.9
	<i>PMS2</i>	550	11.6	180	11.5	370	11.7	312	10.3	238	14.0
	Unknown	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Sex	Male	1824	38.5	629	40.1	1195	37.8	1190	39.3	634	37.2
	Female	2908	61.5	940	59.9	1968	62.2	1838	60.7	1070	62.8
	Unknown	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Age at start of follow-up period	25–34	1208	25.5	363	23.1	845	26.7	805	26.6	403	23.7
	35–44	1209	25.5	398	25.4	811	25.6	781	25.8	428	25.1
	45–54	1034	21.9	376	24.0	658	20.8	702	23.2	332	19.5
	55–64	869	18.4	296	18.9	573	18.1	511	16.9	358	21.0
	65–74	412	8.7	136	8.7	276	8.7	229	7.6	183	10.7
	Unknown	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Ethnicity	White	3908	82.6	1369	87.3	2539	80.3	2651	87.5	1257	73.8
	Asian	207	4.4	58	3.7	149	4.7	108	3.6	99	5.8
	Black	30	0.6	8	0.5	22	0.7	15	0.5	15	0.9
	Mixed	31	0.7	10	0.6	21	0.7	19	0.6	12	0.7
	Other	98	2.1	30	1.9	68	2.1	57	1.9	41	2.4
	Unknown	458	9.7	94	6.0	364	11.5	178	5.9	280	16.4
IMD quintile	Q1—most deprived	727	15.4	240	15.3	487	15.4	452	14.9	275	16.1
	Q2	844	17.8	288	18.4	556	17.6	536	17.7	308	18.1
	Q3	939	19.8	283	18.0	656	20.7	572	18.9	367	21.5
	Q4	1031	21.8	355	22.6	676	21.4	688	22.7	343	20.1
	Q5—least deprived	1042	22.0	363	23.1	679	21.5	702	23.2	340	20.0
	Unknown	149	3.1	40	2.5	109	3.4	78	2.6	71	4.2

Numbers (n) and percentages (%) are provided for the entire cohort (Total) and analysis groups. MMR carriers with no recorded colonoscopies (n=944) are included in the less frequently surveilled groups (MSVI >2 years or MSVI >3 years). Carriers for EPCAM deletions (n=25) are included in the *MSH2* category. Sex is person stated gender. Ethnicity is self-described. IMD quintile is determined by LSOA of residence.

IMD, Index of Multiple Deprivation; LSOA, Lower level Super Output Area; MMR, mismatch repair; MSVI, mean surveillance interval.

25 individuals with *EPCAM* deletions), 39.2%) and *MLH1* (n=1315, 27.8%), followed by *MSH6* (n=1011, 21.4%) and *PMS2* (n=550, 11.6%). Further details are provided in [table 1](#).

Colonoscopy adherence

Across all 4732 MMR carriers, there were a total of 27866 years of follow-up for the colonoscopy analyses (median 4.88) (online supplemental table 2). 3788 MMR carriers (80.1%) had a record of at least one colonoscopy in HES. *MSH2* carriers were most likely to have a record of at least one colonoscopy at 83.0% (n=1541) of individuals, followed by *MLH1* carriers (81.7%, n=1074), *MSH6* carriers (78.5%, n=794) and *PMS2* carriers (68.9%, n=379) (online supplemental table 3). The mean colonoscopies per person for the whole cohort were 2.37, ranging from 1.46 for *PMS2* carriers to 2.68 for *MSH2* carriers. By gene, the MSVI for all MMR carriers combined was 2.51, and 2.58, 2.61, 2.36 and 2.22 for *MLH1*, *MSH2*, *MSH6* and *PMS2* carriers, respectively.

3788 first colonoscopies were conducted in the cohort, of which 65.8% (n=2492) took place within 12 months of the date of eligibility for colonoscopic surveillance. The median time to first colonoscopy from the date of eligibility was 214.5 days. 7413 'subsequent' colonoscopies were conducted in the cohort, of which 91.2% (n=6760) took place within 36 months of the

previous colonoscopy and 41.2% within 24 months (online supplemental table 3). To characterise an individual's adherence to surveillance guidelines throughout the course of the study period, we applied a pragmatically permissive definition, reasoning that while colonoscopies were recommended at 18–24 months' intervals throughout the study period, delays may have occurred. For this reason, we considered individuals to be '3-year-adherent' where their MSVI is ≤3 years across their duration of follow-up.

