Stella A.V. Nieuwenburg

Screening and Surveillance of the Gastrointestinal Tract

Stellingen behorend bij het proefschrift

Screening and Surveillance of the Gastrointestinal Tract

1. The diagnostic yield for detecting clinically relevant premalignant gastric lesion can be improved by adding one extra follow up endoscopy – *this thesis*

2. Optimisation of gastric surveillance based on stratifying patient risk factors will increase surveillance efficiency – *this thesis*

3. High risk regions for gastric cancer may implement dual screening for gastric and colorectal cancer by analysing *H. pylori* in the fecal immunochemical test – *this thesis*

4. Currently available data shows that lowering the start age limit for colorectal cancer screening in the Netherlands from 55 to 50 years is effective – *this thesis*

5. Colon Capsule Endoscopy has proven to be a sufficient screening alternative when colonoscopy is not preferred – *this thesis*

6. Introducing any form of prevention programmes will enhance inequity within societies. *Hofmann, Journal of Evaluation in Clinical Practice, 2016*

7. Robots are taking over the world. *Stidham, Gastroenterology & Hepatology, 2020*

8. Prevention is the key to any health condition - it all starts by living a healthy lifestyle and this is an individuals' responsibility. *Reifegerste, et al. Database of Variables for Content Analysis, 2021*

9. A health screening provides a false feeling of security. *Wieten, Gut, 2019*

10. A PhD trajectory is like running a marathon; remember to pace yourself. *Greep et al., the American Journal of Medicine, 2021*

11. "In de zon zitten kan ook in je achtertuin" – *Papa †*

Screening and Surveillance of the Gastrointestinal Tract

Stella Aurelia Viktoria Nieuwenburg

Screening and surveillance of the gastrointestinal tract

ISBN/EAN: 978-94-6423-818-1

The printing of this thesis has been financially supported by the Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, Rotterdam; Erasmus University Rotterdam; Nederlandse Vereniging voor Gastroenterologie; Chipsoft B.V., Sysmex Nederland, Dr. Falk Pharma Benelux B.V.

Cover design: Viktorija Čeliković VIKA
Layout en design: Dennis Hendriks || ProefschriftMaken.nl
Printing: ProefschriftMaken.nl

Screening and Surveillance of the Gastrointestinal Tract

Screening en surveillance van het maagdarmkanaal

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus

Prof. dr. A.L. Bredenoord

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
vrijdag 24 juni 2022 om 10.30 uur

door

Stella Aurelia Viktoria Nieuwenburg
geboren te Oosterhout (NB)

Erasmus University Rotterdam

Promotiecommissie

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CHAPTER 1.1

General introduction

Nieuwenburg SAV*, Mommersteeg MC*, Spaander MCW, Kuipers EJ

Partially adapted from:

Encyclopedia of Gastroenterology, 2nd edition.
vol. 2, pp. 620-628. Oxford: Academic Press.

The gastrointestinal (GI) tract comprises a significant proportion of the human body. It was the Greek anatomist Herphilos of Chalcedon (335-280 BC) who performed the first dissection of a human body in Western medicine and was able to make several anatomical discoveries with precise descriptions (1). Footprints of his work are still marked in the field of gastroenterology nowadays, for example by naming the first part of the human intestine: the duodenum. This translates into "12 finger-widths long" and was the first step in the years that followed to reveal the complete length and surface area of the human GI tract. From autopsy data, to laparotomy data, towards advanced radiological techniques today, estimations are getting more and more precise. This resulted in the most recent estimation of the total surface of the human GI tract of approximately the size of a half badminton court (30 m^2) (2). After the respiratory tract (containing a total internal surface area of around 150 m^2) (3), the GI tract contains the second largest mucosal surface of the entire human body.

A unique trait of the GI tract is its constant interaction with the inner and outer world. This makes it vulnerable for a widespread variety of exposure to for example hot and cold temperatures, micro-organisms, toxic and carcinogenic substances. Even body's own substances that contain a valuable function in one part of the GI tract might cause damage in other parts of the GI tract, such as bile acid or gastric acid (4, 5). Exogenous substances such as medication that is ingested for any (systemic) disease, have to be absorbed and processed through the GI tract before it can be of use elsewhere. All the above require a dynamic and high-paced modelling of intestinal metabolism, enzyme- and cell turn over (6). Some medications are known to affect the GI tract, such as the association between the use of non-steroidal anti-inflammatory drugs (NSAIDs) and mucosal erosions or the use of proton pump inhibitors (PPIs) and the occurrence of fundic glands polyps in the stomach (7, 8). This thesis will elaborate more on the prevalence of these mentioned lesions (**Part III**).

Unfortunately, the GI tract distincts itself by another characteristic being the most common source of malignancies worldwide. Of the 9.6 million cancer deaths per year over 1/3 is accounted for GI cancers (9). Of these GI cancers, colorectal (CRC) cancer and gastric cancer rank highest being globally placed as the number fourth and fifth (respectively) of cancer related deaths. Both occur through their own carcinogenesis and precursor lesions.

In more detail, gastric carcinogenesis, in particular of the intestinal type, occurs via a cascade of epithelial changes. The endoscopic and histological finding of these epithelial stages are depicted in **Figure 1**. This process is initiated by inflammation most often caused by a *Helicobacter pylori* (*H. pylori*) colonization. Chronic active gastritis may lead to a loss of glandular structures and collapse of the reticulin skeleton of the mucosa, which is defined as atrophic gastritis. Further progression of atrophic gastritis will result

in intestinal metaplasia (IM) characterized by the appearance of intestinal goblet cells. All lesions are associated with an increased risk of development of intestinal type gastric adenocarcinoma (10).

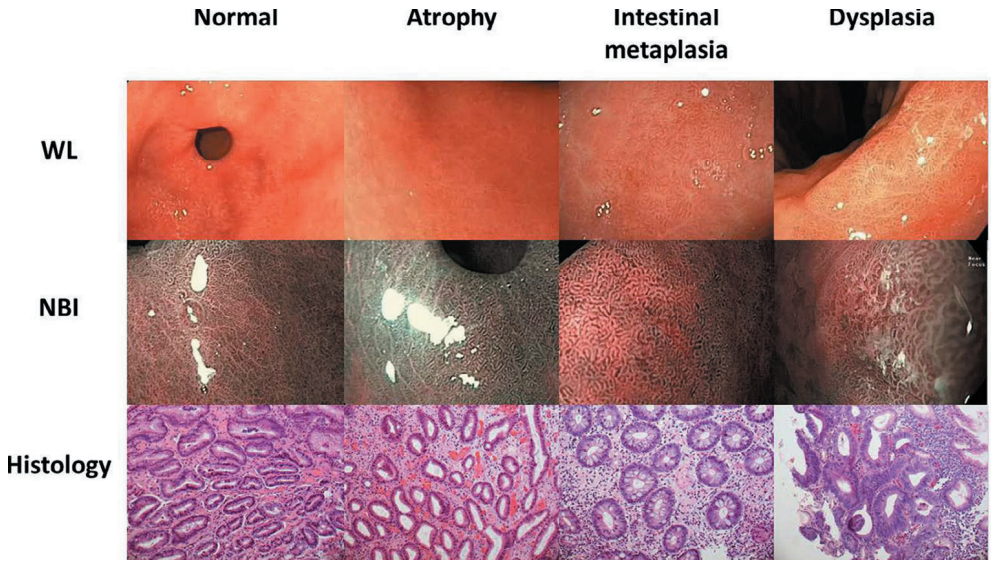

Figure 1. Examples of the gastric epithelium as visualized by white light endoscopy (WLE), narrow band imaging endoscopy (NBI) and histology with hematoxylin/eosin staining (HE histology)

The prevalence of gastric premalignant lesions and the incidence of gastric cancer strongly correlate to the prevalence of *H. pylori* gastritis. The prevalence of *H. pylori* markedly varies worldwide, ranging from <25% in Western Europe and North America to 90% in regions of East Asia and Africa. It is estimated that approximately half of the worlds' population is currently colonized with *H. pylori* (11). In a nationwide Dutch study, the prevalence of atrophic gastritis and intestinal metaplasia increased from approximately 5% at age 40 to 15% in those of 70 years and above (12). A systematic review of 107 studies reported a global prevalence of 35% for atrophic gastritis and 25% for IM in asymptomatic subjects (13). Similar rates are found in symptomatic patients. Prevalence rates of premalignant lesions in regions with low gastric cancer incidence are about 2/3 of the prevalence seen in high incidence countries (13). In 2018, the incidence rate of stomach cancer in Western Europe was 8.2/100.000 for males, and 3.7/100.000 for females. For high incidence regions such as Eastern Asia incidence rates were 32.1/100.000 for males and 13.2/100.000 for females (9).

Detection of gastric cancer at an early stage will dramatically improve 5-year survival to over 90%, as compared to an overall survival of around 25% (14). It also generally allows for less invasive treatment options, such as endoscopic instead of surgical resection of

the cancer. In areas with a high gastric cancer incidence, population screening may be effective and is as such endorsed by the Asia-Pacific consensus guidelines. Japan, Korea and the Matsu Island in Taiwan implemented population-based screening programmes (15). The MAPS guidelines (Management of Precancerous conditions and lesions in the Stomach) were designed and recently updated (2019) to provide a surveillance strategy for gastric premalignant lesions in lower endemic areas (16, 17). It is still a topic of debate if surveillance in low endemic areas will be efficient. The U.S. pleats against surveillance of patients with premalignant gastric lesions, unless specific risk factors are the case (such as Asian heritage or having a first degree relative with gastric cancer) (18). Europe currently performs endoscopic surveillance taking into account the extension of the intestinal metaplasia, in which surveillance intervals are dependent on specific risk factors (family history of gastric cancer, incomplete IM, autoimmune gastritis, persistent *H. pylori* infection). This thesis will elaborate more on the accuracy of current surveillance strategies, risk stratification of patients in need for surveillance and endoscopic techniques used for surveillance (**Part II**).

The colorectal carcinogenesis is also a multistep process. In the so-called adenoma pathway, normal colon epithelial cells changes into aberrant crypt foci, which may form polyps. Subsequently, these can progress into non-advanced adenomas (less than 1 cm in size, tubular histology), advanced adenomas (histology with over 25% of a villous component or high-grade dysplasia or over 10 mm in size), and eventually colorectal cancer (19). This process is gradually and can take up to 10-20 years.

Globally, CRC is the third most commonly diagnosed cancer and comprises 11% of all diagnosed cancers worldwide with up to eight-fold variations between regions (20). In Western Europe, incidence rate of CRC in 2018 was 20.3/100.000 for males, and 15.4/100.000 for females. In lower incidence regions such as Asia and Africa, these rates range between 3.0-12.0/100.000 (9). Incidence of CRC still increases worldwide due to ageing of the population and the rise of several risk factors such as smoking, lack of physical activity and obesity (21-23). These factors can be correlated with a Western lifestyle.

Early detection of CRC will, just like for gastric cancer, dramatically improve 5-year survival rates. In the Netherlands, 5-year survival for early stage CRC is 97%, compared to 19% for late stage CRC (24). This underscores the importance of detecting CRC in the earliest stage as possible. Furthermore, by removal of the premalignant lesions, polyps, CRC development can be prevented.

For this reason, screening programmes are being implemented worldwide (25). In the Netherlands, a biannual faecal immunochemical test (FIT) is offered to individuals aged between 55 and 75 years of age. If tested positive, a subsequent colonoscopy is performed.

In the first year of the national screening programme a total of 2,483 cancers and 12,030 advanced adenomas were detected (26). Data on subsequent rounds hereafter showed consistent diagnostic yield and participation rates (27). There are multiple ways to perform population CRC screening which inherit a large set of variables that could influence the performance of a programme as such. This thesis will provide more insights on this topic by discussing screening target groups, influence of medication use on FIT performance and the use of innovative imaging modalities such as the video capsule (**Part III**).

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CHAPTER 1.2

Aims and outline of this thesis

This thesis is divided into four parts. **Part I** contains an introduction on this thesis. **Chapter 1.1** provides a general introduction on the topic. **Chapter 1.2** describes the aims and outline of this thesis.

Part II of this thesis specifically focuses on gastric premalignant lesions and surveillance strategies. **Chapter 2** provides an overview of recent advances within the detection and management of (pre-) malignant gastric lesions. In **Chapter 3**, we evaluate current European guidelines for the surveillance of premalignant gastric lesions. Through our ongoing prospectively followed cohort, we were able to assess clinical outcome of individuals that were discharged from further surveillance according to guidelines, but received more stringent follow up within the scope of our study.

Especially for low endemic regions it is important to focus on proper risk stratification when identifying the proportion of patients that will truly benefit from surveillance. **Chapter 4** shows a risk stratification that distinguishes between progressors and non-progressors of gastric intestinal metaplasia, using patient baseline characteristics, serological markers and genetic data.

Not only patient factors are important when establishing a proper surveillance programme, also the choice of imaging modality and biopsy strategy play a significant role. **Chapter 5** contains the study protocol of an international, multicenter cohort study which compares the use of white light endoscopy and a random biopsy scheme with the use of narrow band imaging taking targeted biopsies. **Chapter 6** is the final chapter of Part II and links preventive strategies of the upper gastrointestinal (GI) tract with the lower GI tract. Non-invasive methods (the urea breath test, serology and faeces) for the diagnostics of an *Helicobacter pylori (H. pylori)* colonization were compared within one individual. Further, a "proof of concept" was performed to determine *H. pylori* antigen in the faecal immunochemical test (FIT) that is used within the Dutch CRC screening programme.

Part III of this thesis contains studies on CRC and the optimisation of screening. Insights on the prevalence of gastrointestinal (GI) diseases in the general population is important. **Chapter 7** contains a large prospective study on prevalence rates of any lesions found in the entire GI tract within a general population using a colon capsule endoscopy (CCE). This study provides a frame of reference for prevalence rates of GI diseases in general. **Chapter 8** focuses on age-related colorectal cancer incidence and mortality throughout Europe with the use of data registries of over 20 countries. To provide more insights on the aetiology of this age-related colorectal cancer, **chapter 9** zooms in on pathophysiological differences in colorectal tumours at different ages.

Most countries have already implemented a colorectal cancer screening programme consisting of faecal blood testing with the faecal immunochemical test (FIT) and a subsequent colonoscopy when needed. It is important to investigate alternatives for colonoscopy in order to further improve participation rate and to carry the burden of increasing colonoscopy capacity. Therefore, **chapter 10** provides a systematic review that elaborates on the role of the colon capsule endoscopy within CRC screening.

Further, the use of certain medication might influence accuracy of FIT screening and therefore could ask for individualised strategies to optimise screening. Within this scope, **chapter 11** is a systematic review and meta-analysis evaluating the effect of oral anticoagulants and non-steroidal anti-inflammatory drugs (NSAIDs) on accuracy of FIT within CRC screening.

Part IV contains the general summary of this thesis. **Chapter 12** contains a general discussion and future perspectives derived from this thesis.

PART II

Premalignant lesions of the stomach & surveillance

Chapter 2
Recent advances in the detection and management of early gastric cancer and its precursors

Chapter 3
Accuracy of upper endoscopies with random biopsies to identify patients with gastric premalignant lesions who can safely be exempt from surveillance

Chapter 4
Factors associated with the progression of gastric intestinal metaplasia: a multicenter, prospective cohort study

Chapter 5
Accuracy of endoscopic staging and targeted biopsies for routine gastric intestinal metaplasia and gastric atrophy evaluation, study protocol of a prospective, cohort study – the ESTIMATE study

Chapter 6
Accuracy of H. pylori faecal antigen test using faecal immunochemical test (FIT)

CHAPTER 2

Recent advances in the detection and management of early gastric cancer and its precursors

Nieuwenburg SAV*, Waddingham W*, Carslon S, Rodriguez-Justo M, Spaander MCW, Kuipers EJ, Jansen M, Graham DG, Banks M

Frontline Gastroenterology, July 2020

Abstract

Despite declines in incidence, gastric cancer remains a disease with a poor prognosis and limited treatment options due to its often late stage of diagnosis. In contrast, early gastric cancer has a good to excellent prognosis, with 5-year survival rates as high as 92.6% after endoscopic resection. There remains an East-West divide for this disease, with high incidence countries such as Japan seeing earlier diagnoses and reduced mortality, in part thanks to the success of a national screening programme. With missed cancers still prevalent at upper endoscopy in the West, and variable approaches to assessment of the high-risk stomach, the quality of endoscopy we provide must be a focus for improvement, with particular attention paid to the minority of patients at increased cancer risk. High-definition endoscopy with virtual chromoendoscopy is superior to white light endoscopy alone. These enhanced imaging modalities allow the experienced endoscopist to accurately and robustly detect high-risk lesions in the stomach. An endoscopy-led staging strategy would mean biopsies could be targeted to histologically confirm the endoscopic impression of premalignant lesions including atrophic gastritis, gastric intestinal metaplasia, dysplasia and early cancer. This approach to quality improvement will reduce missed diagnoses and, combined with the latest endoscopic resection techniques performed at expert centres, will improve early detection and ultimately patient outcomes. In this review, we outline the latest evidence relating to diagnosis, staging and treatment of early gastric cancer and its precursor lesions.

Introduction

Detection and management of gastric cancer (GC) and its precursors remain a challenge that warrants attention, and recent guidelines support an effort to make our approach in low to intermediate incidence Western countries more standardised (1, 2). Despite declining incidence, gastric adenocarcinoma is still the fifth most common cause of cancer-related death worldwide, accounting for 8.2% of all cancer deaths (3). In the UK, roughly 6700 new cases are diagnosed each year (4). Prognosis remains poor with UK 5-year survival rates of 20.9%, and late stage of diagnosis limits treatment options in a large proportion (46%–57% with stage 4 at diagnosis) (5). Early gastric cancer (EGC), however, has a good prognosis with a 5-year survival rate of between 69% and 82%, demonstrating the importance of early diagnosis and treatment (6). Importantly, a recent study showed that the incidence of non-cardia gastric adenocarcinoma is increasing among young Caucasians in the USA, and an increasing trend of atrophic gastritis in young adults has been described in Sweden (7, 8). These data suggest that the decline in GC incidence over the past decades may be less certain in the future.

The endoscopist's approach to upper endoscopy is a major factor in determining the success of early detection. A recent meta-analysis including 22 studies estimated a rate of missed GC at endoscopy of 9.4% (9). A nationwide GC screening programme in Japan contributes to earlier stage of diagnosis and with that a superior 5-year survival (10, 11). These studies highlight the need for improved strategies to establish early diagnosis and show that the quality of diagnostic upper gastrointestinal (GI) endoscopy for the detection of neoplasia should be a target for quality improvement. Recent British Society of Gastroenterology (BSG) quality standards (2) and newly published 2019 BSG guidelines on the diagnosis and management of patients at risk of gastric adenocarcinoma (12) both address this. There is, however, a dearth of evidence supporting GC screening in intermediate-risk and low-risk countries. Although it has been suggested that screening programmes in intermediate-risk European countries could be cost-effective if combined with a scheduled colonoscopy (13) or targeted to high- risk ethnic groups (14).

Progression to (non-cardia) gastric adenocarcinoma, in the context of Helicobacter pylori-related chronic inflammation, results in pre-neoplastic transformation of the entire mucosal surface. The rugal folds and large surface area of the stomach make identification and demarcation of early premalignant lesions more challenging than in the oesophagus and colon. The time and attention endoscopists currently devote to early detection in the stomach remain far outweighed by our approach to adenoma detection in the colon. In the stomach, chronic atrophic gastritis (CAG) and gastric intestinal metaplasia (GIM) are the two main precursors that precede the development of neoplasia. Currently, the diagnosis and risk stratification of CAG and GIM are dependent on histopathology.

However, improvements in advanced endoscopic imaging techniques, and an increasing body of evidence suggest enhanced imaging or virtual chromoendoscopy, can be used to reliably and accurately identify premalignant changes and indeed EGC. A shift towards an endoscopy-led staging approach in the stomach may facilitate more robust assessment to allow a more accurate and tailored approach to cancer surveillance and early detection for high-risk individuals (15). The advances in therapeutics in endoscopy including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have transformed the management of EGC. ESD has become the technique of choice and is now the gold standard given its high en bloc resection rates, lower local recurrence and excellent 5-year survival rates as high as 92.6%. (16, 17) In this review, we outline the recent advances and recommended approach to endoscopic diagnosis and treatment of EGC and its precursor lesions.

Risk factors for premalignant gastric lesions and EGC

The majority of GCs are sporadic, however, 1%–3% arise in the setting of familial cancer predisposition, including hereditary diffuse GC. This is associated with a germline mutation in the E-cadherin gene (CDH1) and an 80% lifetime cancer risk. Detailed guidelines describing clinical management of rarer hereditary subtypes can be found elsewhere (18). There are several risk factors that endoscopists should consider to assess a patient's risk of CAG, GIM and EGC. The role of H. pylori in gastric carcinogenesis is long recognised (19) with the accepted Correa cascade describing a linear progression from chronic inflammation to atrophic gastritis, intestinal metaplasia and finally neoplasia. Serological studies suggest an underestimation of the association of H. pylori with CAG due to clearance of the infection in advanced stages of CAG (20). Patients with a history of H. pylori infection therefore warrant an additional degree of suspicion and mucosal inspection. Epstein–Barr virus (EBV) may play a role in the pathogenesis of a subset of gastric adenocarcinoma (up to 9%) that are molecularly distinct (21) however, EBV does not lead to an endoscopically detectable precursor.

Both CAG and GIM have a higher incidence in those with a family history of GC (22, 23) Pernicious anaemia is associated with a higher risk of CAG and GIM. A recent meta-analysis of 27 studies estimated the overall relative risk in pernicious anaemia was 6.8 (95% CI 2.6 to 18.1) (24). Advancing age is an important risk factor for gastric premalignant lesions and progression to GC. Three studies showed that patients over 45 years have an increased risk of neoplastic progression (OR 1.92– 3.1) (25–27). Multiple studies have demonstrated increased risk of CAG and GIM in male smokers (25, 28–30) and those with a high salt diet (31). In The Netherlands, a low incidence country, a study including patients with CAG and/or GIM diagnosed at histopathology described annual incidences of GC of 0.1% and 0.25%, respectively (32). Furthermore, ethnicity and geographic location appear to

influence GIM-related and CAG-related cancer risk. A systematic review found higher GC incidence related to CAG and GIM in East Asian countries (33), while a study in the USA showed a sustained increased risk of GC in East Asian immigrants (34). The histological subtype of incomplete GIM may confer a higher risk of cancer progression (35), however, GIM is not routinely subtyped by all pathologists and further studies are warranted to establish this as an additional risk marker.

Assessing cancer risk of premalignant lesions

Japanese data show that the grade and severity of atrophic gastritis are predictive of GC risk (36). However, a recent Dutch study examining surveillance in a low incidence population found that risk stratification based on biopsies alone (antrum and corpus) did not discriminate progression rate; in the low-risk group, 1 out of 86 patients developed invasive cancer compared with 2 out of 125 in the high-risk group. However, combining serology and histopathology did adequately discriminate progression risk with no patients categorised as low risk developing high-grade dysplasia (HGD) or neoplasia during follow-up (37). The histological Operative Link for Gastritis Assessment (OLGA) and Operative Link on Gastric Intestinal Metaplasia (OLGIM) systems have been advocated for staging gastritis (38, 39). While higher stages of CAG and GIM by these methods (stages III and IV) are predictive of increased GC risk, current histopathologic staging methods to risk stratify these patients are all fraught with significant limitations and poor interobserver and intraobserver reproducibility (40). This may explain widely varying estimates of risk between studies.

By contrast, longitudinal studies suggest that endoscopic staging of CAG with the Kimura–Takemoto classification system (41) is a useful stratification tool to predict GC risk (36, 42). This system classifies CAG into six endoscopic stages according to the location of the atrophic border. A simplified, modified Kimura–Takemoto classification is depicted in **figure 1D,E** (43). This modified system resulted in a complete concordance between endoscopic and histological assessment of 69.8% with good reproducibility (weighted kappa of 0.76 (95% CI 0.71 to 0.80)) (43). The Endoscopic Grading of Gastric Intestinal Metaplasia (EGGIM) score is an alternative means for staging the stomach based on the presence of GIM; this relies on enhanced imaging assessment of all five areas of the stomach to score each for the presence of GIM (<30% or>30% of mucosal surface), with targeted biopsies taken to confirm the endoscopic impression. A recent validation study compared the EGGIM score with the histological OLGIM score and suggested that such an endoscopic staging system may be clinically efficacious (44). We strongly advocate a move towards a simplified endoscopic risk stratification system that fits within the constraints of routine (Western) clinical practice to facilitate an endoscopy-led staging paradigm to robustly predict cancer risk in the chronically inflamed stomach.

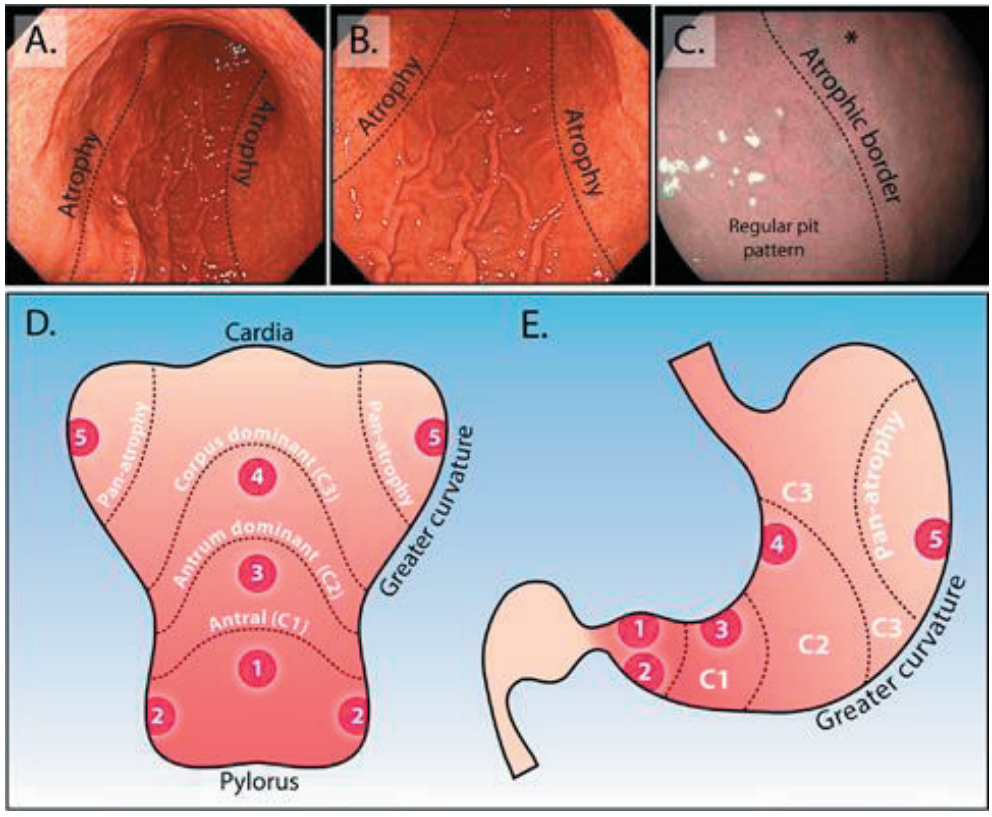

Figure 1. Endoscopic appearance of the atrophic border and modified Kimura–Takemoto classification system. (A and B) Low power view of atrophic gastritis at white light endoscopy. The abrupt transition at the atrophic border is clearly seen (dotted line) with loss of rugal folds, mucosal pallor and increased visibility of vessels. In this example, the atrophic border is located at the transition between the lesser and greater curve. Using the modified Kimura–Takemoto scoring system (45) this patient would be staged 'C3, corpus dominant atrophy'. (C) Appearance of the atrophic border at enhanced imaging (Olympus, NBI), to the right of the dotted line the normal body pit pattern is lost and the mucosa appears paler (asterisk). (D and E) Depicted is the stomach opened up along the greater curvature (D) and in traditional coronal view (E). This schematic representation demonstrates the modified Kimura–Takemoto classification system; antral (C1); antral predominant (C2); corpus predominant (C3) and panatrophy; numbers 1–5 correspond to the location of gastric biopsies, which should be taken according to the updated Sydney system: antrum greater and lesser curve, incisura, corpus greater and lesser curve (images taken from Waddingham et al (15).

Detection and staging of CAG, GIM and EGC

Non-invasive assessment: serology

The best evidenced serological tests for assessing GC risk are pepsinogens. Pepsinogens secreted by gastric chief cells are the inactive proenzymes of pepsin, with hydrochloric acid leading to their conversion to pepsin. Pepsinogen I is predominantly produced in the corpus, while pepsinogen II is produced from the antrum, cardia, fundus and duodenum.

As gastric atrophy progresses to the corpus, pepsinogen I is reduced relative to pepsinogen II. Therefore, a low pepsinogen I, pepsinogen I/II ratio or both are good indicators of functional atrophy. There are several studies evaluating its use in identifying patients with extensive atrophic gastritis and GC. Most recently, a 2015 meta-analysis (45) suggested a good correlation between reduced pepsinogens and presence of gastric atrophy. The summary sensitivity and specificity for GC diagnosis were 0.69 (95% CI 0.60 to 0.76) and 0.73 (95% CI 0.62 to 0.82), respectively; corresponding values for atrophic gastritis diagnosis were 0.69 (95% CI 0.55 to 0.80) and 0.88 (95% CI 0.77 to 0.94), respectively. There were issues with study heterogeneity and varying serum cut-offs (most used pepsinogen I <70 ng/mL and pepsinogen I/II ratio <3). An American cost-effectiveness study found that one time pepsinogen screening at age 50 years reduced the lifetime intestinal-type non-cardia GC risk (0.24%) by 26.4%; however, this was not cost-effective unless targeted to current smokers (46). It is likely that these reasons, in addition to varying methods of laboratory serum analysis, have contributed to serological testing not being taken up in routine use in low-moderate incidence countries. Pepsinogens will likely have a future role for targeted screening of higher risk patients to identifying those who should then be offered an endoscopy.

Endoscopy

The ESGE (2016) (47) and BSG (2017) (2) have listed a number of principles in their recent statements on upper endoscopy. It is recommended that a complete oesophagogastroduodenoscopy should assess and photo-document all relevant anatomical landmarks and high-risk stations, and any detected lesions. Optimal mucosal visualisation is key and should be obtained through a combination of air insufflation, aspiration and the use of mucosal cleansing techniques (eg, sime- thicone, N-acetylcysteine or pronase). A minimum of 7 min procedure time for first diagnostic upper endoscopy and follow-up of GIM improves detection rates of high-risk gastric lesions and is considered a key performance measure (48).

Endoscopic features of CAG and GIM

As atrophy progresses, the gastric rugae are lost; this combined with mucosal pallor, and increased visibility of mucosal vessels, represents the main endoscopic features of CAG (49, 50). The atrophic border (**figure 1A–C**), identified as a line marking the junction of the paler atrophic mucosa and normal mucosa, which moves further proximally as the disease progresses, helps in the diagnosis of gastric atrophy and allows the endoscopist to appreciate the extent of atrophy.

With standard white light endoscopy (WLE), GIM usually appears as paler-white, elevated plaques, surrounded by patchy pink and pale areas of mucosa causing an irregular uneven surface (**figure 2**). Mottled patchy erythema has also been positively associated with GIM

(51), indeed, this could be thought to be a simple gastritis to the unwary endoscopist. Detection of GIM with standard WLE alone is of inferior accuracy compared with enhanced imaging (eg, NBI) (87% vs 53%; p<0.001)(52) and should therefore not be used as the sole endoscopic modality.

Image-enhanced endoscopy (eg, Olympus NBI, Pentax iScan, Fujinon intelligent chromo endoscopy (FICE)) allows more detailed characterisation of the mucosal architecture. With a number of studies suggesting that superior detection rates can be achieved for both CAG and GIM (53–56). In the stomach, as patches of GIM expand, the glands elongate to form a 'groove type pattern' similar to that of the antrum or villiform pattern of the intestine (**figure 2**). Although these changes can easily be distinguished from the normal corpus, GIM in the antrum is more difficult to characterise (49, 57). Additional features of GIM that can aid the endoscopic diagnosis in the antrum include the light blue crest (LBC) and the marginal turbid band (58, 59). Using narrow band imaging (**figure 2**) with magnifying endoscopy (NBI-ME), the LBC appears as a fine, blue- white line on the crest of the epithelial surface and is a highly accurate sign for the presence of intestinal metaplasia at histology (57–59). White opaque substance (lipid droplets) obscuring the subepithelial capillaries is another endoscopic finding associated with GIM (50).

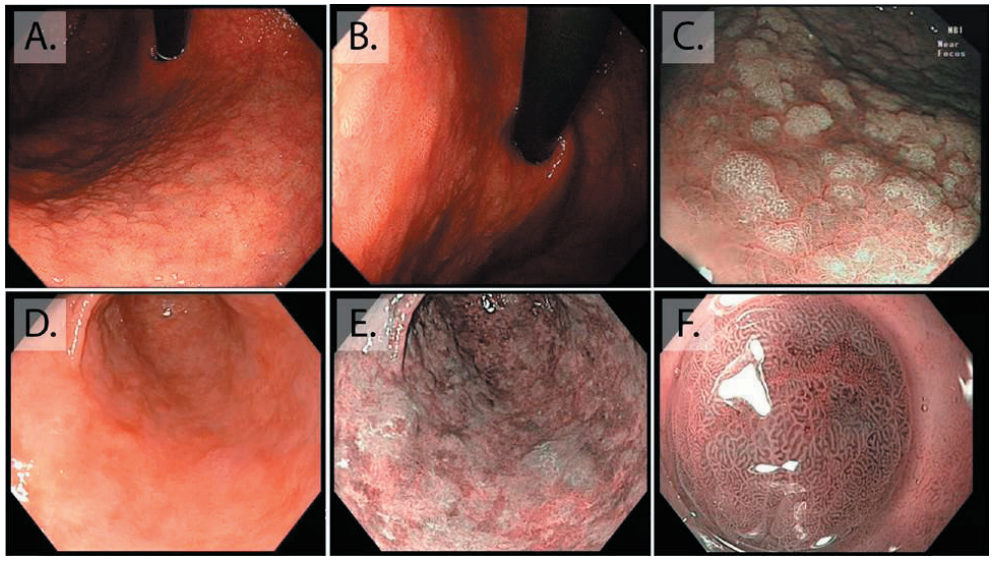

Figure 2. Endoscopic appearance of gastric intestinal metaplasia (GIM). (A and B) Macroscopic appearance of GIM at white light endoscopy, both are retroflexed views of the lesser curve, visible is the irregular uneven surface of GIM, with elongated groove type pit pattern. (C) At enhanced imaging (Olympus, NBI), this is visible as multiple paler elevated patches. (D and E) The difference between white light endoscopy and enhanced imaging in this stomach with extensive GIM seen as a patchwork of multiple paler, blueish patches on the background of atrophic gastritis, (F) magnification NBI allows visualisation of individual elongated metaplastic glands.

