Gastric and duodenal cancer in individuals with Lynch syndrome: a nationwide cohort study

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Summary

Background Lynch syndrome increases the risk of gastric cancer (GC) and duodenal cancer (DC), particularly in individuals with *MLH1* and *MSH2* pathogenic variants (PVs). To provide further insight into whether, and from what age, esophagogastroduodenoscopy (EGD) surveillance may be beneficial, we evaluated the cumulative incidence and tumour characteristics of GC and DC in a large nationwide cohort of Dutch individuals with LS.

Methods For this retrospective nationwide cohort study, clinical data of individuals with LS registered at the Dutch Hereditary Cancer Registry were matched with pathology reports filed by the Dutch Pathology registry. All individuals registered between Jan 1, 1989 and Dec 31, 2021 with proven or putative PVs in one of the mismatch repair genes were included. Cumulative incidences of GC and DC were estimated for high-risk (*MLH1, MSH2* and *EpCAM*) and low-risk (*MSH6 and PMS2*) PVs using competing risk methodology (Fine and Gray method) with death due to other causes as competing risk.

Findings Among 1002 individuals with high-risk and 765 individuals with low-risk PVs, 29 GCs (1.6%) and 39 DCs (2.2%) were diagnosed. Cumulative incidence of GC and DC under the age of 50 was very low (≤1%) for all individuals. At age 70 and 75, cumulative incidence of GC was 3% [95% CI 1%–5%] and 5% [3%–8%] for high-risk PVs and 1% [0%–2%] and 1% [0%–2%] for low-risk PVs (p = 0.006). For DC, cumulative incidence at age 70 and 75 was 5% [3%–7%] and 6% [3%–8%] in high-risk, 1% [0%–1%] and 2% [0%–4%] in low-risk PVs, respectively (p = 0.01). Primary tumour resection was performed in 62% (18/29) of GCs and 77% (30/39) of DC cases. Early-stage GC, defined as TNM stage I, was found in 32% (9/28) of GCs. Early-stage DC, defined as TNM stage I-IIa, was found in 39% (14/36) of DCs.

Interpretation Individuals with *MLH1, MSH2,* and *EpCAM* PVs have an increased risk of developing GC and DC at the age of 70 years, but this risk is very low before the age of 50 years. The age of onset of surveillance, the yield of GC and DC during EGD surveillance, and its cost-effectiveness should be subject of future studies.

Funding None.

Keywords: Lynch syndrome; Gastric cancer; Duodenal cancer

Introduction

Lynch syndrome is a dominantly inherited cancer predisposition syndrome caused by a pathogenic germline variant (PV) in one of the mismatch repair genes (*MLH1, MSH2, MSH6* and *PMS2*) or *EpCAM* gene.[1–5] Individuals with Lynch syndrome have an increased

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Research in context

Evidence before this study

We searched PubMed for prospective and retrospective studies published between January 1 2010 and December 31 2021, using the terms "gastric cancer", "duodenal cancer" and "Lynch syndrome" without language limitations. Gastric cancer risk in Lynch syndrome is estimated to be between 5 and 13%, with higher incidences reported among *MLH1* and *MSH2* carriers. The risk for duodenal cancer in Lynch syndrome can reach up to 7% in *MLH1* carriers. These data are however not corrected for competing risks as death due to other causes, which risk is increased in Lynch syndrome individuals. Despite the known gastric and duodenal cancer risks, there is a lack of consensus among guidelines regarding the necessity of esophagogastroduodenoscopy (EGD) surveillance for Lynch syndrome individuals. The European guideline (ESGE) advises against it, while German and U.S. guidelines advocate for EGD surveillance starting from age 35 years.

Added value of this study

We demonstrated that, after adjusting for deaths due to other causes, the combined risk of gastric and duodenal cancer is 11% at lifetime for individuals with *MLH1* and *MSH2* mutations, but negligible before age 50 for all Lynch syndrome individuals. Over 60% of diagnosed cases of gastric and duodenal cancer were resectable at the time of diagnosis, with approximately one-third of tumours being identified at an early stage. Compared to the general Dutch population, individuals with Lynch syndrome face a sevenfold higher risk of gastric cancer and a 250-fold higher risk of duodenal cancer.

