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CLINICAL AT

No Difference in Colorectal Cancer Incidence or Stage at Detection by Colonoscopy Among 3 Countries With Different Lynch Syndrome Surveillance Policies

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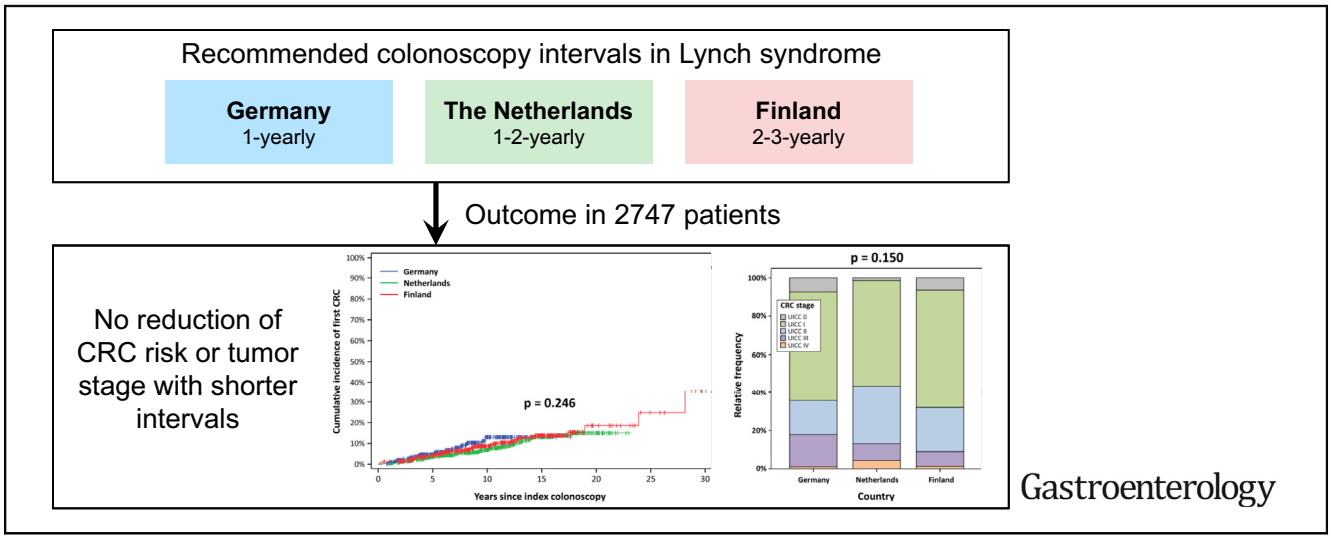
BACKGROUND & AIMS: Patients with Lynch syndrome are at high risk for developing colorectal cancer (CRC). Regular colonoscopic surveillance is recommended, but there is no international consensus on the appropriate interval. We investigated whether shorter intervals are associated with lower CRC incidence and detection at earlier stages by comparing the surveillance policies in Germany, which evaluates patients by colonoscopy annually, in the Netherlands (patients evaluated at 1–2-year intervals), and Finland (patients evaluated at 2–3-year intervals). **METHODS:** We collected data from 16,327 colonoscopic examinations (conducted from 1984 through 2015) of 2747 patients with Lynch syndrome (pathogenic variants in the *MLH1*, *MSH2*, or *MSH6* genes) from the German HNPCC Consortium, the Dutch Lynch Syndrome Registry, and the Finnish Lynch Syndrome Registry. Our analysis included 23,309 person-years of cumulative observation time. Time from the index colonoscopy to incident CRC or adenoma was analyzed using the Kaplan-Meier method; groups were compared using the log-rank test. We performed multivariable Cox regression analyses to identify factors associated with CRC risk (diagnosis of CRC before the index colonoscopy, sex, mutation, age, and presence of adenoma at the index colonoscopy). **RESULTS:** The 10-year cumulative CRC incidence ranged from 4.1% to 18.4% in patients with low- and high-risk profiles, respectively, and varied with age, sex, mutation, and prior detection of CRC or adenoma. Observed colonoscopy intervals were largely in accordance with the country-specific recommendations. We found no significant differences in cumulative CRC incidence or CRC stage at detection among countries. There was no significant association between CRC stage and



time since last colonoscopy. **CONCLUSIONS:** We did not find a significant reduction in CRC incidence or stage of detection in Germany (annual colonoscopic surveillance) than in countries with longer surveillance intervals (the Netherlands, with 1–2-year intervals, and Finland, with 2–3-year intervals). Overall, we did not find a significant association of the interval with CRC risk, although age, sex, mutation, and prior neoplasia were used to individually modify colonoscopy intervals. Studies are needed to develop and validate risk-adapted surveillance strategies and to identify patients who benefit from shorter surveillance intervals.

Keywords: Genetic Risk Factor; Interval; Hereditary Colon Cancer; Tumor.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Individuals with Lynch syndrome are at increased risk for colorectal cancer. Regular colonoscopic surveillance is recommended, but there is no international consensus on the appropriate interval.

NEW FINDINGS

Comparing prospective data from three countries with different surveillance policies (annually, 1–2-yearly, 2–3-yearly), we found that a policy of strict annual colonoscopies was not associated with lower CRC incidence or stage.

LIMITATIONS

Only adenoma detection rate, but no other data on the quality of individual colonoscopies, was available.

IMPACT

Our study contributes to answering the question of how often patients with Lynch syndrome should undergo regular colonoscopies and could help to design further comparative studies in this field.