Univariable logistic regression analyses of persons showed MMR gene, age at start of follow-up period, ethnicity and IMD quintile to be statistically significantly associated with likelihood of being '3-year-adherent' (MSVI ≤3 years), while sex was not. In multivariable logistic regression, including adjustment for all variables, age at start of follow-up was significantly associated with being '3-year-adherent', as well as IMD quintile. The likelihood of being '3-year-adherent' decreased as age increased (p-trend=0.002) and increased as IMD quintile moved from most to least deprived (p-trend=0.001) ([table 2](#)).

Incidence of CRC

334 CRCs were diagnosed in the cohort during the follow-up period: 138 in *MLH1* carriers, 167 in *MSH2* carriers, 23 in *MSH6* carriers and 6 in *PMS2* carriers (online supplemental

Table 2 Univariable and multivariable logistic regression models for '3-year-adherence' (mean surveillance interval ≤ 3 years)

		MSVI ≤ 3 years		MSVI > 3 years		Univariable model			Multivariable model			
		n	%	n	%	OR	95% CI	P value	OR	95% CI	P value	P trend
MMR gene	<i>MLH1</i>	837	63.7	478	36.3							
	<i>MSH2</i>	1224	65.9	632	34.1	1.11	0.95 to 1.28	0.18	1.05	0.89 to 1.23	0.58	
	<i>MSH6</i>	655	64.8	356	35.2	1.05	0.89 to 1.25	0.57	1.07	0.88 to 1.31	0.48	
	<i>PMS2</i>	312	56.7	238	43.3	0.75	0.61 to 0.92	0.005	0.84	0.66 to 1.06	0.14	
Sex	Male	1190	65.2	634	34.8							
	Female	1838	63.2	1070	36.8	0.92	0.81 to 1.03	0.16	0.92	0.80 to 1.05	0.21	
Age at start of follow-up	25–34	805	66.6	403	33.4							0.002
	35–44	781	64.6	428	35.4	0.91	0.77 to 1.08	0.29	0.88	0.72 to 1.08	0.22	
	45–54	702	67.9	332	32.1	1.06	0.89 to 1.26	0.53	1	0.81 to 1.23	0.99	
	55–64	511	58.8	358	41.2	0.71	0.60 to 0.86	<0.001	0.67	0.54 to 0.83	<0.001	
	65–74	229	55.6	183	44.4	0.63	0.50 to 0.79	<0.001	0.6	0.46 to 0.78	<0.001	
Ethnicity	White	2651	67.8	1257	32.2							
	Asian	108	52.2	99	47.8	0.52	0.39 to 0.69	<0.001	0.49	0.37 to 0.66	<0.001	
	Black	15	50	15	50.0	0.47	0.23 to 0.98	0.042	0.48	0.23 to 1.01	0.052	
	Mixed	19	61.3	12	38.7	0.75	0.37 to 1.59	0.44	0.68	0.33 to 1.45	0.30	
	Other	57	58.2	41	41.8	0.66	0.44 to 1.00	0.045	0.67	0.44 to 1.03	0.065	
IMD quintile	Q1—most deprived	452	62.2	275	37.8							0.001
	Q2	536	63.5	308	36.5	1.06	0.86 to 1.30	0.59	1.11	0.89 to 1.38	0.36	
	Q3	572	60.9	367	39.1	0.95	0.78 to 1.16	0.60	1	0.81 to 1.24	0.99	
	Q4	688	66.7	343	33.3	1.22	1.00 to 1.49	0.049	1.24	1.00 to 1.53	0.046	
	Q5—least deprived	702	67.4	340	32.6	1.26	1.03 to 1.53	0.024	1.39	1.13 to 1.73	0.002	

Unadjusted ORs are presented from univariable models, constructed using each variable in turn. Adjusted ORs are presented from multivariable models, including all variables. Individuals with missing data in any of the variables ($n=567$) are excluded, resulting in inclusion of 3824 individuals in the multivariable model. P-values are the result of Wald tests, and p-trend values are calculated using linear polynomial contrasts.

Sex is person stated gender. Ethnicity is self-reported.