Implications of all the available evidence

Combining all evidence, it appears indicated to implement surveillance strategies for gastric and duodenal cancer in *MLH1* and *MSH2* mutation carriers based on the cumulative risks. However, our results do not support starting surveillance at age 35 years. The age of onset, yield and cost-effectiveness of surveillance should be determined in future studies. Whether EGD surveillance is able to prevent gastric and duodenal cancer by detection and resection of precursor lesions or decreasing gastric and duodenal cancer related death by early cancer detection is still unknown.

risk of developing several types of cancer, including colorectal cancer and endometrial cancer, and to a lesser extent, gastric cancer (GC) and duodenal cancer (DC).

The lifetime cumulative incidence of developing GC was previously estimated to be up to 9% in a cohort of 2014 Dutch individuals with Lynch syndrome between 1970 and 2003.[6] For DC, the lifetime cumulative incidence for individuals with Lynch syndrome was estimated between 2 and 6% in a European cohort of 3119 Lynch syndrome individuals.[7] However, these estimates were not adjusted for the competing risk of death due to other causes, which risk is elevated in individuals with Lynch syndrome due to their increased risk for several malignancies. Furthermore, cancer risks in individuals with Lynch syndrome differ per PV. Previous studies have demonstrated that individuals with PVs in *MLH1* and *MSH2* exhibit a similar incidence of GC and DC, and that this risk is substantially higher compared to the risk of GC and DC in individuals with PVs in *MSH6* and *PMS2*.[6–9]

Early detection of both GC and DC may reduce cancer-related mortality in individuals with Lynch syndrome. Biennial surveillance with esophagogastroduodenoscopy (EGD) is therefore recommended by guidelines in Germany and the USA starting at the age of 35 years.[10,11] Other guidelines, however, conclude that there is currently insufficient evidence to support such a recommendation.[12–15]

Before starting a screening or surveillance program, several criteria should be fulfilled. Surveillance should only be offered if the disease is an important health problem in which detection of precursor lesions or early cancer reduces the incidence or improves the prognosis of this disease. Furthermore, an accurate and tolerable screening test for the disease should be available.[16] Lastly, it is essential to tailor the message on the need for surveillance to the target population, ensuring that its relevance is clearly understood.[17] Since EGD is an invasive procedure, it is crucial to weigh harms and benefits, and only offer surveillance to those at high risk of GC and DC. To evaluate if, and from what age, EGD surveillance in individuals with Lynch syndrome would be beneficial, data on the age-specific incidence of GC and DC are essential. Here we present the cumulative incidence of gastric and duodenal cancers for the different PVs in a large nationwide cohort of Dutch individuals with Lynch syndrome.

Methods

Study design and participants

This nationwide cohort study included individuals with Lynch syndrome registered at the Netherlands Foundation for Detection of Hereditary Tumours (StOET). Following a Lynch syndrome diagnosis in the Netherlands, families are invited to register at the nationwide registry of the StOET. Since 1985, the StOET offers information for patients and caregivers, prospectively collects data about the colonoscopic and gynaecological surveillance, and monitors clinical outcomes for all registered individuals with Lynch syndrome.

The clinical data of the individuals registered at the StOET were linked with pathology reports describing histopathologic outcomes of gastric and duodenal tissue sampling from the Dutch Pathology Registry (PALGA) databank in order to evaluate the incidence of histologically proven GC and DC. PALGA is the nationwide network and registry that prospectively enrols all histopathology reports in the Netherlands since 1989.[18] In this study, all individuals registered at the StOET with proven or putative PVs in one of the mismatch repair genes, i.e. *MLH1, MSH2, MSH6, PMS2,* or *EpCAM* gene, were included. We excluded individuals of whom the germline MMR mutation was not specified in the StOET database. Likewise, all individuals registered at the StOET of whom insufficient personal data was available for accurate matching with pathology reports filed by PALGA, were excluded. All data from 1 January 1989 until 31 December 2021 was used for analysis.

Ethics

Written informed consent for recording medical information for future research is obtained at registration at the StOET. The study design was approved by the scientific research boards of the StOET and PALGA (2021-189).