Lynch syndrome (LS) is a dominantly inherited cancer predisposition syndrome caused by a mutation in one of the DNA mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, or *PMS2*.[1] Patients with LS have a 30% to 60% risk of developing colorectal cancer (CRC), depending on the underlying gene defect. Other tumors are also observed in LS, including endometrial cancer, gastric cancer, small bowel cancer, urinary tract cancer, and ovarian cancer.[2,3] LS is the most common hereditary CRC syndrome, responsible for 3% to 5% of all CRC, and it has been estimated that 1 of 279 individuals in the general population carries a pathogenic MMR gene mutation.[4]

Colonoscopic surveillance in these high-risk patients has been recommended for the past 30 years,[5] and a number of studies have shown that surveillance leads to a reduction in CRC-associated mortality.[6–8] However, there is no international consensus on the appropriate surveillance interval, with current recommendations of 1-, 2-, or even 3-yearly intervals.[6,9,10] A prospective, nonrandomized study demonstrated that colonoscopic surveillance at 3-year intervals more than halved the risk of CRC, prevented CRC deaths, and decreased overall mortality by approximately 65% compared with individuals who had no screening.[6] However, no studies have been conducted to date that compare the outcomes of different surveillance intervals.

This prompted us to perform a joint analysis of prospective surveillance data on patients with LS in 3 European countries who underwent colonoscopic screening at intervals varying from 1 to 3 years. The primary aim was to assess

*Authors share co-first authorship; § Authors share co-senior authorship.

Abbreviations used in this paper: **CI, confidence interval; CRC, colorectal cancer; HNPCC, hereditary nonpolyposis colorectal cancer; LS, Lynch syndrome; MMR, mismatch repair; UICC, International Union Against Cancer.**

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whether shorter intervals are associated with a lower CRC incidence and a more favorable tumor stage distribution.

Methods

Study Population

The study population consisted of patients with LS registered in the LS registries of 3 countries: Germany (German Hereditary Nonpolyposis Colorectal Cancer [HNPCC] Consortium, established in 1999), the Netherlands (Dutch Lynch Syndrome Registry, established in 1989), and Finland (Finnish Lynch Syndrome Registry, established in 1982). In all 3 registries, patients with LS are followed prospectively, with documentation on colonoscopic examinations and tumor diagnoses before and after start of surveillance. Different surveillance interval policies are pursued in the 3 countries. In Germany, all patients with LS are advised to undergo strict annual examinations. In the Netherlands, 1- to 2-yearly colonoscopies are recommended, whereas 2- to 3-yearly intervals are recommended in Finland. Colonoscopies are performed according to national standards either in hospitals or by gastroenterologists in private practice. Written informed consent was obtained from all patients with LS who were enrolled in the registries and participated in the prospective surveillance studies.

Patients were eligible for the present analysis if they had (1) a proven pathogenic germline mutation in either the *MLH1*, *MSH2*, or *MSH6* gene; and (2) had completed at least 2 surveillance colonoscopies after registry inclusion. Patients with *PMS2* or *EPCAM* mutations were not included due to low sample size. Patients either had no CRC before the start of prospective observation (cohort 1), or were already diagnosed and treated for CRC before inclusion (cohort 2). For each patient, sex and the type of MMR gene defect were recorded. For each colonoscopy, age at examination and worst finding (normal, adenoma, CRC) were noted, and for each CRC, the age at diagnosis and tumor stage according to TNM, International Union Against Cancer (UICC), or Dukes classification were recorded.

Statistical Analysis

Prospective observation started with the first colonoscopy conducted after enrollment into the LS register (index colonoscopy) and ended with the last colonoscopy or the occurrence of a primary CRC diagnosis. CRCs detected at the index colonoscopy were considered as prevalent cancers. All other CRCs detected at follow-up or due to symptoms during prospective observation were defined as incident cancers. The occurrence of incident extracolonic tumors was ignored, if regular colonoscopies were continued after such an event.

Time to incident CRC or adenoma was analyzed using the Kaplan-Meier method, with time zero at the index colonoscopy and group comparisons made using the log-rank test. Comparisons of categorical data between groups were performed using the χ^2 test or Fisher exact test where appropriate. Multivariable Cox regression analyses were performed to explore the association of CRC risk with the following 5 patient-related factors: prior CRC diagnosis before the index colonoscopy, male sex, presence of *MLH1* or *MSH2* mutation (in contrast to *MSH6*), age $\geq$40 years, and presence of adenoma at the index colonoscopy.

Instrumental variable analysis was used to assess the relationship between the mean of each patient's intervals and CRC risk, using country as an instrument variable and adjusting for the factors that could have an impact both on the physician's decision to individually deviate from the general interval recommendation and CRC risk. This analysis involved a 2-stage regression approach.[11] In the first stage, multivariable linear regression was used to predict the means of each patient's colonoscopy intervals from country and the previously mentioned patient-related factors. In the second stage, multivariable Cox regression analysis was used to estimate the association of the predicted means of each patient's colonoscopy intervals (obtained from the stage 1 regression) on CRC risk, adjusting for the same 5 patient-related factors.

P values less than .05 were considered statistically significant. All analyses were carried out using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY).

Results

Patient Characteristics

The study comprised 2747 patients with LS (1027 from Germany, 806 from the Netherlands, and 914 from Finland). Table 1 shows basic patient characteristics. A total of 1709 individuals (62%) did not have a CRC diagnosis before their index colonoscopy at a mean age of 40 years (cohort 1); 1038 patients (38%) already had a prior CRC (mean age at diagnosis of 43 years) and had their index colonoscopy at a mean age of 50 years (cohort 2). Because of the presence of 2 *MLH1* founder mutations in the Finnish population, the proportion of *MLH1* carriers was higher in Finland (79%) compared with Germany (39%) and the Netherlands (35%). Patients had a median of 5 consecutive colonoscopies (16,327 colonoscopies in total). The median per-patient observation time was 7.8 years (interquartile range 4.2 to 12.0). Because of the later establishment of the German LS registry, the median per-patient observation time was shorter in both cohorts (6.0 years) compared with the Netherlands (9.7 years) and Finland (8.8 years). The cumulative prospective observation time amounted to 23,309 person-years in total. At the index colonoscopy, the frequency of prevalent adenomas was 10.2% and the frequency of prevalent CRC was 2.3%.