IMD, Index of Multiple Deprivation derived from postcode of residence; MMR, mismatch repair; MSVI, mean surveillance interval.

table 4). This low incidence likely reflects the relatively short follow-up period available. 7.7% ($n=233$) of MMR carriers who were '3-year-adherent' were diagnosed with a CRC, compared with 5.9% ($n=101$) of those who were not '3-year-adherent' (online supplemental table 5). Examining individual MMR genes and then all genes combined, comparing MMR carriers who were '3-year-adherent' and those who were not, there was no statistically significant difference in the 5-year AS-AIRs of CRC nor in the cumulative risk of CRC (figure 1, online supplemental tables 6 and 7). There was evidence of a change in the stage distribution of CRCs at diagnosis in *MLH1* carriers who were '3-year-adherent' compared with those who were not ($p=0.024$), with a higher proportion (and absolute number) of stage 1 cancers (online supplemental table 5). There was no evidence for significant change in the stage distribution for other MMR genes. Considering all MMR carriers combined, there was no significant difference between the '3-year-adherent' group compared with the non-'3-year-adherent' for the AS-AIRs for either early-stage (stages 1 and 2 combined) or late-stage (stages 3 and 4) CRCs (figure 2, online supplemental table 8).

Having used a pragmatically permissive definition adherence of MSVI ≤ 3 years, we next sought to examine how CRC incidence was influenced by a more frequent colonoscopy regimen. We repeated the analysis, considering individuals as adherent if their MSVI was ≤ 2 years ('2-year-adherent'). The differences in CRC incidence between analysis groups were more marked: 10.0% ($n=157$) of MMR carriers who were '2-year-adherent' were diagnosed with a CRC, compared with 5.6% ($n=177$) of those who were not (online supplemental table 9). AS-AIR point estimates were higher in '2-year-adherent' MMR carriers for all age groups, with a statistically significant difference for ages

30–34, 40–44, 50–54 and 55–59 (online supplemental table 10). The cumulative risk of CRC diagnosis was higher at all ages in the '2-year-adherent' group for all MMR carriers combined, with the difference in risk increasing with age. At age 50, the cumulative risk of CRC in the '2-year-adherent' group was 33.4% (95% CI 25.5% to 41.4%), and 14.1% (95% CI 10.7% to 17.4%) in 'non-2-year-adherent' group, rising to 63.4% (95% CI 53.3% to 73.5%) and 37.4% (95% CI 31.8% to 42.9%) by age 74, respectively (online supplemental table 11). A similar pattern was present for each MMR gene in isolation (figure 1). There was evidence of a change in the stage distribution of CRCs between the '2-year-adherent' and non-'2-year-adherent' groups for all genes combined ($p=0.040$) and *MLH1* carriers only ($p=0.047$) (online supplemental table 9). AS-AIRs for stage 1 and 2 cancers trended higher across all age groups in '2-year-adherent' MMR carriers, with a statistically significant increase in early-stage cancers in '2-year-adherent' 30–34 year-olds and 55–59 year-olds ($p<0.05$). By contrast, there was no evidence of a statistically significant difference in the AS-AIRs for late-stage cancers between the '2-year-adherent' and '2-year-non-adherent' groups in any age bands (figure 2, online supplemental table 12).

Mortality analyses

There were five CRC-specific deaths among 3028 '3-year-adherent' MMR carriers compared with 17 among 1704 non-'3-year-adherent' MMR carriers. The cumulative risks of CRC-specific death at 5 and 10 years were 0.11% (95% CI 0.00% to 0.24%) and 0.29% (95% CI 0.01% to 0.58%), respectively, in '3-year-adherent' MMR carriers and 0.61% (95% CI 0.15% to 1.07%) and 1.57% (95% CI 0.67% to 2.47%) in