Procedures

In this analysis we classified individuals with PVs in *MLH1* and *MSH2* as "high-risk" and individuals with PVs in *MSH6* and *PMS2* as "low-risk". PVs in the *EpCAM* gene that silences *MSH2,* were grouped with *MSH2*.[4] Data on sex, germline mutation, year of birth, date of last registered contact and, if applicable, date of death were extracted from the clinical records filed at the StOET. Data on histopathological diagnosis, *Helicobacter pylori* and, if applicable, AJCC/UICC TNM tumour stage (8th version) were extracted from the digital excerpts of pathology reports and classified according to the site of origin (e.g. stomach or duodenum).[19] In line with Ladigan-Badura *et al.*, early-stage GC was defined as TNM stage I.[20] Early-stage DC was defined as local disease, TNM stage I-IIb, consistent with Vangala *et al.*[21,22] Of the small bowel carcinomas, only duodenal carcinomas were included because these tumours are within the diagnostic reach of the EGD and the aim of our study is to evaluate if, and from what age, EGD surveillance in individuals with Lynch syndrome would be beneficial. In the same context, tumours in the ampullary region of the duodenum were grouped with duodenal carcinomas.

Statistics

All adenocarcinomas of the stomach and duodenum were defined as events in their respective analyses. Time to carcinoma was defined as the time from 18 years until cancer diagnosis. Lifetime cumulative incidences were defined as the cumulative incidence until 75 years, as beyond this age, less than 10% of the population in our cohort remained at risk. Cumulative incidences of GC and/or DC were estimated using competing risk methodology (Fine and Gray method) with death due to any other cause as competing risk. This approach can accurately estimate the cumulative incidence of GC and DC while considering the influence of other competing events, such as death due to other causes, which may preclude GC and/or DC occurrence. The cumulative incidences of GC and DC with 95% confidence intervals (CI) were analysed separately, as well as combined. Differences between high- and low-risk groups were tested using the Fine and Gray model, estimating the subdistribution hazard ratios (HR) adjusted for year of birth in order to correct for potential missing pathology data on individuals diagnosed with GC and/or DC before the start of the Dutch pathology registry in 1989 and sex. Sensitivity analysis was conducted to rule out selection bias. In the sensitivity analysis we included all individuals registered at the StOET and assumed that all excluded patients without a PALGA excerpt did not undergo EGD and were not diagnosed with GC and/or DC. Standardized incidence ratios (SIR) were determined by dividing the observed number of carcinomas in the study cohort by the expected number of carcinomas per age group based on the annual GC and DC incidence in the general Dutch population between 1989 and 2021. The population estimates of the general Dutch population were derived from the Netherlands Cancer Registry and CBS Statistics Netherlands.[23,24] Exact confidence intervals at 95% were estimated based on the assumption that the number of observed carcinomas followed a Poisson distribution. Statistical significance was set at $p < 0.05$. All analyses were performed using R software version 4.0.3.

Role of funding sources

There was no funding received for this study.

Results

The personal data of 1767 of the 1862 individuals with Lynch syndrome in the StOET registry could be matched with the Dutch Pathology registry (Fig. 1). The final cohort for analyses included 448 (25%) *MLH1,* 539 (31%) *MSH2,* 599 (34%) *MSH6,* 166 (9%) *PMS2* and 15 (1%) *EpCAM* PV carriers. The median age at last registered contact of the final study cohort was 60 (IQR 50–70) years with women accounting for 60% of the cohort. A total of 626 (35%) individuals with Lynch syndrome underwent at least one EGD with biopsy or tissue sampling for histopathological examination (Supplementary Table S1).

Gastric cancer

A total of 29 individuals were diagnosed with GC (1.6%). The median age at diagnosis was 68 (IQR 58–74) years,

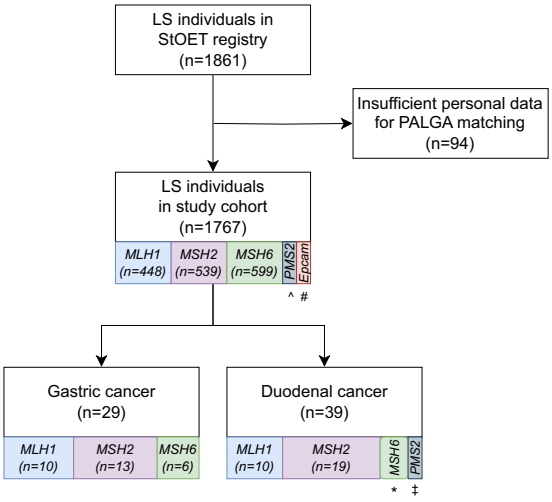

Fig. 1: Flowchart of included patients. LS: Lynch syndrome, ^: (n = 166), #: (n = 15) *: (n = 7), ‡: (n = 3).