Colonoscopy Intervals

To characterize the colonoscopy intervals at the patient level, the median of each patient's intervals was calculated. Figure 1 depicts the distribution of the interval medians by country. We considered a patient to be within the country-specific interval recommendation if their interval median did not differ by more than $\pm$6 months. According to this definition, 76% of the patients in Germany, 87% in the Netherlands, and 88% in Finland were within the recommended interval. Twenty-one percent of the German patients had longer intervals (>1.5 years), and 13% of the patients in the Netherlands (>2.5 years). In Finland, 9% of the patients had shorter intervals than recommended (<1.5 years).

Table 1. Patient Characteristics

	Cohort 1 (no CRC before index colonoscopy)				Cohort 2 (first CRC before index colonoscopy)				Total Cohort 1&2
	Germany	Netherlands	Finland	Total Cohort 1	Germany	Netherlands	Finland	Total Cohort 2	
	n = 387	n = 646	n = 676	n = 1709	n = 640	n = 160	n = 238	n = 1038	n = 2747
Sex, n (%)									
Male	154 (39.8)	255 (39.5)	320 (47.3)	730 (42.7)	369 (57.7)	84 (52.5)	133 (55.9)	585 (56.4)	1315 (47.9)
Female	233 (60.2)	391 (60.5)	356 (52.7)	980 (57.3)	271 (42.3)	76 (47.5)	105 (44.1)	452 (43.6)	1432 (52.1)
Affected MMR gene, n (%)									
MLH1	127 (32.8)	218 (33.7)	536 (79.3)	881 (51.5)	273 (42.7)	67 (41.9)	186 (78.2)	526 (50.7)	1407 (51.2)
MSH2	201 (51.9)	276 (42.7)	104 (15.4)	582 (34.0)	306 (47.8)	60 (37.5)	39 (16.4)	404 (39.0)	986 (35.9)
MSH6	59 (15.2)	152 (23.5)	36 (5.3)	247 (14.4)	61 (9.5)	33 (20.6)	13 (5.5)	107 (10.3)	354 (12.9)
Age at prior CRC, mean (±SD)	—	—	—	—	41.4 (±9.5)	44.0 (±11.4)	44.6 (±11.0)	42.5 (±10.2)	42.5 (±10.2)
Age at index colonoscopy, mean (±SD)	40.9 (±12.0)	41.3 (±12.5)	39.0 (±13.4)	40.3 (±12.8)	48.0 (±11.4)	52.3 (±11.1)	53.5 (±11.8)	49.9 (±11.7)	43.9 (±13.2)
Year of index colonoscopy, mean (±SD)	2006 (±4)	2002 (±5)	2002 (±6)	2003 (±5)	2005 (±4)	2001 (±5)	2002 (±5)	2004 (±5)	2003 (±5)
Number of colonoscopies									
Per patient, median (IQR)	6 (3–8)	6 (4–8)	4 (3–6)	6 (4–8)	6 (4–9)	6 (4–9)	5 (3–7)	6 (4–8)	5 (3–8)
Cumulative	2316	4197	3215	9728	4195	1119	1285	6599	16,327
Observation time, y									
Per patient, median (IQR)	6.2 (3.2–9.8)	9.9 (6.1–14.5)	8.9 (5.0–13.5)	8.6 (4.9–12.8)	6.0 (3.0–9.0)	9.1 (5.8–14.2)	7.8 (4.3–12.3)	6.9 (3.7–10.5)	7.8 (4.2–12.0)
Cumulative	2534	6708	6379	15,621	4061	1575	2053	7689	23,309
Finding at index colonoscopy, n (%)	n = 365	n = 613	n = 676	n = 1,654	n = 594	n = 152	n = 238	n = 984	n = 2639
Normal	305 (83.6)	550 (89.7)	582 (86.1)	1,437 (86.9)	520 (87.5)	138 (90.2)	214 (89.9)	872 (88.5)	2,309 (87.5)
Adenoma	49 (13.4)	55 (9.0)	74 (10.9)	178 (10.8)	56 (9.4)	13 (8.5)	23 (9.7)	92 (9.3)	270 (10.2)
CRC	11 (3.0)	8 (1.3)	20 (3.0)	39 (2.4)	18 (3.0)	2 (1.3)	1 (0.4)	21 (2.1)	60 (2.3)
Adenoma detection rate,[a] %	15.5	15.6	15.6	15.6	13.9	13.5	15.4	14.1	15.0
Incident CRC, no. patients/CRC	29 / 31	54 / 56	61 / 61	144 / 148	71 / 73	23 / 23	34 / 35	128 / 131	272 / 279

IQR, interquartile range; SD, standard deviation

[a]Defined as follow-up colonoscopies with at least 1 adenoma divided by all follow-up colonoscopies.

