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ORIGINAL ARTICLE

Equivalent *Helicobacter pylori* infection rates in Lynch syndrome mutation carriers with and without a first-degree relative with gastric cancer

Eline C. Soer[1] · Laura W. Leicher[1] · Alexandra M. J. Langers[2] · Paul C. van de Meeberg[3] · Egbert-Jan van der Wouden[1] · Jan Jakob Koornstra[4] · Marloes Bigirwamungu-Bargeman[5] · Hans F. A. Vasen[6] · Wouter H. de Vos tot Nederveen Cappel[1]

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Abstract
Background Patients with Lynch syndrome (LS) are at an increased risk of developing gastric cancer. In 2010, a guideline that recommended to screen all patients for *Helicobacter pylori* was implemented in the Netherlands. *H. pylori* is an important risk factor in the development of gastric cancer in the general population, and eradication of the bacterium reduces this risk. We aimed to assess the proportion of LS patients being tested and the yield and also addressed the question whether *H. pylori* infection is more prevalent in LS families with known cases of gastric cancer.
Methods Proven mutation carriers from five different Dutch hospitals were included. The implementation of *H. pylori* screening and its outcome was examined. The observation period was 2008–2013. The presence of first-degree family members with gastric cancer was noted, and it was observed if *H. pylori* infection was more prevalent in Lynch families with known cases of gastric cancer. Obtainable endoscopy reports were reviewed.
Results Four hundred forty-three (male, 184) proven mutation carriers were included. The proportion of patients screened increased after 2010, from 37 to 68 %. Twenty percent of the patients were infected. The 25 patients who had a first-degree family member with gastric cancer did not have a higher infection rate. In 30 % of cases, an endoscopy was performed; in four patients, intestinal metaplasia and in eight patients, gastric cancer was found.
Conclusion The recommendation to screen for *H. pylori* is increasingly followed. The prevalence of infection in this patient group does not differ from the general population. Patients who had a first-degree family member with gastric cancer did not have a higher infection rate.

Keywords Lynch syndrome · Gastric cancer · *Helicobacter pylori*

✉ Eline C. Soer
e.c.soer@amc.uva.nl

[1] Department of Gastroenterology and Hepatology, Isala Clinics, Zwolle, The Netherlands

[2] Department of Gastroenterology and Hepatology, Leiden University Medical Center, Isala Clinics, P.O. box 10400, 8000 GK Zwolle, The Netherlands

[3] Department of Gastroenterology and Hepatology, Slingeland Ziekenhuis, Doetinchem, The Netherlands

[4] Department of Gastroenterology and Hepatology, Groningen University Medical Center, Groningen, The Netherlands

[5] Department of Gastroenterology and Hepatology, Medisch Spectrum Twente, Enschede, The Netherlands

[6] The Netherlands Foundation for the Detection of Hereditary Tumors, Leiden, The Netherlands

Introduction

Lynch syndrome (LS) is an autosomal dominantly inherited syndrome, caused by germ-line mutations in one of the four mismatch repair (MMR) genes (MLH1, MSH2, MSH6, PMS2) or epigenetic inactivation of MSH2 through an EpCAM mutation [1]. Patients with LS are at an increased risk of developing cancer, particularly colorectal cancer and endometrial cancer. Cancers of the stomach, small intestine, liver, gallbladder ducts, upper urinary tract, brain, and skin are observed more frequently as well [2–4].

The lifetime risk of gastric cancer is estimated between 2 and 13 % for LS patients. The 5-year survival rate for gastric cancer is only 15 % [5]. There is no evidence for clustering of gastric cancer within specific families [2, 6, 7]. The risk appears to be highest for MLH1 and MSH2 mutation carriers. The mean age of diagnosis of gastric cancer is 56 years. Higher risks are reported in countries that have other risk factors for gastric cancer such as high incidence of *Helicobacter pylori* infection. This indicates that environmental factors also play a role in the development of gastric cancer in gene carriers [8].

Intestinal-type adenocarcinoma is reported in 73–79 % of gastric cancer cases in patients with LS [6, 9]. This type of cancer is strongly associated with environmental factors, especially *H. pylori* infection. Patients with *H. pylori*-associated chronic gastritis may develop atrophy of the gastric mucosa, followed by intestinal metaplasia. Eventually, adenocarcinoma of the 'intestinal' type can arise [10]. *H. pylori* is classified by the WHO as a group one carcinogen [11]. In contrast, diffuse-type adenocarcinoma is not known to be associated with environmental factors. This type of cancer is notoriously difficult to detect in its early stages.

In 2013, a group of European experts (the Mallorca group) published its revised guidelines for the clinical management of Lynch syndrome [12]. In light of the relatively low risk of gastric cancer and the lack of established benefits, they did not recommend endoscopic surveillance of the upper gastrointestinal (GI) tract. However, they recommended to screen MMR mutation carriers for the presence of *H. pylori* infection and to perform subsequent eradication. For Dutch physicians, the recommendation to screen for *H. pylori* had already been operative since 2010 [13].