55% (16/29) were male, and 14% (4/29) were diagnosed before the age of 50 years. Familial clustering of GC (>1 GC in pedigree) was seen in one family, where 3 cases of GC were found. Among all GC patients, two developed also DC during their lifespan; one patient was diagnosed with GC 6 years after pylorus preserving pancreaticoduodenectomy for DC and one was diagnosed with DC 16 years after partial distal gastrectomy for GC. Of the GC patients, 16/29 (55%) had developed a previous malignancy prior to the diagnosis of GC.

As shown in Table 1, 10/29 of the GC patients (33%) underwent at least one EGD with tissue sampling prior to GC diagnosis with a median time between last EGD and GC diagnosis of 3.5 (range 2–16) years. Details on EGD findings can be found in Supplementary Table S2.

Most GCs (57%) were classified as intestinal type. A total of 18/29 (62%) patients underwent primary tumour resection: one endoscopic submucosal dissection and 17 surgical resections. TNM stage was unknown for one of the resected tumours. Approximately one-third of GCs were resected at an early stage, with TNM stage I tumours accounting for 9/28 (32%) of all GCs. All stage I tumours in our cohort were N0. One patient, who received neo-adjuvant chemotherapy, showed a pathological complete response of the primary tumour (ypT0N0; stage 0). TNM stage II and stage III tumours accounted for 5/28 (18%) and 2/28 (7%) of all GCs, respectively.

Duodenal cancer

In total, 39 individuals were diagnosed with DC (2.2%), including six carcinomas in the ampullary region. Median age at diagnosis was 59 (IQR 53–66) years, and 7/39 (18%) patients were diagnosed before the age of 50. DC was more common in males (62%) than in females with Lynch syndrome (38%). Familial clustering of DC was seen in one family, where two cases of DC occurred. Six carcinomas (15%) were located in the ampullary region of the duodenum. The majority of 26/39 DC patients (66%) had a previous malignancy, most often colorectal cancer. A proportion of 28% of patients (10/39) underwent an EGD with tissue sampling before DC diagnosis with median time between last EGD and DC diagnosis of 6.0 (range 1–20) years (Table 1).

DC was most often moderately differentiated (68%). A majority of 77% of patients (30/39) with DC underwent pancreaticoduodenectomy. Nine out of 39 patients (23%) did no undergo duodenal cancer resection. TNM stage was unknown for three of the resected tumours. Early stage tumours (TNM stage I-IIa) accounted for 39% (14/36) of DCs.

Cumulative incidence of cancer

The highest cumulative incidence of GC was observed among individuals with high-risk PVs as compared to individuals with low-risk PVs (HR 3.70, 95% CI 1.47–9.28; p = 0.005; Fig. 2a). The cumulative incidence at age 70 years was 3% (95% CI 1%–5%) in high-risk and 1% (95% CI 0%–2%) low-risk PVs. Patients with high-risk PVs had a 5% (95% CI 3%–7%) lifetime cumulative incidence of GC. For patients with low-risk PVs, lifetime cumulative incidence was 1% (95% CI 0%–2%).

Individuals with high-risk PVs had a significantly higher risk of DC compared to individuals with low-risk PVs (HR 2.62, 95% CI 1.27–5.34; p = 0.008; Fig. 2b). At age 70 years, the cumulative incidence of DC was 5% (95% CI 3%–7%) in high-risk and 1% (95% CI 0%–2%) low-risk PVs. Lifetime cumulative incidence of DC was 6% (95% CI 3%–8%) for individuals with high-risk PVs compared to 2% (95% CI 0%–4%) for individuals with low-risk PVs.

Taken together, individuals with high-risk PVs harbour a significantly higher risk of developing GC and/or DC compared to individuals with low-risk PVs (HR 2.97, 95% CI: 1.68–5.24, p < 0.001), as shown in Fig. 2c, with lifetime cumulative incidences of 10% (95% CI 7%–14%) and 3% (95% CI 1%–5%), respectively.

Sensitivity analyses

When including the 94 individuals that could not be matched with PALGA (no prior histology or no matching possible), the lifetime risk of GC and/or DC was 10% in individuals with high-risk and 3% in low-risk PVs. The sensitivity analysis shows that the exclusion of patients without pathology/PALGA data did not impact cumulative incidences.