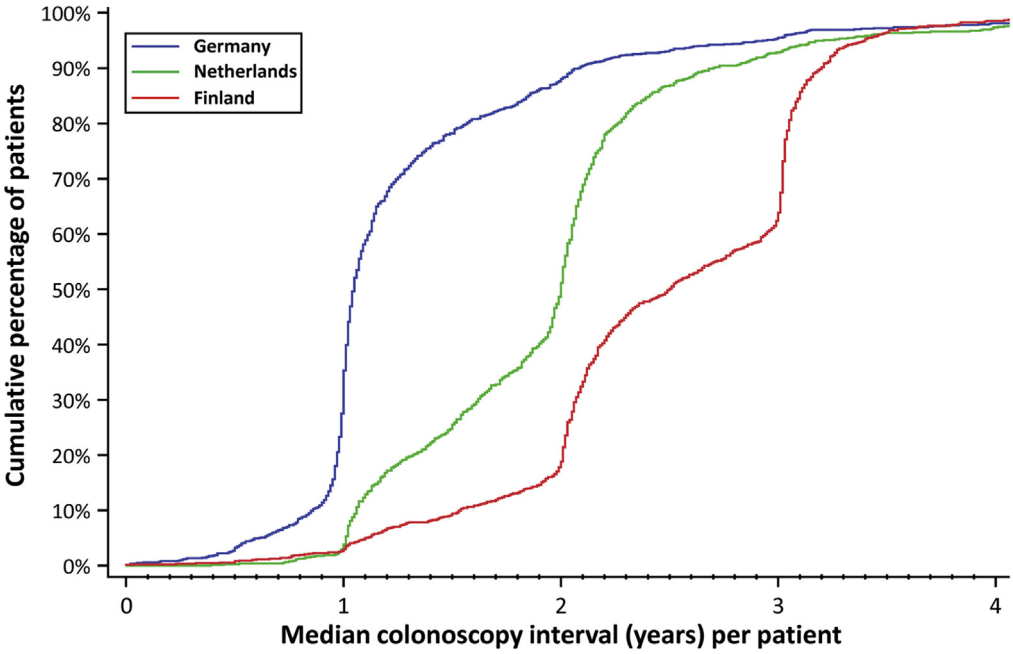


Figure 1. Distribution of colonoscopy intervals by country.

Adenoma Detection Rate and Cumulative Adenoma Incidence

The adenoma detection rate in the follow-up colonoscopies was 15.6% in cohort 1 and 14.1% in cohort 2 (Table 1). There were no significant differences between countries ($P = .996$ for cohort 1, and $P = .411$ for cohort 2). The cumulative incidence of adenomas 10 years after the index colonoscopy was 39.4% (95% confidence interval [CI] 36.6%–42.3%) in cohort 1 and 46.0% (95% CI 42.1%–50.0%) in cohort 2 (Figure 2*A* and *B*). The highest cumulative adenoma incidence was observed in the German cohort both in cohort 1 and cohort 2. Supplementary Figure 1 shows the time-dependent cumulative incidence for advanced adenomas only. Again, the highest incidence was observed in Germany both in cohort 1 and cohort 2.

Cumulative Incidence and Stage Distribution of CRC

During prospective follow-up, 144 patients in cohort 1 and 128 patients in cohort 2 were diagnosed with incident CRC. Among these, 4 patients in cohort 1 and 3 patients in cohort 2 had diagnoses of 2 synchronous CRCs, resulting in a total of 148 incident CRCs in cohort 1 and 131 in cohort 2 (Table 1). The location of the CRCs is shown in Supplementary Table 1. The time-dependent cumulative incidences of first (cohort 1) or metachronous (cohort 2) CRC were not significantly different among the 3 countries (Figure 2*C* and *D*). There were also no significant differences among the 3 countries in a multivariable analysis adjusting for sex, mutated gene, age at the index colonoscopy, and the presence of an adenoma at the index colonoscopy. After 10 years of follow-up, the cumulative CRC incidence was 8.4% (95% CI 7.1%–10.2%) for first CRC and 14.1% (95% CI 11.5%–16.8%) for metachronous CRC. Multivariable Cox regression analysis revealed that male sex, *MLH1/MSH2* mutation (in contrast to *MSH6*), age at index colonoscopy $\geq$40 years, and a prevalent adenoma at the index colonoscopy were independently associated with a higher cumulative CRC incidence (Table 2). Figure 3 shows the cumulative CRC incidence by the number of risk factors. Patients in the lowest risk group with none or only 1 risk factor had a 10-year CRC risk of 4.1% (95% CI 2.1%–6.1%), whereas the risk was 18.4% (95% CI 14.2%–22.6%) in patients in the highest risk group with 4 or 5 risk factors.

To assess the relationship between the mean of each patient's intervals (exposition) and CRC risk (outcome), an instrumental variable analysis was performed using country as instrument and the following 5 patient-related factors as influential variables both for the exposition and the outcome: prior CRC diagnosis before the index colonoscopy, male sex, presence of *MLH1* or *MSH2* mutation (in contrast to *MSH6*), age $\geq$40 years, and presence of adenoma at the index colonoscopy. The first stage of this analysis revealed that, besides country, each of these factors was independently associated with a shorter mean of each patient's intervals (Supplementary Table 2). However, there was no significant association between the predicted mean of each patient's intervals and CRC risk in the second stage of this analysis adjusting for the same 5 risk factors (Supplementary Table 3).