We recommend endoscopists to routinely use enhanced imaging to make an endoscopic assessment of both GIM and atrophy. These findings should be documented with their location and extent, including the simplified Kimura–Takemoto system (**figure 1D,E**) (normal; limited atrophy: antral (C1); antral predominant (C2); and extended atrophy: corpus predominant (C3) and panatrophy) and finally, obtain targeted biopsies from areas endoscopically suspicious for GIM in areas of the updated Sydney protocol (15).

Detection of neoplasia

High-definition endoscopy with enhanced imaging is also superior for the detection of dysplasia and early cancer. Changes in the mucosa that suggest neoplasia include irregular vessels and glands, as lesions progress this can lead to complete loss of glands and the normal mucosal and vascular pattern (**figure 3**). These appearances warrant photo-documentation and targeted biopsy sampling. It should be borne in mind that up to 25% of low-grade dysplasia (LGD) is upstaged after endoscopic resection.

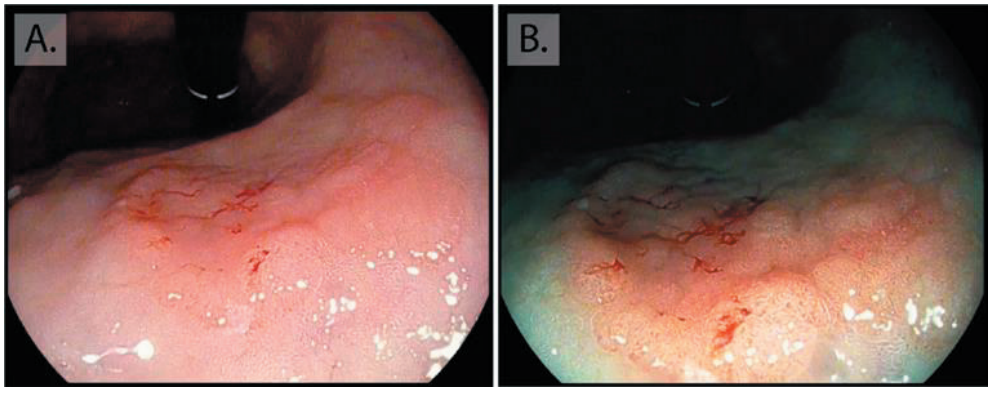

Figure 3. Early gastric cancer. Intramucosal cancer located in the inferior body of the stomach. Although visible at white light endoscopy (A) with nodularity, rolled edges and central depression, the lesion is more clearly demarcated with enhanced imaging (Pentax, OE) (B), showing a greater contrast of the erythematous neoplastic mucosa, irregularity in the mucosal pit pattern and loss of normal gland architecture.

LGD lesions larger than 2 cm and those with mucosal nodularity or depression all have a higher risk of upstaging (60). Non-healing gastric ulcers are also a feature of neoplasia and malignancy, and multiple biopsies should be taken from the ulcer edge for confirmation, preferably targeted to areas of abnormal mucosa with irregular vascular and mucosal patterns. NBI-ME combined with conventional WLE yields a higher accuracy for detection of depressed EGCs (median 64.8%–96.6%, $p<0.001$) (61). A 2016 meta-analysis confirmed that NBI-ME had a very high diagnostic efficacy for diagnosing early gastric adenocarcinoma (pooled sensitivity 0.83 (95% CI 0.79 to 0.87; I2=79.8%), pooled specificity 0.96 (95% CI 0.95 to 0.97; I2=89.3%)), this outperformed WLE although comparison was

limited by study heterogeneity (62). Combining autofluorescence imaging with NBI has also shown very high sensitivity and specificity for dysplasia (83.33% and 98.51%) and EGC (90.91% and 99.22%) (63). Other modalities that improve detection include blue laser imaging-bright; a Japanese randomised control trial showed that this was superior to WLE for real-time detection of EGC. Despite the high diagnostic advantage these imaging modalities afford, the majority are not widely available in Western centres and the endoscopist should therefore be advised during assessment of high-risk patients to use a combination of HD-WLE and enhanced imaging (eg, Olympus NBI, Pentax iScan or FICE) where magnification is available this can supplement the approach. The presence of atrophy and GIM should alert the endoscopist to an increased likelihood of neoplasia, initiating a more thorough mucosal assessment.

Biopsy strategies

At first endoscopy, assessment of the high-risk stomach should include biopsies to assess for H. pylori and to stage the extent of atrophic gastritis (1). The recent 2019 BSG guidelines (12) on diagnosis and management of patients at risk of GC recommend that patients with image-enhanced features of CAG should undergo biopsies for confirmation of endoscopic diagnosis. Biopsies should be directed at sites within Sydney protocol areas where enhanced imaging suggests GIM. Biopsy samples should be collected in separate containers and labelled as either 'directed' or 'random' to corroborate endoscopic staging Updated 2019 guidelines from the ESGE stipulate biopsies from at least two sites (antrum and corpus, lesser and greater curvature for each) (1). Additionally, where enhanced imaging is available and with the appropriate expertise, targeted biopsies to visible mucosal abnormalities should also be taken. There is evidence that taking an incisural biopsy may increase the proportion of patients diagnosed with higher-risk gastritis (OLGA III/IV or OLGIM III/IV) (64, 65) this also facilitates histopathological staging with the OLGA or OLGIM, which correlate with cancer risk (39, 66, 67). Random sampling carries a significant risk of sampling error leading to inaccurate and potentially missed diagnoses; therefore, the highest yield for advanced gastritis and early neoplasia is currently with a combination of random mapping biopsies plus targeted biopsies with enhanced imaging. A drive to improve clinicians' confidence in the recognition of mucosal patterns of the stomach, as has been the case for colonic polyp classification, would enable a move towards an endoscopy-led staging protocol where biopsies are taken for confirmatory purposes or to exclude H. pylori and neoplasia.

Surveillance

CAG and GIM

Recently updated European Society of Gastrointestinal Endoscopy (ESGE MAPS 2) guidelines (1, 68) and new BSG guidelines on patients at risk of gastric adenocarcinoma (12) recommend 3 yearly surveillance for patients with extensive CAG or GIM, that is, that affecting antrum and corpus (**figure 4**). Although the majority of GC is sporadic, 10% show familial aggregation. Those with a family history have an additionally increased cancer progression risk, an affected first-degree relative is associated with a relative risk of 1.8–3.5 (69). Therefore, in cases with extensive CAG or GIM and a family history, these patients should be considered for more intensive surveillance every 1–2 years, while patients with a family history and CAG or GIM limited to one area of the stomach may be counselled for the benefits of surveillance every 3 years (**table 1**). Carcinoma in the gastric remnant of patients who have had previous surgery for benign disease (eg, peptic ulcer disease) is rare, there are currently no consensus guidelines for this patient group; however, patients are often recommended endoscopy at 15 years post-surgery, additionally if they are known to have mucosal abnormalities such as CAG or GIM they should also be considered for surveillance on an individual basis.

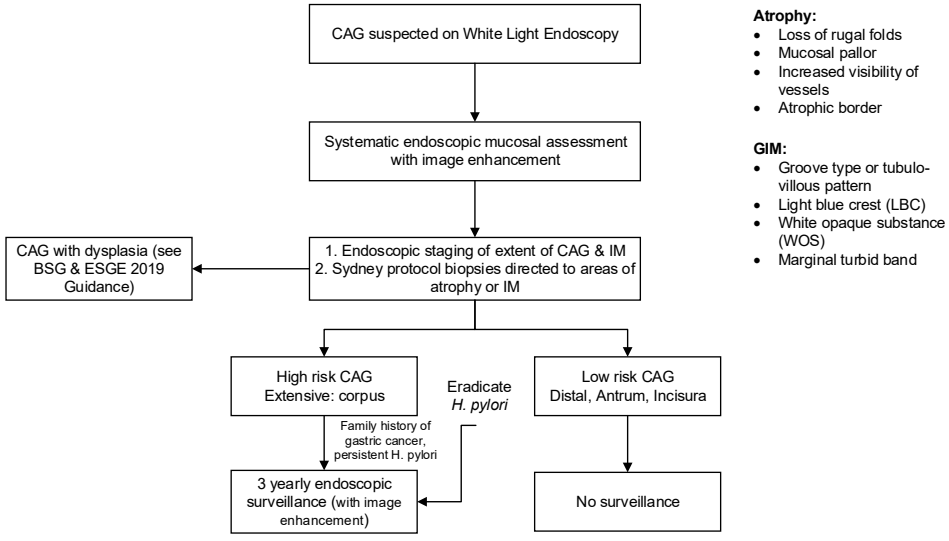

Figure 4. Flowchart of management of atrophic gastritis. Adapted from BSG Guidelines 2019 (12)
BSG; British Society of Gastroenterology, CAG: Chronic Atrophic Gastritis, ESGE; European Society of Gastrointestinal Endoscopy, GIM: Gastric Intestinal Metaplasia

Table 1. Summary of relevant updated guideline recommendations for diagnosis and surveillance of precancerous conditions of the stomach

Guidelines	Year	Summary of recommendations
BSG guidelines on the diagnosis management of patients at risk of gastric adenocarcinoma.[12]	2019	**Diagnosis and staging** • 'Patients at higher risk for gastric adenocarcinoma, including GA and GIM, systematic endoscopy of the stomach with clear photo-documentation of gastric pathology. We suggest a minimum examination time of 7 min. (*evidence level: moderate quality; grade of recommendation: strong; level of agreement: 100%*) • 'Patients with image-enhanced features of CAG should undergo biopsies for confirmation of endoscopic diagnosis; biopsies are directed at mucosal sites within Sydney protocol areas where enhanced imaging discloses GIM. Biopsy samples should be collected in separate containers and labelled as either 'directed' or 'random' to corroborate endoscopic staging assessment.' (*evidence level: low quality; grade of recommendation: strong; level of agreement: 93%*) **Surveillance** • 'Endoscopic surveillance every 3 years should be offered to patients diagnosed with extensive CAG or GIM, defined as that affecting the antrum and body.' (*evidence level: low quality; grade of recommendation: strong; level of agreement: 100%*). • 'We do not recommend surveillance in patients with GA or GIM limited just to the gastric antrum unless there are additional risk factors, such as a strong family history of gastric cancer or persistent H. pylori infection, then we suggest 3 yearly surveillance.' (*evidence level: low quality; grade of recommendation: strong; level of agreement: 93%*)
Management of epithelial precancerous conditions and lesions in the stomach (MAPS 2) update; ESGE.[1]	2019	**Diagnosis and staging** • 'high definition endoscopy with chromoendoscopy (CE) is better than high light endoscopy alone for the diagnosis of gastric precancerous conditions and lesions.'(*high quality evidence*) • 'For adequate staging of gastric precancerous conditions, a first time diagnostic upper gastrointestinal endoscopy should include gastric biopsies both for Helicobacter pylori infection diagnosis and for identification of advanced stages of atrophic gastritis'. (*moderate quality evidence, strong recommendation*) • 'Biopsies of at least two topographic sites (from both the antrum and the corpus, at the lesser and greater curvature of each) should be taken and clearly labelled in two separate vials. Additional biopsies of visible neoplastic suspicious lesions should be taken.' (*moderate quality evidence, strong recommendation*) • 'Systems for histopathological staging (eg, Operative Link on Gastritis Assessment (OLGA) and Operative Link on Gastric Intestinal Metaplasia (OLGIM) assessment) can be used to identify patients with advanced stages of gastritis. If these systems are used to stratify patients, additional biopsy of the incisura should be considered.' (*moderate quality evidence, weak recommendation*) **Surveillance** • 'In patients with IM at a single locations with a family history of gastric cancer, or with incomplete IM, or persistent H. pylori gastritis, endoscopic surveillance with CE and guided biopsies in 3 years' time may be considered.' (*low quality evidence, weak recommendation*) • 'Patients with advanced stages of atrophic gastritis (severe atrophic changes or intestinal metaplasia in both antrum and corpus, OLGA/OLGIM III/IV) should be followed up with a high-quality endoscopy every 3 years.' (*low quality evidence, strong recommendation*) • 'Patients with advanced stages of atrophic gastritis and with a family history of gastric cancer may benefit from a more intensive follow-up (eg, every 1-2 years).' (*low quality evidence, weak recommendation*)

Autoimmune gastritis

There is some evidence that patients with autoimmune gastritis have an increased risk of GC and may therefore benefit from endoscopic surveillance. At present, there is no clearly defined follow-up interval. Screening endoscopy at the time of diagnosis is important to secure the diagnosis but also for estimating risk as this may be the period of greatest excess cancer risk (1). The 2019 updated ESGE MAPS 2 guidelines recommend that patients may benefit from endoscopic follow-up every 3–5 years, however, this was a weak recommendation based on low-quality evidence.

Dysplasia

Patients with any evidence of dysplasia should be assessed at a specialist centre with expertise in enhanced imaging assessment. All visible dysplastic lesions should be resected where possible. If there is no endoscopically visible lesion, a repeat enhanced imaging endoscopy should be performed in 6 months for HGD and 6–12 months for LGD (1). Revision of pathology slides by a GI pathologist with special expertise should be considered, especially in the scenario where no lesion is visible after a high-quality endoscopy. Post endoscopic resection for neoplasia, patients should remain under yearly surveillance as long as this remains clinically appropriate.

Treatment of neoplasia

H. pylori eradication

Eradication of H. pylori heals non-atrophic chronic gastritis, may lead to regression of atrophic gastritis and reduces the risk of GC in patients with these conditions and is therefore recommended (1). H. pylori eradication is also recommended for patients with neoplasia after endoscopic therapy. Although there is some contradicting evidence for eradication in this setting, two meta-analyses analysing 10 studies (eight non- randomised, two randomised) (70, 71) and a more recent meta-analysis analysing 17 studies reached the same conclusion that H. pylori eradication reduces the risk of metachronous cancer; the most recent study found a 50% lower odds of metachronous events (RR=0.50; 95 % CI 0.41 to 0.61) (72). Subsequent to these meta-analyses, a 2018 study from South Korea, performed in a prospective, double-blind, placebo-controlled, randomised manner; again confirmed that H. pylori eradication after endoscopic resection for EGC lead to reduced rates of metachronous cancer (HR in the treatment group, 0.50; 95% CI 0.26 to 0.94; p=0.03) and a better chance of improvement in histological grades of atrophy (15% in placebo vs 48.4% in treatment group, p<0.001) (73).

Endoscopic therapy

The MDT plays a vital role in deciding on management of gastric neoplasia, facilitating decisions involving endoscopists, pathologists and surgeons, in centres with appropriate

expertise. There is no role for endoscopic therapy in the setting of CAG or GIM; however, guidelines state that all visible gastric neoplasia should be resected in an en bloc fashion (74). This is in contrast to Barrett's oesophagus where eradication of residual Barrett's after treatment of neoplasia is recommended to reduce the risk of metachronous neoplasia. In the stomach, an ablative approach to eradicate GIM is currently neither practical nor has evidence to support it. Surveillance rather than resection for visible HGD or LGD should only be chosen if it is the patient's preference or the risk of resection is felt to not be justifiable due to the patient's comorbidities. ESD is the preferred technique for endoscopic resection (**figure 5**). Prior to performing endoscopic resection, a high-quality endoscopy should be performed with contrast or digital chromoendoscopy, by an experienced endoscopist to assess suitability (ESGE Guidelines 2015) (74). ESD achieves significantly higher en bloc resection with lower recurrence rates than EMR and is therefore recommended by both Japanese and Western guidelines for treatment of superficial gastric neoplasia (low-grade or high- grade non-invasive neoplasia, adenocarcinoma with no evidence of deep submucosal invasion).

The standard indication for endoscopic resection of gastric dysplasia and invasive cancer includes the following criteria:

- Low-grade dysplasia.
- High-grade dysplasia.
- Well or moderately differentiated intramucosal adenocarcinoma, irrespective of size and without ulceration.
- Well or moderately differentiated intramucosal adenocarcinoma, <3.0 cm in size if ulcerated.
- Well or moderately differentiated submucosal adenocarcinoma, <3.0 cm in size, with superficial submucosal invasion (Sm1; <500 micron submucosal invasion as measured in a vertical line from the deepest fibre of the muscularis mucosae).
- Poorly differentiated intramucosal adenocarcinoma, ≤2.0 cm in size

Lesions endoscopically resected with these pathological features should be considered to have been curatively treated.

Conclusion

An awareness of higher risk patient groups combined with reliable endoscopic diagnosis and accurate assessment of the chronically inflamed stomach is essential to the early detection and successful treatment of GC. Careful mucosal examination using a combination of high-definition WLE and enhanced imaging (eg, NBI, iScan, FICE and magnification where available) should be carried out for high-risk patients. Where

endoscopic signs of CAG and/or GIM are present, a combination of random mapping biopsies in the areas of the Sydney protocol and biopsies targeted with enhanced imaging provides the best chance of accurate staging and risk assessment. Gastric neoplasia should be managed by referral centres with expertise in enhanced imaging endoscopy and endoscopic resection for early cancers. Further research is needed to define the feasibility and reproducibility of an endoscopy-led staging paradigm for the premalignant stomach. This approach would help tackle the challenge of early detection, allowing more accurate risk assessment, while reducing the biopsy burden placed on patients under surveillance and on pathology services.

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CHAPTER 3

Accuracy of upper endoscopies with random biopsies to identify patients with gastric premalignant lesions who can safely be exempt from surveillance

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Gastric Cancer, May 2021

Abstract

Introduction

Guidelines recommend endoscopy with biopsies to stratify patients with gastric premalignant lesions (GPL) to high and low progression risk. High-risk patients are recommended to undergo surveillance. We aimed to assess the accuracy of guideline recommendations to identify low-risk patients, who can safely be discharged from surveillance.

Methods

This study includes patients with GPL. Patients underwent at least two endoscopies with an interval of 1–6 years. Patients were defined 'low risk' if they fulfilled requirements for discharge, and 'high risk' if they fulfilled requirements for surveillance, according to European guidelines (MAPS-2012, updated MAPS - 2019, BSG). Patients defined 'low risk' with progression of disease during follow-up (FU) were considered 'misclassified' as low risk.

Results

334 patients (median age 60 years IQR11; 48.7% male) were included and followed for a median of 48 months. At baseline, 181/334 (54%) patients were defined low risk. Of these, 32.6% were 'misclassified', showing progression of disease during FU. If MAPS-2019 were followed, 169/334 (51%) patients were defined low risk, of which 32.5% were 'misclassified'. If BSG were followed, 174/334 (51%) patients were defined low risk, of which 32.2% were 'misclassified'. Seven patients developed gastric cancer (GC) or dysplasia, four patients were 'misclassified' based on MAPS-2012 and three on MAPS-2019 and BSG. By performing one additional endoscopy 72.9% (95% CI 62.4–83.3) of high-risk patients and all patients who developed GC or dysplasia were identified.

Conclusion

One-third of patients that would have been discharged from GC surveillance, appeared to be 'misclassified' as low risk. One additional endoscopy will reduce this risk by 70%.

Introduction

Prognosis of advanced gastric cancer is poor, with a five-year-survival rate of 20% (1). However, if gastric cancer is detected at an early stage, survival rates improve up to 90% (2, 3). Chronic atrophic gastritis (CAG) and intestinal metaplasia (IM) are precursor lesions of gastric adenocarcinoma (GC) (4). These premalignant lesions make gastric cancer suitable for screening and surveillance, depending on the regional prevalence of (pre-)malignant lesions and progression rates to cancer. Nationwide screening strategies are mainly relevant for high-GC prevalence regions such as East-Asia, where population-based screening programs are implemented (5). In case advanced premalignant lesions are detected, patients are eligible for surveillance and early intervention when possible (6). For regions with low prevalence rates, such as Western Europe and North America, nationwide screening is not recommended due to a low a priori risk. However, when patients of these regions are inadvertently diagnosed with advanced premalignant lesions, for instance, during routine endoscopy, surveillance should be considered given the risk of progression to cancer. The debate about the balance between harms and benefits of surveillance strategies is still ongoing (7). To this end, US guidelines state that surveillance is not indicated except for individuals with a known increased gastric cancer risk, such as persons of Asian ancestry or patients with a positive family history (8). European MAPS (management of epithelial precancerous conditions and lesions in the stomach) as well as the British guidelines, recommend surveillance in patients with a premalignant gastric lesion (9– 11). These surveillance recommendations depend on the extent and severity of these premalignant lesions. The MAPS- 2012 guideline recommended surveillance for patients with extensive CAG or IM. In the updated MAPS-2019 guideline, surveillance was extended to patients with CAG and IM limited to either the antrum or the corpus and presence of incomplete intestinal metaplasia (in any of the biopsies), autoimmune gastritis, persistent Helicobacter pylori (H. pylori) infection or a first degree relative with gastric cancer. In 2019, the British Society of Gastroenterology also published a guideline (BSG) on the management of gastric premalignant lesions. The recommendations on surveillance of premalignant lesions were mostly identical to the revised MAPS-2019 guideline. The only difference with the MAPS guideline is that patients with autoimmune gastritis and CAG or IM limited to the antrum or corpus were not referred for further surveillance. To assess the extent and severity of premalignant gastric lesions, endoscopic surveillance is advised. However, endoscopic recognition of gastric premalignant lesions can be difficult. Therefore, obtaining random biopsies throughout the stomach according to the updated Sydney protocol is recommended (12). Nevertheless, due to the uneven distribution of gastric premalignant lesions, random biopsies may not properly reflect the extent of the lesions and subsequently the individual gastric cancer risk (13). Since only a few patients will develop gastric cancer, it is essential that surveillance strategies in practice lead to the identification of those few cases. While the addition of new risk factors to the MAPS-2019 and BSG potentially allows better stratification of at-risk

patients, thus far, there is only limited data describing to what extent we can accurately dismiss patients with premalignant gastric lesions from surveillance, based on their low risk of gastric cancer development. The aim of this study was to assess to what extent we can accurately identify low-risk patients who can safely be discharged from gastric surveillance according to the recommendations of MAPS-2012, MAPS-2019 and BSG guideline.

Methods

Study design

This study is based on the Proregal study (Progression and Regression of precancerous Gastric Lesions). The design of the study has been described previously (14). In short, this study was initiated in 2009 and is an ongoing prospective cohort study carried out in six hospitals (one academic, five regional) in the Netherlands and one regional hospital in Norway. Patients are eligible for inclusion if they are over 18 years of age and diagnosed with one of the following conditions at routine endoscopy (t0): atrophic gastritis, intestinal metaplasia and/or dysplasia in any part of the gastric mucosa. Patients are excluded from participation if they have: (1) previously undergone upper gastrointestinal surgery, (2) a previous diagnosis of gastric carcinoma, or any other malignancy not being in remission, (3) severe comorbidity limiting their expected survival to less than 2 years, (4) portal hypertension, or (5) a proven CDH1 mutation. In case H. pylori was present, H. pylori eradication was provided, and eradication was verified in all patients (20 patients had persistent H. pylori colonization). H. pylori eradication was eventually achieved in all patients. In all subjects, a surveillance endoscopy is performed at one (t1) and three (t2) years after the initial endoscopy. Random biopsy samples are obtained according to the Proregal biopsy protocol with targeted biopsies in case of visible gastric lesions (**Figure 1**).

In case of low-grade dysplasia (LGD) or high-grade dysplasia (HGD), the surveillance interval is shortened to twelve and six months, respectively. In case a visible lesion is detected, endoscopic resection of the lesion is performed. After t2, continuation or cessation of surveillance is decided based on the recommendations of the MAPS guideline. For the purpose of this study, subjects who were discharged from further surveillance based on the MAPS guideline recommendation at t2 were re-invited for endoscopy (t3).

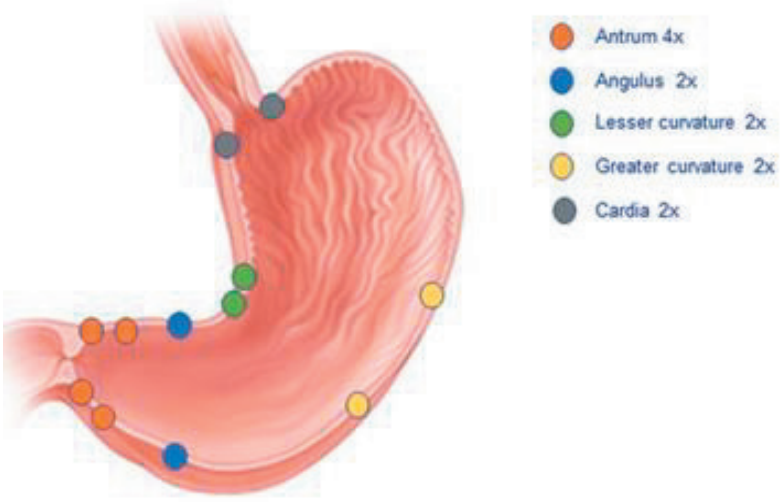

Figure 1. Locations of standardised random gastric biopsies obtained during endoscopy for this study

Patient selection

All patients from the Proregal cohort were eligible for inclusion provided patients had at least one follow-up endoscopy. Patients were classified as low or high risk. Low-risk patients were defined as patients with premalignant gastric lesions, who do not fulfil the requirements for surveillance (i.e. IM limited to the antrum). 'High risk' patients are patients with premalignant gastric lesions who are advised to undergo surveillance (i.e. IM in both antrum and corpus). Requirements for surveillance are described in more detail in **Supplementary Table 1**.

At baseline, patients were defined as 'low risk' for progression of disease if they fulfilled requirements for discharge based on the European guidelines MAPS-2012, MAPS-2019 or the BSG guideline. Patients were defined as 'high risk' if further surveillance was indicated according to these guidelines.

To assess the safety of discharging patients from further surveillance based on MAPS/BSG guideline recommendations, we included the 'low risk' patients who had no indication for further surveillance according to the guidelines at t1 or t2 (e.g. limited extension of IM), but underwent a surveillance endoscopy within the scope of this study. We correlated the findings with the outcome of the endoscopy performed at t2 and t3, respectively. In case lesions were found at the follow-up endoscopy for which surveillance is recommended, the patient was defined as 'misclassified' as low risk for gastric cancer development.

Furthermore, we linked all patients to the Netherlands Cancer Registry, managed by the Netherlands Comprehensive Cancer Organisation (IKNL) to account for all (interval) gastric cancers even after surveillance was stopped. Since 1989, the Netherlands Cancer Registry

registers all participants diagnosed with cancer in the Netherlands. The study design is depicted in **Figure 2**. The study protocol was approved by the Institutional Review Board (MEC-2009-090).

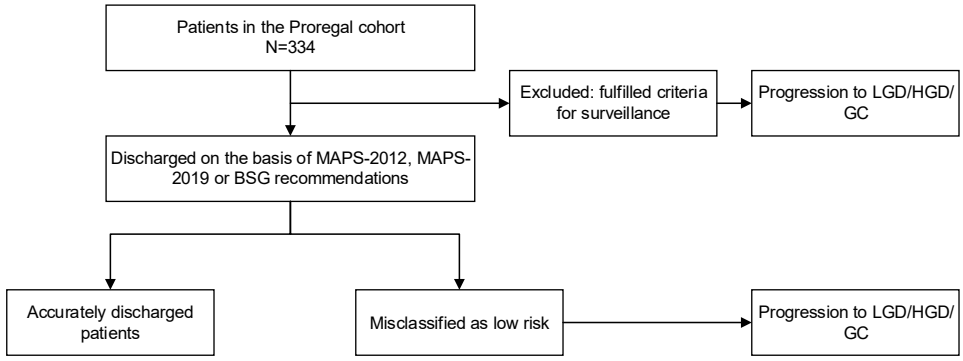

Figure 2. Flowchart of the study design. GC gastric cancer; HGD high-grade dysplasia; LGD low-grade dysplasia; MAPS management of precancerous conditions and lesions in the stomach; Proregal progression and regression of precancerous lesions

MAPS-2012

The MAPS guideline recommendations were first published in 2012 (9). Chronic atrophic gastritis (CAG) or intestinal metaplasia (IM) confined to the antrum did not require further surveillance. CAG or IM in both antrum and corpus or only in the corpus required endoscopic surveillance every three years (**Supplementary Table 1**).

MAPS-2019

The MAPS guideline recommendations were updated in 2019 (10). CAG or IM limited to the antrum or corpus does not require further surveillance. However, surveillance every three years is recommended if the subject meets one of the following criteria: first degree family history of gastric cancer, autoimmune gastritis, persistent H. pylori infection or incomplete IM (Table 1). Surveillance every 1–2 years is recommended in case of a first degree relative with GC (**Supplementary Table 1**).

BSG

The BSG guideline recommendations were published in 2019 (11). In this guideline, CAG or IM limited to the antrum or corpus does not require further surveillance. However, surveillance every three years is recommended if the subject meets one of the following criteria: first degree family history of gastric cancer or persistent H. pylori infection.

Statistical analyses

Baseline characteristics are presented as mean with standard deviation (SD) or median with interquartile range (IQR) when appropriate. Kaplan–Meier curves were performed

on the proportion of patients identified as still at risk after (supposed) discharge of surveillance per year and per endoscopy for MAPS-2012, MAPS-2019 and BSG guidelines. The analyses were performed using SPSS v.24 statistical package (SPSS Inc, Chicago, IL).

Results

Patient characteristics

In total, 334 patients were included. Median age was 60 years (IQR 11) and 48.7% were men. This cohort captured seven cases of dysplasia or gastric cancer. Baseline characteristics of the entire cohort are shown in **Table 1** and were described in more detail previously (14).

Following the MAPS-2012 guideline recommendation

At baseline, 153/334 (45.8%) patients were correctly defined as high risk (i.e. already fulfilled the criteria for surveillance according to the guideline) and therefore excluded. Of the remaining 181 low-risk patients (i.e. would have been discharged from further surveillance according to the guideline), 59 patients (32.6%) were misclassified as low risk because they had gastric lesions at subsequent endoscopies that gave reason to continue surveillance (i.e. gastric premalignant lesions not limited to the antrum) see also **Figure 3a**. This included four out of the total seven cases of LGD/HGD/gastric cancer cases. LGD was found in one patient, HGD was found in two patients, and one patient developed gastric cancer. One of the patients with HGD underwent endoscopic resection and died from causes unrelated to gastric cancer or the procedure. The other patient with HGD underwent a successful gastrectomy. The patient with gastric cancer and the patient with LGD underwent an endoscopic resection and are currently in remission for over two years. Patient characteristics of these cases are available in **Table 2**.

Table 1. Baseline characteristics of the total Proregal cohort. H. pylori Helicobacter pylori; IQR inter quartile range; GC gastric cancer; HGD high-grade dysplasia; LGD low-grade dysplasia; OLGIM operative link on gastric intestinal metaplasia assessment; Proregal cohort total number of the prospective cohort that are or have been under surveillance for their gastric premalignant lesions (31)

	Proregal cohort (n=334)
Gender (male, %)	48.7
Age (median, IQR)	60 (11)
Follow up months (median, IQR)	48 (24)
Most severe lesion recent endoscopy*	
OLGIM 0	123 (36)
OLGIM I	55 (16)
OLGIM II	81 (24)
OLGIM III	51 (15)
OLGIM IV	9 (3)
Lesions requiring treatment	
LGD	1
HGD	2
GC	4

Following the MAPS-2019 guideline recommendation

At baseline, 165/334 (49.4%) patients were correctly defined as high risk (i.e. already fulfilled the criteria for surveillance according to the guideline) and therefore excluded. Of the remaining 169 low-risk patients (i.e. would have been discharged from further surveillance according to the guideline), 55 patients (32.5%) were misclassified as low risk because they had gastric lesions at subsequent endoscopies that gave reason to continue surveillance (i.e. gastric pre-malignant lesions not limited to the antrum). This included three out of the total seven cases of LGD/HGD/gastric cancer (one case of LGD, HGD and gastric cancer each) see also **Figure 3b**. These patients were also misclassified by the MAPS-2012 guideline. The correctly classified patient with HGD (that was misclassified in MAPS-2012) was included for surveillance according to MAPS -2019 because of a first degree relative with gastric cancer. This patient had HGD, but declined further therapy due to comorbidities and age, although (endoscopic) resection might have been possible. Another patient with carcinoma who would have been discharged according to the extent of his lesions (limited to the corpus) was recommended to undergo surveillance according to the MAPS-2019 guideline, also because of a first degree relative with gastric cancer. Patient characteristics of these cases are depicted in **Table 2**.

Following the BSG guideline recommendation

At baseline, 160/334 (47.9%) patients were correctly defined as high risk (i.e. already fulfilled the criteria for surveillance according to the guideline) and therefore excluded. Of the remaining 174 low-risk patients (i.e. would have been discharged from further surveillance according to the guideline), 56 patients (32.2%) were misclassified as low risk because they had gastric lesions at subsequent endoscopies that gave reason to continue surveillance (i.e. gastric premalignant lesions not limited to the antrum). This included three out of the total seven cases of LGD/HGD/ gastric cancer (one case of LGD, HGD and gastric cancer each) see also **Figure 3c**. These patients were also misclassified by the MAPS -2012 and MAPS - 2019 guideline. The correctly classified HGD patient (who was misclassified in MAPS-2012) was included for surveillance according to BSG because of a first degree relative with gastric cancer. This patient had HGD, but declined further therapy due to comorbidities and age, although (endoscopic) resection might have been possible. Another patient with carcinoma who would have been discharged according to the extent of his lesions (limited to the corpus) was recommended to undergo surveillance according to the BSG guideline, also because of a first degree relative with gastric cancer. Patient characteristics of these cases are depicted in **Table 2**.