Standardized incidence ratio

Table 2 shows the standardized incidence ratios (SIR) of GC and DC. The GC risk was 4.9 (95% CI 3.3–7.0) times

	Gastric cancers (n = 29)	Duodenal cancers (n = 39)
Age at diagnosis		
Median (IQR)	68 (58–74)	59 (53–66)
Sex		
Male	16 (55%)	24 (62%)
Female	13 (45%)	15 (38%)
EGD in history		
1 EGD	4 (14%)	8 (20%)
2 EGDs	3 (10%)	3 (8%)
≥3 EGDs	3 (20%)	1 (<1%)
No	19 (66%)	28 (72%)
Years since EGD		
Median (IQR)	3.5 (2.3–12.3)	6 (3.5–9)
Helicobacter pylori		
Positive	5 (17%)	–
Negative	15 (52%)	–
Unknown	9 (31%)	–
Malignancy prior to GC/DC		
Colorectal cancer	10 (35%)	13 (33%)
Endometrial cancer	1 (3%)	3 (8%)
Multiple malignancies	2 (7%)	6 (15%)
Other	3 (10%)	4 (10%)
No	13 (45%)	13 (33%)
Histological subtype (Lauren)		
Intestinal	16 (57%)	–
Diffuse	8 (29%)	–
Mixed	3 (11%)	–
Mucinous	1 (4%)	–
Unknown	3	–
Differentiation grade		
Good	–	3 (11%)
Moderate	–	19 (68%)
Poor	–	6 (21%)
Unknown	–	11
Primary tumour resection		
Yes	18 (62%)	30 (77%)
No	11 (38%)	9 (23%)
UICC TNM Stage		
0	1 (4%)	0
I	9 (32%)	4 (11%)
II	5 (18%)	14 (39%)
III	2 (7%)	8 (22%)
IV	0	1 (3%)
No resection	11 (39%)	9 (25%)
Unknown	1	3

IQR: interquartile range; EGD: esophagogastroduodenoscopy; UICC: Union for International Cancer Control.

Table 1: **Gastric cancer (GC) and duodenal cancer (DC) patient and tumour characteristics.**

higher in individuals with Lynch syndrome compared to the general Dutch population. High-risk PV carriers had a standardized incidence ratio of 7.8 (95% CI 4.9–11.6). Low-risk PV carriers had a three times higher risk of GC compared to the general Dutch population (SIR 3.0, 95% CI 0.7–4.4), but without reaching statistical significance.

The DC risk was substantially higher in individuals with Lynch syndrome compared to the general Dutch population with a standardized incidence ratio of 250 (95% CI 178–290). The risk of DC was even more outspoken in high-risk PV carriers (SIR 396, 95% CI 265–446) than in low-risk PV carriers (SIR 121, 95% CI 58–157).