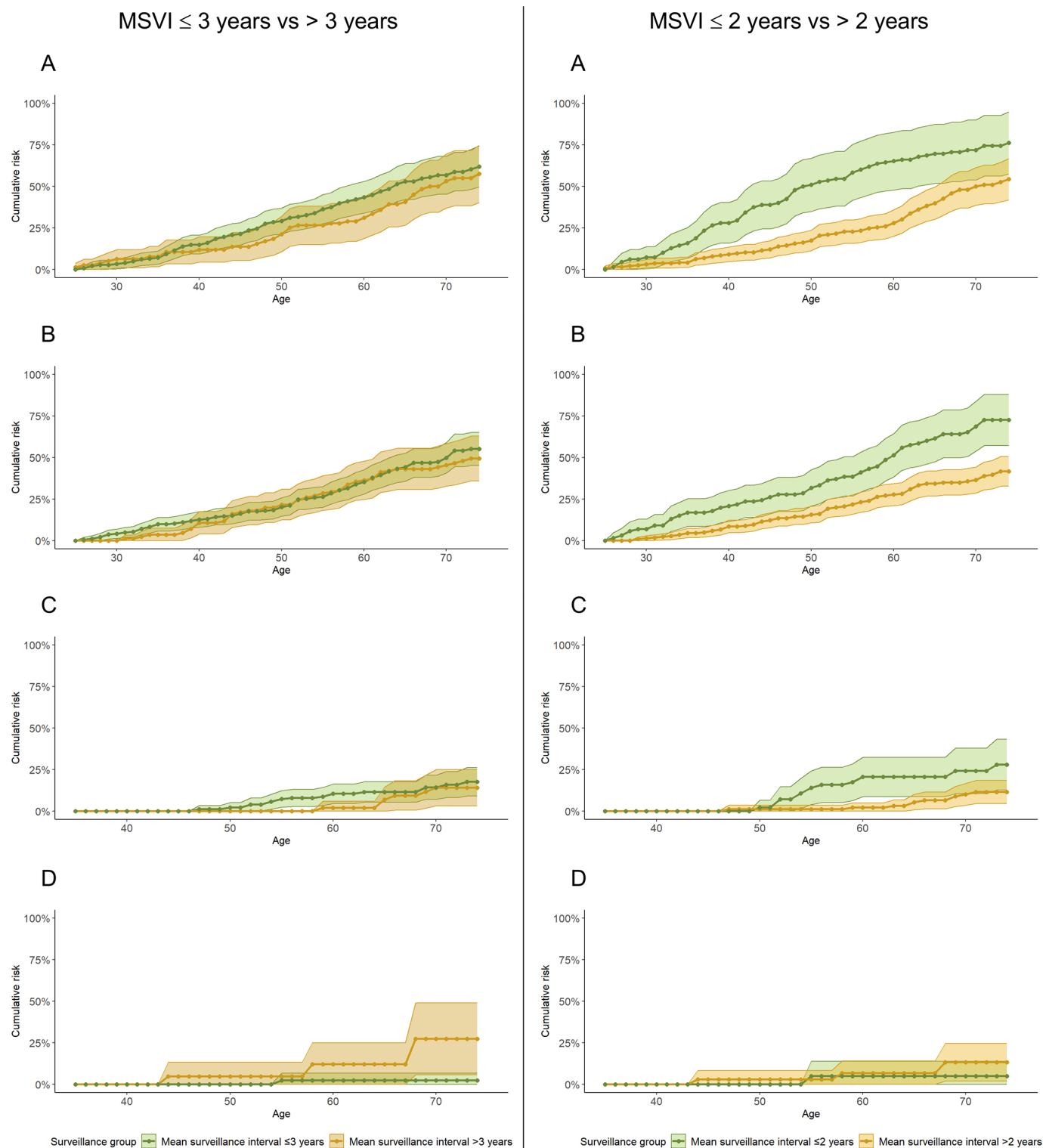


Figure 1 Cumulative risk (in %) of colorectal cancer in (A) *MLH1*, (B) *MSH2*, (C) *MSH6* and (D) *PMS2* MMR pathogenic variant carriers by MSVI: left panel ≤ 3 years vs > 3 years, right panel ≤ 2 years vs > 2 years. Solid points represent estimates of the cumulative risk, calculated using the life table method. Shaded bands represent the 95% CI, estimated from the SE derived using Greenwood's formula. Assumed zero risk below the age of 25 for *MLH1/MSH2* carriers and below the age of 35 for *MSH6/PMS2* carriers. MMR, mismatch repair; MSVI, mean surveillance interval.

non-‘3-year-adherent’ MMR carriers ($p < 0.001$) (online supplemental table 13, figure 3). Following adjustment for sex, age at follow-up start and IMD quintile, an MSVI ≤ 3 years was associated with a reduction in risk of CRC-specific death (HR 0.14, 95% CI 0.05 to 0.39) (online supplemental table 14).

There was a lower risk of death from any cause among individuals who were ‘3-year-adherent’ compared with those who were not ($p < 0.0001$) (figure 3). There were 68 deaths among 3028 ‘3-year-adherent’ MMR carriers (2.2%) and 80 deaths among 1704 non-‘3-year-adherent’ MMR carriers (4.7%). The