Information on UICC tumor stage was available for 242 (89%) of 272 patients with an incident CRC after their index colonoscopy. Figure 4 shows the distribution of UICC stages by country and by time interval between CRC diagnosis and the preceding colonoscopy. In total, 33 (14%) of 242 patients had advanced stage (UICC III/IV) carcinomas. No significant differences were observed among countries ($P = .150$) or by the interval since the last colonoscopy ($P = .240$). There was also no significant association between

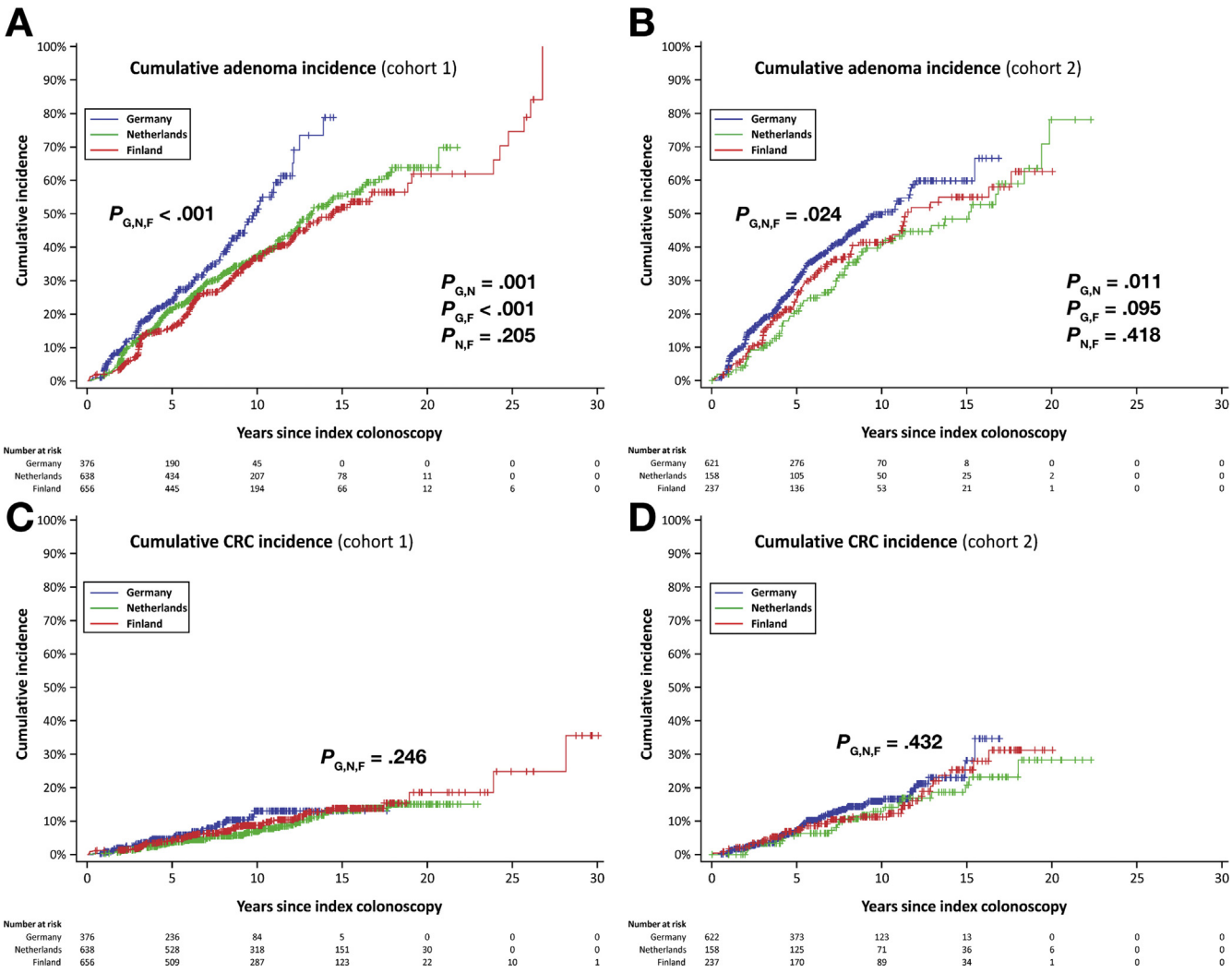


Figure 2. Cumulative incidences of adenoma and CRC. Cumulative incidence of adenoma (*A*) cohort 1 and (*B*) cohort 2. Cumulative incidence of CRC (*C*) cohort 1 and (*D*) cohort 2.

UICC stages and the mean colonoscopy interval of each patient (Supplementary Figure 2).

Discussion

The present joint analysis of colonoscopy data from prospective cohort studies in 3 countries demonstrated that a policy of strict annual surveillance intervals as recommended in Germany was not associated with a reduction in CRC incidence or the detection of earlier stages of CRC in patients with LS compared with the surveillance policies pursued in the Netherlands with 1- to 2-yearly examinations and in Finland with 2- to 3-yearly intervals.

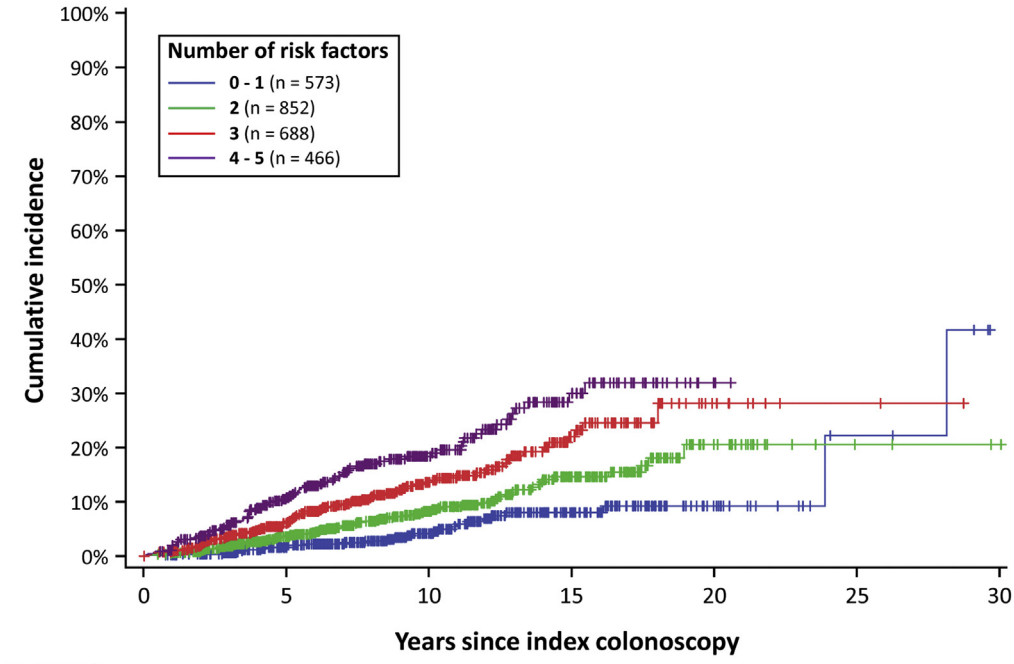
Table 2. Multivariable Cox Regression Analysis of Risk Factors for CRC (Adjusted for Country)