Table 2. Characteristics of patients identified with a resectable lesion in the complete proregal cohort including which guideline would have accurately identified these patients being at risk GPL gastric premalignant lesion; MAPS management of precancerous conditions and lesions in the stomach; BSG British society of Gastroenter-ology guideline; N/A not applicable; GC gastric cancer; AI autoimmune †Patient is deceased.

#	Age Diagnosis	Gender	First diagnosis of GPL	Guideline recommending surveillance	Lesions at end of surveillance	Lesion found in follow-up	Therapy
1	78 †	male	1996	none	moderate intestinal metaplasia of antrum and angulus	High grade dysplasia antrum	endoscopic resection
2	59	male	2010	none	moderate intestinal metaplasia of antrum and angulus	Intestinal type adenocarcinoma angulus	endoscopic resection
3	71	female	2009	none	Slight intestinal metaplasia of the antrum	Low grade dysplasia of the antrum	endoscopic resection
4	77	male	1996	MAPS-2019	Chronic gastritis of antrum and corpus	High grade dysplasia of the antrum	no therapy
5	46	male	2008	MAPS-2019 MAPS-2012	N/A	Intestinal type adenocarcinoma antrum	endoscopic resection
6	53	female	2009	MAPS-2012 MAPS-2019	N/A	Diffuse type gastric cancer N/A	Total gastrectomy
7	72 †	Male	2006	MAPS-2012 MAPS-2019	N/A	Intestinal type adenocarcinoma Lesser curvature/Angulus	Total gastrectomy

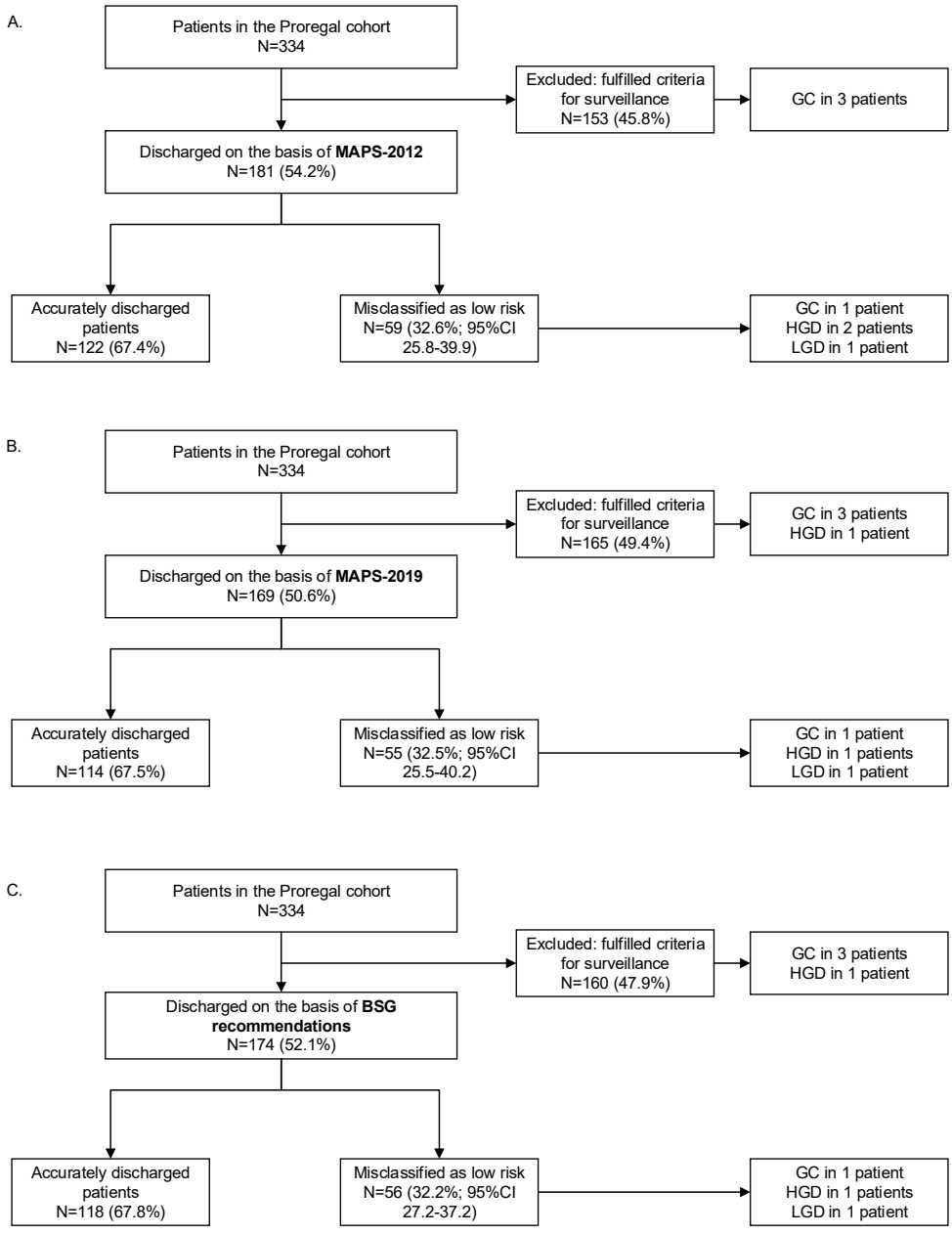

Figure 3. Schematic visualization of surveillance of patients with pre-malignant gastric lesion according to the MAPS-2012 guideline (a), according to the MAPS-2019 guideline (b) and according to the BSG (c). LGD low-grade dysplasia; HGD high-grade dysplasia; GC gastric cancer; CI confidence interval; MAPS management of precancerous conditions and lesions in the stomach; Proregal progression and regression of precancerous lesions

Longitudinal follow-up

Figure 4 shows a graphical presentation of the results of each endoscopy according to the MAPS-2019 guideline. As can be appreciated from this figure, several patients continuously switch between high and low risk of progression. The number of endoscopies or time necessary to correctly identify low-risk patients was visualized by a Kaplan–Meier curve. As seen in **Figure 5a, c, e**, one additional endoscopy identifies over 75.4% (95% CI 64.3–86.6), 72.9% (95% CI 62.4–83.3) and 73.2% (95% CI 59.7–84.2) of high -risk patients according to the MAPS-2012, MAPS -2019 or BSG guideline, respectively. After two additional endoscopies, this percentage increases to 89.5% (95% CI 81.5–97.5), 85.7% (95% CI 77.5–93.9) and 85.7 (95% CI 73.8–93.6 or BSG, respectively. **Figure 5b, d, f** shows patients who were defined as low risk according to MAPS-2012, MAPS-2019 or BSG by years of follow-up. After 3 years, the percentage of correctly identified patients at low gastric cancer development risk is 77.2% (95% CI 66.3–88.1), 80.9% (95% CI 74.1–91.7) and 80.4% (95% CI 67.6–89.8) as shown in **Figure 5b, d, f**. In this period, all patients underwent either one or two additional endoscopies. All of the misclassified low-risk patients, who were diagnosed with GC or dysplasia during follow-up, would have been correctly classified as high risk in case one additional endoscopy between two and four years was performed (following any guideline).

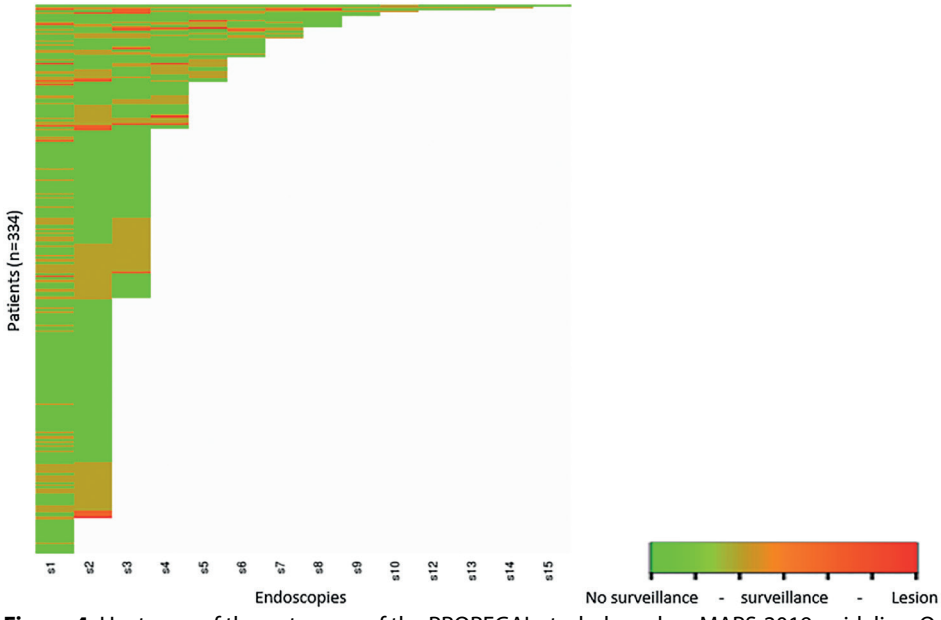

Figure 4. Heat map of the outcomes of the PROREGAL study, based on MAPS-2019 guideline. On the Y-axis, all individual patients have been plotted, on the X-axis, the endoscopies are shown. A green colour indicates that MAPS-2019 would not recommend an endoscopy, an orange colour represents a recommendation of surveillance. A red colour represents detection of lesions that should be considered for (endoscopic) resection (i.e. LGD, HGD, gastric adenocarcinoma). Several patients who would have been discharged based on the lesion found and according to MAPS-2019 guideline did show lesions warranting surveillance in subsequent endoscopies

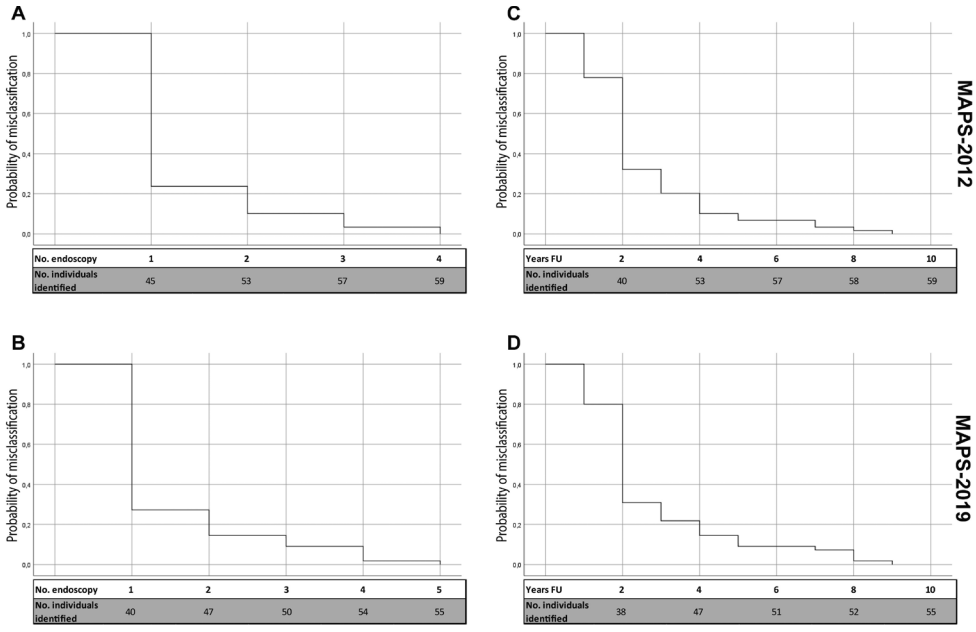

Figure 5. Kaplan–Meier analysis of the probability of patients being misclassified as low risk for gastric cancer. a Patients who were misclassified as low risk according to MAPS-2012, distinguished by number of endoscopies needed until identified as still at risk. b Patients who were misclassified as low risk according to MAPS-2012, distinguished by years of follow-up until identified as still at risk. c Patients who were misclassified as low risk according to MAPS-2019, distinguished by number of endoscopies needed until identified as still at risk. d Patients who were misclassified as low risk according to MAPS-2019, distinguished by years of follow-up until identified as still at risk. e Patients who were misclassified as low risk according to BSG, distinguished by number of endoscopies needed until identified as still at risk. Of Patients who were misclassified as low risk according to BSG, distinguished by years of follow-up until identified as still at risk. No. number of; FU follow-up; MAPS management of precancerous conditions and lesions in the stomach

Discussion

To the best of our knowledge, this is the first study that evaluates how accurate we can identify low-risk GPL patients, and whether they can be safely discharged from further surveillance based on guideline recommendations. Due to the addition of several risk factors in MAPS-2019 and BSG as compared to MAPS-2012, MAPS-2019 and BSG improve the identification of high-risk patients who develop lesions requiring treatment, while reducing the amount of patients under surveillance. Nevertheless, a large proportion of patients at risk of neoplastic progression are still missed. Up to 32% of patients who are discharged from gastric cancer surveillance appeared to be misclassified as 'low risk' on subsequent endoscopy, including three out of the total of seven HGD/GC cases following the current European guidelines (MAPS-2019 and BSG). By adding one additional endoscopy, all patients who developed dysplasia or cancer were correctly

identified as high risk and risk of misclassification was reduced by 72.9%. Dismissing patients from further surveillance after two 'negative' endoscopies is already common practice in colonic polyp surveillance and might be considered in the setting of gastric premalignant lesions (15). Currently, extension and severity of gastric premalignant lesions are determined by upper endoscopy with random biopsies. This might cause sampling error and with that, underestimation of the true extent of lesions (16, 17). This could explain the number of patients who were misclassified as low risk in our study, based on the subsequent endoscopy results. It has been described previously that conventional white light endoscopy (WLE) findings do not correlate well to histological findings in gastric premalignant lesions (18, 19). Advanced endoscopic techniques such as high-definition endoscopes and imaging enhancement technologies have improved markedly in the past years (20, 21). High-Definition-White Light Endoscopy (HD-WLE) has improved the correlation between endoscopic and histological diagnosis, with a sensitivity ranging between 75% and 92.7% and a specificity ranging between 92.7% and 100% (20, 21). However, when measured in daily clinical practice, this accuracy decreases to 53% sensitivity and 98% specificity (22). The addition of Narrow band imaging (NBI) to high-resolution endoscopy can further enhance accuracy up to a sensitivity of 85% and a specificity of 77% (23). Our study highlights the importance of embracing and further investigating endoscopic improvement tools to stratify at-risk individuals with better accuracy and make surveillance guidelines more efficient (23). These improvements in endoscopic techniques opens possibilities for targeted biopsies during surveillance endoscopies, which is expected to lower sampling error. On the other hand, improvements in endoscopic techniques will only lead to a decrease in sampling error if endoscopist is trained to correctly interpret endoscopic images and identify the gastric lesions. MAPS-2019 guidelines recommend the use of NBI or chromoendoscopy as it outperforms the use of WLE alone as described above. However, the use of other virtual chromoendoscopy such as i-Scan or FICE is less well investigated. These new developments may contribute to a better detection of premalignant gastric lesions, but therefore further research is necessary, especially to assess the usability and yield in daily practice in non-expert hands before recommendations can be made.

Another potential explanation for the apparent changes in perceived severity of lesions during follow-up is that it represents regression of lesions, rather than sampling error. H. pylori eradication effectively blocks progression of intestinal metaplasia and reduces the risk of gastric cancer (24). While regression of (chronic) atrophic gastritis has been suggested (25–27), actual regression or disappearance of IM has only been described in several individual studies. Indeed, several meta -analyses show no significant regression of IM even after H. pylori eradication and long-term treatment with a Cox2 inhibitor (28, 29). This held true for premalignant lesions in all the different locations of the stomach and supports the idea that sampling error contributes more to the fluctuating severity of

lesions in our cohort than biological pro- or regression of disease (29, 30). This raises the question whether histology from the last available endoscopy only is sufficient to identify patients who are at risk for gastric cancer development. According to our data, performing one additional endoscopy will identify the majority of patients who otherwise would have been inappropriately discharged. A surveillance strategy in which longitudinal data of all previous endoscopies are taken into account in risk assessment should be a future step.

The main challenge of surveillance strategies, especially in low-risk areas, is to identify the small proportion of patients that will benefit from surveillance while circumventing the burdens of such strategy. No surveillance strategy will perfectly identify all patients at risk. Therefore, it is important to take into account the risk of progression of premalignant lesions, the availability of a relatively safe and effective method to treat (early) cancers and the burden due to surveillance for both patient as well as health care. In three (43%) out of the seven patients who developed gastric cancer or dysplasia, at least one high-risk feature was present. Our study shows that the addition of risk factors (autoimmune gastritis, first degree family history and persistent H. pylori infection) in MAPS-2019 and BSG indeed increases the yield of the current surveillance strategy and highlights the importance of continuing this improvement of risk stratification.

Several limitations have to be taken into account. First, this is an observational study which is not powered to make specific recommendations to improve current guidelines. This study solely provides descriptive information. Larger sample size in a randomized controlled trial setting would be needed to truly investigate the risk of misclassification and improve on guideline recommendations regarding biopsy strategies and surveillance (intervals). Furthermore, misclassification of patients is unavoidable and what percentage is deemed acceptable is debatable. This will depend on the costs health systems are willing to bear. Also, even though (almost) half of the dysplasia/gastric cancer cases in our cohort would never have received a surveillance endoscopy if guidelines were followed, these patients may have presented themselves when complaints would have arisen. Inevitably, this would have caused some delay in their treatment. However, the possibility of endoscopic treatment and outcome can only be speculated upon.

In conclusion, cancer detection improved with the updated MAPS-2019 and BSG guidelines, however, still three out of seven dysplasia/GC cases were missed. Furthermore, one-third of patients were misclassified as low risk for gastric cancer development and therefore would have inappropriately been discharged from further surveillance. The majority of these patients could be identified by performing one additional endoscopy within three years. Our study emphasizes the need for further improvement of stratifying at-risk individuals and improved endoscopic recognition of premalignant gastric lesions.

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Supplementary material

Supplementary Table 1. Recommended management of premalignant stomach lesions according to the MAPS guideline 2012, the updated MAPS guideline 2019 and BSG guideline; AIG; auto immune gastritis, CAG; chronic atrophic gastritis, GC; gastric cancer, IM; intestinal metaplasia, MAPS; management of epithelial precancerous conditions and lesions in the stomach

	MAPS-2012	MAPS-2019	BSG
	Surveillance (yes/no)	**Surveillance (yes/no)**	**Surveillance (yes/no)**
CAG/IM antrum	No	Yes: every 3 years, if: Family history of GC Incomplete IM AIG Persistent Hp infection Absence of above = no surveillance	Yes: every 3 years, if: Family history of GC Persistent Hp infection Absence of above = no surveillance
CAG/IM corpus	Yes: every 3 years	Yes: every 3 years, if: Family history of GC Incomplete IM AIG Persistent Hp infection Absence of above = no surveillance	Yes: every 3 years, if: Family history of GC Persistent Hp infection Absence of above = no surveillance
CAG/IM antrum + corpus	Yes: every 3 years	Yes: every 1-2 years, if: First degree relative with GC Absence of above = every 3 years	Yes: every 3 years

CHAPTER 4

Factors associated with the progression of gastric intestinal metaplasia: a multicenter, prospective cohort study

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Endoscopy International Open, March 2021

Abstract

Introduction

Gastric cancer (GC) is usually preceded by premalignant gastric lesions (GPLs) such as gastric intestinal metaplasia (GIM). Information on risk factors associated with neoplastic progression of GIM are scarce. This study aimed to identify predictors for progression of GIM in areas with low GC incidence.

Methods

The Progression and Regression of Precancerous Gastric Lesions (PROREGAL) study includes patients with GPL. Patients underwent at least two upper endoscopies with random biopsy sampling. Progression of GIM means an increase in severity according to OLGIM (operative link on gastric intestinal metaplasia) during follow-up (FU). Family history and lifestyle factors were determined through questionnaires. Serum Helicobacter pylori infection, pepsinogens (PG), gastrin-17 and GC-associated single nucleotide polymorphisms (SNPs) were determined. Cox regression was performed for risk analysis and a chi-squared test for analysis of single nucleotide polymorphisms.

Results

Three hundred and eight patients (median age at inclusion 61 years, interquartile range (IQR: 17; male 48.4%; median FU 48 months, IQR: 24) were included. During FU, 116 patients (37.7%) showed progression of IM and six patients (1.9%) developed high-grade dysplasia or GC. The minor allele (C) on TLR4 (rs11536889) was inversely associated with progression of GIM (OR 0.6; 95%CI 0.4–1.0). Family history (HR 1.5; 95%CI 0.9–2.4) and smoking (HR 1.6; 95%CI 0.9–2.7) showed trends towards progression of GIM. Alcohol use, body mass index, history of H. pylori infection, and serological markers were not associated with progression.

Conclusion

Family history and smoking appear to be related to an increased risk of GIM progression in low GC incidence countries. TLR4 (rs11536889) showed a significant inverse association, suggesting that genetic information may play a role in GIM progression.

Introduction

Gastric cancer (GC) of the intestinal type is often initiated by chronic Helicobacter pylori infection through gastritis eventually leading to the development of gastric premalignant lesions (GPLs). These in particular include atrophic gastritis (AG), gastric intestinal metaplasia (GIM), and dysplasia (1, 2). These premalignant lesions make GC suitable for screening and surveillance. In high endemic GC regions such as Asia, population-based screening for GC has been implemented in certain regions (3). Due to low prevalence rates of GC, screening programs are not effective in low endemic areas such as the Northern European countries. These regions rely on surveillance programs of at-risk individuals with GPL identified during routine endoscopy.

The balance between burden and benefit of such endoscopic surveillance in low endemic regions is still under debate. While US guidelines do not recommend endoscopic surveillance, European guidelines recommend surveillance dependent on the extent and severity of GPL (4-7). The American Gastroenterological Association (AGA) recently published clinical practice guidelines on the management of GIM. The AGA suggests against routine endoscopic surveillance for patients with GIM unless a higher risk of GC is the case (i.e. incomplete GIM, extensive GIM, a family history of GC or of Asian heritage) (8). While European guidelines do opt for endoscopic surveillance, they recognize that a more individualised surveillance strategy distinct based on risk factors for disease progression is needed and will maximise the yield and reduce the burden of surveillance endoscopies. The recently updated European guideline takes risk factors such as a positive family history for gastric cancer into account (9).

Evidence suggests that patients who have a first-degree relative with gastric cancer (diffuse type [hereditary] gastric cancer excluded) have an increased risk for neoplastic progression compared to GIM patients who have no first-degree relative with gastric cancer (10-12). Single nucleotide polymorphisms (SNPs) are common genetic variants among individuals and are frequently inherited within families. SNPs are increasingly being studied in association with H. pylori infection and gastric cancer. SNPs that have been associated with non-cardia gastric carcinogenesis are located in toll like receptor 4 (TLR4) rs11536889, toll like receptor 1 (TLR1) rs28393318 (both having a signalling function in initiating immune responses), autophagy 16 like 1 (ATG16L1) rs2241880, and neutrophil cytosolic factor 4 (NCF4) rs482154 genes (playing a part in activity of granulocytes) (13-15). Besides genetic factors, smoking, alcohol use and increased BMI have also been identified as possible risk factors for neoplastic progression of GPL, in particular in high-risk populations (16, 17). Serum pepsinogen (ratios) and gastrin levels are markers for current presence of an atrophic stomach (18). Pepsinogen I/II ratio is increased, and gastrin level decreased in

case of gastric atrophy (19). However, it is not known if these serological markers have a predictive value for progression of intestinal metaplasia over time.

All in all, information on risk factors of neoplastic progression of GIM is limited and they have not been tested systematically in a prospective cohort of premalignant gastric lesion in patients living in a low GC incidence country. Many patients are followed intensively without risk stratification, causing a significant burden to patients and health care systems. From 2009, a prospective cohort of over 300 patients with premalignant gastric lesions was initiated in the Netherlands and Norway. This study aims to reveal potential risk factors associated with the progression of GIM, including analyses on SNPs and serological markers, in a country with low GC risk.

Methods

Patient selection

The PROREGAL study (Progression and Regression of precancerous Gastric Lesions) was initiated in 2009 and is an ongoing prospective cohort study in six hospitals (one academic, five regional) in the Netherlands and one regional hospital in Norway. The study design has been described previously (20). In short, patients over 18 years of age and with atrophic gastritis, gastric intestinal metaplasia and/or dysplasia are eligible for inclusion. Patients are excluded from participation if they have: 1) previously undergone upper gastrointestinal surgery, 2) a previous diagnosis of gastric carcinoma, or any other malignancy not being in remission, 3) severe comorbidity limiting their expected survival to less than 2 years, 4) portal hypertension, or 5) a proven CDH1 mutation. Eligible patients are included after written informed consent. The study protocol was approved by the Erasmus MC Institutional Review Board (MEC-2009-090).

Baseline data collection

Information on lifestyle factors, medical history, medication use and family history of gastric cancer were obtained through questionnaires. Pepsinogens-I/II (PG-I/II), gastrin-17 and H. pylori status blood samples were collected at baseline. Any active H. pylori infections were eradicated and confirmed afterwards.

Endoscopy procedures

All patients underwent at least one surveillance endoscopy after the index endoscopy (t0). First surveillance endoscopy (t1) was performed one year after the index endoscopy and the second surveillance endoscopy (t2) 3 years after the index endoscopy, except if low-grade dysplasia (within 1 year) or high-grade dysplasia (within 6 months) was present. Further follow-up surveillance endoscopies were decided according to the Management of epithelial precancerous conditions and lesions in the stomach (MAPS)

guideline recommendations that became available during the study (4). Every gastric lesion found at endoscopy was reported. Gastric biopsies were sampled in a standardised manner at every endoscopy. This included biopsies from any visible lesion and twelve random biopsies from five areas in the stomach: four quadrant biopsies of the antrum, two biopsies from the incisura, two from the lesser curvature, two from the greater curvature and two from the cardia.

Pathology

The biopsy specimens were fixed in buffered formalin and embedded in paraffin and then assessed by pathologists from the participating hospitals. The presence and grade of the different stages of GGIM were classified according to the OLGIM (Operative Link of Gastric Intestinal Metaplasia) classification. The scoring of lesions is divided into mild-moderate-severe IM in both antrum and corpus, providing a score between 0–IV with IV having the highest risk of gastric cancer development (21).

Enzyme linked immunosorbent assay

Serum was collected from patients at the first surveillance endoscopy and was aliquoted and stored at −80°C until analysis. Enzyme linked immunosorbent assay (ELISA) for H. pylori IgG, gastrin and pepsinogen I/II was performed according to manufacturer's protocol (Gastropanel, Biohit oyi, Finland). In short, precoated plates were incubated with patient sera or standardized controls. Plates were washed and subsequently incubated with the conjugated antibody. After another wash step the substrate was added after which the readout could be performed at a frequency of 450nm. Optical density (OD) measurement and 8 subsequent quantification of plates was performed with the infinite 200 pro ELISA reader (TECAN, Mannedorf, Switzerland).

Identification of SNPs

Several SNPs associated in the past with H. pylori infection and an increased risk of gastric cancer were selected (22-25). We first tested if there was a difference in the minor allele frequency (MAF) of the selected SNPs between the PROREGAL cohort and the general population. For this purpose, we compared the MAF of the PROREGAL cohort with the MAF found in the Rotterdam Study 1 cohort (RS1). The Rotterdam Study is a prospective cohort study of healthy persons living in a well-defined district in Rotterdam (Ommoord), more details on this study are described elsewhere (26). The cohort reflects the general Dutch population. In short, it comprises almost 6,500 healthy participants aged between 45–75 years. Participants are followed throughout life every 3–4 years with emphasis on collecting bio specimens that enable molecular and genetic analysis.

To determine a significant difference between the SNPs in the PROREGAL cohort versus the general population (RS1) a chi squared test was performed. The ATG16L1 (rs2241880)

SNP MAF was 0.465 in the RS1 cohort versus 0.528 in the PROREGAL cohort (P=0.016). The NCF4 (rs482154) SNP MAF was 0.292 in the RS1 cohort versus 0.311 in the PROREGAL cohort (P=0.530). The TLR1 (rs28393318) SNP MAF was 0.266 in the RS1 cohort versus 0.374 in the PROREGAL cohort (P>0.001). The TLR4 (rs11536889) SNP MAF was 0.147 in the RS1 cohort versus 0.192 in the PROREGAL cohort (P=0.048). Based on these results we included rs2241880, rs28393318 and rs11536889 SNPs for the current study.

DNA isolation and SNP identification in the PROREGAL cohort

At baseline blood was collected from each patient. DNA was isolated using the Kleargene XL blood DNA extraction kit (LGC limited, Teddington, UK). Quantity and quality of isolated DNA was measured on the nanodrop and DNA samples were normalized to 10ng/ul. SNPs were determined using Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP). In short DNA fragments were amplified using regular PCR for 35 cycles. After quality control by performing gel electrophoresis on 2% Tris-Borate-EDTA (TBE) agarose gel, samples that provided a well-defined band are digested overnight using a restriction enzyme that specifically digest one allele of the appropriate SNP (**Supplementary Table1**). These samples were then used in TBE gel electrophoresis and presence of the SNP in one or two alleles was determined by identifying the number of bands: one band for homozygously undigested, two bands for homozygously digested, three bands for heterozygous patients.

Statistical analyses

Baseline characteristics are presented as mean with standard deviation (SD) or median with interquartile range (IQR). Categorical variables were reported as percentages. Progression of GIM was defined as progression of the OLGIM classification at any time point between follow-up (FU) endoscopies. Potential risk factors (RF) for progression were analysed by Cox-regression with a two-sided significance level of 0.05 and providing hazard ratios (HR) 95% CI. To further substantiate the genetic role on one's progression risk, interdependence of SNP distributions for progressors and non-progressors was calculated using the chi squared test and providing odds ratio (OR) with 95% confidence intervals (95% CI). Analyses were performed in IBM SPSS v.24. Figures were drafted in R V.3.4.2.

Sample size and seletion of predictors

To avoid overfitting of the Cox regression model we have used an event per variable (EPV) of>10 with a central limit theorem of 10 cases as generally proposed in sample size considerations for proportional hazards analysis (27). This entails that for every ten cases of progression of GIM one predictor was added to the cox model starting from the 10th case. The current study contains 81 cases of progression with complete data. This

translates into the inclusion of seven predictors (81 cases minus 10 cases as being the central limit of theorem, adding 1 variable per 10 cases) in our Cox regression model.

We pre-selected possible predictors that can be determined prior to one's first upper endoscopy, based on available literature and guidelines. Previously, our study group and many others have shown a correlation between OLGIM stage and values of the serological markers pepsinogen I, pepsinogen II, and gastrin-17 (20, 28). It is therefore that we included these serological markers in the current study to evaluate if these factors might also be associated with the progression of GIM over time.

Further, family history has been an increased focus of research and was recently added as a risk factor in the updated surveillance guidelines (9). However, it is still rated as "low quality evidence" for which prospective data is needed.

Several trials have been performed on the effects of H. pylori eradication and the progression to gastric cancer. The benefits of H. pylori eradication were mostly seen in patients without premalignant gastric lesions at baseline (29, 30). We have added history of an (confirmed eradicated) H. pylori infection to evaluate if this might affect progression of GIM over time. Lifestyle factors such as smoking, use of alcohol and body mass index (BMI) remain understudied with controversial results and mainly focus on the occurrence of gastric cancer. Associations with the progression of premalignant lesions might just be as important (31-34).

Results

Baseline characteristics

A total of 308 patients were included (**Figure1**). Their median age was 61 years (IQR: 17) and 48.4% were male. Baseline characteristics of the study population are shown in **Table1**. Median follow-up (FU) time was 48 months (IQR 24), with a median of three endoscopies (IQR: 1) performed per patient. One hundred and sixteen patients (38.0%) showed progression of OLGIM stage, two (0.6%) patients showed progression to high-grade dysplasia, and four patients (1.3%) developed gastric cancer. The distribution of progression within specific OLGIM stages of these progressors is shown in **Figure 2**.

Risk factors

Smoking (HR 1.6; 95%CI 0.9–2.7, P=0.079) and having a family member (first- and/or second-degree) with gastric cancer (HR 1.5; 95% CI 0.9–2.4, P=0.076) was associated with an increased risk of progression of GIM, but statistically non-significant (**Figure 3**). Serum PG I, PG II and their PG I/II ratio (HR 1.0; 95%CI 0.9–1.1, P=0.420) as well as serum gastrin-17 (HR 1.0; 95%CI 0.9–1.1, P=0.854) did not significantly correlate with the risk of

GIM progression. Also, history of an H. pylori infection (HR 1.1; 95%CI 0.6–1.7, P=0.953), alcohol use (HR 0.7; 95%CI 0.4–1.1, P=0.103), and BMI (HR 1.0; 95%CI 0.9–1.1, P=0.947) showed no association with progression of GIM.