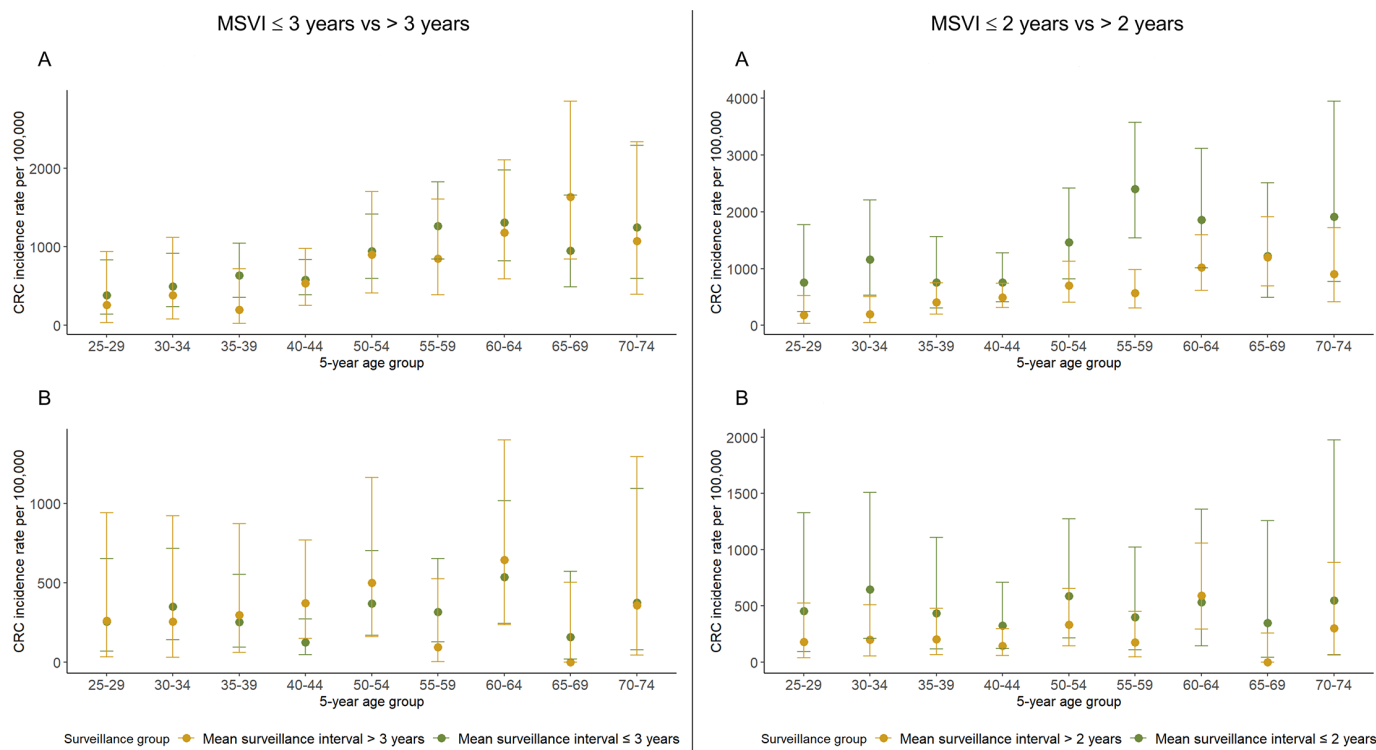


Figure 2 Stage-specific and age-specific 5-year annual incidence rates for (A) early-stage (stages 1 and 2) CRCs and (B) late-stage (stages 3 and 4) CRCs by MSVI: left panel ≤ 3 years vs > 3 years, right panel ≤ 2 years vs > 2 years. Only first cancers are included. Tumours are staged at diagnosis. 95% CIs are calculated using Byar's method. CRC, colorectal cancer; MSVI, mean surveillance interval.

cumulative risks of death at 5 and 10 years were 1.25% (95% CI 0.80% to 1.70%) and 3.61% (95% CI 2.63% to 4.58%) for those who were '3-year-adherent' and 3.75% (95% CI 2.65% to 4.84%) and 7.81% (95% CI 5.89% to 9.69%) for those who were not (online supplemental table 15). Following adjustment for MMR gene, sex, age at follow-up start and IMD quintile, an MSVI ≤ 3 years was associated with a reduction in risk of death

from any cause (HR 0.44, 95% CI 0.31 to 0.61) (online supplemental table 16).