Risk factor	HR	95% CI	*P*
Prior CRC	1.32	1.00–1.77	.056
Male sex	1.51	1.17–1.93	.001
MLH1/MSH2 mutation	2.33	1.30–4.19	.005
Age[a] ≥40 y	1.73	1.29–2.30	<.001
Adenoma[a]	1.55	1.09–2.20	.015

HR, hazard ratio.
[a]At index colonoscopy.

There is general agreement that sporadic CRCs originate from adenomatous polyps and that removal of polyps reduces the incidence of CRC.[12] A controlled trial by Järvinen et al.[6] showed that regular colonoscopies and removal of adenomas led to a lower CRC incidence, suggesting that CRC development in LS follows the classic adenoma-carcinoma sequence. Moreover, previous studies have reported a higher frequency of adenomas in LS compared with controls,[13,14] and the adenomas in LS more often show high-grade dysplasia and a villous structure, especially in right-sided adenomas.[14–16] Loss of mismatch repair function is also observed in most adenomas.[14,17,18]

Surveillance of patients with LS has been recommended since the early 1980s.[19] In 1990, the International Collaborative Group on HNPCC (now International Society for



Number at risk

0 - 1	573	452	243	105	24	5	0
2	852	636	345	140	23	3	1
3	688	479	220	68	9	2	0
4 - 5	466	300	139	43	2	0	0

Figure 3. Cumulative incidence CRC by number of risk factors (prior CRC, male sex, *MLH1/MSH2* mutation, age ≥40 years at index colonoscopy, presence of adenoma at index colonoscopy).

Gastrointestinal Hereditary Tumours, InSiGHT) recommended a surveillance interval of 2 to 3 years.[5] However, a few years later, reports appeared describing patients who seemed to have developed a cancer within 2 to 3 years after a normal colonoscopy.[20] Other studies also indicated that the adenoma-carcinoma sequence in LS might be accelerated.[21–23] Therefore, shorter intervals of 1 to 2 years are currently recommended in most countries.

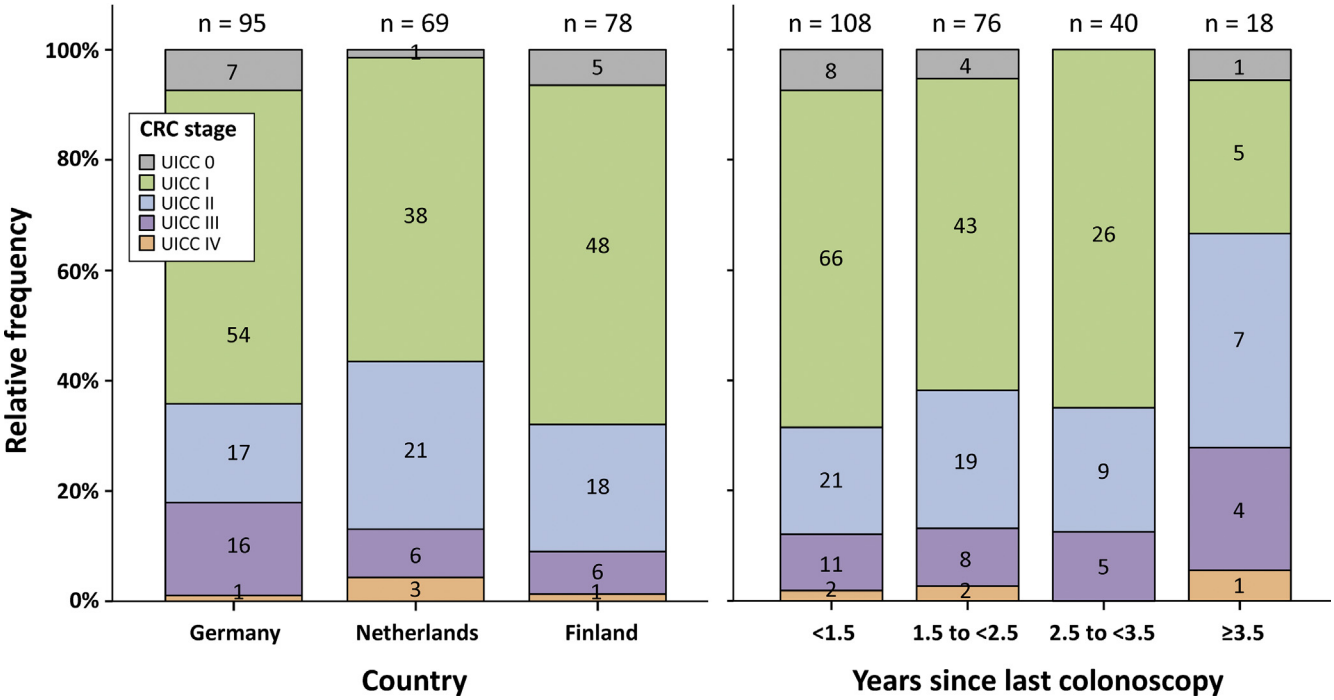


Figure 4. UICC stages of incident CRC. No significant differences were observed between countries ($P = .150$) or by time interval since last colonoscopy ($P = .240$).