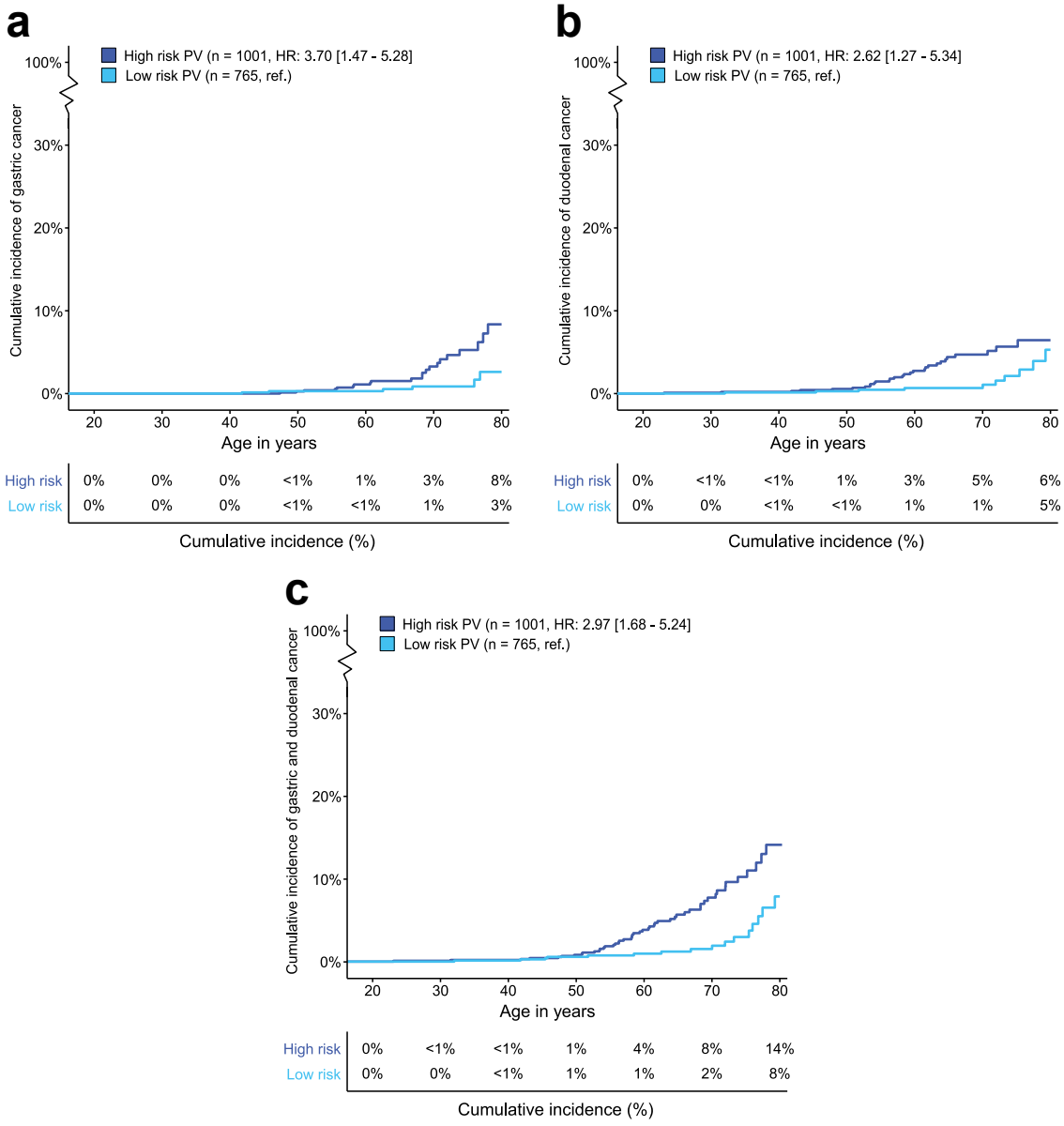

Fig. 2: a. Cumulative incidence of gastric cancer in individuals with high-risk (MLH1, MSH2 and EpCAM) and low-risk (MSH6 and PMS2) pathogenic variants (PVs). p = 0.006. HR: hazard ratio, ref.: reference. b. Cumulative incidence of duodenal cancer in individuals with high-risk (MLH1, MSH2 and EpCAM) and low-risk (MSH6 and PMS2) pathogenic variants (PVs). p = 0.01. HR: hazard ratio, ref.: reference. c. Cumulative incidence of gastric and duodenal cancer in individuals with high-risk (MLH1, MSH2 and EpCAM) and low-risk (MSH6 and PMS2) pathogenic variants (PVs). p < 0.001. HR: hazard ratio, ref.: reference.

Discussion

This study provides insight into tumour characteristics and age-specific cumulative incidence of GC and DC in individuals with Lynch syndrome. In the Netherlands, EGD surveillance is currently not recommended for Lynch syndrome individuals due to lack of clear evidence of its benefit. Both GC and DC are within reach of EGD and thus both cancers could potentially be detected by this procedure. The cumulative incidence of both cancers together was significantly increased in high-risk Lynch syndrome PV carriers: 8% at age 70 years and 10% lifetime. In low-risk PV carriers, cumulative incidence of GC and DC at age 70 years and lifetime was 2% and 3%, respectively. Furthermore, our results highlight that individuals with Lynch syndrome are at 4.9 times higher risk for GC and 250

	SIR gastric cancer	SIR duodenal cancer
All individuals with LS (95% CI)	**4.9** (3.3–7.0)	**250** (178–290)
High-risk PV (95% CI)	**7.8** (4.9–11.6)	**396** (265–446)
Low-risk PV (95% CI)	**3.0** (0.7–4.4)	**121** (58–157)

LS: Lynch syndrome; PV: pathogenic variant.

Table 2: **Standardized incidence ratios (SIR) of gastric and duodenal cancer compared to the general Dutch population between 1989 and 2021.**

times higher risk for DC compared to the general population.