To date, there are no data on the results of this recommendation. The aims of the present study were to assess (1) the proportion of LS patients being tested for *H. pylori* infection, (2) the yield of *H. pylori* screening, and (3) the results of upper GI endoscopy if performed. We also address the question whether *H. pylori* infection is more prevalent in Lynch families with known cases of gastric cancer.

Material and methods

In this retrospective observational cohort study, we examined the medical records of Lynch patients from five Dutch hospitals. Patients were eligible for inclusion if they were proven mutation carriers. The observation time was from December 2008 until December 2013. The study was approved by the ethics committees of the respective centers. The implementation of *H. pylori* screening, the type of test (serology, rapid urease test), urea breath test (UBT), stool antigen test or histology and its outcome were examined within the observation period. No data was available on the specific type of *H. pylori* strain. Unfortunately, due to the retrospective nature of the study, it was impossible to discern if the test was undertaken for screening purposes or due to the presence of symptoms. However, we assume that in the vast majority of the patients, the test was done for screening purposes. The presence of first-degree family members with gastric cancer was evaluated; the reports of upper GI endoscopy were collected and reviewed. Patients were excluded in case of incomplete medical records, i.e., if two major parameters were unknown.

Results

Baseline characteristics

In total, the medical records of 443 (male, 184) proven mutation carriers were reviewed. The mean age was fifty-three (range, 22–90 years). Twenty-three patients had died. There were almost equally as many MLH1, MSH2, and MSH6 mutation carriers (Table 1).

H. pylori screening

Screening for *H. pylori* was performed in 206 mutation carriers (46 %). A total of forty-two (20 %) patients were found to be infected. Serological testing was performed most often. For three mutation carriers, the type of test that was performed could not be determined (Table 2).Of the patients ascertained to be mutation carriers before 2010, 37 % was screened for *H. pylori*. After 2010, the percentage increased to 68 %. The percentage of mutation carriers screened varied across the five different hospitals, from 68 to 37 %.

Table 1 Baseline characteristics of all mutation carriers

Characteristic	Total, *n*	Percentage	Gastric cancer, *n*
All	443		8
Gender			
Male	184	42	5
Female	258	58	4
Alive			
Yes	421	95	5
No	22	5	4
Mutation status			
MLH1	125	28	1
MSH2	140	32	6
MSH6	128	29	1
PMS2	34	8	–
EpCAM	16	4	–

Table 2 Mutation carriers screened for *H. pylori*

Characteristic	Total, *n*	Percentage
All	206	
Hp status		
Positive	42	20
Negative	161	78
Unknown	3	2
Type of test[a]		
Serology	94	42
RET	21	9
UBT	4	2
Stool antigen	42	19
Histology	55	24
Unknown	6	3

RET rapid urease test, *UBT* urea breath test

[a] In 16 cases, two tests were performed

Table 3 Characteristics of patients with a positive family history for gastric cancer

Characteristic	Total, *n*	%
All	25	
Type of mutation		
MLH1	6	24
MSH2	12	48
MSH6	5	20
PMS2	1	4
EPCAM	1	4
Number of family members		
One	18	72
Two	7	28
H. pylori status		
Positive	5	20
Negative	14	56
Unknown	6	24
Age of family member at diagnosis		
Average	53	

Gastric cancer

Only eight (1.8 %) of 443 mutation carriers were diagnosed with gastric cancer. The mean age at diagnosis was sixty-four (range, 51–84 years). Four of eight patients had died, all within one year of diagnosis. Four patients were still alive after a follow-up of one to eleven years after treatment. Five patients with gastric cancer were MSH2 mutation carriers, one of whom developed diffuse-type gastric cancer. Seven patients were screened for *H. pylori*: three by serology and four by histology. One patient was found to be infected. Only one patient had a positive family history for gastric cancer.

Family history (first degree)

For 356 mutation carriers, the family history was available. Twenty-five of them had at least one first-degree family member with gastric cancer, and seven had more than one first-degree relative with gastric cancer. The infection rate of *H. pylori* in patients with a first-degree relative was 20 %, similar to the total group. The age at diagnosis was known for thirty-one family members; the mean age was fifty-three (range, 16–78 years). Of the twenty-five mutation carriers with a positive family history, twelve had an MSH2 mutation. MSH2 mutation carriers were 1.6 times (95 % CI 0.7–4.4) more likely to have a positive family history, when compared to the other mutation carriers. However, this difference did not reach statistical significance. See Table 3.

Upper endoscopy

In 132 patients (30 %), upper GI endoscopy was performed. In fifty-six cases (42 %), no abnormalities were found and no biopsy was taken. In seventy-six patients (58 %), one or more biopsies were taken; the results are shown in Table 4.

In 54 % of the cases, the biopsy revealed no abnormalities. Active inflammation was the most commonly found abnormality (30 %) and was seen significantly more often in *H. pylori*-positive patients (OR 11.0; 95 % CI 3.1–36.0). Intestinal metaplasia was present only in four (5 %) of the seventy-six patients. Three of these patients were tested negative for *H. pylori*, using serological testing.