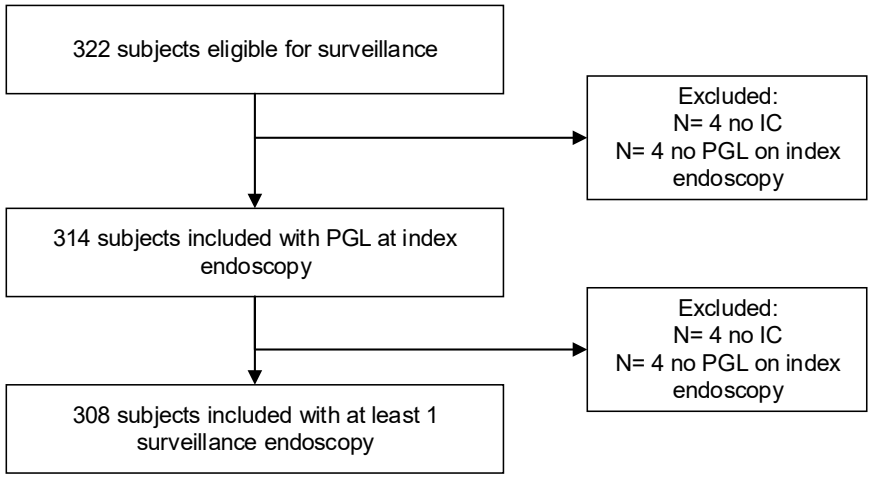

Figure 1. Flowchart of the included subjects. IC, informed consent; PGL, premalignant gastric lesion; MALT, mucosa-associated lymphoid tissue

Table 1. Baseline characteristics of the PROREGAL cohort; IQR: interquartile range, IM: intestinal metaplasia, HGD: high grade dysplasia

Baseline characteristics	PROREGAL cohort	Available data N (% from total)
Male n (%)	148 (48)	308 (100)
Age at baseline (years) median (IQR)	61 (17)	308 (100)
Ethnicity (Caucasian), n (%)	242 (79)	308 (100)
Follow up (months) median (IQR)	48 (24)	308 (100)
OLGIM stage at baseline n (%)		308 (100)
0	54 (21)	
I	83 (32)	
II	67 (26)	
III	42 (16)	
IV	10 (4)	
Progression of IM n (%)	116 (38)	308 (100)
Progression to HGD n (%)	2 (0.6)	308 (100)
Progression to gastric cancer, n (%)	4 (1.3)	308 (100)
History of H. pylori -infection, n (%)	148 (62)	237 (77)
Pepsinogen I (µg/L) mean (SD)	128 (99)	301 (98)
Pepsinogen II (µg/L) mean (SD)	18 (13)	303 (98)
Pepsinogen I/II (µg/L) mean (SD)	9 (11)	301 (98)
Gastrin-17 (pmol/L) mean (SD)	19 (25)	296 (96)
Smoking status (ever), n (%)	151 (60)	250 (81)
Alcohol use (yes), n (%)	132 (53)	249 (81)
Family history of gastric cancer, n (%)	76 (29)	262 (85)
First degree	50 (16)	
Second degree	26 (8)	

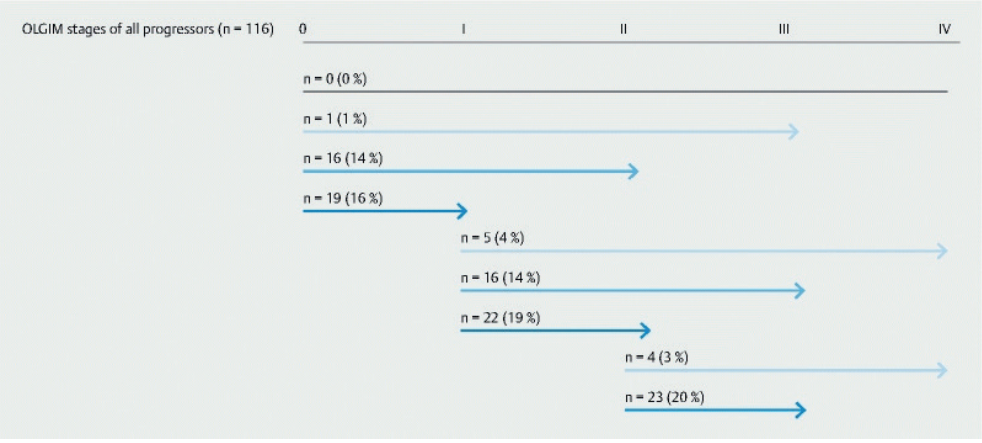

Figure 2. Percentages of progressors per OLGIM stage at baseline and the maximal OLGIM stage at the first time point of progression during follow up

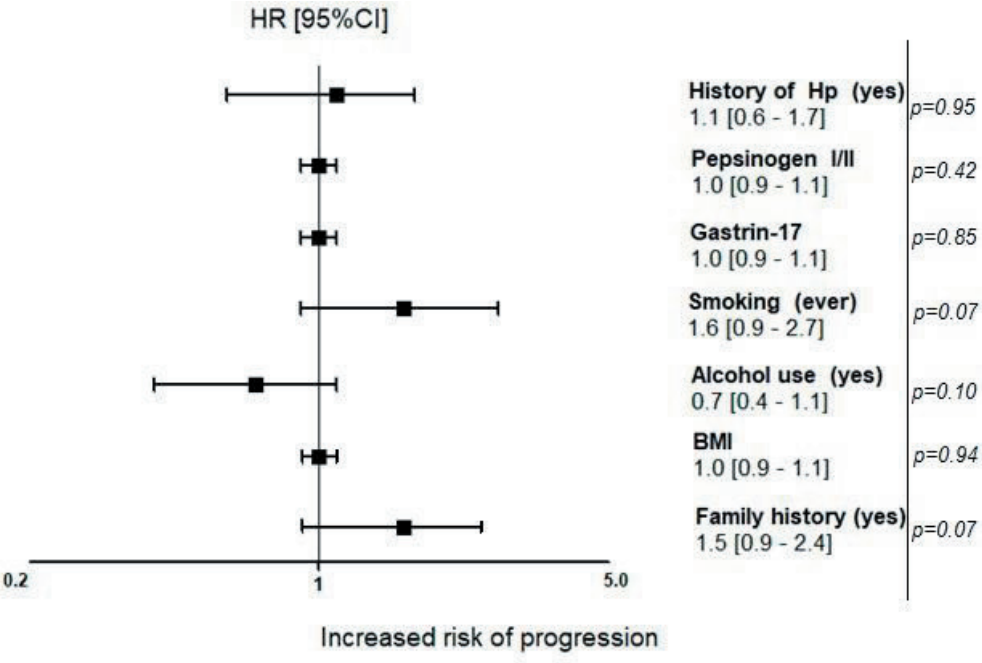

Figure 3. Analysis of risk factors associated with progression of intestinal metaplasia. BMI, body mass index; CI, confidence interval; Hp, Helicobacter pylori; HR, hazard ratio.

Family history of gastric cancer

Information on family history was available for 266 subjects (86%). Fifty subjects had a first-degree relative with gastric cancer (of whom 48.0% showed progression of IM), 26 had a second-degree relative with gastric cancer (of whom 50.0% showed progression of IM), and 190 did not have a family history of gastric cancer (of whom 36.3% showed progression of IM) (**Figure 4**).

Single nucleotide polymorphisms

The genotype distribution of the SNPs within our cohort is represented in **Table 2**. Also, this demonstrates the minor allele frequencies for all variants between the non-progressor and progressor groups. The minor allele (C) on the TLR4 gene (rs11536889) was inversely associated with the progression of GIM showing an odds ratio (OR) of 0.6 (P=0.042).

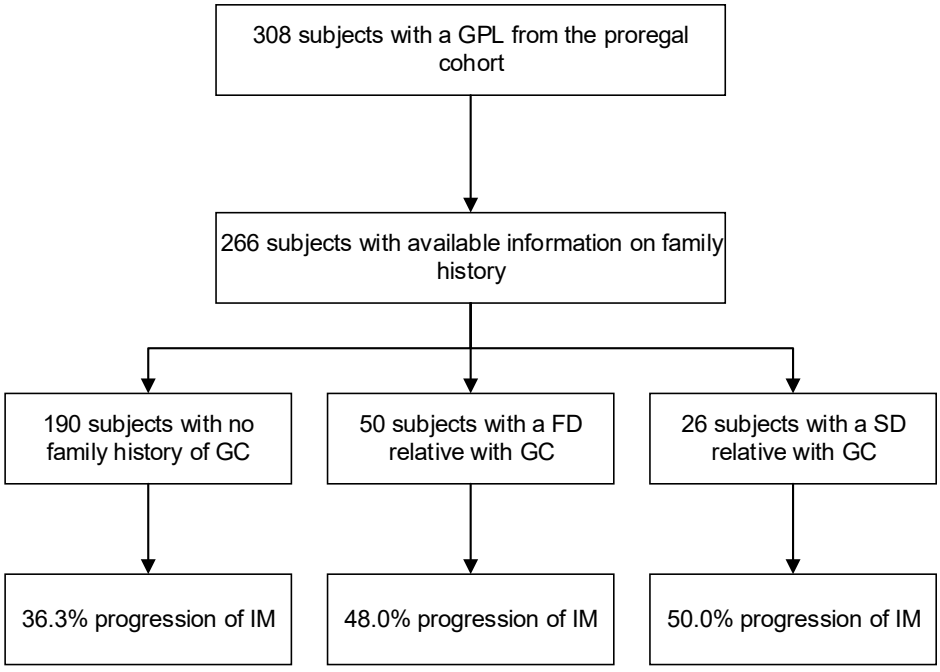

Figure 4. Flowchart of available information on family history. Subjects of the PROREGAL cohort with known gastric premalignant lesions and the proportion of subjects with a positive family history. FD, first-degree relative; GC, gastric cancer; IM, intestinal metaplasia; SD, second-degree relative.

Table 2. Summary of the genotypes associated with progression in the PROREGAL cohort and comparison of the minor allele frequencies (MAF) in the non-progression and progression groups. PROREGAL, Progression and Regression of Precancerous Gastric Lesions; MAF, minor allele frequency; OR, odds ratio.

	Genotype	Non-progression (%)	Progression (%)	OR (95%CI)	p-value
ATG16L1	AA	30 (18.6%)	23 (21.3%)		
	AG	91 (56.5%)	57 (52.8%)		
	GG	40 (24.8%)	28 (25.9%)		
MAF		0.469	0.477	1.0 (0.8-1.4)	0.808
TLR1	AA	57 (35.4%)	36 (33.6%)		
	GA	92 (57.1%)	59 (55.1%)		
	GG	12 (7.5%)	12 (11.2%)		
MAF		0.360	0.388	1.1 (0.8-1.5)	0.572
TLR4	GG	95 (59.4%)	80 (74.1%)		
	GC	56 (35.0%)	25 (23.1%)		
	CC	9 (5.6%)	3 (2.8%)		
MAF		0.231	0.144	0.6 (0.4-1.0)	0.042

Discussion

To our knowledge, this is the first study that prospectively assessed multiple risk factors, including SNP analysis, for progression of gastric intestinal metaplasia in a population with a low gastric cancer incidence. SNP analysis showed that the minor allele (C) on TLR4 (rs11536889) was negatively associated with progression of GIM. This result suggests genetic information may play a role in GIM progression. Possible risk factors that were previously identified in high-risk GC populations were not predictive for progression in our low-risk population. However, a positive family history of gastric cancer and smoking status might be associated with an increased risk of progression.

Lifestyle factors such as the use of alcohol and smoking were previously studied in association with gastric cancer. A large meta-analysis including 59 studies showed a correlation between heavy drinking (>4 drinks/day) and progression to non-cardia gastric cancer with a relative risk (RR) of 1.39 (95%CI 1.14–1.69) among non-Asian studies and 0.90 (95%CI 0.65–1.25) among Asian studies (34). In our study we did not find any correlation between alcohol consumption and progression of IM. However, our data did not allow for discrimination between amounts of consumption, which might neglect the influence of heavy drinking in our cohort.

A large Korean cohort study including almost 200,000 subjects found smoking as an independent risk factor for the development of IM by measuring urinary cotinine levels. Heavy smoking (i.e. nicotine level >500ng/mL) corresponded to an hazard ratio (HR) of 1.54 (95%CI 1.44–1.64) for men, and 1.57 (95%CI 1.07–2.30) for women (35). In a study from a low risk area, a HR of 1.13 (95%CI 1.00–1.27, P=0.05) was found for the progression

to gastric cancer in male smokers with normal serum PGI levels (36). A recent meta-analysis pooled the published studies on smoking and alcohol use and their relation with the presence of GIM (37). By pooling these results (n=7971 subjects in eight studies) the Relative Risk (RR) of ever or former smoking versus never smoked and the presence of GIM was 1.57 (95% CI 1.24–1.98). For ever or former alcohol use versus no alcohol use (n=6775 subjects in five studies) RR was 1.29 (95% 1.12–1.50). Although not significant, we found similar trends for the risk of progression of GIM in smokers.

Serum markers such as gastrin-17 and pepsinogen I and II are well correlated with the presence and severity of premalignant lesions (18, 20, 38). This study aimed to evaluate if serological markers at baseline might have a predictive value for future progression of IM. This would substantiate proper risk stratification at initial diagnosis. However, our results did not show any significant associations between serology levels at baseline and progression of GIM during follow up. It is still to be tested if longitudinal data assessment of serological markers during every FU endoscopy might be of value.

In both the American Gastroenterological Association (AGA) and European guidelines, routine surveillance endoscopies are not recommended for all patients with GPL. Both guidelines advise a more individualized strategy where accurate risk stratification is the key. Both emphasize the importance of having a positive family history of gastric cancer as being a risk factor. Although not significant, the recent meta-analysis showed that a positive family history was associated with the presence of GIM (RR1.46, 95%CI 0.97–2.21) (37). Both the AGA guidelines as well as the updated MAPS guidelines recommend providing more intensive surveillance in this at-risk population (8, 9). Our results indeed point in the direction of an increased risk of progression of GIM in case of a positive family history. The current study helps strengthen the currently available literature by further elucidating these risk factors, as well as showing that familial predisposition might also contribute to the course of disease.

These results are in line with previous literature. A prospective cohort study from Italy also showed that neoplastic progression in AG patients was two-fold more frequent among patients with a first degree relative with gastric cancer compared to patients with a negative family history (23.5% vs. 12.6%, P=0.4867) (39). In a retrospective study from the United States, over 900 subjects with IM were included. Of these, 25 subjects progressed to gastric cancer, with family history being a significant risk factor (incidence rate ratio, 8.87; 95%CI 1.5–23.5; P=0.012) (40).

The ATG16L1 SNP rs2241880 previously has been associated with gastric cancer (25). In the PROREGAL cohort, variation at rs2241880 was associated with the presence of intestinal metaplasia when compared to a general population control group.Rs2241880 is

a functional SNP that results in an amino acid change of threonine to alanine at position 300 in the ATG16L1 protein, which in turn causes impaired autophagy (41). Increasing evidence links the autophagy pathway to H. pylori pathogenesis (42). Variation in the TLR1 gene at rs28393318 is in linkage disequilibrium with the functional SNP rs4833095 which has previously been negatively associated with H. pylori serology and positively associated with gastric cancer (43, 44). In our study, rs28393318 was also associated with the presence of gastric premalignant lesions. Although the consequences of this SNP remain largely unclear, it is biologically plausible that innate immune signaling through TLR1 may contribute to the inflammatory environment in which gastric premalignant lesions may occur.

Of the analyzed SNPs, only variation at TLR4 (rs11536889) showed a significant inverse association with the progression of IM. Just as with TLR1, TLR4 is a pattern recognition receptor and can initiate the innate immune response in the host colonized with H. pylori. This SNP might thus affect the intensity of the host response against H. pylori and thus modify the severity of chronic H. pylori gastritis (13). The association of rs11536889 with IM and the inverse relationship with progression of IM may seem contradictory. However, several explanations can be found for these conflicting results. First, all previous studies that found an increased risk of gastric cancer associated with rs11536889 were restricted to patients of Chinese descent (13, 45). Second, the highest risk that could be found was in individuals that, aside from the variation at rs11536889, were also infected with H. pylori. This is also biologically plausible since TLR signalling is important in the early response to H. pylori infection. Several studies suggest that over the long term, modest regression of gastric premalignant lesions may be expected after eradication of H. pylori (46, 47). If the association of this TLR4 SNP with gastric cancer is co-dependent on H. pylori infection, one might expect some regeneration or stabilization when H. pylori has been eradicated.

Our study also has some limitations. First, our median follow-up period is 4 years. To draw firm conclusions on the course of disease with concomitant risk factors, a longer follow-up period is needed. Second, lifestyle risk factors and family history were obtained through questionnaires, making that information subject to patient interpretation. Third, due to a limited number of cases we were not able to add more potential risk factors. Because the PROREGAL study is an ongoing prospective study that will be continued and expanded in the future, more long-term data with larger sample size are awaited. Fourth, the association between smoking and a positive family history was not statistically significant, with a P=0.07; it may, however, point in the direction of an indicated effect. Furthermore, our primary endpoint was progression of OLGIM stage instead of progression to gastric cancer because of the small number of neoplastic lesions. Location, therefore, could not to be added as independent factor in the Cox model. For low-risk regions, it is just as

important to focus on the identification of progression of premalignant lesions as to stop further surveillance in patients with a very low risk of gastric cancer development.

In conclusion, this multicenter, prospective cohort study on the surveillance of gastric premalignant lesions in an area with a low gastric cancer incidence shows that both a positive family history of gastric cancer and a history of smoking are indicated to have an effect on the progression of GPL. This study further substantiates the possible underlying role of SNPs in (non-)progression of GPL, suggesting that genetic information may play a role in the risk stratification of patients with GIM.

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CHAPTER 5

Accuracy of endoscopy staging and targeted biopsies for routine gastric intestinal metaplasia and gastric atrophy evaluation, study protocol of a prospective, cohort study – the ESTIMATE study

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BMJ Open, September 2019

Abstract

Introduction

Patients with chronic atrophic gastritis (CAG) and intestinal metaplasia (IM) are at risk of developing gastric adenocarcinoma. Their diagnosis and management currently rely on histopathological guidance after random endoscopic biopsy sampling (Sydney biopsy strategy). This approach has significant flaws such as under- diagnosis, poor reproducibility and poor correlation between endoscopy and histology. This prospective, international multicentre study aims to establish whether endoscopy- led risk stratification accurately and reproducibly predicts CAG and IM extent and disease stage.

Methods and analysis

Patients with CAG and/or IM on standard white light endoscopy (WLE) will be prospectively identified and invited to undergo a second endoscopy performed by an expert endoscopist using enhanced endoscopic imaging techniques with virtual chromoendoscopy. Extent of CAG/IM will be endoscopically staged with enhanced imaging and compared with standard WLE. Histopathological risk stratification through targeted biopsies will be compared with endoscopic disease staging and to random biopsy staging on WLE as a reference. At least 234 patients are required to show a 10% difference in sensitivity and accuracy between enhanced imaging endoscopy-led staging and the current biopsy-led staging protocol of gastric atrophy with a power (beta) of 80% and a 0.05 probability of a type I error (alpha).

The study was approved by the respective Institutional Review Boards (Netherlands: MEC-2018-078; UK: 19/LO/0089). The findings will be published in peerreviewed journals and presented at scientific meetings. Trial registration number NTR7661.

Introduction

Gastric adenocarcinoma remains a major cause of cancer mortality and is the most commonly diagnosed malignant condition of the gastrointestinal (GI) tract (1-4). Although incidence rates had previously been declining, recent studies demonstrated this differs among population subgroups. For example, an increasing incidence of gastric adenocarcinoma among young white cohorts in Western countries was objectified. This may be due to an increasing prevalence of gastric cancer precursors among younger adults, in particular chronic atrophic gastritis (CAG), intestinal metaplasia (IM) and dysplasia (5, 6). These studies suggest that gastric cancer incidence rates may plateau or even increase again in the upcoming years. Importantly, with the exception of Japan and Korea, the majority of gastric cancers worldwide are diagnosed at later stage. This results in a poor prognosis with less than 30% 5 year survival (1, 2, 7). Japan's earlier stage of diagnosis and superior 5 year survival high-light the need for earlier recognition and treatment (8).

Endoscopic recognition of the premalignant stomach has long been problematic and limited by the ability of endoscopist and the imaging tools. A previous study demonstrated that 22% of high-grade dysplastic lesions and early gastric cancers were missed (9, 10). A meta-analysis and systematic review of endoscopy follow-up studies confirmed that a marked proportion of early gastric cancers are missed at endoscopy (10). Therefore, current practice uses histology-based staging (11, 12). However, endoscopic imaging has significantly improved with high-definition endoscopes and imaging enhancement technologies now routinely available. Some recent studies already suggested that accurate endoscopic staging of CAG and gastric intestinal metaplasia (GIM) is achievable and can robustly predict gastric adenocarcinoma risk. Importantly, the interobserver and intraobserver reproducibility characteristics of endoscopic CAG and GIM severity assessment are in experienced hands moderate to excellent (13-18). These marked improvements in endoscopic technology and the shift towards an endoscopy-led approach will empower the endoscopist to risk stratify individuals with greater accuracy and decrease the already huge burden placed on our endoscopy and histopathology departments. Therefore, the aim of this study is to evaluate if enhanced endoscopic imaging, including high-definition white light endoscopy (WLE) and virtual chromoendoscopy, alongside targeted biopsies, provides an accurate and reproducible assessment of CAG and IM disease extent and staging, when compared with the current practice of WLE and random biopsies through the Sydney protocol biopsy strategy.

Methods and analysis

Aims

The primary aim of this study is to assess the diagnostic accuracy for the endoscopic diagnosis of IM in Sydney biopsy locations comparing standard endoscopic staging with random biopsies with enhanced imaging with biopsies targeted to GIM (19). The Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines were followed (20). Study sites are located in the Netherlands and the UK. Secondary objectives are to evaluate (a) reproducibility of endoscopic staging after expert review, (b) reproducibility of histopathology for detection of IM, (c) the number of dysplastic or neoplastic lesions detected and (d) effects of inspection time of gastric mucosa on diagnostic accuracy.

Design

This is a prospective, multicentre registry study on the accuracy and reproducibility of enhanced endoscopic imaging, including high-definition WLE and virtual chromoendoscopy, for the staging of CAG and IM. Two upper endoscopies will be performed on two separate occasions (6–12 months in between) using standard white-light endoscopy plus random biopsies (current diagnostic strategy) at the first endoscopy and enhanced endoscopic imaging with targeted biopsies (proposed diagnostic strategy) at the second endoscopy. We will compare both approaches using histopathology as a reference and assess the accuracy and reproducibility of enhanced endoscopic imaging (figure 1).

Patient and public involvement

We maintained close links with patient alliances and interest groups, both in the Netherlands as well as in the UK. This close relationship informs our practice and is the basis for the current study design. We will engage closely with patient interest groups to communicate research findings and ensure that our deliverables are fit for purpose.

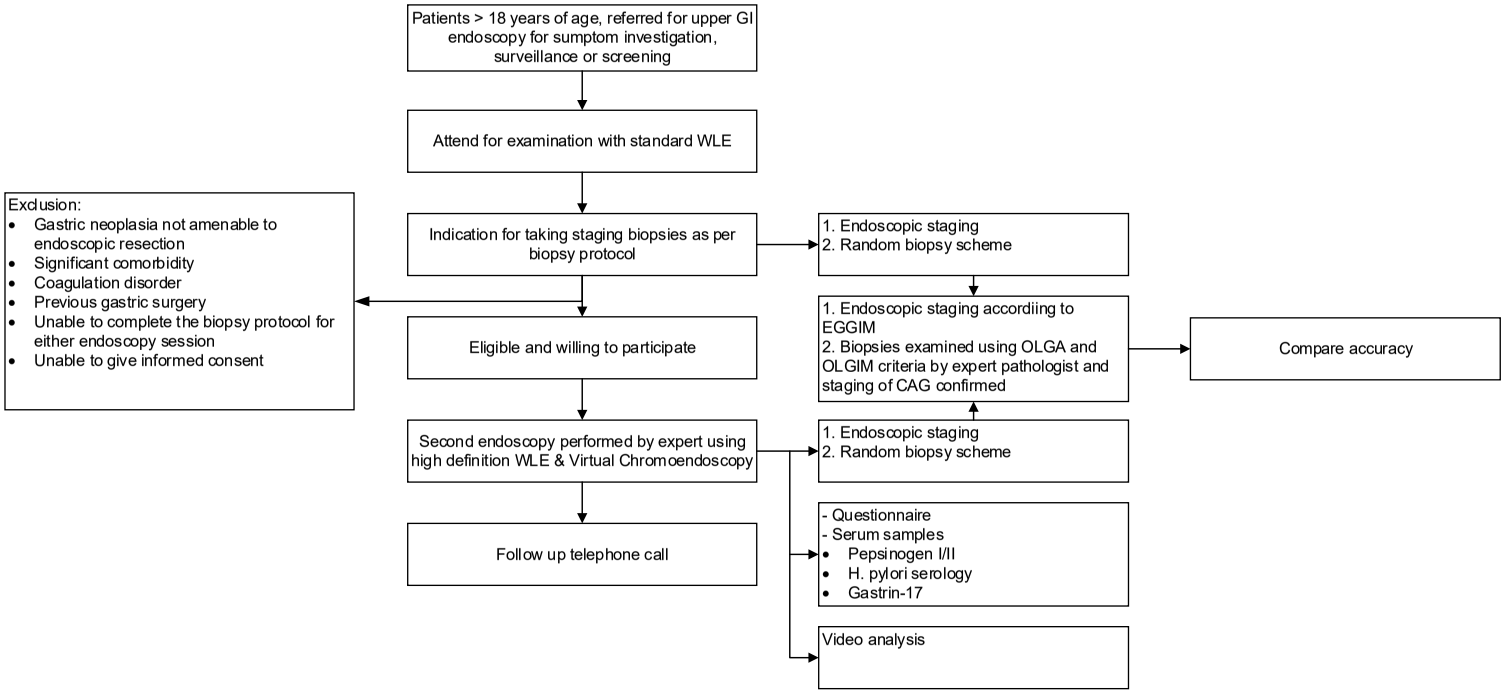

Figure 1. Flowchart of the study design. CAG, chronic atrophic gastritis; EGGIM, endoscopic grading of gastric intestinal metaplasia; GI, gastrointestinal; H. pylori, Helicobacter pylori; OLGA, operative link for gastritis assessment; OLGIM, operative link for gastric intestinal metaplasia assessment; WLE, white light endoscopy.

Participants

Sample size

For estimation of sample size, we assume that the diagnosis of CAG or IM on enhanced imaging and targeted biopsies must be set with at least a 90% sensitivity with WLE and random biopsies as a reference (15). A power (beta) of 80% and a probability of type I error (alpha) of 0.05 will be handled. That purpose requires at least 234 patients to be recruited to show a 10% difference in sensitivity between enhanced endoscopy-led staging and the standard WLE.

Recruitment

All patients (>18 years of age) referred to the endoscopy department for routine diagnostic upper GI endoscopy and diagnosed with CAG or IM between November 2018 and June 2020 are eligible for inclusion if able to give informed consent. Patients are excluded when having (1) gastric neoplasia not amenable to endoscopic resection, (2) no indication for Sydney biopsy staging on standard WLE, (3) significant comorbidity, a coagulation disorder, (5) previous gastric surgery or (6) are unable to complete the biopsy protocol in either endoscopy session.

Interventions

Baseline characteristics

All patients are asked to complete a questionnaire on life-style factors, medical history, past interventions, medication use and family history of gastric cancer.

White light endoscopy

Patients referred to the endoscopy department for upper GI endoscopy for investigation of symptoms or for surveillance of a known condition will undergo their procedure on a standard diagnostic gastroscopy list. Patients found to have CAG or IM will be prospectively identified. During the initial procedure, patients will receive the current recommended practice. Current practice is to initially identify if gastric atrophy is present and to inspect the gastric mucosa for areas suspicious for dysplasia or malignancy. Any mucosal abnormalities suspicious for dysplasia or malignancy are biopsied with tissue biopsies placed in separate containers. Following this, 10 random biopsies are taken according to the Sydney protocol (**see also figure 2**): 4 quadrant biopsies of the antrum, 2 biopsies from the incisura and 4 biopsies from the body of the stomach, respectively, 2 from the lesser curve, and 2 from the greater curve.

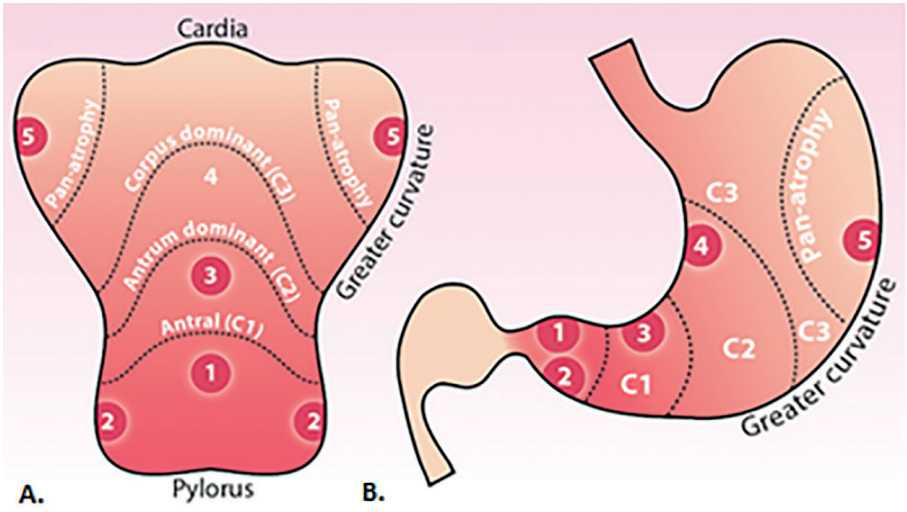

Figure 2. Biopsy strategy. (A) Sydney protocol biopsy sites in the opened stomach along the greater curvature; (B) biopsy sites in the anatomical view.

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Enhanced imaging endoscopy

Patients who opt to be recruited to the study will be invited for a second endoscopy at 6–12 months interval. This will be performed by one of the experts on this protocol. The endoscopists will be blinded to any previous endoscopy or biopsy results. This second endoscopy will be recorded and performed using enhanced endoscopic imaging. Given that these patients will have recently undergone a complete upper GI endoscopy, while all anatomical land-marks will be viewed, the focus of this examination will be on the gastric mucosa. The endoscopist will record (1) the extent of gastric atrophy, (2) the presence and extent of IM in each of the aforementioned areas. This will be done using our simplified endoscopic metaplasia scoring system (GRAHAM Score) (**table 1**).

Biopsies will then be taken in the following manner: (1) areas of IM found in any of the Sydney protocol areas, (2) Sydney areas negative for GIM will be randomly biopsied, as control, to complete the assessment and (3) lesions suspicious for dysplasia or malignancy.

Table 1. Simplified endoscopic gastric intestinal metaplasia staging system: 'GRAHAM Score'

	Focal / Minimal metaplasia (<1/3 of surface coverage)	Moderate / extensive metaplasia (>1/3 surface coverage)
Antrum & incisura	1	2
Lesser curve	1	2
Greater curve	1	2

Histopathological assessment

Each biopsy will be reviewed at the teaching hospital by one of the expert GI histopathologists named on this protocol according to the established operative link for gastritis assessment and operative link for gastric intestinal metaplasia assessment staging systems (21). Histopathologists will be blinded to whether biopsies were directed at areas suspicious for IM and to the biopsy results of WLE staging. A proportion of biopsy samples will be reviewed and rescored by a second expert GI histopathologist, who is blinded to the initial results. This is to ensure interobserver reproducibility for histopathological detection of IM.

Serology assessment

A proportion of the collected serum will be used to assess Helicobacter pylori serology, pepsinogen I/II ratio and gastrin-17. The remaining serum will then be stored for use in future studies exploring the development of molecular biomarkers for gastric atrophy risk stratification.

Data collection and management

All data collected for this study will be recorded in an anonymised format on a centralised, secure webbased platform (OpenClinica). Source data will be recorded in patients' notes or electronic health records, and hard copies of consent forms will be stored in a secure locked cabinet per site. All study data will be stored in a linked anonymised fashion against a study number, with the registry of study numbers stored separately on an encrypted database.

Statistical analyses

For descriptive statistics, mean (±SD) will be used in case of a normal distribution of variables and median (25–75%) will be used for variables with a skewed distribution. Where appropriate, the Student's ttest or Mann– Whitney U test will be used.

Diagnostic accuracy of endoscopic diagnosis of CAG and IM is defined as the total number of directed biopsies that confirm the endoscopic impression of the presence or absence of IM divided by the total number of biopsies (accuracy=true positives+true negatives/ all biopsies). Results will be compared with the histopathology outcomes using the $\chi 2$ test after multiple testing correction as well as kappa values for interobserver agreement among endoscopists and histopathologists.

After study completion, all videos will be collated and anonymised prior to expert panel review and estimation of the severity and extent of atrophy as well as IM. Five expert reviewers will review 50 videos each (kappa 0.4) for the purposes of assessing interobserver reliability. Sensitivity, specificity and global accuracy along with the 95%

confidence intervals will be established. Duration of inspection time of gastric mucosa and its relation to diagnostic accuracy will be evaluated using, when appropriate, a paired t-test or Wilcoxon test. All tests will be two-sided.

Ethics and dissemination

Results will be disseminated to potential users in academia and medical industries, through the standard routes of presentations, oral and posters, at local, national and international conferences, undergraduate and graduate teaching and through peerreviewed publication. Efforts will be made to present work in a timely manner at key international meetings to encourage collaboration with research partners.

Discussion

The recently updated European MAnagement of Precancerous conditions and lesions in the Stomach (MAPS) guidelines recommend surveillance of patients with premalignant gastric mucosal lesions by performing endoscopy (preferably with advanced imaging) and taking random biopsies of the stomach for histopathological assessment. This enables the detection of progression to high-risk lesions and eventually cancer (22). However, various studies indicate that a marked proportion of advanced gastric lesions are missed at a stage when these lesions are potentially still amenable to endoscopic management. This implies that the risk of undertreatment is undeniable (9). The development of high-definition endoscopy and virtual chromoendoscopy has been a main focus of research in the past years and it has revolutionised the endoscopic assessment of the premalignant stomach by being superior to white light imaging (23). The updated MAPS guidelines opt for the use of advanced imaging as the preferred surveillance method. Recently, Esposito et al showed a scoring tool based on endoscopic staging using Endoscopic Grading of Gastric Intestinal Metaplasia (EGGIM) with advanced imaging as a promising decision tool to identify patients at risk of gastric cancer (24). However, currently there are no studies on how the use of advanced endoscopic imaging to detect IM of the stomach can be applied in countries with a low prevalence of IM. Still, histological confirmation is needed through random biopsies. Future steps are to evaluate the possible shift towards an endoscopy-led strategy now these marked improvements in endoscopic technology are within our reach. This prospective study was therefore designed to determine the validity of endoscopy-led staging of the premalignant stomach using advanced imaging and taking targeted biopsies for histological.confirmation.

A previous comparative study between white light and high-definition endoscopy for the diagnosis of premalignant gastric lesions indeed showed a superior diagnostic accuracy of high-definition endoscopy (15). However, one limitation was that WLE and high-definition endoscopy were performed during one occasion, which implied that the endoscopist was

not blinded to the WLE results. Within the current protocol, we choose to perform the procedures on two separate occasions with blinding of the expert endoscopist to the previous WLE results.

Over the years, serological markers have shown major promise for predicting the presence and severity of gastric premalignant lesions (25-27). Pepsinogens are serological markers for atrophy in the stomach and can be divided into pepsinogen I and II. A decreased PG I/II ratio indicates the presence of atrophic changes. Gastrin serum levels are indicative for gastric acid output and are increased in the presence of atrophic changes (27). The collection of serum samples was included in our protocol to strengthen risk stratification for progression of premalignant gastric lesions.