To our knowledge, our study is the first to describe the cumulative incidence of gastric and duodenal carcinomas in individuals without EGD surveillance corrected for competing risks, which leads to more accurate estimations of gastric and duodenal carcinoma incidence in a study population at an increased risk for other carcinomas. When comparing our results to previous studies conducted by Capelle *et al.* and Møller *et al.*, the cumulative incidences of GC and DC appear to be lower in our study.[6,7] However, their results were not corrected for competing risks. We deliberately used competing risk methodology to account for deaths due to other causes that could prevent the occurrence of GC and/or DC. If competing events were not accounted for, by censoring survival outcomes at the time of death, the cumulative incidences of GC and DC align with the studies of Capelle *et al.* and Møller *et al.*[6,7] (Supplementary Figure S1). Capelle *et al.*'s study focused on the Dutch LS population between 1970 and 2003, showing a cumulative incidence of up to 9% at 80 years. Comparing these results to our cohort, it appears that there is no decline in GC incidence among individuals with LS. This is in contrast to the decline in gastric cancer incidence in the general Dutch population. None of the abovementioned studies, however, presented the cumulative incidence of GC and DC combined. Since GC and DC are both in the yield of EGD surveillance, combining the cumulative incidences may be the preferred approach for providing further insight into if, and from what age, surveillance would be appropriate.

The benefit of EGD surveillance in individuals with Lynch syndrome is still a topic of debate.[25] Considering the invasive nature of the procedure, the patients' burden, and—albeit small–the risks associated with conscious sedation and the procedure itself, it is essential to provide EGD surveillance only to individuals at high risk of developing GC and DC who could benefit from this procedure. Whether EGD surveillance is indeed capable of adequately detecting benign precursor lesions or early cancers, particularly in LS, remains a subject of ongoing discussion.[26] The known precursor lesions of the intestinal type GC, such as intestinal metaplasia and dysplasia, require thorough and time-consuming examination of the gastric mucosa, preferably performed in expert centres.[27] Surveillance guidelines for Lynch syndrome patients with these high-risk features are unavailable. Our study lacks the necessary data to assess the risk of potential precursor lesions progressing to cancer in Lynch syndrome, while it's worth noting that the risk of these lesions progressing to cancer is estimated to be rather low in the general population.[28] Furthermore, we showed that 29% of the identified GCs in Lynch syndrome were of the diffuse type, for which literature on precursor lesions in Lynch syndrome is lacking. In individuals with hereditary diffuse gastric cancer (HDGC), intramucosal diffuse GC foci have been observed.[29] However, the optimal approach to managing these foci and assessing their potential progression into cancer remains unclear. Concerning DC in LS, no prevalence data about its precursor lesion, duodenal adenoma, are available. Furthermore, no data showing the effect of duodenal adenoma resection in preventing DC in Lynch syndrome are available. This complexity underscores the ongoing discussion surrounding surveillance strategies for GC and DC in Lynch syndrome. The question is whether EGD surveillance should primarily focus on preventing GC and DC by detecting and resecting precursor lesions, or emphasize the detection of carcinomas at an early stage.

Early detection of GC and DC is desirable as patients diagnosed at an early stage have a better prognosis. The 3-year survival is estimated to be over 72% and 73% for early stages (stage I GC and stage I-IIa DC), and less than 5–52% and 15–51% for advanced stages (stage II-IV) of GC and DC, respectively.[24,30] Despite the fact that EGD surveillance for Lynch syndrome is not offered in the Netherlands, the majority of GC and DC (62% & 77%) diagnosed in our cohort were resectable at time of diagnosis. Approximately one-third of tumours, i.e. 32% of GCs and 39% of DCs, were in an early stage. This may reflect that individuals with Lynch syndrome have a high cancer awareness and undergo an EGD as soon as they experience symptoms. Ladigan-Badura *et al.* and Vangala *et al.* recently described a higher proportion of early stage cancers (83% of GCs and 77% of DCs) among individuals who underwent surveillance in their cohort of 2009 German Lynch syndrome individuals compared to those who did not (25% of GCs and 29% of DCs), suggesting a beneficial effect of EGD surveillance in LS.[20,22] However, among the 1128 and 1338 individuals with at least one EGD, only six cases of GC and 13 cases of DC were diagnosed under surveillance respectively, limiting the strength of these data.