Contrary to our initial expectations, we did not detect an association of shorter intervals with a lower incidence of CRC. There are 2 possible explanations for this finding. In sporadic CRC, it is generally agreed that the development of CRC from adenomas takes 10 years or more. In LS, however, small adenomas may develop and convert to CRC much faster, perhaps even within 1 to 2 years. As a consequence, the time window for detection of adenomas might be so short that most adenomas become malignant before detection, even with annual colonoscopy. An alternative explanation for the lack of efficacy of shorter colonoscopy intervals is that LS-associated CRCs may also develop directly from the normal mucosa or from precursor lesions growing under the mucosal surface and therefore escape colonoscopic detection.[24–27] However, further research is required to clarify which of these routes plays the major role in LS.

A second important finding of the present study was that the stage distribution of incident CRC was independent of the surveillance interval. We were not able to demonstrate that the proportion of metastatic CRC (stage III/IV) detected 1.5 years or less after the last colonoscopy was lower than after longer intervals. One possible explanation is that the progression of CRC from localized to metastatic CRC is too slow to detect clinically relevant staging differences within 1- to 3-yearly intervals. These findings are in agreement with previous studies that reported a better survival for patients with LS.[28] LS-associated CRCs appear to be less aggressive cancers, probably due to the well-known increased immunological defense mechanisms in LS.[29,30]

Our study also showed a high incidence of metachronous CRC, which is in agreement with previous studies.[31,32] The elevated risk of developing a second CRC might be due to the presence of the same genetic and environmental factors that contributed to the development of the first tumor. An important finding was that CRC risk was largely dependent on a number of independent risk factors, namely (1) the presence of a prior CRC diagnosis, (2) male sex, (3) *MLH1* or *MSH2* carrier status (in contrast to *MSH6* carrier status), (4) age $\geq$40 years at the index colonoscopy, and (5) presence of an adenoma at the index colonoscopy. Other studies suggested that *MLH1* and *MSH2* mutation carriers have a higher risk of developing CRC compared with carriers of an *MSH6* mutation.[10,33] This finding can be explained by the fact that CRC in *MSH6* carriers develops 5 to 10 years later than in *MLH1* or *MSH2* carriers.[2] We show that a simple risk score based on the number of risk factors allows the stratification of patients into risk groups with 10-year CRC risks ranging from 4.1% in the lowest risk group (with none or only 1 risk factor) up to 18.4% in the highest risk group (with 4 or 5 risk factors). This risk score might be used to individually adjust the surveillance intervals. Further well-defined studies are needed to develop and validate such risk-adapted surveillance protocols.

The current study had several strengths, as well as some limitations. Strong aspects of the study were the use of prospective data and the long duration of follow-up. A limitation was that data on the quality of the individual colonoscopies were not available. However, adenoma detection rates during follow-up were very similar in the 3 countries, suggesting a comparable quality of colonoscopies. In contrast, the cumulative adenoma incidence was significantly higher in the German cohort compared with the cohorts in the Netherlands and Finland, which might be explained just by the higher frequency of colonoscopies in the German cohort.

Our study does not provide insight into the direct association between interval lengths and CRC risk. Such an analysis is hampered by the fact that the interval length might be modified by the same factors that are associated with CRC risk in an uncontrolled way, because such modifications were not part of the national protocols. Therefore, we deliberately compared the country-specific CRC risks under the specific distribution of intervals in each country. However, these distributions were largely in accordance with the recommendation (ie, the proportion of patients with longer or shorter intervals was small).

What are the implications of our findings for general practice? Although there was no significant difference in the stage distribution of incident CRC, intervals of $>$3.5 years may lead to an increased rate of CRCs with more advanced stages. Based on our findings, strict annual surveillance of all patients with LS without any interval adjustment based on individual risk factors seems not to be justified. An interval of 2 years might be appropriate, and shorter intervals are needed only for patients predicted to have a high CRC risk based on individual risk factors, and longer intervals may be advised in patients with a low CRC risk.

It has been shown that colorectal neoplasms in LS are more likely to have a nonpolypoid shape, especially in the proximal colon.[34] Thus, to detect small or flat adenomas and CRC, a high-quality colonoscopy is of the utmost importance. The use of chromoendoscopy might improve the detection of such lesions.[35] Attention also should be paid to quality measures of colonoscopy, including the Boston Bowel Preparation Scale, withdrawal time, and other parameters.[36]

In conclusion, combining prospective cohort data from 3 countries, this study showed that a policy of strict annual colonoscopic surveillance, as practiced in Germany, was not associated with lower CRC incidence or earlier stages of CRC in patients with LS compared with a policy of 1- to 2-year intervals in the Netherlands or 2- to 3-year intervals in Finland. There was also no significant association of the colonoscopy interval with CRC risk when taking into account that patient-related CRC risk factors, such as age, sex, mutation, and prior detection of CRC or adenoma, were used to individually modify colonoscopy intervals. An interval of 2 years might be sufficient, and only patients predicted to have a high CRC risk based on individual risk factors may benefit from shorter intervals. To identify such patients and to design risk-adapted surveillance policies, appropriate predictive risk models need to be developed. Moreover, further well-designed prospective studies with suitable endpoints need to be conducted to validate the efficacy and safety of such novel surveillance strategies.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.07.030.