A few limitations of the study should be mentioned. All highdefinition endoscopies will be performed by expert endoscopists at either site. A potential caveat with this design is the generalisability of the study outcomes to nonexpert settings. To test this, we selected a panel of independent endoscopists who will review recorded endoscopy videos in order to assess interobserver variability. The same limitation holds for the histopathological evaluation of the biopsy samples. Therefore, a proportion of the samples will be reviewed and rescored by a blinded second expert GI histopathologist.

In conclusion, prospective validation of endoscopy-led staging of the premalignant stomach will provide the needed evidence for an endoscopy-led risk stratification of patients at risk for gastric adenocarcinoma. This will allow rational design of tiered screening and surveillance protocols to benefit early stage gastric cancer detection within at-risk populations. This will cause major implications for affected patients and general healthcare resource utilisation.

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CHAPTER 6

Accuracy of H. pylori faecal antigen test using faecal immunochemical test (FIT)

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Gastric Cancer, October 2021

Abstract

Introduction

Gastric and colorectal cancer (CRC) are both one of the most common cancers worldwide. In many countries faecal immunochemical tests (FIT) based CRC screening has been implemented. We investigated if FIT can also be applied for detection of H. pylori, the main risk factor for gastric cancer.

Methods

This prospective study included participants over 18 years of age referred for urea breath test (UBT). Patients were excluded if they had used antibiotics/bismuth in the past four weeks, or a proton pomp inhibitor (PPI) in the past two weeks. Participants underwent UBT, ELISA stool antigen test in standard feces tube (SAT), ELISA stool antigen test in FIT tube (Hp-FIT), blood sampling, and completed a questionnaire on user friendliness. UBT results were used as reference.

Results

A total of 182 patients were included (37.4% male, median age 52.4 years (IQR 22.4)). Of these, 60 (33.0%) tested H. pylori-positive. SAT and Hp-FIT showed comparable overall accuracy 71.1% (95%CI 63.2-78.3) vs. 77.6% (95%CI 70.4-83.8), respectively (p=0.597). Sensitivity of SAT was 91.8% (95%CI 80.4-97.7) versus 94.2% (95%CI 84.1-98.9) of Hp-FIT (p=0.998). Serology scored low with an overall accuracy of 49.7% (95%CI 41.7-57.7). Hp-FIT showed highest overall user convenience.

Conclusion

FIT can be used with high accuracy and sensitivity for diagnosis of H. pylori and is rated as the most convenient test. Non-invasive Hp-FIT test is highly promising for combined upper and lower gastrointestinal (pre-) cancerous screening. Further research should investigate the clinical implications, benefits and cost-effectiveness of such an approach.

Introduction

Helicobacter pylori (H. pylori) is the most important risk factor for intestinal type gastric adenocarcinoma and classified as a class 1 carcinogen by the World Health Organization (WHO) (1). Current practice recommends eradicating H. pylori when identified in order to prevent H. pylori-associated disease (2). Some studies even advocate a "screen-and-treat" program to reduce gastric cancer burden (3). However, in low incidence gastric cancer regions the low prevalence rates of H. pylori infections limit cost efficiency of such a strategy (4). For high incidence regions screening might be effective (5-7).

Several non-invasive diagnostic tests are already available. The urea breath test (UBT) has the highest sensitivity (90-96%) and specificity (88-98%) and has similar accuracy to the stool antigen tests (SAT) using ELISA (enzyme immune assay). Serology testing for H. pylori antibodies is easy to perform, but does not distinguish between active or prior infection, as antibodies can persist in the blood after eradication (2). Previous studies compared invasive and non-invasive methods for the diagnosis of H. pylori in terms of sensitivity and specificity (8, 9). Importantly, in order for a test to be effective, patient preference and acceptance are just as important as test performances (10).

Faecal immunochemical tests (FIT) are used in colorectal cancer (CRC) screening and are known for their ease of use (11). Simultaneous non-invasive screening for gastric and colorectal cancer is potentially very attractive, in particular in populations with a higher incidence of both cancers. In addition, it may be cost effective (12, 13). FIT sampling may be a suitable medium for both goals. But also, for clinical purposes to diagnose Hp infection by a non-invasive, easy to perform test at home. However, the potential to determine the presence of faecal H. pylori stool antigen in FIT has thus far not been investigated. While analyses of the faecal microbiome have already been proven promising and feasible in FIT and feces, suggesting that FIT might be a good tool to study bacterial presence (14, 15).

We therefore investigated whether H. pylori stool antigen can be detected in FIT and how this outcome relates to the other non-invasive H. pylori tests. Furthermore, we assessed patient preferences for these tests.

Methods

Study design

This prospective study was performed in two hospitals (one academic and one regional) in the Netherlands. Patients were eligible for inclusion if they were over 18 years of age and were referred for UBT at the general practitioner's discretion. They were identified through the outpatient clinic of the participating hospitals and contacted by telephone.

After informed consent, patients were sent a first questionnaire and feces sampling kits with instructions. Patients were excluded if they had used antibiotics/bismuth in the past four weeks, or a proton pomp inhibitor (PPI) in the past two weeks. All participants underwent UBT, SAT, Hp-FIT and blood sampling. Patient inclusion took place between February 2018 and December 2020. UBT results were used as reference. The performers of the SAT, Hp-FIT and blood sampling were blinded to the UBT results. The institutional review boards of both participating hospitals approved the study (MEC-2017-528). This trial was registered in the Dutch trial register (NTR7052). All co-authors had access to the study data and had reviewed and approved the final manuscript.

Baseline data collection

All participants completed two questionnaires, one before and one after performing the tests. The first questionnaire concerned details about age, sex, ethnicity and items about lifestyle factors, medical history, family history and medication use. Expected convenience and burden of the tests were assessed. The second questionnaire was handed out after all tests had been performed and included questions about actual experienced convenience and burden of each test.

Expected and actual experienced convenience and burden were asked in the following manner: patients were asked about pain, embarrassment and overall burdensome for all tests. All aspects had to be rated on a scale from zero to four. Zero being "not at all painful/embarrassing /burdensome, and four being extremely painful/embarrassing / burdensome (**Supplementary material 1**).

Sampling collection

Feces sampling for Hp-FIT and SAT was performed at home on the same stool and collected within 24 hours of the scheduled UBT. Patients were instructed to keep the stool at -4°C until the hospital visit. A blood sample was drawn during the hospital visit. Feces and blood samples were stored at - 80°C until analysis. Serological testing of H. pylori antibodies was performed by commercial ELISA tests (H. pylori IgG ELISA, Gastropanel, Biohit Oyi, Helsinki Finland). All tests were performed according to the manufacturer's instructions, which allowed for a one-time -80°C storage and defrosting.

Serum samples

Serum samples were diluted 1:200 in sample diluent, 100µl of this solution was added to the H. pylori antigen coated microplates. After 30 minutes of incubation, samples were washed, and conjugate solution was added. After another 30 minutes of incubation samples were washed and the substrate solution was added. Quantification of the optical density was performed using a spectophomometer (Infinite M Nano Tecan group ldt.;

Mannedorf, Switzerland) at a wavelength of 450nm. For the serology test a cutoff of 30 EIU was used as per the manufacturers' protocol.

Stool antigen ELISA

For the stool antigen ELISA a commercial kit was used (Faecal Helicobacter pylori Antigen, ref KT 826, Epitope Diagnostics Inc.; San Diego, USA). In short, 40mg of faecal material was suspended in 1ml of assay buffer. A total of 100µl of this sample was added to monoclonal antibody coated microwell plates and incubated for 60 minutes. After washing the plate, the tracer antibody was added to the wells and incubated for 30 minutes. The plates were washed again and the HRP substrate was added for 10 minutes to develop the wells. Quantification of the optical density was performed using a spectophomometer (Infinite M Nano Tecan group ldt.; Mannedorf, Switzerland) on a wavelength of 450nm. For the stool antigen ELISA test a cutoff of 3 ng/mL was used as per the manufacturers' protocol.

For measurement of the FIT (OC-Sensor, Eiken) samples the same procedure was followed, except for sample preparation. For FIT, 100uL of undiluted, centrifuged FIT fluid was used. Clean FIT fluid was compared to assay buffer to confirm there was no interference of the FIT assay buffer on the procedure (not shown).

Sample size

Based on previous reports, we estimated the prevalence of H. pylori in the Dutch population at 30% (16). Sensitivity rates for the different non-invasive tests for H. pylori are 90-96% for the UBT, 86-94% for serological testing, and 81-98% for SAT. Sensitivity of Hp-FIT was unknown. Similar sensitivity rate as for the SAT was used (92%) to perform power calculations using the UBT as reference standard. For a one-sided non-inferiority margin of 10%, a total of 55 H. pylori-positive subjects and 110 controls were required (using a ratio of 1:2) to have 80% power to detect an effect for which the upper limit of a one-sided 95% confidence interval will exclude a difference in favour of the standard test of more than 10%.

Statistical analyses

Positivity rate (PR) was defined as the proportion of positive tests in participants with an analyzable test. The positive predictive value (PPV) comprised all participants diagnosed with H. pylori UBT by the studied test proportionally to participants with a positive H. pylori UBT result. The negative predictive value (NPV) comprised all participants with a negative H. pylori UBT result by the studied test proportionally to participants with a negative H. pylori UBT result. Sensitivity was calculated by dividing true positives by true positives plus false negative results, multiplied by 100. Specificity was calculated by dividing true negatives by true negatives plus false positives, multiplied by 100. Overall accuracy was calculated by dividing true positives and true negatives by all performed tests. Confidence

intervals for sensitivity, specificity and accuracy are "exact" Clopper-Pearson confidence intervals. For all tests, Receiver Operating Characteristic (ROC) curves with their Area Under the Curve (AUC) were calculated. An AUC > 0.9 was considered as "outstanding discrimination", 0.8-0.9 as "excellent discrimination", 0.7-0.8 as "acceptable discrimination", 0.5-0.7 as "poor discrimination" and 0.5 as "no discrimination" (17). Differences between categorical variables, such as patient preferences in questionnaires, were evaluated using a chi squared test or McNemar test when appropriate. Differences between means were evaluated using a t-test. A two-sided significance level of $p<0.05$ for all tests was used.

Results

Baseline characteristics

In total, 222 patients were considered for this study of which 182 patients were included based on the in- and exclusion criteria (37.4% male, median age 52.4 years (IQR 22.4)) (**Figure 1**). Of these, 60 (33.0%) tested positive for H. pylori by UBT (**Table 1**).

Test accuracy

All tests were plotted in a ROC curve (**Figure 2**). The SAT showed the highest AUC with 0.91, the Hp-FIT showed an AUC of 0.85. The serology test had an AUC of 0.68.

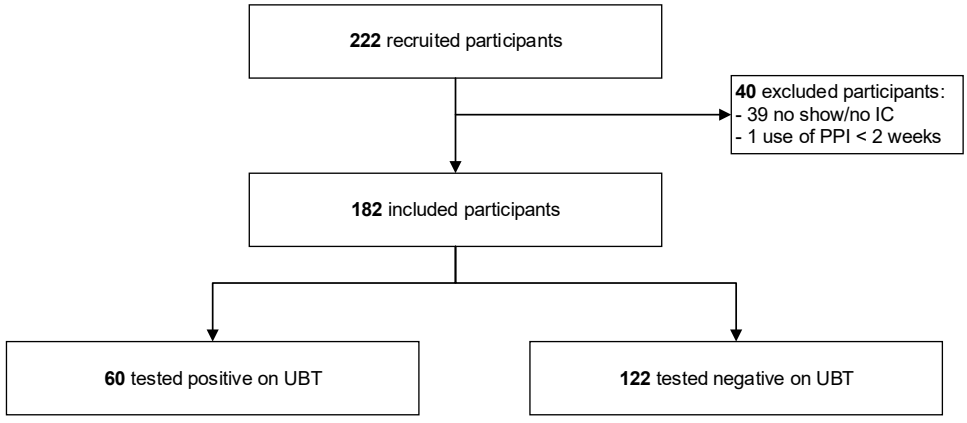


Figure 1. Flowchart of study inclusions; PPI; proton pump inhibitor, IC; informed consent, UBT; urea breath test

Cutoff points

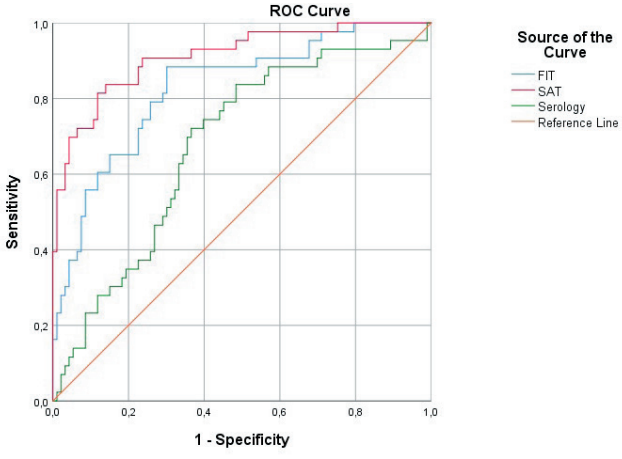
Since use of FIT in this context is newly investigated, a cutoff is not yet established. **Table 2** shows all test outcomes for Hp-FIT when the same cutoff is used as for SAT (i.e. 3 ng/mL). Under these conditions, SAT and Hp-FIT showed comparable overall accuracy; 71.1% (95%CI 63.2-78.3) vs. 7.·6% (95%CI 70.4-83.8), respectively (p=0.597). The sensitivity rate for SAT was 91.8% (95%CI 80.4-97.7) versus 94.2% (95%CI 84.1-98.9) for Hp-FIT (p=0.998).

Both tests however had a low specificity rate of 61.0% (95%CI 50.7-70.6) and 69.7% (95%CI 60.2-78.1) for SAT and Hp-FIT, respectively (p=0.442). The serology test scored low on all primary outcomes, with an overall accuracy rate of 49.7% (95%CI 41.7-57.7).

Means of absolute stool antigen concentration were compared for Hp-FIT and SAT for false positive and true positive test results. Absolute stool H. pylori antigen concentration in false positive Hp-FIT versus true positive Hp-FIT was 9.3 ng/mL (95%CI 8.6-12.3) vs 30.9 ng/mL (95%CI 19.0-45.3) (p<0.001), respectively. For SAT this was 8.6 ng/mL (95%CI 5.4-9.8) for false positives, and 46.2 ng/mL (95%CI 32.4-58.3) for true positives (p<0.001).

Table 1. Baseline characteristics of the study population FIT; Faecal Immunochemical Test, IQR; Inter Quartile Range, UBT; Urea Breath test, SAT; Stool Antigen Test

	Study participants (n=182)
Sex: male (%)	68 (37·4)
Age: median (IQR)	52·4 (22·4)
Ethnicity n (%)	
Western Europe	110 (61·0)
Middle East	12 (6·5)
Western Africa	9 (4·8)
Latin America	7 (3·7)
Asian	8 (4·3)
Missing	36 (19·7)
Indication of UBT n (%)	
Diagnostic	53 (35.8)
Eradication	76 (51.4)
Lynch Screening	19 (12.8)
Positive test n (%)	60 (33·0)
Complete sampling n (%)	
FIT	161 (88·5)
SAT	149 (81·8)
Serum	159 (87·4)



	AUC (95%CI)
FIT	0.85 (0.78–0.92)
SAT	0.91 (0.86–0.97)
Serology	0.68 (0.59-0.78)

Figure 2. ROC curves for all tests AUC; Area Under the Curve, FIT; Faecal Immunochemical test, ROC; Receiver Operating Characteristics, SAT; Stool Antigen

Table 2. Primary outcomes measures of all tests at a cutoff of 3 ng/mL for SAT and Hp-FIT and 30 EIU for serology, CI; Confidence Interval, FIT; Faecal Immunochemical Test, NPV; Negative Predictive Value, PPV; Positive Predictive Value, PR; Positivity Rate, SAT; Stool Antigen Test

Test	PR (%) (95%CI)	PPV (%) (95%CI)	NPV (%) (95%CI)	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	Accuracy (%) (95%CI)
Hp-FIT	50.9 (43.0-58.9)	59.8 (52.6-66.6)	96.2 (89.4-98.7)	94.2 (84.1-98.9)	69.7 (60.2-78.1)	77.6 (70.4-83.8)
SAT	56.4 (48.0-64.5)	53.6 (47.1-59.9)	93.9 (85.5-97.5)	91.8 (80.4-97.7)	61.0 (50.7-70.6)	71.1 (63.2-78.3)
Serology	73.6 (66.0-80.3)	35.9 (32.3-39.7)	88.1 (75.6-94.6)	89.4 (76.9-96.5)	33.0 (24.4-42.6)	49.7 (41.7-57.7)

Choosing different cut-off levels affects performance of the test. Test outcomes at different cutoff points for Hp-FIT are therefore shown in **Table 3**. When the cutoff of Hp-FIT was raised up to 4 ng/mL or higher, the overall accuracy was lower. By raising the cutoff up to 6 ng/mL specificity rate increased to 74.6% (95%CI 65.9-82.0), however this came at the cost of a considerable decrease in the sensitivity rate (67.3% 95%CI 53.3-79.3). Lowering the cutoff to 2 ng/mL resulted in a lower overall accuracy due to a decrease in specificity rate (47.5% 95%CI 38.4-56.8).

Patient preferences

Expected and perceived burdens were compared for all participants using questionnaires before and after performing all tests. UBT was rated best, with only 13.8% of the participants perceiving moderate to severe overall inconvenience (ranking 3 or 4 on a scale from 0 to 4 with 0 being "no burden" and 4 " severe burden"), followed by Hp-FIT with 27.3%, the serum test 29·4% and lastly SAT with 40.9% (**Figure 3**). Inconvenience in SAT was mostly due to embarrassment due to the execution of the test (scooping feces (SAT) vs. picking feces (Hp-FIT)). Expected and perceived convenience was similar across most aspects. Overall, UBT was perceived as more convenient than expected.

Table 3. Test outcomes of FIT with different cutoffs, CI; Confidence Interval, FIT; Faecal Immunochemical Test, NPV; Negative Predictive Value, PPV; Positive Predictive Value, PR; Positivity Rate

Cutoff (ng/mL)	PR (%) (95%CI)	PPV (%) (95%CI)	NPV (%) (95%CI)	Sensitivity (%) (95%CI)	Specificity (%) (95%CI)	Accuracy (%) (95%CI)
2	62.1 (54.1-69.6)	47.1 (42.7-51.6)	95.1 (86.3-98.3)	95.0 (86.1-99.0)	47.5 (38.4-56.8)	63.2 (55.7-70.2)
4	44.7 (36.9-52.8)	57.0 (50.3-63.5)	92.1 (85.2-96.0)	88.3 (77.4-95.2)	67.2 (58.1-75.4)	74.2 (67.2-80.4)
5	39.1 (31.6-47.1)	59.5 (52.0-66.7)	89.8 (83.2-94.0)	83.3 (71.5-91.7)	72.1 (63.3-79.9)	75.8 (68.9-81.9)
6	34.2 (26.9-42.0)	59.2 (50.9-67.0)	85.9 (79.5-90.5)	67.3 (53.3-79.3)	74.6 (65.9-82.0)	74.7 (67.8-80.9)

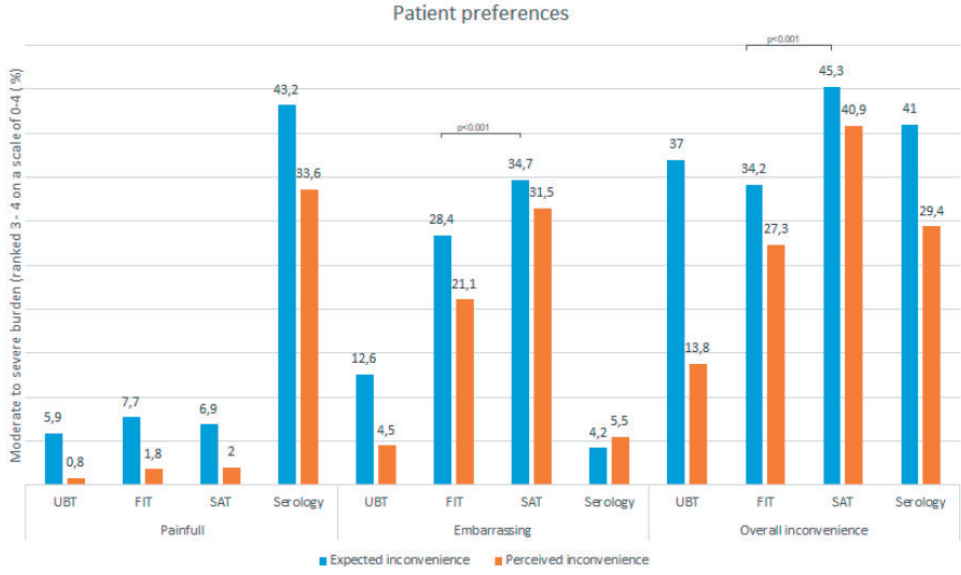


Figure 3. Histogram of patient preferences retrieved through questionnaires UBT; urea breath test, Hp-FIT; faecal immunochemical test for H. pylori

Discussion

We investigated FIT as a new non-invasive test for diagnosis of H pylori infection and compared the outcome of Hp-FIT directly to the other available non-invasive diagnostic H. pylori tests. This is the first study to show that it is possible to determine H. pylori antigen in FIT. Furthermore, we show that Hp-FIT has comparable accuracy and sensitivity rates to SAT and was perceived as a more convenient test. This study is an important stepping-stone towards (cost-efficient) combined upper and lower gastrointestinal pre- cancerous screening. As the FIT test is already widely used in current practice it can therefore easily

be adopted for such an expanded indication in general practitioners' offices, hospitals as well as in screening programs.

In previous studies, diagnostic tests for diagnosis of H. pylori showed that accuracy rates of stool antigen tests using ELISA are comparable with UBT (8, 9). The current Maastricht V consensus report therefore states that SAT and UBT can be used interchangeably (2). Our results showed lower specificity rates. This might be due to the fact that 45% of the study population underwent eradication therapy prior to testing. It is known that this could affect accuracy of stool antigen tests (9).

Both Hp-FIT and SAT showed a high rate of false positivity. This has been established before in a Cochrane meta-analysis in which the results of 101 different studies were compared (18). Unfortunately, all but one of these studies were of poor methodological quality, for which reason only a suboptimal indirect comparison could be made. A few possible explanations for the high rate of false positives were discussed in this meta-analysis. First, UBT was considered the golden standard for H. pylori positivity. However even though UBT is an outstanding test, false negative UBT results do occur (19). Second, there was large heterogeneity of cut off points used for each of the tests. The current study investigated the accuracy rates at different cutoff points. The currently used cutoff point of 3 ng/mL showed the most favorable accuracy rates. However, different cutoff points might be preferred for different purposes such as H. pylori eradication verification tests compared to diagnostic tests or screening purposes. For actual implementation of Hp-FIT in screening issues such as subsequent intervention after a positive test should be addressed (i.e. esophagogastroduodenoscopy, direct eradication therapy) taking into account already available guidelines per country.

As already stated, in order for a test to be widely adopted and effective, ease of use and non-invasiveness are likely as important as test accuracy (10). Therefore, this study also investigated patient preferences. The UBT showed to have the best overall convenience. When both faecal tests were compared, Hp-FIT appeared to be perceived as most convenient. From previous CRC screening studies we already have learned that feces tests with a pricker instead of a scoop are more convenient in use (11). There are some clear benefits of using SAT or Hp-FIT over UBT in particular for patients since the test can easily be performed at home. Further also particularly from a socioeconomic point of view since there is no need for advanced expensive technical materials or direct contact with a technician or nurse.

This study has several limitations. First, the UBT was used as the golden standard instead of biopsy confirmation. This might skew the overall results by a small margin of a 96% sensitivity of UBT compared to biopsy testing (2). This happens most profoundly in the case

of concurrent use of PPIs (20). Recent use of PPIs or bismuth was therefore an exclusion criterium in our study. Furthermore, UBT is known to produce rare false positive results in the presence of non-H. pylori urease producing bacteria or fungi (i.e. Proteus mirabilis, Citrobacter freundii, Klebsiella pneumoniae, Enterobacter cloacae and Staphylococcus aureus) in either the stomach or the oral cavity (21, 22).

Second, for Hp-FIT analysis 100uL of undiluted, centrifuged FIT fluid was used. This might not always fully correspond with the same amount of feces. Hence, this also might affect test results. However, our study endpoints are based on binomial results (either positive or negative for H. pylori), which makes the absolute amount of feces per test of less relevance. Future studies should compare different kits for both FIT and SAT. Third, patient preferences results might be biased since study drop-outs could not be questioned about preferences. Fourth, the use of PPI, antibiotics or bismuth was an exclusion criterium of the study tested through a questionnaire. This might cause reporting bias. In a real life (screening) setting it should be accounted for that the use of PPIs will not always be ceased and therefore will affect accuracy.

This study is the first to show that Hp-FIT can be used as a new and convenient test within daily practice. With this, it is an important step within screening, being a first step towards a potential cost-efficient, dual screening program of the upper and lower gastrointestinal tract.

Acknowledgements

The authors would like to acknowledge B.H.C.M. Roovers, J. Francke, M. Ouwendijk and F. van Deurzen for their assistance in the execution of the tests in the Erasmus MC. We would also like to acknowledge A. van Liere-Baron for her assistance in organizational tasks and logistics at the Albert Schweitzer Hospital.

This study was supported by the Dutch Digestive Foundation (D18-02).

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Supplementary material

Supplementary material 1 Questionnaires (in Dutch)

Toelichting op deze vragenlijst
U heeft een uitnodiging ontvangen om mee te doen aan de studie die onderzoekt of de maagbacterie Helicobacter Pylori (Hp) in de FIT ontlastingstest bepaald kan worden. Graag willen wij weten wat u van onderzoek vindt.

Wij vinden uw mening erg belangrijk, ook als u besloten heeft om niet mee te doen of als u nog geen keuze gemaakt heeft.

Het is belangrijk dat de vragenlijst wordt ingevuld door degene aan wie de brief is geadresseerd. Controleer daarom of uw naam in de brief is vermeld. Is dit niet het geval, wilt u dan de vragenlijst aan de persoon geven voor wie deze is bestemd?

Er zijn geen goede of foute antwoorden, het gaat om uw persoonlijke ervaring. Uw vragenlijst zal anoniem worden verwerkt.

Invulinstructie
- In deze vragenlijst kunt u uw antwoord geven door een antwoordvakje aan te kruisen.
- Als u al een vakje heeft aangekruist en u wilt uw antwoord wijzigen, dan moet het foutief aangekruiste vakje geheel zwart/blauw gemaakt worden – vervolgens kunt u het juiste antwoordvakje aankruisen.
- Bij vragen waar u zelf iets moet opschrijven, schrijft u dan in blokletters.
- Wij verzoeken u alle vragen te beantwoorden.

Met reguliere ontlastingstest (SAT) wordt bedoeld:

Met de te onderzoeken test (FIT) wordt bedoeld:

Hartelijk dank voor uw medewerking.

Mw. Dr. M.C.W. Spaander, Maag-, Darm-, Leverarts, Erasmus MC
Mw. Drs. S.A.V. Nieuwenburg, arts-onderzoeker Maag- Darm- en Leverziekten, Erasmus MC

Voor vragen over deze vragenlijst of over eventuele deelname aan het onderzoek kunt u bellen met de studietelefoon, te bereiken op werkdagen op telefoonnummer 06-50033983

Vragenlijst Hp bepaling in FIT - Verwachtingen

1. Hoe duidelijk vond u de uitleg over het onderzoek?

☐	☐	☐	☐	☐
zeer duidelijk	duidelijk	onduidelijk	zeer onduidelijk	niet gelezen

2. Waarover had u graag meer informatie gekregen? (U mag meerdere antwoorden geven)

- ☐ het doel van het onderzoek
- ☐ hoe vaak maagaandoeningen voorkomen
- ☐ de voordelen van deelname
- ☐ de nadelen van deelname
- ☐ de vrijwilligheid van deelname
- ☐ niets, de informatie was voor mij voldoende
- ☐ anders, namelijk…

Onderstaande vragen gaan over uw verwachtingen van de te ondergane onderzoeken voor de Helicobacter pylori bepaling in bloed, ontlasting en uitgeademde lucht. Wilt u bij elke uitspraak aangeven in hoeverre u het eens dan wel oneens bent met de volgende uitspraken. Het is belangrijk dat u hierbij uw eigen mening of gevoel weergeeft. Er zijn geen goede of foute antwoorden.

1. In hoeverre verwacht u dat <u>de ademtest</u> belastend zal zijn?

☐	☐	☐	☐	☐
helemaal niet belastend	een beetje belastend	Enigszins belastend	Tamelijk belastend	Zeer belastend

2. In hoeverre verwacht u dat <u>de ademtest</u> pijnlijk zal zijn?

☐	☐	☐	☐	☐
Helemaal niet pijnlijk	Een beetje pijnlijk	Enigszins pijnlijk	Tamelijk pijnlijk	Zeer pijnlijk

3. In hoeverre verwacht u dat <u>de ademtest</u> beschamend/gênant zal zijn?

☐	☐	☐	☐	☐
helemaal niet beschamend	een beetje beschamend	enigszins beschamend	tamelijk beschamend	zeer beschamend

4. In hoeverre verwacht u dat <u>de reguliere ontlastingstest (SAT)</u> belastend zal zijn?

☐	☐	☐	☐	☐
helemaal niet belastend	een beetje belastend	Enigszins belastend	Tamelijk belastend	Zeer belastend

5. In hoeverre verwacht u dat <u>de reguliere ontlastingstest (SAT)</u> pijnlijk zal zijn?

☐	☐	☐	☐	☐
Helemaal niet pijnlijk	Een beetje pijnlijk	Enigszins pijnlijk	Tamelijk pijnlijk	Zeer pijnlijk

6.	In hoeverre verwacht u de reguliere ontlastingstest (SAT) beschamend/gênant zal zijn?				
	☐	☐	☐	☐	☐
	helemaal niet beschamend	een beetje beschamend	enigszins beschamend	tamelijk beschamend	zeer beschamend
7.	In hoeverre verwacht u dat de te onderzoeken test (FIT) belastend zal zijn?				
	☐	☐	☐	☐	☐
	helemaal niet belastend	een beetje belastend	Enigszins belastend	Tamelijk belastend	Zeer belastend
8.	In hoeverre verwacht u dat de te onderzoeken test (FIT) pijnlijk zal zijn?				
	☐	☐	☐	☐	☐
	Helemaal niet pijnlijk	Een beetje pijnlijk	Enigszins pijnlijk	Tamelijk pijnlijk	Zeer pijnlijk
9.	In hoeverre verwacht u de te onderzoeken test (FIT) beschamend/gênant zal zijn?				
	☐	☐	☐	☐	☐
	helemaal niet beschamend	een beetje beschamend	enigszins beschamend	tamelijk beschamend	zeer beschamend
10.	In hoeverre verwacht u dat de bloedtest belastend zal zijn?				
	☐	☐	☐	☐	☐
	helemaal niet belastend	een beetje belastend	Enigszins belastend	Tamelijk belastend	Zeer belastend
11.	In hoeverre verwacht u dat de bloedtest pijnlijk zal zijn?				
	☐	☐	☐	☐	☐
	Helemaal niet pijnlijk	Een beetje pijnlijk	Enigszins pijnlijk	Tamelijk pijnlijk	Zeer pijnlijk
12.	In hoeverre verwacht u dat de bloedtest beschamend/gênant zal zijn?				
	☐	☐	☐	☐	☐
	helemaal niet beschamend	een beetje beschamend	enigszins beschamend	tamelijk beschamend	zeer beschamend

Tot slot nog enkele vragen over uzelf.

13. Wat is uw burgerlijke staat?

- ☐ alleenstaand
- ☐ samenwonend/gehuwd
- ☐ duurzame relatie, maar niet samenwonend
- ☐ anders, namelijk…

14. Welke situatie is voor u op dit moment het meest van toepassing?

- ☐ ik heb betaald werk voor ____ uur per week (graag invullen)
- ☐ ik doe geen betaald werk want ik zorg voor de huishouding en evt. kinderen
- ☐ ik doe geen betaald werk vanwege gezondheidsproblemen
- ☐ ik doe geen betaald werk om andere redenen (bijv. onvrijwillig werkloos, vrijwilligerswerk)
- ☐ ik ben gepensioneerd of met de VUT

15. Tot welke bevolkingsgroep voelt u zich behoren?

- ☐ Nederlands
- ☐ Turks
- ☐ Marokkaans
- ☐ Hindoestaans
- ☐ Creools
- ☐ Surinaams
- ☐ anders, namelijk…

16. Welke taal spreekt u thuis?

- ☐ alleen Nederlands
- ☐ Nederlands en een andere taal
- ☐ andere taal, namelijk…

17. Heeft u moeite bij het lezen van kranten, brieven of folders in het Nederlands?

- ☐ ja, altijd
- ☐ ja, vaak
- ☐ ja, soms
- ☐ nee, nooit

18. Kent u mensen die (ook) hebben meegedaan aan dit onderzoek

☐ ja ☐ nee

19. Hoe vaak bezoekt u gemiddeld een dokter? (uitgezonderd de artsen die u in het kader van dit onderzoek ziet)

- ☐ ongeveer 1 maal per maand of vaker
- ☐ om de paar maanden
- ☐ ongeveer 1 maal per jaar
- ☐ eens in de 2 tot 5 jaar

20.	Hoe zou u over het algemeen uw gezondheid noemen?				
	☐	☐	☐	☐	☐
	slecht	matig	goed	zeer goed	Uitstekend
21.	Heeft u wel eens last van:				
	Zuurbranden	☐		☐	
		ja		nee	
	Misselijkheid	☐		☐	
		ja		nee	
	Braken	☐		☐	
		ja		nee	
	Snel vol gevoel	☐		☐	
		ja		nee	
	Pijn in de maag	☐		☐	
		ja		nee	
	Andere klachten	☐		☐	
		Ja, namelijk:		nee	

22.	Gebruikt u pijnstillers zoals ibuprofen/diclofenac/neurofen/advil/aspirine? (NSAID's)		
	☐		☐
	Ja, namelijk .. keer/week		nee
23.	Gebruikt u zuurremmers zoals Rennies, gaviscon, omeprazol, pantoprazol, nexium, pariet?		
	☐		☐
	Ja, namelijk .... keer/week		Nee
24.	Bent u ooit eerder behandeld met antibiotica vanwege een maagbacterie?		
	☐		☐
	Ja, geschatte maand/jaartal:		nee
25.	Rookt u?		
	☐	☐	☐
	Ja, namelijk .... sig/per dag, sinds 19..	nee	niet meer, gestopt sinds 19..
26.	Drinkt u alcohol?		
	☐		☐
	Ja, namelijk .... glazen/week		Nee
27.	Komen er in de familie maagklachten voor?		
	☐		☐
	Ja, namelijk bij....		nee
28.	Is er bij een familielid wel eens een antibioticakuur voorgeschreven voor een maagbacterie?		
	☐		☐
	Ja, namelijk bij ..		nee

29.	Komt er in de familie maagkanker voor?		
		☐	☐
		Ja, namelijk bij ..	nee

Tot slot.