There was thus a lower risk of non-CRC death among individuals who were '3-year-adherent' compared with those who were not ($p < 0.0001$). There were 63 non-CRC deaths among 3028 '3-year-adherent' MMR carriers (2.1%) and 63 deaths among 1704 non-'3-year-adherent' MMR carriers (3.7%). The

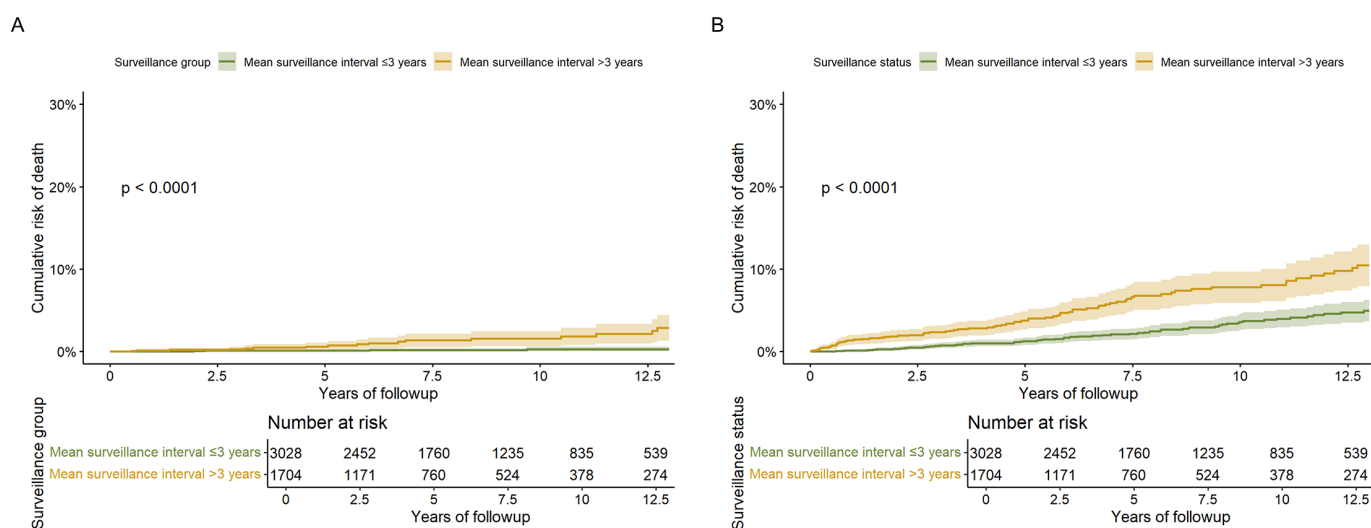


Figure 3 Cumulative risk of death from (A) CRC and (B) any cause in MMR pathogenic variant carriers with a mean surveillance interval of ≤ 3 years compared with MMR pathogenic variant carriers with a mean surveillance interval of > 3 years. CRC-specific deaths are defined as any death where a CRC ICD-10 code (C18, C19, C20) appears as a cause code in any section (1A, 1B, 1C or 2) of the death certificate. A total of 22 CRC-specific deaths occurred in the cohort (5 in the ≤ 3 years' interval group, 17 in the > 3 years' group). A total of 148 deaths from any cause occurred in the cohort (68 in the ≤ 3 years' interval group, 80 in the > 3 years' group). P-values are the result of the log-rank test. CRC, colorectal cancer; ICD-10, International Classification of Diseases, 10th Revision; MMR, mismatch repair.

cumulative risks of non-CRC death at 5 and 10 years were 1.14% (95% CI 0.71% to 1.57%) and 3.33% (95% CI 2.38% to 4.26%) for those who were '3-year-adherent' and 3.16% (95% CI 2.15% to 4.16%) and 6.33% (95% CI 4.59% to 8.04%) for those who were not.

Sensitivity analyses

To mitigate the impact of short follow-up periods on CRC incidence results, we performed sensitivity analyses using the cohort of 4129 individuals who had at least 1 year of follow-up (603 individuals excluded, online supplemental table 17). There were 254 CRC diagnoses (online supplemental table 18). Comparison of AS-AIRs, cumulative incidence rates and stage distributions produced similar, though attenuated, results, with fewer statistically significant differences (online supplemental tables 19–21).

To investigate whether inclusion of 'prevalent' CRCs affected CRC incidence results, we performed sensitivity analyses using a cohort of 4665 individuals who were not diagnosed with a CRC within 90 days of their first recorded colonoscopy (67 individuals excluded, online supplemental table 22). There were 267 'incident' cancers, with no statistically significant difference in the stage distribution of 'prevalent' and 'incident' cancers ($p=0.308$, online supplemental tables 23 and 24). Comparison of AS-AIRs, cumulative incidence rates and stage distributions produced similar, though attenuated, results, with fewer statistically significant differences (online supplemental tables 25–27, online supplemental figures 1–4).