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Conflicts of interest
The authors disclose no conflicts.

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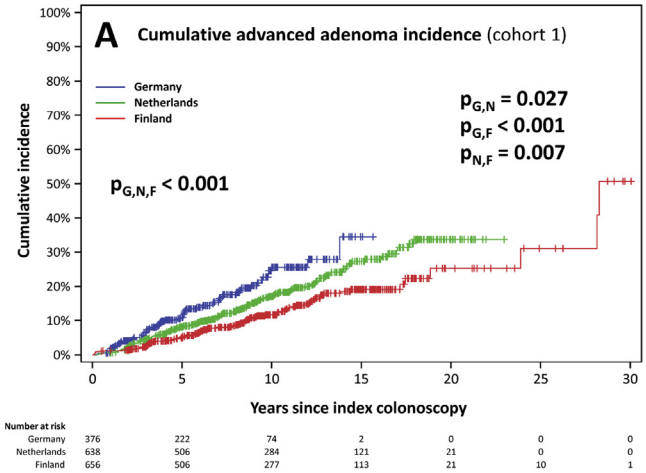
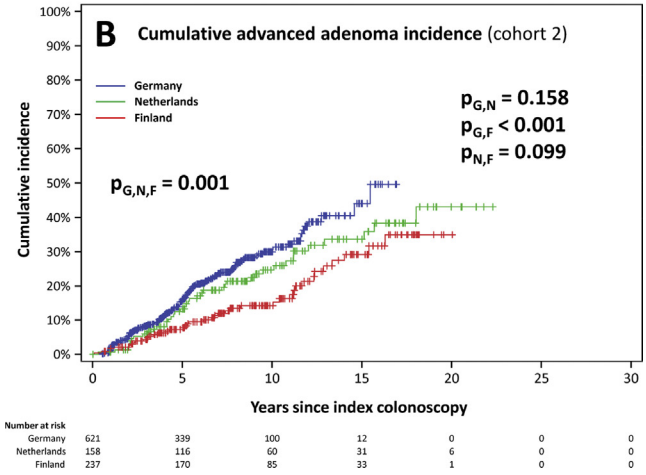
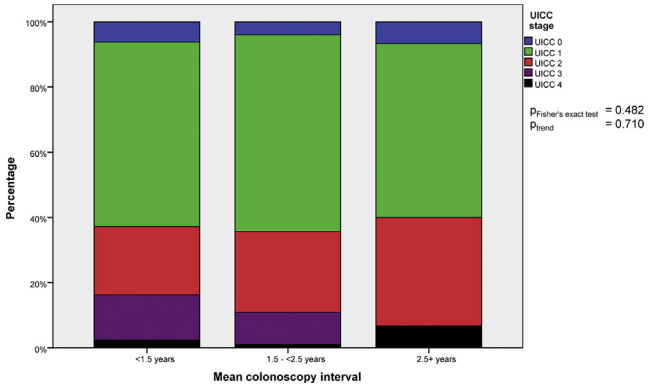




Supplementary Figure 1. Cumulative incidences of advanced adenoma. (*A*) Cohort 1; (*B*) cohort 2.



Supplementary Figure 2. UICC stages of incident CRC by mean interval.

Supplementary Table 1. Location of Incident CRC, n (%)

Location of CRC	Germany n = 104	Netherlands n = 79	Finland n = 96	Total n = 279
Caecum	10 (9.6)	22 (27.8)	17 (17.7)	49 (17.6)
Colon ascendens	21 (20.2)	16 (20.3)	23 (24.0)	60 (21.5)
Flexura hepatica	8 (7.7)	6 (7.6)	4 (4.2)	18 (6.5)
Colon transversum	17 (16.3)	11 (13.9)	16 (16.7)	44 (15.8)
Flexura lienalis	4 (3.8)	3 (3.8)	6 (6.3)	13 (4.7)
Colon descendens	7 (6.7)	3 (3.8)	6 (6.3)	16 (5.7)
Rectosigmoid	1 (1.0)	1 (1.3)	3 (3.1)	5 (1.8)
Rectum	13 (12.5)	5 (6.3)	11 (11.5)	29 (10.4)
Unknown	5 (4.8)	3 (3.8)	2 (2.1)	10 (3.6)

Supplementary Table 2. Instrumental Variable Analysis (Stage 1)

Risk factor	B	95% CI	*P*
Country: Netherlands (ref: Germany)	+0.497	+0.413 to +0.582	<.001
Country: Finland (ref: Germany)	+0.981	+0.902 to +1.061	<.001
Prior CRC	−0.252	−0.328 to −1.761	<.001
Male sex	−0.072	−0.136 to −0.008	.027
MLH1/MSH2 mutation	−0.149	−0.246 to −0.051	.003
Age[a] ≥40 y	−0.101	−0.170 to −0.032	.004
Adenoma[a]	−0.191	−0.295 to −0.087	<.001

NOTE. Results of linear regression of the mean colonoscopy interval dependent on country (instrumental variable) and patient-related factors.
[a]At index colonoscopy.

Supplementary Table 3. Instrumental Variable Analysis (Stage 2)

Risk factor	HR	95% CI	*P*
Predicted mean colonoscopy interval	0.782	0.568–1.076	.131
Prior CRC	1.313	0.960–1.796	.088
Male sex	1.492	1.163–1.914	.002
MLH1/MSH2 mutation	2.355	1.315–4.218	.004
Age[a] ≥40 y	1.665	1.248–2.221	.001
Adenoma[a]	1.498	1.046–2.145	.027

NOTE. Results of Cox regression of time-to-CRC dependent on the predicted mean colonoscopy (exposure variable) and patient-related factors.
HR, hazard ratio.
[a]At index colonoscopy.