30. Wat is de datum van invullen van deze vragenlijst?

_____ - _____ - _____ (dag-maand-jaar)

Wilt u alstublieft controleren of u alle vragen heeft ingevuld en geen bladzijden heeft overgeslagen.

HARTELIJK DANK VOOR UW MEDEWERKING

Vragenlijst Hp bepaling in FIT - Ervaringen

Onderstaande vragen gaan over uw verwachtingen van de reeds ondergane onderzoeken voor de Helicobacter pylori bepaling in bloed, ontlasting en uitgeademde lucht. Wilt u bij elke uitspraak aangeven in hoeverre u het eens dan wel oneens bent met de volgende uitspraken. Het is belangrijk dat u hierbij uw eigen mening of gevoel weergeeft. Er zijn geen goede of foute antwoorden.

1. In hoeverre vond u de ademtest belastend?

☐	☐	☐	☐	☐
helemaal niet belastend	een beetje belastend	Enigszins belastend	Tamelijk belastend	Zeer belastend

2. In hoeverre vond u de ademtest pijnlijk?

☐	☐	☐	☐	☐
Helemaal niet pijnlijk	Een beetje pijnlijk	Enigszins pijnlijk	Tamelijk pijnlijk	Zeer pijnlijk

3. In hoeverre vond u de ademtest beschamend/gênant?

☐	☐	☐	☐	☐
helemaal niet beschamend	een beetje beschamend	enigszins beschamend	tamelijk beschamend	zeer beschamend

4. In hoeverre vond u de reguliere ontlastingstest (SAT) belastend?

☐	☐	☐	☐	☐
helemaal niet belastend	een beetje belastend	Enigszins belastend	Tamelijk belastend	Zeer belastend

5. In hoeverre vond u de reguliere ontlastingstest (SAT) pijnlijk?

☐	☐	☐	☐	☐
Helemaal niet pijnlijk	Een beetje pijnlijk	Enigszins pijnlijk	Tamelijk pijnlijk	Zeer pijnlijk

6. In hoeverre vond u de reguliere ontlastingstest (SAT) beschamend/gênant?

☐	☐	☐	☐	☐
helemaal niet beschamend	een beetje beschamend	enigszins beschamend	tamelijk beschamend	zeer beschamend

7. In hoeverre vond u de te onderzoeken test (FIT) belastend?

☐	☐	☐	☐	☐
helemaal niet belastend	een beetje belastend	Enigszins belastend	Tamelijk belastend	Zeer belastend

8. In hoeverre vond u de te onderzoeken test (FIT) pijnlijk?

☐	☐	☐	☐	☐
Helemaal niet pijnlijk	Een beetje pijnlijk	Enigszins pijnlijk	Tamelijk pijnlijk	Zeer pijnlijk

9. In hoeverre vond u de te onderzoeken test (FIT) beschamend/gênant?

☐	☐	☐	☐	☐
helemaal niet beschamend	een beetje beschamend	enigszins beschamend	tamelijk beschamend	zeer beschamend

10.	In hoeverre vond u <u>de bloedtest</u> belastend?				
	☐	☐	☐	☐	☐
	helemaal niet belastend	een beetje belastend	Enigszins belastend	Tamelijk belastend	Zeer belastend
11.	In hoeverre vond u <u>de bloedtest</u> pijnlijk?				
	☐	☐	☐	☐	☐
	Helemaal niet pijnlijk	Een beetje pijnlijk	Enigszins pijnlijk	Tamelijk pijnlijk	Zeer pijnlijk
12.	In hoeverre vond u <u>de bloedtest</u> beschamend/gênant?				
	☐	☐	☐	☐	☐
	helemaal niet beschamend	een beetje beschamend	enigszins beschamend	tamelijk beschamend	zeer beschamend

Tot slot.

13. Wat is de datum van invullen van deze vragenlijst?
_____ - _____ - _____ (dag-maand-jaar)

Wilt u alstublieft controleren of u alle vragen heeft ingevuld en geen bladzijden heeft overgeslagen.

HARTELIJK DANK VOOR UW MEDEWERKING

PART III

Pre- and malignant lesions of the colon & screening

Chapter 7
Population-based prevalence of gastrointestinal abnormalities at colon capsule endoscopy

Chapter 8
Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years

Chapter 9
Pathology characteristics of colorectal cancer in young adults in the Netherlands

Chapter 10
The role of colon capsule endoscopy in colorectal cancer screening: a systematic review

Chapter 11
Effects of anticoagulants and NSAIDs on accuracy of a faecal immunochemical test (FIT) in colorectal cancer screening – a systematic review and meta-analysis

CHAPTER 7

Population-based prevalence of gastrointestinal abnormalities at colon capsule endoscopy

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Clinical Gastroenterology & Hepatology, October 2020

Abstract

Introduction

The population prevalence of gastrointestinal (GI) disease is unclear and difficult to assess in an asymptomatic population. The aim of this study was to determine prevalence of GI lesions in a largely asymptomatic population undergoing colon capsule endoscopy (CCE).

Methods

Participants aged between 50-75 years were retrieved from the Rotterdam Study, a longitudinal epidemiological study, between 2017-2019. Participants received CCE with bowel preparation. Abnormalities defined as clinically relevant were Barrett segment >3cm, severe ulceration, polyp >10 mm or ≥3 polyps in small bowel (SB) or colon, and cancer.

Results

Of 2800 invited subjects, 462 (16.5%) participants (mean age 66.8 years, female 53.5%) ingested the colon capsule. A total of 451 videos were analyzed, and in 94.7% the capsule reached the descending colon. At least 1 abnormal finding was seen in 448 (99.3%) participants. The prevalence of abnormalities per GI segment, and the most common type of abnormality, were as follows: Esophageal 14.8% (Barrett's esophagus <3 cm in 8.3%), gastric 27.9% (fundic gland polyps in 18.1%), SB abnormalities 33.9% (erosions in 23.8%), colon 93.3% (diverticula in 81.2%). A total of 54 participants (12%) had clinically relevant abnormalities, 3 (0.7%) in esophagus/stomach (reflux esophagitis grade D, Mallory Weiss lesion and severe gastritis), 5 (1.1%) in SB (polyps > 10 mm; n = 4, severe ulcer n = 1,) and 46 (10.2%) in colon (polyp > 10 mm or ≥3 polyps n = 46, colorectal cancer n = 1).

Conclusions

GI lesions are very common in a mostly asymptomatic Western population, and clinically relevant lesions were found in 12% at CCE. These findings provide a frame of reference for the prevalence rates of GI lesions in the general population.

Introduction

A considerable proportion of patients with gastrointestinal (GI) abnormalities remain undiagnosed because they do not always present with symptoms for which endoscopy is deemed necessary. Therefore, prevalence rates of GI diseases in the general population are unknown. What we do know is that GI diseases increase with age and that life expectancy is steadily expanding leading to an increased elderly population (1). For this reason, it is expected that the prevalence of GI disease will rise (2, 3). Learning the prevalence rates of GI mucosal abnormalities in an asymptomatic population will help to set a frame of reference of GI lesions that may be found during endoscopy, which is of interest especially in a screening setting. Furthermore, it may help to better inform patients about the (non-relevant) lesions found during endoscopy, when this could be compared against a general asymptomatic population.

Multigenerational prospective cohort studies with healthy participants that are followed throughout life are of paramount importance. In order to assess the etiology, contributing factors and burden of a certain disease, a frame of reference within a healthy population is essential. For example, the Framingham Heart Study has already shown us that monitoring healthy participants provided breakthroughs on the occurrence and natural course of cardiovascular diseases (4). Further, biobank studies such as the Lifelines cohort are becoming the core of clinical research worldwide (5). Nowadays, research that focuses not only on the disease, but also the healthy individual is just as important for unraveling pathologies.

The Rotterdam study is a prospective cohort study including healthy individuals 45 years of age and older that are followed throughout their lives (6). The current study is embedded within this cohort study. By the use of colon capsule endoscopy (CCE), we were able to image the entire GI tract of the participants. The colon capsule has 2 cameras on each side of the capsule and is able to acquire images with a frame rate of 4–35 frames/s. The CCE can be adequately used as pan-endoscopy (7, 8). The aim of this study was to assess the prevalence of any GI lesion in a general asymptomatic population-based study using CCE.

Materials and Methods

Study Design

This trial is embedded within the Rotterdam study. The rationale and design of the Rotterdam study have been described previously (6). The current study aims to evaluate the prevalence of GI lesions in a largely asymptomatic population using CCE between 2017 and 2019. The study has been approved by the Medical Ethics Committee of Erasmus MC (registration number MEC-2015-453). The protocol was registered in the Netherlands Trial

Register (NTR6321). All participants signed written informed consent before participation in the study. The authors of this manuscript had access to the study data and have read and approved this manuscript.

Participants

In the Rotterdam study, participants were recruited from 1990 onward (6). People participating in the Rotterdam study were eligible to participate in this study if between 50 and 75 years of age and able to give informed consent. Participants were excluded when meeting 1 of the following criteria: (1) unable or unwilling to sign written informed consent, (2) severe or terminal disease with a life expectancy <5 years, (3) allergy or known contraindication to the medications used in this study, (4) chronic heart failure New York Heart Association functional class III or IV, (5) severe kidney insufficiency (glomerular filtration rate<30 ml/min/1.73 m3), (6) dysphagia or swallowing disorder, (7) increased risk for capsule retention (M. Crohn, prior abdominal surgery likely to cause bowel obstruction), (8) pacemaker or other implantable cardioverter-defibrillator, (9) magnetic resonance imaging scheduled within 14 days after ingestion of the capsule, (10) risk of congenital extended QT syndrome or medication known to extend the QT interval, and (11) diabetes mellitus with use of insulin.

Participants received an announcement by post, followed by an invitation 2 weeks later, which included the patient information letter. In case of nonresponse, a reminder was sent after 6 weeks. Positive responders were invited for an interview to explain the CCE procedure and sign informed consent. A second appointment was made for the ingestion of the capsule. Both appointments took place in the study center, a specialized research facility in Ommoord, the Netherlands .

CCE Procedure

The second-generation colon capsule (PillCam COLON 2; Medtronic, Minneapolis, MN) was used. The ingestion of the capsule took place between 9 Am and 11 Am in the presence of a physician. After successful ingestion of the capsule, participants went home. The sensor belt, which is attached to the participant before ingesting the colon capsule and receives transmission data from the colon capsule, was taken off by participants at 8 pm or earlier when the capsule had left the body before 8 pm (for a detailed description of the CCE device, see the Supplementary Methods). Bowel preparation regimen for CCE consisted of 2 L of polyethylene electrolyte glycol plus ascorbic acid (Moviprep; Norgine, Amsterdam, the Netherlands) plus 2 L of water in split dose. A sulfate-based solution (Eziclen, Zambon, the Netherlands) was used as booster. After the capsule exited the stomach, the participant ingested the booster, which propelled the capsule through the small bowel and added fluid to the colon. The exact bowel preparation regimen is shown in **Supplementary Table 1**.

Reading Technique

CCE reading and evaluation was performed by a specially trained Erasmus MC study team, which consisted of 1 certified gastroenterologist, 3 medical doctors, and 1 endoscopy nurse. After a 2-day CCE masterclass, the participating readers practiced with an e-learning program. In total, they spent 30 hours evaluating videos each. Finally, the study team followed a course for 3 days at the Royal Free Hospital in London, United Kingdom. They were required to identify pathological features of the entire digestive tract in the videos and indicate the type, location, and size of the lesions.

In case of uncertainty, an international external reading expert team was consulted (C.S., I.F.-U., O.E.). The first 20 videos of each reader were re-evaluated by a second, experienced reader for quality control. All findings were saved as thumbnails, with a detailed description of each finding. The upper GI tract was defined as esophagus, stomach, and small bowel. The lower GI tract was defined as all segments of the colon and rectum. Each video was evaluated within 3 weeks of receipt.

Cleansing of the stomach, small bowel, and colon was graded according to 3 different grading scales (**Supplementary Table 2**). Colon cleansing grades of good and excellent were considered adequate bowel preparation, and grades of poor and fair were considered inadequate. A video was considered complete when the anal verge was observed.

Findings and Follow-Up

All findings are listed in **Supplementary Table 3**. In case an abnormality was found with potential clinical consequences, the finding was shared with the participant and the general practitioner. Only in those cases in which a clinically relevant finding was found was an endoscopy with or without biopsies or polypectomy performed. Clinically relevant findings were defined as the following: Barrett's segment >3 cm, severe ulceration >1 cm, polyp >10 mm or ≥3 polyps in the small bowel, or polyp >10 mm or ≥3 polyps in the colon and cancer (**Supplementary Table 4**). Barrett's esophagus (BE) will only be ascertained when the Z-line is visible. The participant received an appointment at the gastroenterology outpatient clinic of the Erasmus MC or another hospital in the Netherlands, where—in accordance with the participant—further investigations were planned.

Prevalence rates were based upon the findings of CCE and the additional endoscopy in cases of clinically relevant findings found by CCE.

Statistical Analysis

To assess prevalence estimates with a good and acceptable precision, the sample size must be large enough. For diseases with an estimated prevalence under 10%, it is advised to use a precision of half the prevalence. (9,10) For a valid estimate of prevalence rates of

≥3.3% with a precision of 0.0165, a sample size of 450 participants is needed. Descriptive statistics were used to describe the results. Statistical analyses were performed with SPSS software version 25 (IBM Corporation, Armonk, NY).

Results

Study Population

A total of 2800 subjects between 50 and 75 years of age were invited to participate, of whom 462 (16.5%) ingested the colon capsule (**Figure 1**). No difference in sex, age, tobacco use, and alcohol intake was found between participants and non-participants (**Supplementary Table 5**). However, participants had a lower body mass index, more often had a paid job, and were more often highly educated compared with the non-participants. Owing to a technical failure, 11 videos could not be assessed, resulting in a total of 451 participants for further analyses. The majority of participants were Caucasian with a mean age of 67.4 ± 4.9 years, and 53.7% were female (**Table 1**). A medical history of GI disease was reported in 17.7% of the participants, most commonly colon polyps removed in the past (8.9%), hemorrhoids (2.4%), and diverticulosis (2.2%) (**Table 1**). In 84.8% of the participants, no GI symptoms or complaints were present at time of the interview. Some participants (15.2%) presented with only minor symptoms for which they would not seek a doctor: heartburn, changed defecation pattern, and gastric complaints.

Prevalence of All GI Findings

In this study cohort, 448 (99.3%) participants had any abnormality in the GI tract. In total, 1948 abnormalities were found, with a mean number of 4.3 ± 2.5 abnormalities per participant (**Figure 2A**). Both men and women were equally affected, 99.5% of all men had any abnormality vs 99.2% of all women. However, the distribution of abnormalities was different between men and women (**Figure 2B and C**). In 304 of the 451 (67.4%) participants, abnormalities were found in the upper GI tract, with a total of 553 abnormalities. In the lower GI tract 1395 abnormalities were found in 419 (93.3%) participants.

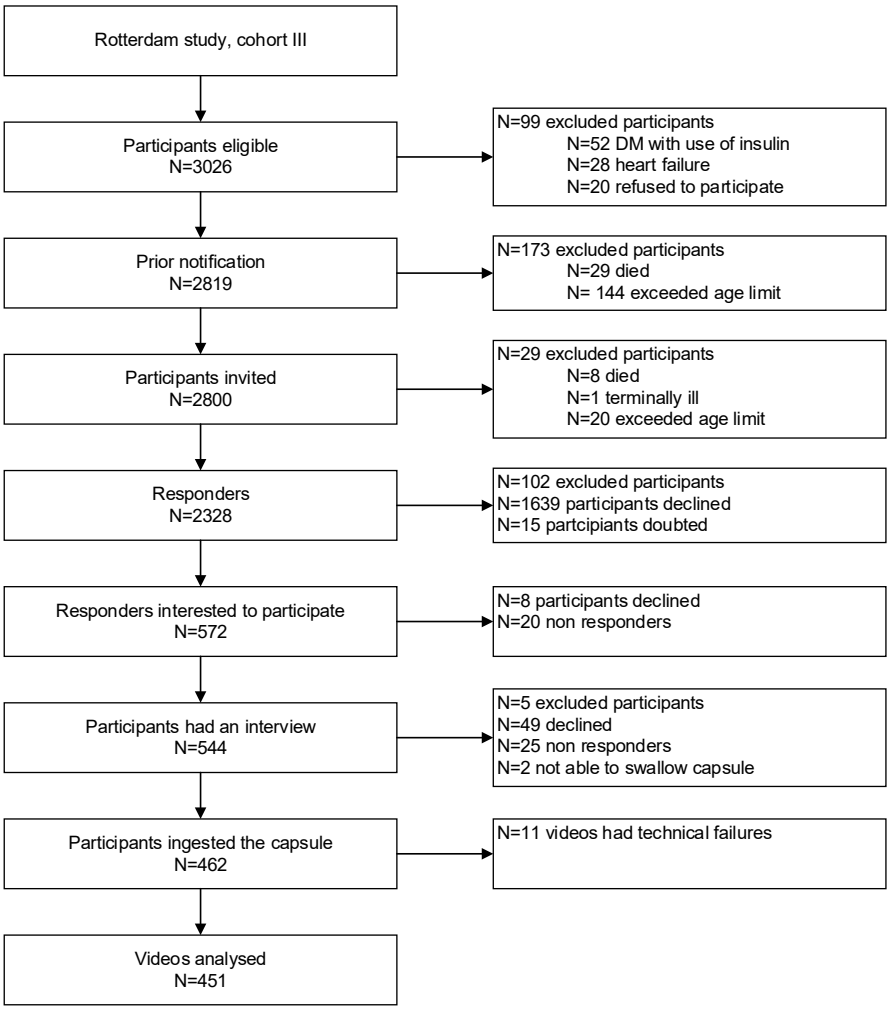

Figure 1. Study flow chart. DM, diabetes mellitus

Table 1. Medical history of participants (N = 462) GI, gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug.

	Total	N	%
Male/female	462	214 / 248	46.3 / 53.7
Mean age, years (SD)	462	67.4 (4.9)	
Ethnicity	462		
European		400	86.6
East-Asian		2	0.4
African		8	1.7
Mixture		5	1.1
Missing		47	10.2
GI symptoms	454		
None		385	84.8
Heartburn		20	4.4
Changed defecation pattern		15	3.3
Gastric complaints		10	2.2
Other		24	5.3
Medical history	462		
None		205	44.4
GI disease		82	17.7
Cardiac disease		95	20.6
Pulmonary disease		35	7.6
Cerebral disease		20	4.3
Endocrine		41	8.9
Malignancy in the past		44	9.5
Medication use	459		
Antihypertensive		159	34.6
Proton pomp inhibitor		108	23.5
Statin		106	23.1
Platelet aggregation inhibitor		43	9.3
β_2 adrenergic receptor agonist		35	7.6
Laxative		27	5.9
NSAID		27	5.9
Antidiabetic		17	3.7
Grading general health	411		
Poor		3	0.7
Fair		33	8.0
Good		257	62.5
Very good		95	23.1
Excellent		23	5.6

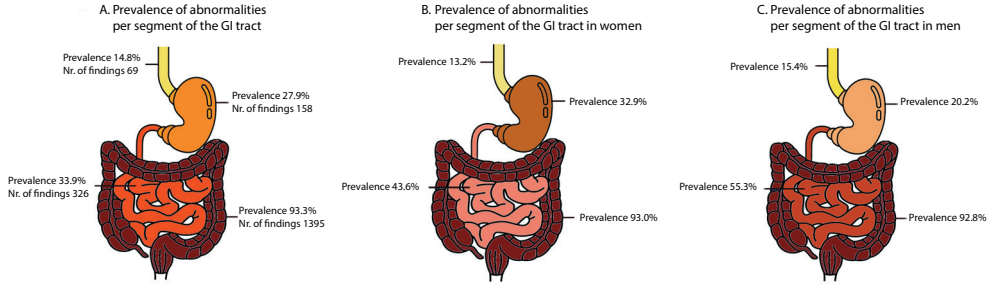

Figure 2. Heatmap of the prevalence rates of abnormalities per segment of the GI tract observed by CCE. (A) Prevalence rate per GI segment of all 451 participants with total number of findings per segment. Prevalence rate per segment in (B) women (n = 243) and (C) men (n = 208).

Upper GI Tract

Esophageal abnormalities were found in 64 (14.8%) participants, with a total number of 69 findings. BE <3 cm and esophagitis were the most common abnormalities, with prevalence rates of 8.3% and 5.5%, respectively (**Figure 3** and **Supplementary Tables 6** and **7**). Gastric abnormalities were found in 122 (27.9%) participants. In total, 158 abnormalities were found in the stomach. Most frequent abnormalities were fundic gland polyps (FGP) (prevalence of 18.1%) and end erosions (prevalence of 6.6%). In total, 326 small bowel abnormalities were found in 151 (33.9%) participants with erosions (23.8%) being the most common lesions. Although not defined as an abnormality, lymphangiectasis was observed in 30.7% of the participants.

Lower GI Tract

Colon abnormalities were present in 419 (93.3%) participants, with a total of 1395 abnormalities. (**Figure 3** and **Supplementary Tables 6** and **7**). Abnormalities were found less frequently in the cecum (25.4% of the participants). In 44.8% of the participants, any abnormality was found in the ascending colon, and in 41.8% of participants, any abnormality was found in the transverse colon. Compared with the other segments of the colon, most abnormalities were found in the descending colon (82.7% of the participants). Most common findings were diverticula (prevalence of 71.4%) and polyps (prevalence of 34.0%), both having a specific distribution (**Figure 4**). In the rectum, 181 abnormalities were found in 127 (50.8%) participants. Most frequent findings were hemorrhoids (36.4%) and polyps (16.0%).

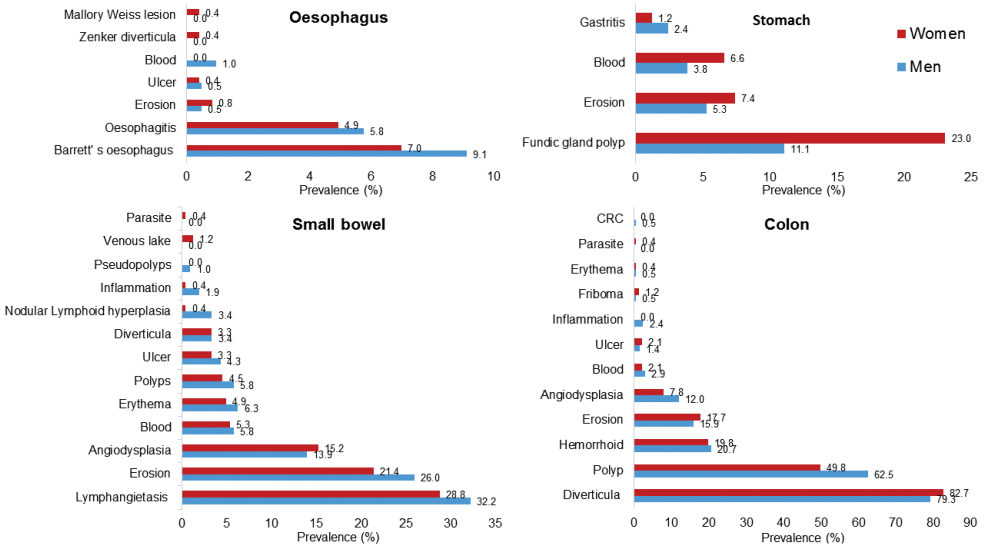

Figure 3. Prevalence rates of any abnormality in the GI tract divided by men (blue) and women (pink).

Prevalence of Clinically Relevant Findings and Clinical Follow-Up

A total of 54 (12%) participants had clinically relevant abnormalities, 3 (0.7%) findings in the stomach, 5 (1.1%) findings in the small bowel and 46 (10.2%) findings in the colon (**Table 2** and **Supplementary Table 8**). In 2 participants, bleeding in the stomach was detected by CCE. At endoscopy, it was found that a Mallory-Weiss lesion and reflux esophagitis grade D had caused the bleeding. The third participant had a severe gastritis. Of the 5 participants with clinically relevant findings in the small bowel, 1 participant had a severe ulcerative lesion and 4 participants had a polyp larger than 10 mm. Of the 46 participants with clinically relevant abnormalities in the colon, 46 participants had 1 polyp larger than 10 mm or 3 or more polyps and 1 participant had also a colorectal carcinoma (CRC).

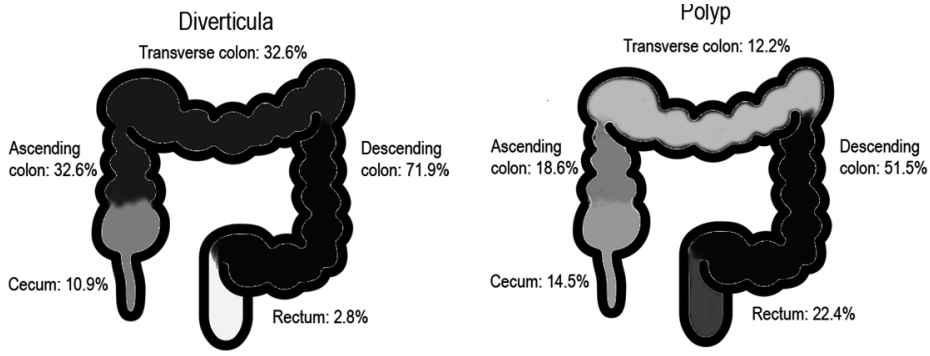

Figure 4. Distribution of colonic diverticula and polyps among participants.

Additional Findings

In the participants with clinically relevant findings, additional imaging tests were performed. Findings observed at upper endoscopy and not by CCE were a reflux esophagitis grade D and a Mallory-Weiss lesion in the esophagus. In the small bowel, no additional findings were observed by magnetic resonance imaging and follow-up CCE. In the colon, 53 additional polyps were found at colonoscopy (OC), of which 45 were ≤9 mm and 8 were >10 mm (**Table 2**).

One participant was diagnosed with a CRC in the sigmoid 6 months after the CCE procedure. CCE had missed the CRC due to the fact that the battery life of the colon capsule had ended in the descending colon, and therefore, the CRC located in the sigmoid was not visualized.

Quality Parameters of Colon Capsule

The gastric cleansing was considered good in 304 (69.6%) participants, the small bowel cleansing was good or excellent in 442 (99.1%) participants, and the overall colon cleansing was adequate in 344 (76.6%) participants. The Z-line, the gastroesophageal junction, was observed in 44.8% of the participants. The capsule reached the descending colon in 94.7% and completion was achieved in 51.9% of the participants. The number of visualized segments of the GI tract are described in **Supplementary Table 9**. No difficulties in swallowing the capsule were observed. No procedure-related serious adverse events occurred.

Table 2. Clinical Follow-Up of Clinically Relevant Findings at CCE by Endoscopy and Histology

Esophagus/Stomach, N = 3	CCE	Endoscopy		Histology
		Type	Finding	
	Bleeding	Gastroscopy	Reflux esophagitis grade D	
	Bleeding	Gastroscopy	Mallory Weiss lesion and erythema of antrum and corpus with two small erosions	Chronic active inflammation. Helicobacter pylori organisms
	Severe gastritis	Gastroscopy	Mild erosive antrum gastritis	Intestinal metaplasia antrum
Small bowel, N = 3*	Ulcer >10mm	MRI	Hyperaemia and bowel wall thickening	NA
	Polyp >10mm	MRI	No abnormalities	NA
	Polyp >10mm	CCE follow up	No change in size or appearance	NA
Colon	**CCE**	**Endoscopy**		**Histology**
		Type	**Finding**	
Total polyps detected, N	135	Colonoscopy	163	
Size, N (%)				
≤5 mm	49 (36.3)		69 (42.3)	HP 16, SSA 1, TA 38, TVA 2 No dysplasia 18, LGD 42
6-9 mm	45 (33.3)		41 (25.2)	HP 7, SSA 4, TA 24, TVA 1 No dysplasia 11, LGD 26, HGD 1
≥10 mm	41 (30.4)		37 (22.7)	HP 1, SSA 8, TA 15, TVA 11, CA 1 No dysplasia 6, LGD 27, HGD 1
Location, N (%)				
Cecum	17 (12.6)		18 (11.0)	SSA 4, TA 8, TVA 1 No dysplasia 3, LGD 9, HGD 1
Ascending colon	23 (17.0)		32 (19.6)	HP 1, SSA 3, TA 15, TVA 3 No dysplasia 4, LGD 19
Transverse colon	23 (17.0)		37 (22.7)	HP 7, SSA 1, TA 26, TVA 1 No dysplasia 8, LGD 26, HGD 1
Descending colon/ sigmoid	54 (40.0)		51 (31.3)	HP 11, SSA 3, TA 27, TVA 6 No dysplasia 12, LGD 34

Table 2. Continued

Colon	CCE	Endoscopy		Histology
		Type	Finding	
Rectum	18 (13.3)		25 (15.3)	HP 8, SSA 1, TA 5, TVA 4, CA 1 No dysplasia 10, LGD 8, HGD 1
Appearance, N (%)				
Sessile	94 (69.6)		92 (56.4)	HP 20, SSA 18, TA 41, TVA 4 No dysplasia 25, LGD 57, HGD 1
Pedunculated	39 (28.9)		21 (12.9)	HP 1, SSA 1, TA 10, TVA 8 No dysplasia 2, LGD 17, HGD 1
Flat	1 (0.7)		23 (14.1)	HP 4, SSA 1, TA 9, TVA 2 No dysplasia 5, LGD 10, HGD 1

Discussion

True population prevalence data of GI disease are scarce, as most prevalence studies are based on select, often symptomatic populations. This study provides prevalence rates of GI lesions in a general mostly asymptomatic population. GI lesions appeared to be a very common condition in a Western population. Prevalence of BE was 8.3%, esophagitis 5.8%, FGP in 18.1%, and diverticula in 81.6%, and prevalence of colon polyps was 56%. In 12%, clinically relevant findings were detected. The most common clinically relevant lesions found were colon polyps >10 mm.

GI diseases are usually detected when patients undergo a diagnostic procedure because of symptoms. Prevalence of GI lesions in asymptomatic population are difficult to assess. Most people perceive endoscopies as burdensome and invasive and are therefore reluctant to undergo such procedure in case no symptoms are present. Therefore, studies assessing prevalence of GI lesions are mainly performed in screening or symptomatic patients who already have to undergo an endoscopy.

Our findings are not in line with previous literature. One Swedish study has assessed the prevalence of BE in a general population and found a rate of 1.6% (11). Other studies have reported significantly higher prevalence rates of BE, ranging from 6.8% to 25% (12, 13). We found a prevalence rate of 8.3% in the adult general population. On the one hand, this prevalence may be underestimated because the Z-line was observed in only 44.8% of the participants. On the other hand, BE was defined on macroscopic findings only. The difference in prevalence rates could be explained by time, as the Swedish publication was in 2005. It is known that the prevalence of gastroesophageal reflux disease, which is often accompanied with BE, has increased over the last 20 years (14).

An Italian study focused on gastroesophageal reflux symptoms and esophagitis in a general Italian population and found prevalence of esophagitis of 11.8%. The prevalence of reflux symptoms in their population was 44.3%, which could explain the higher prevalence numbers in comparison to our findings (prevalence of 5.5%) (15).

We found an FGP prevalence rate of 18.1% in our population, and 40% of them used a proton pump inhibitor. True prevalence of gastric polyps is not well known, as they are rarely symptomatic (16). The prevalence rates of all gastric polyps range between 0.5% and 14%, of which FGP are the most common types, with prevalence rates varying from 21% to 47% in symptomatic populations (17, 18).

In a study from the United States among Kaiser Permanente members, the colon adenoma prevalence was estimated based on 20.792 patients undergoing a screening

OC. They found an adenoma prevalence of 20.2% in women and 30.6% in men (19). A meta-analysis reporting on the prevalence of colon adenomas and CRC in an average risk population by OC concluded that the pooled prevalence of adenomas was 30.2% (range, 22.2–58.2%) (20). In our study, the prevalence of all polyps was 57% and the prevalence of polyps >10 mm was 10%. Our polyp detection rate (PDR) is higher compared with the adenoma detection rate (ADR) found with OC.20 This difference could be explained by 2 reasons. First, it is known that the detection rate of polyps by CCE is different from OC. A Danish study reported that the PDR was significantly higher in CCE vs OC (74% vs 64%, respectively) (21). Second, to assess the ADR, it is essential to have pathology results, which cannot be performed by CCE. A recently performed meta-analysis calculated a conversion factor of 0.68 to calculate the ADR from PDR (22). If we apply this to our data, then an ADR of 38% is found, which is then in line with previously mentioned literature.

Finally, colonic diverticula was the most common clinically non-relevant finding in our study. Although it is generally known that diverticulosis is common and more prevalent at older ages, the true prevalence of diverticula is difficult to determine because most estimates were subjected to selection bias (23). In a recently performed study from the United States, it was shown that in a screening population older than 60 years of age, diverticula were present in 58% of the screened individuals. The prevalence of diverticula was the highest in the sigmoid (24). Our study reported a prevalence of 81.2%. The difference in distribution of diverticula between the study from the United States and our study was remarkable. In the former study, most diverticula were found in the sigmoid, with <11% in other segments of the GI tract, while in our study the highest prevalence was found in the descending colon and around 30% in the ascending and transverse colon. The difference in distribution could be explained by the difference in diagnostic tool: in the U.S. study, OC was used vs CCE in our study.