DISCUSSION

The uptake and frequency of colonoscopy align with previously published regional estimates of adherence among MMR carriers in England and internationally, which range from 50% to 80%.^{23–25} Using an MSVI of ≤ 3 years as a standard of adherence, increased age was associated with a lower likelihood of adherence, while being of white ethnicity or living in a lower deprivation quintile was associated with a higher likelihood, findings which are consistent with previous literature describing participation in population-level national CRC surveillance programmes in England and abroad.^{26 27}

It is generally assumed that regular colonoscopies with polypectomies would reduce the incidence of CRC, as demonstrated in other at-risk populations. However, in these analyses, there was no clear reduction in CRC incidence for MMR carriers who were '3-year-adherent' compared with 'non-adherent' individuals. When tightening the definition of adherence to MSVI ≤ 2 years, in those having more frequent colonoscopies ('2-year-adherent') there was a *higher* overall cumulative risk of CRC compared with 'non-adherent' individuals, with a higher incidence of CRCs observed in most age groups. This pattern could be explained by (a) failure of surveillance colonoscopy to effectively prevent CRC development due to (1) an accelerated adenoma-carcinoma sequence leading to interval cancers, (2) poor-quality colonoscopy or (3) an alternative mechanism(s) of cancer development in LS which is not amenable to secondary prevention via endoscopy, and/or (b) identification of an increased number of early-stage cancers in regularly screened individuals due to (1) stage shift, (2) overdiagnosis, (3) limited duration of follow-up and study design attenuating observed impacts of interventions and/or (4) spectrum bias relating to indication for or timeliness of colonoscopies. Also potentially relevant is tumour biology: there is interesting gene-specific evidence of variation in the pathways to CRC in LS and the efficacy of CRC prevention by colonoscopy.^{28 29} However, the gene-specific sojourn time of adenomas

and other precursors in LS, and their transition to adenomas, remains largely uncharacterised.

Even in the absence of CRC prevention (and a consequent reduction in CRC incidence), more frequent colonoscopies potentially could result in diagnosis of CRCs at an earlier stage than they would otherwise have been (altered stage distribution or 'stage-shift'). Detection of CRC at earlier stage may yield mortality reduction, while also requiring less aggressive clinical management. A change in the relative stage distribution of CRCs, for example, an increase in the relative proportion of stage 1 and 2 cancers, may be indicative of stage-shift, but may also be influenced by underlying changes in CRC incidence, and thus does not robustly demonstrate that stage-shift is occurring. Indeed, the true presence of stage-shift can only be robustly demonstrated by evidence of an increase in the rate of diagnosis of early-stage cancers alongside a decrease in the rate of late-stage cancers, indicating that not only have more early-stage cancers have been identified, but also that they have been prevented from developing into late-stage cancers.

In '3-year-adherent' MMR carriers, there was a change in stage distribution that was statistically significant for *MLH1* carriers ($p=0.024$). However, on analysis of stage-specific AS-AIRs no significant changes were observed for any gene. Comparison of '2-year-adherent' and 'non-2-year-adherent' MMR carriers demonstrated both a change in the distribution of CRC stage at diagnosis ($p=0.040$), with higher AS-AIRs for early-stage CRCs in more frequently surveilled individuals. However, there was no corresponding decrease in late-stage AS-AIRs observed.

This pattern may indicate that an increased number of early-stage cancers have been identified, but that the follow-up period was not sufficient for this to be reflected in a concomitant reduction in late-stage cancers. Alternatively, it may reflect the influence of lead time bias, whereby earlier detection increases the apparent incidence of early-stage disease or nuances in the biology of LS-associated tumours, including biological heterogeneity associated with specific causative MMR genes, for example, in *MLH1* carriers in whom submucosal tumours are observed which develop via a non-polypoid pathway.³⁰ This pattern would also be consistent with overdiagnosis, namely that surveillance is detecting cancers which would not otherwise have progressed to a late stage on account of being indolent or transitory. This is consistent with findings from the PLSD, though PLSD examined CRC incidence according to the surveillance recommendations by area of residence, not by individual-level uptake.³¹ Notably, we were unable to explore factors which may have a bearing on the risks and benefits of earlier diagnosis, such as rates of cure, organ preservation, or any adverse events or morbidity associated both with treatment and with lack of treatment.