Discussion

This is the first study to report the outcome of *H. pylori* screening in a large series of LS mutation carriers. The study demonstrates that a substantial proportion of mutation carriers are being tested for *H. pylori.* The recommendation to screen for *H. pylori* has been operative since 2010, and the proportion of patients being tested increased from 37 % before 2010 to 68 % after 2010. However, we cannot rule out that a small percentage of the tests was performed for complaints instead of for screening purposes. Serology and histology were the tests most commonly used. In 20 % of the mutation carriers, *H. pylori* infection was diagnosed, a proportion that is similar to the general population [14, 15]. Assuming *H. pylori* is an important risk factor in the development of gastric cancer in Lynch patients, we expected to find a higher infection rate in mutation carriers with a positive family history, as *H. pylori* clusters within families [16, 17]. However, a similar percentage of 20 % in the group mutation carriers with and without a positive family history tested positive for *H. pylori.*

H. pylori is a proven carcinogen in the general population. The role of *H. pylori* in the pathogenesis of gastric cancer in

Table 4 Patient characteristics and results of histological examination of biopsies in seventy-six Lynch syndrome patients who underwent an upper GI endoscopy

Characteristics	Inflammation	Intestinal metaplasia	Intestinal-type adenocarcinoma	Diffuse-type adenocarcinoma	No abnormality
All	23	4	7	1	41
Gender					
Male	7	3	4	1	15
Female	16	1	3	0	26
Type of mutation					
MLH1	6	2	1	–	11
MSH2	8	0	5	1	16
MSH6	7	2	1	–	13
PMS2	2	0	–	–	1
Family history					
Positive	4	2	1	–	6
Negative	17	2	5	1	31
Unknown	2	–	1	–	4
Hp status					
Positive	15	1	1	–	6
Negative	8	3	5	1	34
Unknown	–	–	1	–	1

Lynch syndrome is however still unknown. The fact that gastric cancer in mutation carriers occurs more frequently in countries with a higher prevalence of *H. pylori* infection coupled with fact that the incidence of gastric cancer in Western countries has decreased parallel to the decline of *H. pylori* infection, strongly suggest an important role for this bacterium in the carcinogenesis. There exists ample research that underlines the cost-effectiveness of *H. pylori* screening in the general population. A recent meta-analysis showed that even in low-prevalence countries (America, Canada, UK, and Finland), screening the general population for *H. pylori* was cost-effective in the prevention of gastric cancer [18]. Taking into consideration the benefit of screening the general population for *H. pylori* in the prevention of gastric cancer, obviously, screening Lynch syndrome patients would also be beneficial.

In our study population, the incidence of gastric cancer and intestinal metaplasia was much lower than expected, only eight of the mutation carriers had a malignancy; four patients had intestinal metaplasia. The majority of these patients were negative for *H. pylori*. Only one of eight patients with a malignancy was found positive. However, it should be noted that using histology to search for *H. pylori* in the presence of intestinal metaplasia or gastric cancer may produce a false-negative outcome.

A Finnish study examined the value of upper GI endoscopy surveillance in seventy-three MLH1 mutation carriers and thirty-two mutation-negative family members [9]. It showed a substantial proportion of precursor lesions: *H. pylori* infection was observed in 26 %, atrophy in 14 %, and intestinal metaplasia also in 14 %. However, in the control group, similar proportions were found. They concluded upper GI endoscopy surveillance was likely not beneficial in MLH1 mutation carriers.

The prevalence of stomach cancer in Lynch patients is lower in the Netherlands than in its surrounding countries. Engel et al. reported Dutch patients to be 76 % less likely to develop gastric cancer than German patients [19]. The cause of this difference is unknown. We included only eight patients with stomach cancer. This low incidence (2 %) is at least partially attributable to the fact that the registries we used were compiled recently, thereby not including those patients which had already died from stomach cancer.

It is well known that the different mutations have a different phenotype. Various studies have observed that MSH2 mutation carriers have a higher risk for gastric cancer than carriers of the other MMR mutations [6, 12]. In our study, almost half of the mutation carriers with a positive family history are MSH2-positive, and of eight patients with gastric cancer, five had an MSH2 mutation. While our sample size is too small to make conclusions, it supports the assumption that MSH2 mutation carriers are at greatest risk for gastric cancer.

In conclusion: a substantial and increasing proportion of mutation carriers is tested for *H. pylori*, and a similar percentage of 20 % in the group mutation carriers with and without a positive family history was tested positive. The yield of upper GI endoscopy for finding precursor lesions for gastric cancer is low, in accordance to previous studies. In light of the low risk of gastric cancer and the low yield of precursor lesions, we do not recommend regular upper GI endoscopy for any of the MMR mutations in countries with a low prevalence of gastric cancer. Our data do not seem to support the recommendation for routine *H. pylori* screening in Lynch syndrome

patients. It should however be noted that the low incidence of gastric cancer makes a type 2 statistical error likely. Therefore, we think it is presumptuous to make any claims regarding the effectiveness of screening. To answer this question, a large prospective randomized study would be necessary and such a trial would be unethical in a population at an increased risk of gastric cancer. Therefore, we recommend to continue *H. pylori* screening in Lynch syndrome patients.

Compliance with ethical standards The study was approved by the ethics committees of the respective centers.

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