CCE is a noninvasive method to assess the mucosal surface of the entire GI tract. Multiple studies have reported on the usefulness of the colon capsule, especially in the detection of colonic polyps and to observe the colonic mucosa of patients with inflammatory bowel disease (25, 26). Two studies assessed the use of CCE in evaluating the mucosal surface of the entire GI tract. The first study included 21 symptomatic patients and concluded that a CCE is a feasible method (7). The second study included 165 patients to rule out pathology and used both first and second generation colon capsules (8).

The strength of this study is that this study is the first to set a frame of reference of the prevalence of GI abnormalities in the entire GI tract within 1 person. This study also has several limitations. First, 16.5% of the invited subjects participated in our study, which could lead to a selection bias. However, when inviting Dutch individuals, 50–75 years of age, for primary CRC screening with colonoscopy, the participation rate was comparable

(22%) (27). Second, the completion rate of CCE was only 51.9%. However, the descending colon was seen in 94.7% of the participants and therefore almost the entire GI tract was observed. Also, the sleep mode (the default setting of the colon capsule in order to save battery life to observe the entire colon by taking only 4 pictures/min in the stomach) was not turned off. Therefore, the stomach was in some participants less accurately visualized. The sleep mode saves battery allowing an almost complete evaluation of the colon. CCE is not the preferred method to observe the esophagus; in our study, the Z-line was observed in 44.7% of the participants. The 3 previously mentioned limitations may have led to an underestimation of prevalence rates found. Third, the prevalence rates are dependent on the experience of the reader of the videos. Special attention was given to train the readers. An expert team (O.E., C.S., I.F.-U.) was installed and advised when reviewers were having doubts. Fourth, owing to the design of the study, not all abnormalities were confirmed by histopathology, unless clinically relevant lesions were found and the participant had to undergo an endoscopy. This may have overestimated the prevalence of BE. Last, the CCE software has an polyp estimation tool to measure polyps in the colon. For this study, the tool was used to measure all abnormalities, which may have affect the accurate size of findings.

In conclusion, this study provides an overview of the prevalence of GI findings in a largely asymptomatic average-risk population. GI findings are commonly found in a Western population, with 12% having a clinically significant abnormality. This study has set a frame of reference for the prevalence and distribution of GI abnormalities in a general Western population.

Acknowledgments

The authors thank Sophia van Baalen-Van Daalen and the endoscopy nurses of Camerapil for their contribution reviewing the colon capsules videos. They also thank all employees of the Rotterdam Study working in health care center Ommoord for their help in the logistics of this study.

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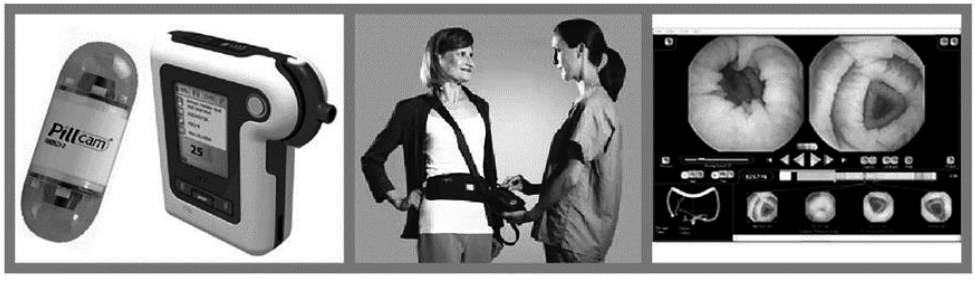
Supplementary materials

Supplementary methods

Technical features of colon capsule endoscopy

Colon capsule endoscopy consists four main components: PillCamTM COLON2 capsule (Medtronic), a sensor belt which is worn, a data-recorder and a workstation with RAPID™ 7.0 software (Supplementary image 1). The colon capsule is 11.6 × 31.5 mm^2 in size and equipped with two head cameras with 168° angle of view. The colon capsule has a feature of an adaptive frame rate (AFR). The AFR is activated once the capsule is in the small bowel and alternates between 4 images per second when the capsule is stationery and changes to 35 images per second when the capsule is moving. The data recorder allows real-time review of images during examinations. The RAPID™ software includes a graphical interface tool for polyp size estimation which allows the reviewer to measure polyps. Furthermore, the capsule provides feedback through the recorder and when capsule enters the small bowel, the recorder provides a notification.[1]



Supplementary figure 1. An image of the colon capsule and data recorder (left image), the sensor belt (image in the middle) and the Rapid™ software (right image).

Supplementary table 1. Bowel preparation schedule for colon capsule endoscopy.
PEG = polyethylene electrolyte glycol solution. OSS = oral sulphate solution

Day	Time	Bowel preparation and booster
Day -2	8 p.m.	1 bisacodyl 5 mg tablet
Day -1		Light breakfast + lunch
	1 p.m.	Clear liquid diet
	6 – 8 p.m.	1L PEG+ 1L clear liquid diet
Day 0	6 – 8 a.m.	1L PEG + 1L clear liquid diet
	~ 9 a.m.	Ingestion capsule
	1 hour after ingestion capsule	10 mg metoclopramide (only if capsule is still in stomach)
	Small bowel detection	250ml OSS + 0.5L clear liquid diet
	3 hours after small bowel detection	250ml OSS + 0.5L clear liquid diet
	8 p.m.	Sensor belt removed by participant

Supplementary table 2. Definition of the cleansing grading scales of the stomach, small bowel and colon

Gastric grading scale	
Good	>90% of the mucosa was observed
Fair	70%-90% of the mucosa was observed
Poor	<70% of the mucosa was observed
Small bowel grading scale	
Proportion of visualized mucosa	
Excellent	> 75%
Good	50-75%
Fair	25-50%
Poor	<25%
The degree of bubbles, debris and bile	
Excellent	<5%, no obscuration
Good	5-25%, mild obscuration
Fair	25-50%, moderate obscuration
Poor	>50%, severe obscuration
Colon grading scale	
Cleansing level grading scale	
Poor	Large amount of faecal residue precluding a complete examination
Fair	Enough feces or dark fluid present to prevent a reliable exam
Good	Small amount of feces or dark fluid not interfering with examination
Excellent	No more than small bits of adherent feces
Bubbles interfering effect scale	
Significant	Bubbles/content/blurry images that interfere with the examination More than 10% of surface area is obscured
Insignificant	No bubbles/content/blurry images or so that they do not interfere with the examination. Less than 10% of surface area is obscured

Supplementary table 3. List of gastrointestinal lesions

All findings	Definition
Barrett's esophagus	Distal esophagus is lined with columnar epithelium with a minimum length of 1 cm
Esophagitis	Mucosal break of the esophagus
Erosion	Circumscribed area of mucosal disruption
Ulcer	Large erosion with a central area with exudates
Inflammation	Redness and/or swelling of the tissue
Polyp	Protuberance into the lumen above the surrounding of the mucosa
Blood	Free intraluminal blood
Zenker diverticulum	Diverticulum of the mucosa and submucosal layers above the pharyngoesophageal junction
Mallory Weiss Lesion	Linear mucosal lacerations of distal esophagus or upper stomach
Fundic gland polyp	Sessile, shiny, translucent and pale polyp
Gastritis	Inflammation of the lining of the stomach
Erythema	Reddening of the mucosa
Angiodysplasia	Aberrant blood vessel
Diverticula	Sac-like protusion of the colonic wall
Nodular Lymphoid Hyperplasia	Multiple small nodules
Pseudopolyp	Projecting mass of granulation tissue
Vascular lesion	Vascular lesion consisting of arterioles, capillaries and venules
Venous Lake	Dilated veins
Parasite	An organism living in the gastrointestinal tract
Hemorrhoid	Abnormal swelling of the anal vascular cushions
Fibroma	Benign tumors composed of fibrous tissue

Supplementary table 4. Definition of significant lesions

Significant Lesions	Definition
Long segment Barrett's esophagus	Segment ≥ 3cm
Severe ulceration of the digestive tract	Segment > 1cm, whether or not containing sigs of blood loss
Marked villous atrophy in the small intestine	-
Polyps in the small bowel or colon	Polyp ≥ 10mm, or three or more polyps
Esophagus tumour, gastric tumour or intestinal tumour	-

Supplementary table 5. Baseline characteristics participants and non-participants

	Participants		Non-participants		P-value
	Total	N (%)	Total	N (%)	
Male/female	462	214 (46.3) / 248 (53.7)	2327	970 (41.7) / 1357 (58.3)	0.066
Mean age, years (SD)	462	67.4 (4.9)	2323	67.1 (4.8)	0.158
Mean BMI, kg/m² (SD)	462	26.9 (4.0)	2323	27.6 (4.6)	0.003
Smoking, ever	460	331 (67.6)	2321	1560 (67.2)	0.869
Total alcohol intake in g/day, mean (SD)	456	8.5 (8.9)	2321	8.0 (9.0)	0.432
Ethnicity	462		2323		0.039
European		400 (86.6)		2010 (86.5)	
East-Asian		2 (0.4)		39 (1.3)	
African		8 (1.7)		30 (1.3)	
Mixture		5 (1.1)		7 (0.3)	
Missing		47 (10.2)		237 (10.2)	
Job	428		2119		0.001
Paid job		334 (78.0)		1394 (65.8)	
Unemployed		10 (2.3)		76 (3.6)	
Housewife/househusband		41 (9.6)		342 (16.1)	
Incapacitated		20 (4.7)		128 (6.0)	
Annuitant		0 (0.0)		9 (0.4)	
Early retirement		20 (4.7)		158 (7.5)	
Retirement		3 (0.7)		10 (0.5)	
unknown		0 (0.0)		2 (0.0)	
Education	428		2119		0.012
Elementary school		28 (6.5)		174 (8.2)	
Primary vocational school		54 (12.6)		336 (15.9)	
General secondary school		69 (16.1)		415 (19.6)	
Secondary vocational school		103 (24.1)		471 (22.2)	
General higher education		22 (5.1)		122 (5.8)	
Higher vocational education		108 (25.2)		465 (21.9)	
University education		42 (9.8)		121 (5.7)	
Different		2 (0.5)		15 (0.7)	

N=number , SD = standard deviation , BMI = body mass index

Supplementary table 6. prevalence rates of gastrointestinal (GI) disease and total number of findings observed with colon capsule endoscopy (CCE). N = number. * = lymphangiectasis were presented in this table but not defined as abnormal and therefore not included in the calculation of the number of participants with findings and total number of findings. CRC = colorectal cancer

Segment GI tract, Number of observed segments, n	**Esophagus, N =433**		**Stomach, N=437**		**Small bowel, N=446**		**Cecum, N=449**		**Ascending colon, N=442**		**Transverse colon, N=433**		**Descending colon, N=427**		**Rectum, N=250**	
TOTAL																
Number of participants with findings, n (%)	64 (14.8)		122 (27.9)		151 (33.9)		114 (25.4)		198 (44.8)		180 (41.6)		353 (82.7)		127 (50.8)	
Total number of findings	69		158		326		144		248		212		610		181	
TYPE OF FINDING																
	Nr. of participants with findings, n(%)	All findings, n	Nr. of participants with findings, n(%)	All findings, n	Nr. of participants with findings, n(%)	All findings, n	Nr. of participants with findings, n(%)	All findings, n	Nr. of participants with findings, n(%)	All findings, n	Nr. of participants with findings, n(%)	All findings, n	Nr. of participants with findings, n(%)	All findings, n	Nr. of patients with findings, n(%)	All findings, n
Barrett's esophagus <3cm	36 (8.3)	36														
Esophagitis	24 (5.5)	24														
Erosions	3 (0.7)	3	29 (6.6)	29	106 (23.8)	119	10 (2.2)	10	9 (2.0)	9	6 (1.4)	6	42 (10.7)	48	16 (6.4)	16
Ulcer	2 (0.5)	2			17 (3.8)	19	5 (1.1)	7	1 (0.2)	1	1 (0.2)	1	3 (0.7)	3	1 (0.4)	1
Inflammation					5 (1.1)	5	2 (0.4)	2					2 (0.5)	2	1 (0.4)	1
Polyp					23 (5.2)	27	56 (12.5)	65	73 (16.5)	82	44 (10.2)	53	145 (34.0)	220	40 (16)	56
CRC													1 (0.2)	1		
Blood	2 (0.5)	2	24 (5.5)	24	25 (5.6)	25	3 (0.7)	3	2 (0.5)	2	2 (0.5)	2	3 (0.7)	3	4 (1.6)	4
Zenker diverticulum	1 (0.2)	1														
Mallory Weiss lesion	1 (0.2)	1														
Fundic gland polyp			79 (18.1)	97												
Gastritis			8 (1.8)	8												
Erythema					25 (5.6)	25							2 (0.8)	2		
Lymphangiectasis*					137 (30.7)	190										
Angiodysplasia					66 (14.8)	75	6 (1.3)	7	10 (2.3)	10	9 (2.1)	9	22 (5.2)	24	1 (0.4)	1
Diverticula					15 (3.4)	16	49 (10.9)	49	144 (32.6)	144	141 (32.6)	141	304 (71.4)	307	(3.2)	7
Nodular lymphoid hyperplasia					8 (1.8)	8										
Pseudo polyps					2 (0.4)	3										
Venous lake					3 (0.7)	3										
Parasite					1 (0.2)	1	1 (0.2)	1								
Hemorrhoids															91 (36.4)	91
Fibroma															4 (1.6)	4

Supplementary table 7. Distribution of relevant findings based on gender and age

Clinical relevant findings	Male/ Female	55-60 years	60-65 years	65-70 years	70-75 years
Barret segment >3cm	-				
Severe ulceration >1cm	1/0			1	
Polyp >10mm or ≥3 polyps in the small bowel	3/1	1		1	2
Polyp >10mm or ≥3 polyps in the colon	26/20	5	5	17	19
Colon cancer	1/0			1	
Total	31/21	6	5	20	21

Supplementary table 8. Observed segment of the gastrointestinal tract (total of 451 videos), observed Z-line and transit times of colon capsule endoscopy

	N	%
Z-line observed	202	44.8
Completion rate	234	51.9
Number of visualized segments of the GI tract		
Esophagus	433	96.0
Stomach	437	96.9
Small bowel	446	98.9
Colon	449	99.6
Cecum	449	99.6
Ascending colon	442	98.0
Transverse colon	433	96.0
Descending colon	427	94.7
Rectum	250	55.4
Reach		
Stomach	1	0.2
Small bowel	1	0.2
Cecum	5	1.1
Ascending colon	10	2.2
Transverse colon	7	1.6
Descending colon	118	26.2
Sigmoid	59	13.1
Rectum	15	3.3

GI = gastrointestinal. CCE = colon capsule endoscopy. IQR = inter quartile range.

CHAPTER 8

Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years

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Gut, October 2019

Abstract

Introduction

The incidence of colorectal cancer (CRC) declines among subjects aged 50 years and above. An opposite trend appears among younger adults. In Europe, data on CRC incidence among younger adults are lacking. We therefore aimed to analyse European trends in CRC incidence and mortality in subjects younger than 50 years.

Methods

Data on age-related CRC incidence and mortality between 1990 and 2016 were retrieved from national and regional cancer registries. Trends were analysed by Joinpoint regression and expressed as annual percent change.

Results

We retrieved data on 143.7 million people aged 20–49 years from 20 European countries. Of them, 187 918 (0.13%) were diagnosed with CRC. On average, CRC incidence increased with 7.9% per year among subjects aged 20–29 years from 2004 to 2016. The increase in the age group of 30–39 years was 4.9% per year from 2005 to 2016, the increase in the age group of 40–49 years was 1.6% per year from 2004 to 2016. This increase started earliest in subjects aged 20–29 years, and 10–20 years later in those aged 30–39 and 40–49 years. This is consistent with an age-cohort phenomenon. Although in most European countries the CRC incidence had risen, some heterogeneity was found between countries. CRC mortality did not significantly change among the youngest adults, but decreased with 1.1%per year between 1990 and 2016 and 2.4% per year between 1990 and 2009 among those aged 30–39 years and 40–49 years, respectively.

Conclusion

CRC incidence rises among young adults in Europe. The cause for this trend needs to be elucidated. Clinicians should be aware of this trend. If the trend continues, screening guidelines may need to be reconsidered.

Introduction

The overall crude incidence of colorectal cancer (CRC) increased in most European countries over the last decade. The annual increase ranged in different countries between 0.4% and 3.6% (1). The recent introduction of CRC screening in most European countries will likely reverse this trend (2, 3). These screening programmes typically target subjects aged 50 years and above. In several parts of the world, the CRC incidence has also risen in individuals below 50 years of age. In the USA, the incidence of colon cancer increased since 1974 with 1.0%–2.4% annually and the incidence of rectal cancer with 3.2% (4).The possible reasons for this increasing incidence are unknown, but may be related to the increasing prevalence of obesity, lack of exercise and to dietary factors such as alcohol and processed meat (3). Furthermore, urbanisation and pollution have been implicated in the overall increase in cancer incidence (5). CRC in young adults is in part due to hereditary cancer syndromes, but most cases are sporadic (6). The changing epidemiology of CRC may also have practical implications, in particular for age to start screening. With the use of the Microsimulation Screening Analysis simulation model, we previously showed that screening initiation at age 45 years had in the US population a favourable balance between screening benefits and burdens (7). This finding supported the American Cancer Society to recommend starting screening at age 45 years instead of 50 years (8). Whether the incidence of CRC also increases among young adults in Europe has not been investigated. We therefore analysed trends in CRC incidence in this population.

Methods

Study design and data source

Data on age-specific incidence and mortality of CRC by year of diagnosis were retrieved from national and regional Euro-pean cancer registries with a time frame of at least 10 years (online supplementary table 1). We evaluated incidence and mortality of CRC, colon cancer (ICD-O-3 codes C18) and rectal cancer (C20) between 1990 and 2016. Data were collected for subjects aged 20–49 years. Five-year incidence and mortality rates were collected and expressed per 100 000 persons.

Statistical analysis

Temporal trends in CRC incidence within the study period were investigated using Joinpoint regression analyses, applying an algorithm to define significant changes in temporal trends on a logarithmic scale. The annual percent change (APC) in each Joinpoint segment represents the rate of change in cancer incidence per year in a given time period. The analyses were performed using the Joinpoint Regression Programme 4.5.0.1, National Cancer Institute. All tests of statistical significance were two-sided; a p value of <0.05 was considered significant. Incidence rates were calculated for three age groups

(20–29, 30–39, 40–49 years), presented per 100 000 persons and adjusted to population numbers for each country.

As not all countries could provide data over the entire time period, a sensitivity analysis was performed with data from countries that covered the entire time frame.

We set out to distinguish between a period effect and a cohort effect. While a period effect results from external factors that equally affect all age groups at a particular time period, a cohort effect represents variations resulting from unique exposure of a specific birth cohort. To this aim, we identified for each age group the year in which the increase in CRC incidence, if any, had started. If it were to be the same for the three age groups, the increase in incidence was considered to be a period effect. If the starting year were to be more recent in the older age groups, the increase was considered to be a cohort effect.

Results

Incidence data were available from 20 European countries (**figure 1**); mortality data from 16 of those (not including Belgium, France, the UK and Ireland). In 2009, the population of these 20 countries numbered 91 842 346 individuals aged 20–39 years, of whom 47 364 were diagnosed with CRC from 1990 to 2016, and 51 868 457 individuals aged 40–49 years, of whom 140 554 were diagnosed with CRC from 1990 to 2016.

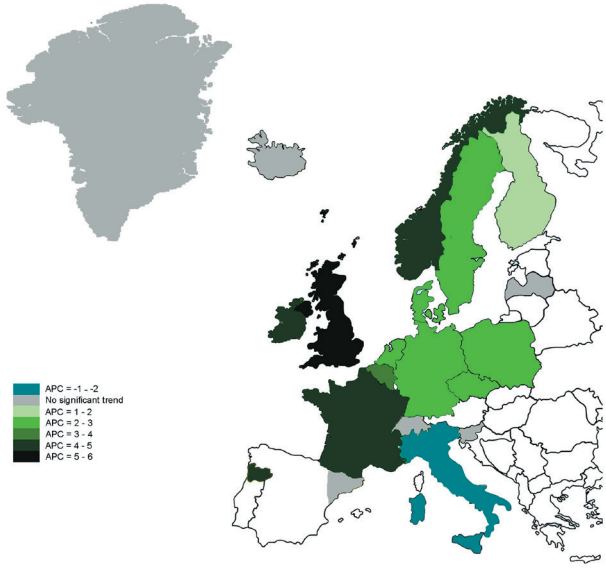

Figure 1. Annual percent change (APC) in colorectal cancer (CRC) incidence from the European countries included in the analysis in adults aged 20–39 years, 1990–2016. Light green to dark green: significant increase in CRC incidence rate; blue: significant decrease in CRC incidence rate; grey: no significant trend.

Incidence of colorectal cancer

Age group 20-29 years

For both sexes combined, CRC incidence increased from 0.8 to 2.3 cases per 100.000 persons between 1990 and 2016. This increase was 1.7% per year between 1990 and 2004, and then rose to 7.9% increase per year between 2004 and 2016 (**figure 2**). In men, the CRC incidence increased with 2.6% per year between 1992 and 2005. This increase rose to 7.4% per year between 2005 and 2016. In women, the CRC incidence increased with 1.8% per year between 1990 and 2003 and with 8.1% per year between 2003 and 2016. The incidence of colon cancer rose more markedly (2.7% per year between 1990 and 2005 and 9.3% per year between 2005 and 2016) than the incidence of rectal cancer. The latter increased with 3.5% annually throughout the whole period without an acceleration over time.

Age group 30–39 years

For both sexes combined, in age group 30–39 years the CRC incidence increased, although less steeply than in age group 20–29 years (**figure 2**). In men, the CRC incidence increased with 3.4% per year between 2001 and 2016 (from 3.7 to 7.1 cases per 100 000 persons between 1990 and 2016). In women, no significant change in trend was observed between 1990 and 2005, but the CRC incidence increased with 6.8% annually between 2005 and 2016 (from 2.8 to 6.4 cases per 100 000 persons between 2006 and 2016). The colon cancer incidence increased between 2006 and 2016 with 6.4% per year; that of rectal cancer with 1.6% per year between 1990 and 2016.

Age group 40–49 years

In age group 40–49 years, the CRC incidence decreased with 0.8% between 1990 and 2004, but increased with 1.6% per year between 2004 and 2016 (incidence increased from 15.5 to 19.2 cases per 100 000 persons between 2005 and 2016). The same trend was observed for colon cancer: the incidence decreased with 1.3% per year between 1990 and 2004 and then increased with 1.6% annually between 2004 and 2016. No significant change in trend was observed for rectal cancer (**figure 2**).

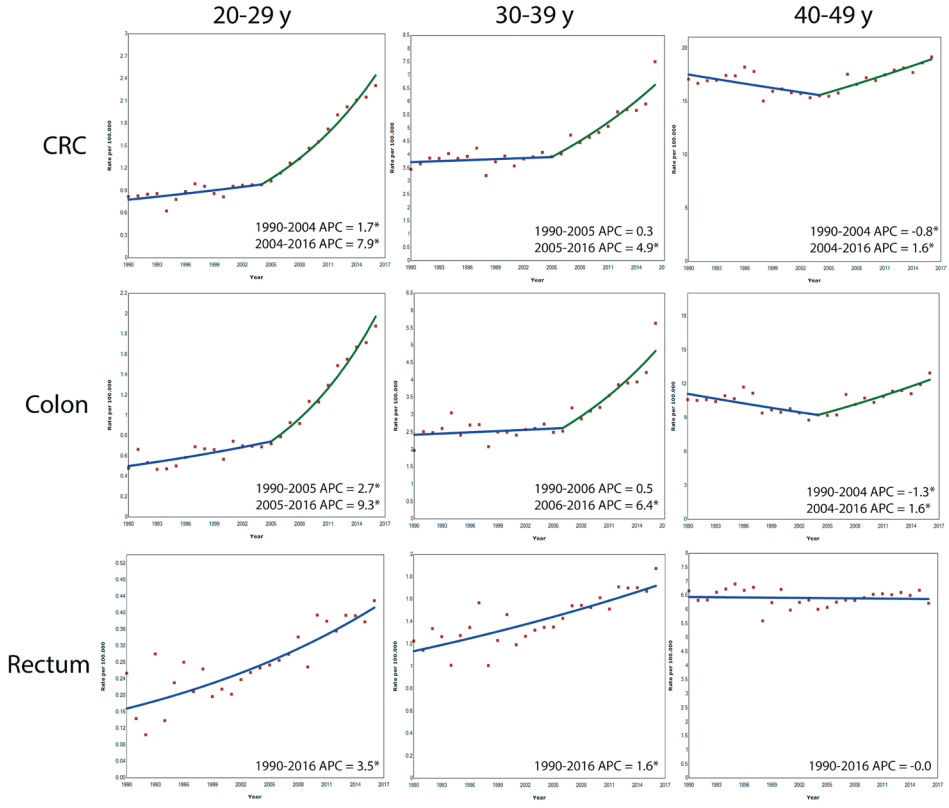

Figure 2. Annual percent change (APC) in age-specific colorectal cancer (CRC), colon cancer and rectal cancer incidence rates in Europe, 1990–2016.
*Indicates that APC is statistically significant different from zero

Country-specific trends

Trends in incidence of CRC per European region are shown in **figure 1**. CRC incidence increased significantly among subjects aged 20–39 years in 12 countries: Belgium, Germany, the Netherlands, the UK, Norway, Sweden, Finland, Ireland, France, Denmark, Czech Republic and Poland. Italy showed a decrease in incidence in this age group. No significant change was observed in the remaining six countries (online **supplementary figure 1**).

CRC incidence increased significantly among subjects aged 40–49 years in eight countries: the UK, Greenland, Sweden, Slovenia, Germany, Finland, Denmark and the Netherlands. Only Czech Republic showed a significant decrease in incidence from 1997 to 2015. No significant change was observed in the remaining 11 countries (online **supplementary figure 2**).

Sensitivity analyses

Not all countries could provide data over the entire time period of 1990 to 2016. We therefore performed sensitivity analyses for the longest possible time frame: 1991 to 2014. Data from nine countries were included: Denmark, Finland, Norway, Sweden, the Netherlands, Greenland, Slovenia, Czech Republic and Switzerland. The outcomes indicated increases in the incidence of both colon and rectal cancer in all age groups (**figure 3**).

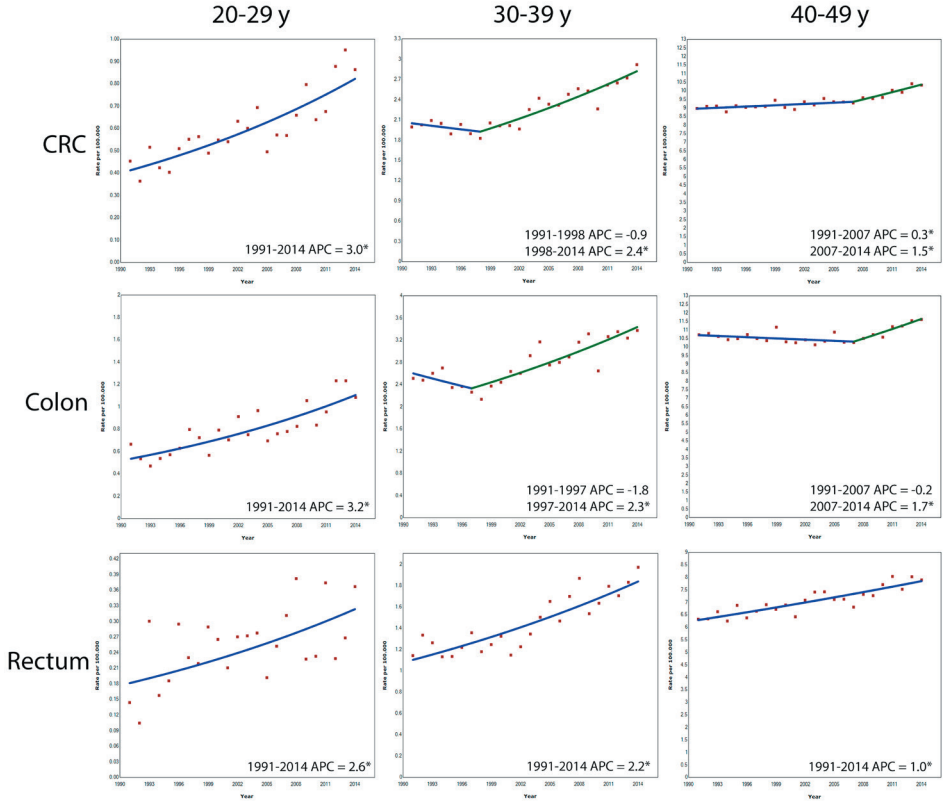

Figure 3. Annual percent change (APC) in age-specific colorectal cancer (CRC), colon cancer and rectal cancer incidence rates in nine European countries, 1991–2014. Analyses on trend in incidence of CRC was based on nine countries: Slovenia, Norway, Denmark, Sweden, Finland, the Netherlands, Czech Republic, Switzerland and Greenland. Analyses on trend of incidence of colon cancer and rectum cancer was based on eight countries: Slovenia, Norway, Denmark, Sweden, Finland, the Netherlands, Czech Republic and Greenland.
*Indicates that APC is statistically significant different from zero

We assessed by means of sensitivity analysis whether the increase in incidence was a period or a cohort effect (**figure 3**). This showed that adults aged 20-29 years had an increase in CRC incidence from 1991 to 2014. In age group 30-39 years, a rise in incidence started in 1998 and exactly 10 years later (2007) a rise in incidence was observed among those aged 40-49 years. This difference in starting points is compatible with a cohort effect.

Mortality due to colorectal cancer

Age group 20–39 years

The mortality rate for CRC did not significantly change in the age group 20–29 years. In the age group 30–39 years, the mortality decreased with 1.1% per year (**figure 4**). The mortality rate of colon cancer decreased with 9.7% per year between 1990 and 1993, and with 0.5% per year between 1993 and 2014, to remained stable from 2014 onwards. No significant change in mortality was observed for rectal cancer.

Age group 40–49 years

The overall mortality of CRC in the age group 40–49 years decreased with 2.4% per year between 1990 and 2009, but increased with 1.1% per year between 2009 and 2016 (**figure 4**).

The mortality rate of colon cancer decreased with 2.4% per year between 1990 and 2010, and remained stable between 2010 and 2016. The mortality rate of rectal cancer decreased with 2.6% per year between 1990 and 2006, and remained stable between 2006 and 2016.

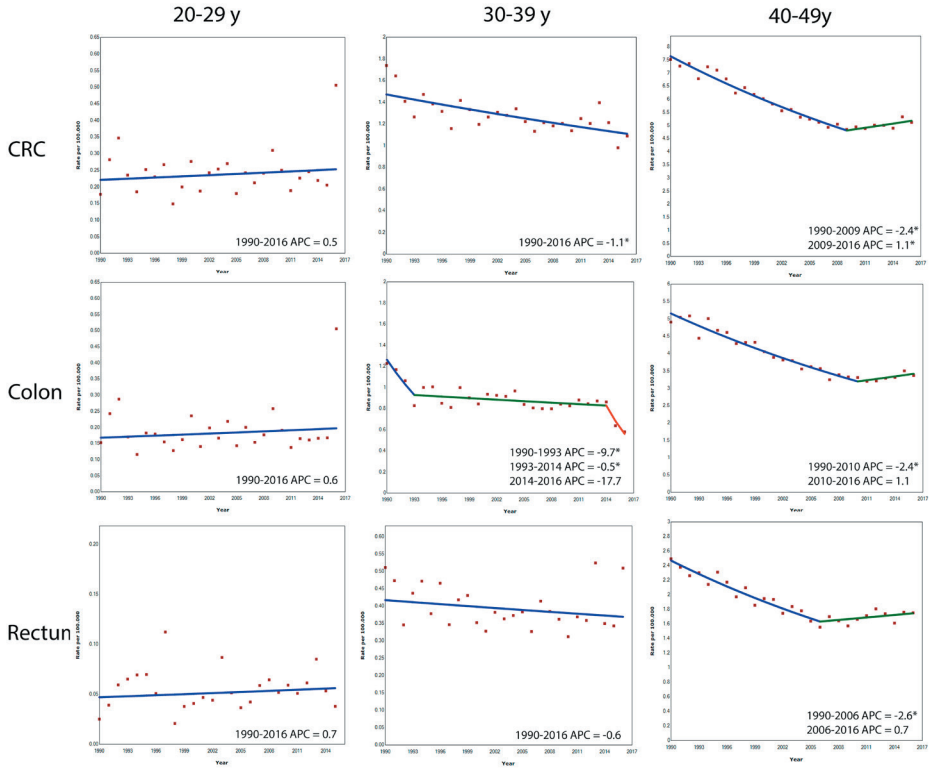

Figure 4. Annual percent change (APC) in age-specific colorectal cancer (CRC), colon cancer and rectal cancer mortality rates in Europe, 1990–2016.
*Indicates that APC is statistically significant different from zero.

Discussion

Our study showed an increase in CRC incidence in adults aged 20–49 years in Europe. The largest increase in CRC incidence occurred among subjects aged 20–39 years. The incidence of colon cancer increased with 6.4%–9.3% annually; that of rectal cancer with 1.6%–3.5% per year. The causes of this increase are yet unknown. Awareness of this trend is relevant to identify patients at risk. Further research is needed to determine whether the trend can be reversed, among others by lowering the age to start screening.

In the past years, an increase in CRC incidence in young adults has been observed in different parts of the world, such as the USA (4). In Canadian subjects aged 20–29 years, the incidence of colon cancer rose faster than that of rectal cancer (APC 6.2%, respectively 1.5%). CRC incidence in young adults also rises in Australia and China. In the latter country, adoption of a Western lifestyle is thought to contribute to this trend (9, 10). In the USA, the increase in CRC incidence was explained by a cohort effect. Our data support a similar effect in Europe. The incidence started to rise exactly 10 years earlier in the age groups 30–39 years than in the group of 40–49 years. CRC incidence also rose among those aged 20–29 years, however, with no turning point during the study period. This suggests that the turning point already occurred before 1990. The cause of this trend is unknown. A combination of factors is likely to have contributed. This includes the increasing prevalence of obesity. The latter parallels the increase in CRC incidence in young adults (11). A meta-analysis showed that weight gain is associated with an increased risk of CRC (12). Excess nutrients may initiate a chronic low-grade inflammatory response in metabolic cells (13). Also, other risk factors such as lack of physical activity, increased alcohol intake and cigarette smoking may play a role (14–17).