'3-year-adherence' was associated with a significant reduction in the risk of death from CRC and from any cause even after adjustment for MMR gene, sex, age at start of follow-up period and IMD quintile. The reduction in risk of death from any cause may indicate a possible impact of colonoscopy on CRC-specific survival. However, in the context of a non-randomised study, the observed reductions in both CRC-specific and non-CRC-related mortality in the surveilled group may be indicative of fundamental differences between analysis groups, whereby healthier individuals were more likely to participate in surveillance (the 'healthy screenee effect'). Length and lead bias may also be present. Notably, it might be hypothesised that these same uncaptured socioeconomic and behavioural factors in a group compliant with screening would correlate with behavioural and environmental exposures reducing their risk of CRCs; this adds

further weight to the observation of higher CRC incidence in surveillance-compliant groups.

To our knowledge, this is the first large study to directly compare CRC outcomes in MMR carriers with regular recorded colonoscopic surveillance to those without. The primary limitation of this work is its observational nature: it is thus subject to the limitations of a non-randomised approach. While known relevant covariates were incorporated in the regression analyses, uncaptured confounding differences between those compliant and non-compliant with surveillance cannot be accounted for and are likely to have a substantial impact. There is potential for misclassification in the approach used to define analysis groups: the MSVI is a mean and thus does not capture nuance in the distribution of surveillance colonoscopies in each individual, particularly in individuals with short follow-up periods (though this is likely mitigated by grouping colonoscopies into 90-day events). Individuals dying or developing a CRC quickly will be classified as non-adherent, which may bias results towards surveillance benefits. To account for these influences, sensitivity analyses were conducted in a cohort of MMR carriers with ≥ 1 year of follow-up, which produced similar results to the main analyses.

This analysis was limited by our ability to distinguish robustly between surveillance colonoscopies and colonoscopies conducted for other purposes (eg, as part of a clinical diagnosis or in response to symptoms), thus potentially leading to spectrum bias. While OPCS-4 codes (and hence procedures) definitely not constituting surveillance events were removed a priori, this is unlikely to have comprehensively removed all non-surveillance colonoscopies, which may impact our findings if symptomatic individuals are more likely to receive additional colonoscopies and be classified as '2-year-adherent' or '3-year adherent'. To explore this, we conducted sensitivity analyses which excluded any individuals diagnosed with a CRC within 90 days of their first colonoscopy, on the assumption that they may have attended due to experiencing symptoms. The results of these analyses produced similar results to the main analyses, though these were attenuated due to reduced statistical power and cannot fully resolve this limitation.

Reported colonoscopic findings were not available but may potentially influence clinician surveillance recall timing. Similarly, information on colonoscopy quality and findings was not available, thus we were unable to include factors such as bowel preparation, withdrawal time or the identification and management of lesions in our analyses. Such factors that influence the effectiveness of surveillance but were not taken into account may confound results. While colonoscopy quality data are not available for our study period, work to prospectively evaluate the quality of colonoscopy has recently been initiated but remains at an early stage.³² Family cancer history was not available but may be an additional covariate influencing adherence to colonoscopy recommendations and possibly even clinician recall timing: factors both potentially contributing to spectrum bias. We did not make specific adjustments in our analyses for variations in colonoscopy activity consequent from the COVID-19 pandemic.³³ Private colonoscopies or colonoscopies conducted outside of England may not be captured in HES and thus are not included.

In this study, we used linked electronic health data to assess the adherence of surveillance colonoscopies in the English LS population to national guidelines and to determine the impact of regular surveillance on CRC incidence as well as CRC-specific and overall mortality. To our knowledge, this is the first national study of LS surveillance adherence in England and the largest

study internationally to date of CRC outcomes in MMR carriers analysing records of colonoscopies.

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Contributors CH and CT designed the analyses. CH accessed the underlying data, coded the analyses and generated the tables and figures for presentation. CM extracted the data from the ENLSR. TR performed the linkage of LS data to HES. PP, KM, AA, MT, RH and EM provided critical feedback to inform the research and analysis. BT provided project management for data access and analyses. DT, LP and SV provided data expertise. CH and CT wrote the manuscript. All authors reviewed the manuscript. CT is the guarantor for this work.

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Competing interests KM acts as a medical advisor for Bowel Cancer UK, Lynch Syndrome UK and NHS England.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval Data used in these analyses were collected and stored securely within NDRS under the legal permissions afforded by Section 254 of the Health and Social Care Act 2012, which permits the collection of patient data without requiring informed consent. This analysis was approved by the NDRS analytical project panel (WP00481).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. All data relevant to the study are included in the article or uploaded as supplementary information. Summary data relevant to the study are included in the article or supplementary information. Individual-level data used in this study are held within NDRS under robust privacy, security and confidentiality procedures and only available to properly authorised analysts and researchers under access arrangements through the NHS England Data Access and Release Service.

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