Currently, no other surveillance strategies for GC and DC in Lynch syndrome are available. The yield of

small bowel neoplasia's detected by video capsule endoscopy (VCE) has been previously studied by Haanstra *et al*. In their research, two cases of DC were identified by VCE. One patient was diagnosed with DC by EGD just seven months after negative VCE.[31] Based on this study, VCE does not appear to be the optimal approach for DC surveillance in individuals with Lynch syndrome. Furthermore, VCE is not suitable for detection of GC as the gastric lumen is too wide to monitor the gastric mucosa. Since we have shown that the combined cumulative incidence of GC and DC is considerable, EGD would be the optimal approach for surveillance as the stomach and duodenum can be simultaneously inspected. However, careful inspection including deep insertion of the duodenum, extended mucosal inspection, and targeted biopsies of the gastric mucosa is essential. For optimal duodenal inspection a transparent cap at the tip of the endoscope may be helpful for better inspection of the ampullary region. A high quality EGD should fulfil all criteria as described by the ESGE guideline.[32] Yield and long-term efficacy with regard to reduction of incidence, and/or reduction of GC and DC related mortality of EGD surveillance should first be evaluated before universal EGD surveillance in high-risk PV and low-risk PV Lynch syndrome carriers can be recommended. The optimal starting age should be related to the cumulative incidence. Our data do not support the current gastric surveillance guidelines advocating a starting age of 35 years in the LS population, as is currently standard of care in Germany and the USA.[10,11] Based on our results, starting after the age of 50 years in individuals with high-risk PVs could be considered. Cost effectiveness analyses should determine the optimal interval and stopping age. To minimize the burden on patients, gastroduodenoscopy could be combined with the already established colonoscopic surveillance in Lynch syndrome.

Although no direct evidence exists, most guidelines on surveillance in Lynch syndrome individuals recommend *H. pylori* screening and eradication to lower GC risk.[10,12–14] Our study faced limitations as information on *H. pylori* colonization was frequently unknown due to the use of histology data in patients undergoing EGD, hence lacking data on *H. pylori* serology and faecal *H. pylori* antigen testing results. This hindered the examination of its association with GC risk. The significance of *H. pylori* in GC carcinogenesis, particularly of the intestinal type, has long been established as the Correa cascade.[33] However, our observation reveals that 29% of GCs within Lynch syndrome were of the diffuse type, and over 50% of all patients tested negative for *H. pylori* on histology, indicating potential variations in GC development in this context.

Another limitation arises from the retrospective nature of our study. As EGD reports are not routinely collected by the StOET, only data on EGDs with tissue sampling were available from the pathology reports filed by PALGA. This likely led to underreporting of negative EGDs (without pathological findings), hindering further analysis on the number of EGDs in the LS population.

In summary, individuals with *MLH1*, *MSH2,* and *EpCAM* pathogenic variants have a substantial risk of developing GC and DC at the age of 70 years, opposed to individuals with *MSH6* and *PMS2* pathogenic variants. For all Lynch syndrome individuals, this risk was negligible before the age of 50. The majority of GC and DC were detected at a relatively early stage. The actual yield of EGD surveillance in detecting GC, DC, and their precursor lesions as well as cost-effectiveness, should be determined in future studies.

Contributors

M.E. van Leerdam and A. Cats contributed equally to this study. I.A. Caspers: Conceptualization, Data curation, Formal analysis, Investigation, Writing—original draft; E.L. Eikenboom: Data curation, Writing—review & editing; M. Lopez-Yurda: Methodology, Formal analysis, Writing—review & editing; N.C.T. van Grieken: Writing—review & editing; T.M. Bisseling: Writing—review & editing; E. Dekker: Writing—review & editing; B.A.J. Bastiaansen: Writing—review & editing; A. Cats: Conceptualization, Methodology, Investigation, Writing—review & editing, Supervision; M.E. van Leerdam: Conceptualization, Data curation, Methodology, Investigation, Project administration, Writing—review & editing, Supervision. All authors had full access to all the data in the study and had responsibility for the decision to submit for publication.

Data sharing statement

The data supporting the findings of this study are available upon request from MEvL.

Declaration of interests

IAC, ELE, MLY, NCTvG, TB, BJAB and AC declare no conflicts of interests. ED has received a research grant from FujiFilm; reports consulting fees from Olympus, Fujifilm, Ambu and InterVenn; has served as speaker for Olympus, GI Supply, Norgine, IPSEN, PAION, and Fujifilm; has received payments as a member of the supervisory board of the eNose company; and has endoscopic equipment on loan from Fujifilm. MEvL is medical director of the Netherlands Foundation for Detection of Hereditary Tumours (unpaid function).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102494.

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