We found that the rate of increase differed for colon and rectal cancer, ranging from 1.6% to 9.3% for colon cancer vs 0% to 3.5% for rectal cancer. Although the above-mentioned risk factors apply to both colon and rectal cancer, some factors are strongly associated with colon cancer only. Lifestyle factors such as diet, physical activity and alcohol have been associated with risk of colon cancer, but not with rectal cancer (18). Also, a meta-analysis showed that obesity was in particular associated with an increased risk of colon cancer. For rectal cancer this association was less apparent in men, and absent in women (19). This might in part be explained by the greater susceptibility of the colon to the effects of insulin in comparison with the rectum (20). The increasing use of colonoscopy for diagnostic and screening purposes may have been responsible for a proportion of the detected CRCs in young adults. Nevertheless, detection bias is probably not the driving factor for this trend, since young adults are less likely to be screened for CRC, the rise was most marked in the youngest age group and the turning points differed between age groups.

Current guidelines in Europe recommend CRC screening from the age of 50. In 2018, the American Cancer Society recommended to start screening at the age of 45. This recommendation was based on the burden of disease, the increasing incidence among younger subjects, the results of modelling and the assumption that screening the age group 45–49 years will have preventive effect as screening those 50 years and above. The American Cancer Society's analyses showed a favourable benefit-to-burden balance with an expected reduction in CRC mortality and incidence (8). For several reasons, the results of our study provide no argument for starting screening at the age of 45 years in Europe. First, the largest increase in CRC incidence rate was observed in the age group of 20–39 years. Second, the rate of change in CRC incidence differed between countries. Third, the absolute numbers of CRC in these age groups still remain low in comparison with elderly subjects. Fourth, most European countries struggle to find the resources to properly screen the age group of 50–75 years, or are in the process of implementing screening for this group. For these reasons, it is too early to use our data to support screening for those aged 45–50 years. However, it is relevant to research to monitor this trend, and repeatedly assess whether screening practice needs to be adapted. Furthermore, we should find underlying causes, and identify high-risk subjects who might benefit from earlier screening. A first step to reach this goal is to make clinicians aware that the CRC incidence in young adults is rising quite rapidly.

Italy is the only country that showed a significant decrease in CRC incidence among subjects aged 20–39 years. This occurred at a rate of 1.8% per year from 1998 onwards. We should be careful with data interpretation though, because the observation might be due to selection bias. The Italian data were retrieved from the AITRUM database, covering only nine regions from 1996 to 2009 instead of the entire country over a longer period. The incidence trend did not significantly change in Greenland, Iceland, Slovenia, Catalonia, Latvia and Switzerland. This can likely be explained by the low population numbers in these countries, affecting power of our calculations.

This study is the first to give an overview of CRC incidence and mortality rates in younger adults in Europe. A major strength is the use of data from 20 European counties. Still, several limitations need to be addressed. First, not all European Union member countries could be included, either because of the lack of a national cancer registry or inaccessibility of the data. Also, for some countries (Portugal, Spain and Italy), data were only available for only a limited number of regions. Second, not all countries could provide data over a period of 25 years, because some national cancer registries were set up in a later year. In all countries, however, data were available for at least 10 years. The analysis of data from countries with a longer observation period (1991–2014) consistently showed the same trends. Third, the quality of data differed between countries. Data quality was estimated in terms of microscopically verified (MV) and death certificate only (DCO). The German

data, for example, had an MV rate of 85.6% and a DCO rate of 13%. The Latvian data had an MV rate of 80.7% and a DCO rate of 5.5%. Fourth, the national cancer registries from Switzerland and Germany present estimated nationwide data on CRC incidence, because not all regions can provide CRC incidence and mortality rates. Fifth, individual data were not accessible. It was not possible, therefore, to differentiate between left and right colon cancers and pathological characteristics of patients with CRC could not be retrieved.

In conclusion, the incidence of CRC is rising in Europe among subjects aged 20–49 years. If this trend continues, screening guidelines may need to be reconsidered. Until the underlying cause of this trend is clarified, it would be commendable to raise clinicians' awareness and identify factors possibly associated with this trend.

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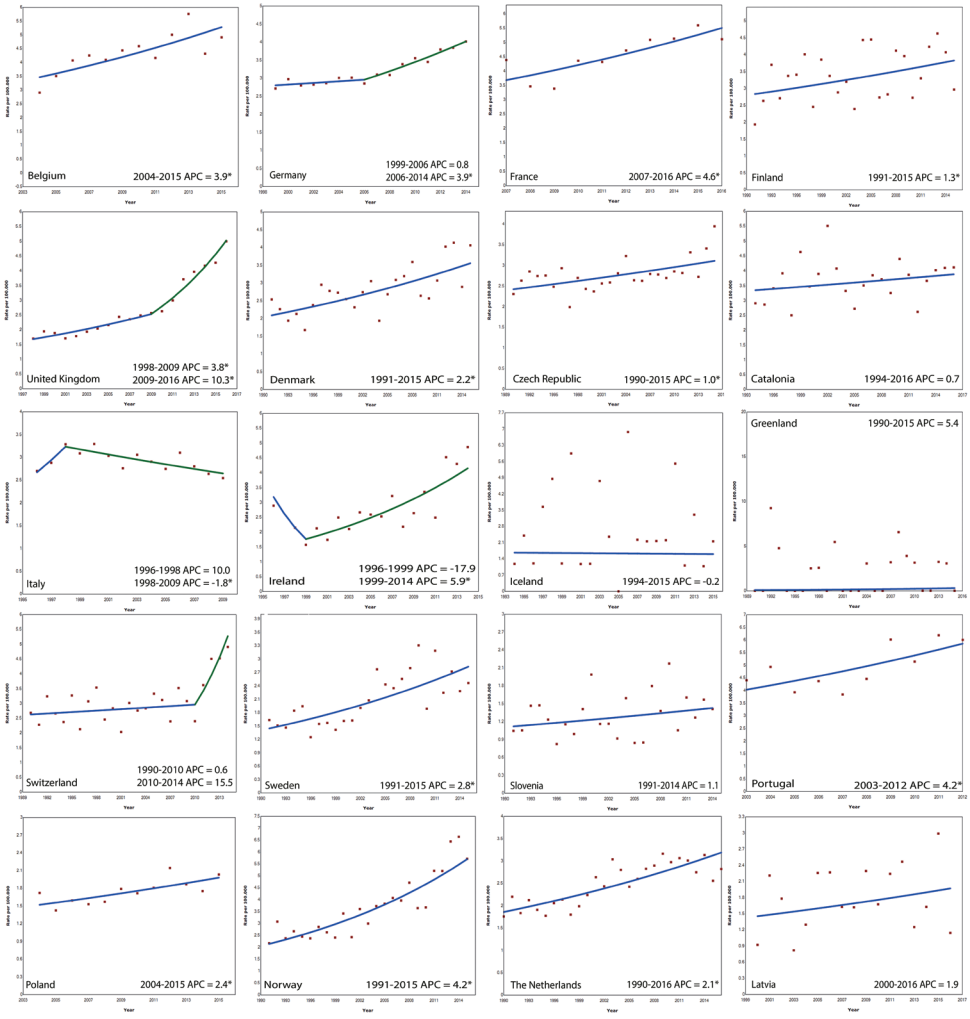
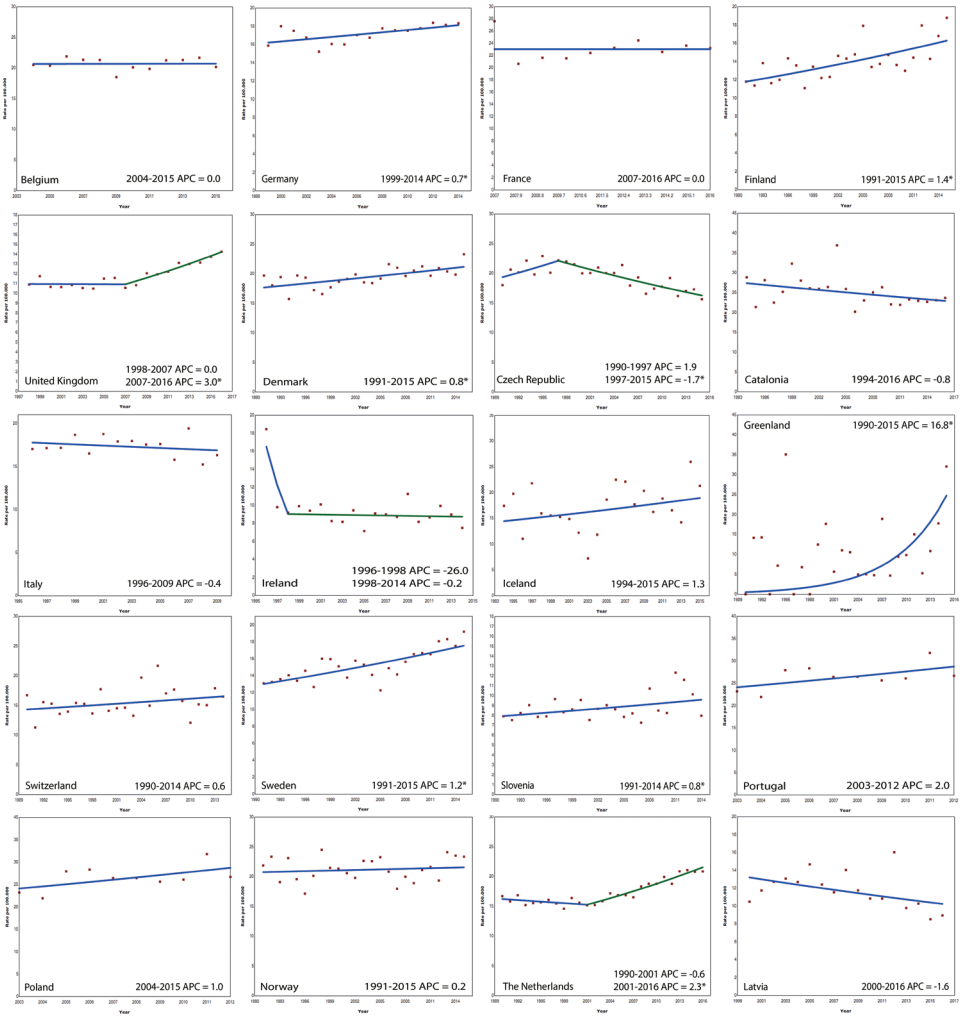
Supplementary material



Supplementary Figure 1. Incidence annual percent change (APC) per country in age group 20 to 39 year *Statistical significant change in trend



Supplementary Figure 2. Incidence annual percent change (APC) per country in age group 40 to 49 year * Statistical significant change in trend

CHAPTER 9

Clinicopathological characteristics of early onset colorectal cancer

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Aliment Pharmacol Ther, October 2021

Abstract

Introduction

The rising incidence of early onset colorectal cancer (EOCRC) might reflect a novel tumour entity. The aim of this study is to evaluate clinicopathological characteristics of sporadic EOCRC (in patients < 50 years old) and investigate changes over time.

Methods

All patients with sporadic EOCRC between 1989 and 2016 were included and divided by age: 20-29 years (group I), 30-39 years (group II) and 40-49 years (group III).

Results

We included 6400 patients. The presence of signet-ring cells and more poorly differentiated tumours were more common in the younger age groups: 5.4% and 3.7% for signet-ring cells in group I and II vs 1.4% in group III ($P < 0.01$), and 28.5% and 20.3% for poorly differentiated in group I and II vs 16.6% in group III, ($P < 0.01$ group I; $P = 0.07$ group II). Positive lymph nodes were more frequently observed in the younger age groups: 16.2% in group I vs 9.3% in group II ($P = 0.01$) and 7.9% ($P < 0.01$) in group III. Over time, a greater proportion of CRCs were diagnosed in women in group I (34.5% < 2004 vs 54.9%>2005, $P = 0.09$), and a higher percentage of rectal cancer was found in age group III (34.3% < 2004 vs 40.7% > 2005, $P < 0.01$). Mean overall survival was 6.3 years and improved over time.

Conclusions

EOCRC is not only characterised by age of onset but also by the more frequent presence of signet-ring cells, more poorly differentiated tumours, and higher risk of lymph node metastases. In the most recent years, a higher proportion of rectal cancer was found from the age of 30 years, and a higher proportion of CRCs were diagnosed in females below the age of 30 years.

Introduction

Colorectal cancer (CRC) incidence and mortality are decreasing in adults older than 50 years due to screening and improvements in CRC treatment in both the US and Europe (1, 2). Conversely, CRC incidence in young adults, early-onset CRC (EOCRC), is rising in several parts of the world (2, 3). It is known that individuals with Lynch syndrome (LS) or familial adenomatous polyposis (FAP) are more likely to develop CRC at a relatively young age. However, this group accounts for only 2%-3% of all CRC cases (4). Most of EOCRCs are sporadic cases. The underlying factors contributing to the increasing incidence of sporadic CRC in young adults are still incompletely understood but seem to include obesity, lack of physical activity, alcohol intake and cigarette smoking (5-7). Also, several drugs have been reported to be associated with CRC risk. The use of oral antibiotics is associated with an increased CRC risk, while the use of statin and aspirin might decrease this risk (8-10). Association studies on sporadic EOCRC show that male gender, being black or Asian, having inflammatory bowel disease (IBD) or a family history of CRC might be associated with an increased EOCRC risk (11). To fully elucidate causes and mechanisms of EOCRC, it is important to have more insight into both patient and tumour characteristics of these CRCs. Data on location, histology, and tumour stages of sporadic EOCRC compared to late-onset CRC are scarce and conflicting. Some studies indicate a higher prevalence of right-sided CRC in EOCRC while other studies showed a higher prevalence of a more distal location (12, 13). Signet-ring cells were described to be more prominent in EOCRC, while conflicting studies were published on KRAS, NRAS and BRAF mutations among EOCRC patients (14, 15). These conflicting data might be a result of differences between and within EOCRC cohorts. For example, the very young patients (below the age of 30 years) might have a different type of CRC than the slightly older EOCRC patients (30-50 years of age). The latter might resemble more the sporadic CRC in adults above the age of 50 years of age. Furthermore, it is questioned whether the rising incidence of sporadic EOCRC might reflect the rise of a novel tumour entity. Therefore, the aim of this study was to assess the clinicopathological characteristics of sporadic EOCRCs within different age categories (20-29 years vs 30-39 years vs 40-49 years) and investigate changes over time.

Methods

Study population

All CRC patients below the age of 50 years were identified from the Netherlands Cancer Registry (NKR) and the Dutch national pathology registry PALGA, the nationwide network and registry of histo- and cytopathology in the Netherlands between 1989 and 2016 with follow-up of each case until 31 January 2018. EOCRCs were defined as sporadic cancers of the colon or rectum in individuals under the age of 50 years that were tested for LS and showed an MSS phenotype. Patients were divided into three age groups:

group I (20-29 years); group II (30-39 years) and group III (40-49 years). All patients with an adenocarcinoma located in the colon and/or rectum were included. Excluded from this study were patients with LS tumours, neuroendocrine tumours, neuroendocrine carcinomas and squamous cell carcinomas.

The study was conducted in accordance with the Declaration of Helsinki Principles and approved by the ethical committee of the Erasmus University Medical Center, Rotterdam (MEC-2020-0048).

Data source

Data on age-related histopathological features were retrieved from the NKR and the Dutch national pathology registry PALGA (16, 17). NKR complies clinical data of all newly diagnosed patients with cancer in the Netherlands since 1989. The PALGA database covers all pathology laboratories in the Netherlands. Summaries of all histopathology and cytopathology reports are generated automatically at the laboratories and transferred to the central databank of PALGA.

Data collection

Tumours on which molecular analyses were performed and were negative for a hereditary disorder, were defined as sporadic CRC. Clinical characteristics included gender, age at diagnosis, tumour location and tumour stage. Tumour location was grouped by primary site, where cecum to sigmoid (ICD-O-3 codes C180, C182-C187 and C199) was defined as colon and rectum (C209) was defined separately. Pathological characteristics included histopathology, degree of differentiation, presence of (lymph node) metastasis, lymphatic invasion and angioinvasion. For N stage the UICC 7th edition was used (18). Lymph node metastasis were categorised in two groups: patients with no or <7 lymph nodes (≤N2a) or patients with >7 lymph nodes (N2b)

TNM stage was based on histopathologic examination (pTNM). In case pTNM stage was not available, TNM stage before treatment (cTNM) was used. Data on the presence of lymphatic invasion and angioinvasion was only available for the years 2015 and 2016. Furthermore, the prevalence of the following genes was examined: BRAF, NRAS and KRAS. Overall survival (OS) was defined as the time between the date of diagnosis to the date of death from any cause or the end of follow-up.

Statistical analyses

The proportions between age categories were compared using chi-squared or Fishers exact tests when appropriate. Group-wise comparisons were performed when the overall P-value of a group was $P < 0.10$. To elucidate the clinical and histopathological characteristics of patients with sporadic EOCRC over time, the study period was divided

into two time periods (period 1: 1989-2004 and period 2: 2005-2018) comparing the first 15 years of data to the second 15 years. Differences between the time periods were compared using the chi-squared test. Kaplan-Meier curves and log-rank tests were used to evaluate differences in survival. A two-sided P-value of less than 0.05 was considered statistically significant. Data analyses were performed using spss version 25.

Results

Baseline characteristics

In total, 15.925 CRC patients under the age of 50 years were identified between 1989 and 2016 (52% male, mean age 43 years, SD 5.8) (**Figure 1**). No molecular diagnostics were performed on 7.905 (49.6%) patients. Differences in characteristics between patients with and without molecular diagnostics are depicted in **Table S1**. Patients tested for MSI were slightly older 43.5 years vs 42.7 years ($P < 0.01$), were more often females 49.5% vs 46.5% ($P < 0.01$), had more often more than seven positive lymph nodes (8.1% vs 5.9%, $P < 0.01$) and had a well-differentiated tumour (80.1% vs 78.1%, $P < 0.01$). Of the other 8020 patients, 69 patients were excluded because the tumour was not an adenocarcinoma.

Of the remaining 7951 patients with an adenocarcinoma and MSI tested, 6400 (80.5%) was a sporadic EOCRC, 681 patients (8.6%) were diagnosed with LS, and of 870 patients (10.9%) the result of molecular diagnostics was unknown.

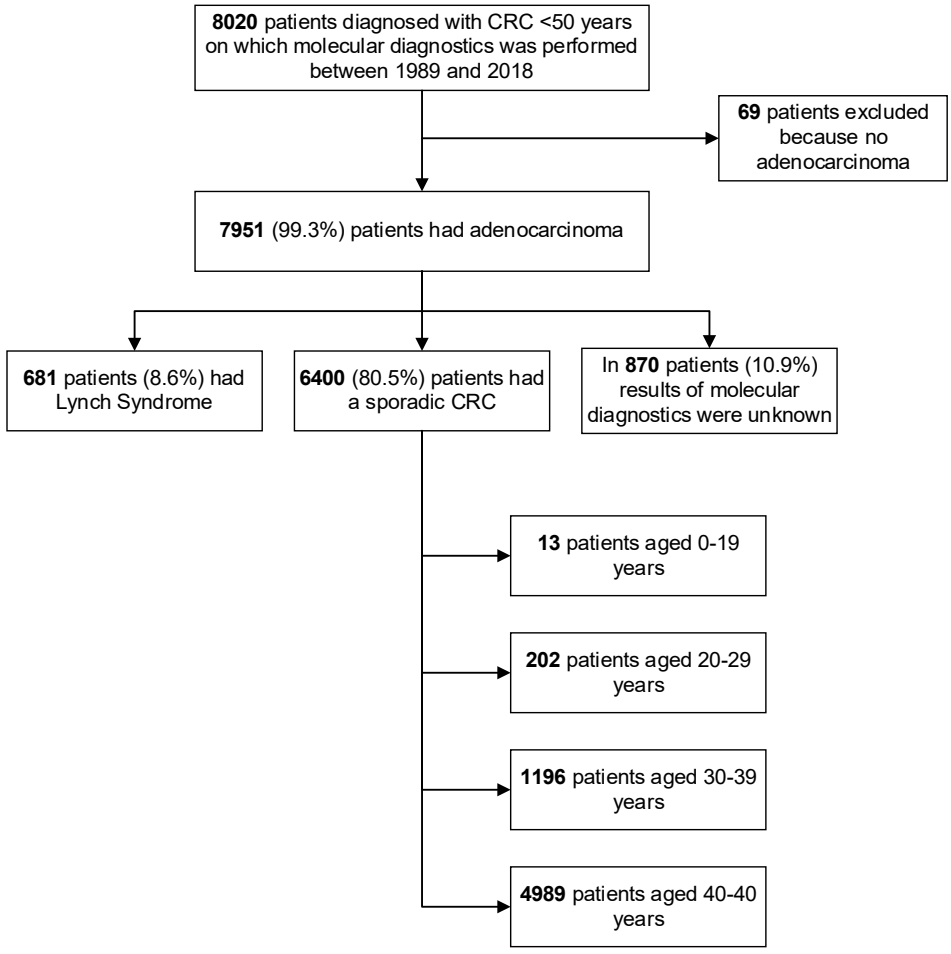

Figure 1. Flowchart, CRC; colorectal cancer

Sporadic EOCRC

When focusing on the 6400 sporadic EOCRC patients, 49.2% was male with a mean age of 43 years (SD 5.6). In total, 202 (3%) patients were diagnosed at the age of 20-29 years old (group I); 1196 (19%) patients at the age of 30-39 years old (group II) and 4.989 (78%) patients at the age of 40-49 years old (group III). Due to the low number of patients in age group 0-19 years of age (n = 13 [0.2%]), clinicopathological features were described and not included in the comparison analyses.

Clinical and pathological characteristics of patients with sporadic EOCRC

Characteristics per age group

In the youngest sporadic EOCRC age group (0-19 years) patients had a mean age of 16 years (SD 2.2), 61.5% was female, and in 38.5% the tumour was located in the rectum. CRC was poorly differentiated in 46.2% and in 38.5% signet-ring cell carcinoma was present.

Between age groups I, II and III no difference in gender ($P = 0.43$) and location ($P = 0.10$) was observed (**Table 1**). More often positive lymph nodes were diagnosed in group I, 16.2% vs 9.3% in group II ($P = 0.01$) and 7.9% ($P < 0.01$) in group III. Also, in group I more poorly differentiated tumours 28.5% were found, followed by 20.3% in group II and 16.6% in group III ($P < 0.01$). Both in groups I and II more signet-ring cell carcinomas 5.4% and 3.7% vs 1.4% in group III ($P < 0.01$) were present (**Figure 2**). The only differences between age groups and TNM stage, were more prevalent TNM stage I tumours in age group III compared to age group II (13.0% vs 11.1%, $P = 0.04$) and more frequently diagnosed TNM stage III tumours in age group II compared to age group III (9.9% vs 6.8%, $P < 0.01$). No differences in the number of metastases were observed between the age groups. Also, no difference in the number of mucinous carcinoma and presence of angioinvasion was observed. Lymphatic invasion was more commonly found in groups I and II compared to group III, 33.3% and 28.0% vs 20.3% ($P = 0.09$) respectively. No difference was observed in the number of KRAS, NRAS and BRAF mutations.

Table 1. Clinical and pathological features of sporadic EOCRC divided in three age groups.
†Data of lymphatic invasion and angioinvasion was only available for years 2015 and 2016

Characteristic of EOCRC patients	Group I 20-29 years	Group II 30-39 years	Group III 40-49 years	P-value	Group I vs group II	Group I vs group III	Group II vs group III
Total number	202	1196	4989				
Gender							
Male	103 (51.0)	569 (47.6)	2470 (49.5)	0.43			
Female	99 (49.0)	627 (52.4)	2519 (50.5)				
Location							
Colon	133 (68.6)	714 (61.0)	2977 (61.0)	0.10	.	.	.
Rectum	61 (31.4)	456 (39.0)	1905 (39.0)				
Mucinous histology							
Absent	188 (93.1)	1126 (94.1)	4741 (95.0)	0.25			
Present	14 (6.9)	70 (5.9)	248 (5.0)				
Signet-ring cell histology							
Absent	191 (94.6)	1152 (96.3)	4919 (98.6)	<0.01	0.23	<0.01	<0.01
Present	11 (5.4)	44 (3.7)	70 (1.4)				
Differentiation grade							
Well/moderate	108 (71.5)	721 (79.7)	3206 (83.4)	<0.01	0.02	<0.01	<0.01
Poor	43 (28.5)	184 (20.3)	636 (16.6)				
TNM stage							
I	30 (14.9)	133 (11.1)	668 (13.0)	0.08	0.13	0.55	0.04
II	12 (5.9)	71 (5.9)	238 (4.8)	0.21			
III	13 (6.4)	118 (9.9)	340 (6.8)	<0.01	0.12	0.83	<0.01
IV	26 (12.9)	174 (14.5)	633 (12.7)	0.23			
Number of metastasis							
0	146 (72.3)	886 (74.1)	3795 (76.1)	0.19			
1	35 (17.3)	204 (17.1)	745 (14.9)	0.14			
2	11 (5.4)	71 (5.9)	306 (6.1)	0.90			
3	9 (4.5)	31 (2.6)	130 (2.6)	0.27			
Number of positive lymph nodes							
<7 positive lymph nodes	129 (83.8)	816 (90.7)	3599 (92.1)	<0.01	0.01	<0.01	0.16
>7 positive lymph nodes	25 (16.2)	84 (9.3)	307 (7.9)				
Lymphatic invasion*							
No	16 (66.7)	67 (72.0)	468 (79.7)	0.09	0.61	0.12	0.09
yes	8 (33.3)	26 (28.0)	119 (20.3)				
Angioinvasion							
No	14 (66.7)	41 (69.5)	331 (74.4)	0.56			
yes	7 (33.3)	18 (30.5)	114 (25.6)				
KRAS mutation							
Absent	14 (58.3)	72(63.2)	261 (55.9)	0.37			
Present	10 (41.7)	42 (36.8)	206 (44.1)				
NRAS mutation							
Absent	13 (92.9)	64(98.5)	244 (94.6)	0.38			
Present	1(7.1)	1 (1.5)	14 (5.4)				
BRAF mutation							
Absent	18 (100)	73 (93.6)	299 (91.8)	0.42			
Present	0 (0)	5 (6.4)	26 (8.0)				

EOCRC characteristics over time

In age group I, 34.5% of the cancers were diagnosed in women in time period 1989-2004 compared to 54.9% in time period 2005-2018 (P = 0.01) (**Figure 3** and **Table S2**). In age groups II and III no differences in gender were observed over time. For tumour location age group I showed the highest percent of cancers located in the colon in both men and women, and this did not change over time. In age group II the percent of rectal cancer was 33.8% in time period 1989-2004 and 41.6% in period 2005-2018 (P = 0.01) and in age group III the percent of rectal cancer was 34.3% in period 1989-2004 and 40.7% in period 2005-2018 (P < 0.01). The percent of poorly differentiated CRCs remained stable in age group I. In age groups II and III a decline over time was observed, 25.1% of the patients were diagnosed with a poorly differentiated CRC in age group II between 1989 and 2004 and declined to 17.4% between 2005 and 2018 (P = 0.05) and in age group III 20.3% had a poorly differentiated CRC between 1989 and 2004 and declined to 15.0% between 2005 and 2018 (P < 0.01). A higher proportion of patients had lymph nodes metastases after 2005 in all three age groups.

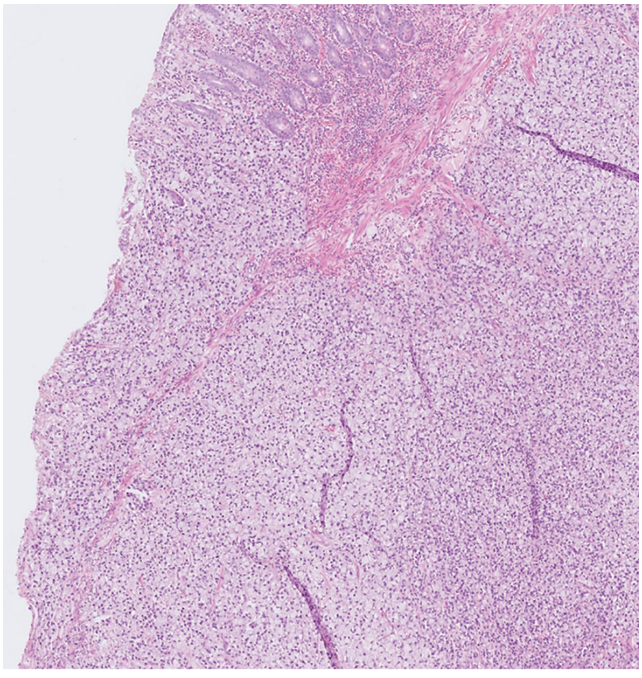

Figure 2. Microscopic image of a signet-ring cell carcinoma in the colon

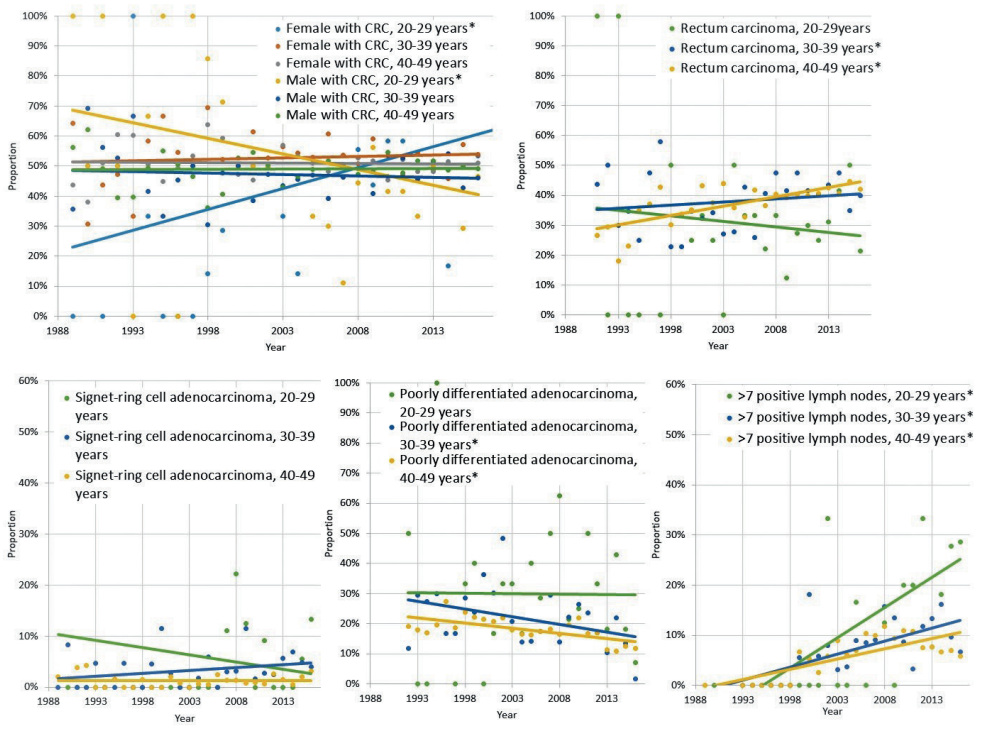

Figure 3. Proportion of female and male patients with colorectal cancer (CRC), rectum carcinomas, signet-ring cell adenocarcinomas, poorly differentiated CRC and CRC with more than 7 positive lymph nodes over time divided into three age groups. *Significant difference

Overall survival outcome

Mean OS time was 6.3 years (SD 6.2). Overall 5-year disease-free survival rates were 60.9% in group I, 62.7% in group II, and 64.2% in group III. OS did not significantly differ between the three groups (P = 0.72) (**Figure 4**). A better survival rate was found for patients diagnosed with CRC between 2005 and 2018, with an overall 5-year disease-free survival rate of 65.8% vs 58.4% for patients diagnosed between 1989 and 2004 (P < 0.01; **Figure 4**).

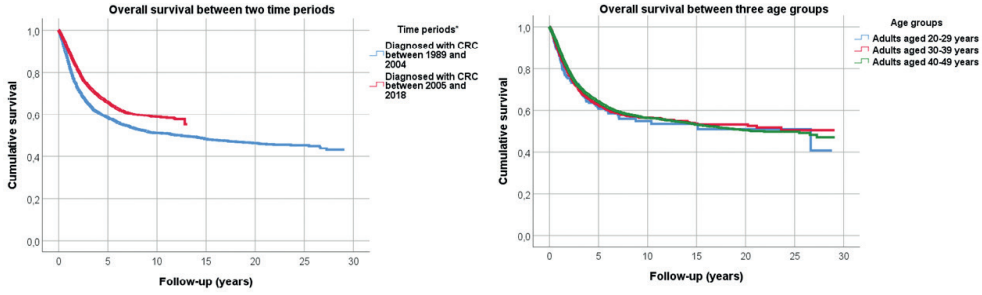

Figure 4. Overall disease-free survival analyses in sporadic early-onset colorectal cancer (EOCRC) patients per time period (1989-2004 vs 2005-2018) and per age group. *Significant difference

Discussion

This study presents a nationwide analysis of clinical and histopathological characteristics of CRC in patients <50 years of age over the past 30 years. Poorly differentiated tumours, presence of signet-ring cells, and higher number of lymph node metastasis were significantly more prevalent in 20-39 years old compared to the 40-49 years old. Over time, a higher proportion of EOCRCs were diagnosed in women below the age of 30 years, while a higher proportion of tumours were located in the rectum in the older group, 30-49 years old. OS was 6.3 years and improved over time.

This is the first study to assess clinicopathological features between different age groups of true sporadic EOCRC patients, without obscuration of patients with LS-CRC. Identification of EOCRC remains a major challenge and is expected to become more prevalent in the upcoming years. Insights about EOCRC both from a patient and tumour perspective may help to better recognise EORCC patients.

The results from our study confirm the observations of two other studies from the US. In one study 55 EOCRC patients below the age of 40 years were compared to sporadic CRC patients older than 40 years of age (15). In the other US study, more than 36 000 patients were included (19). Both studies showed a higher prevalence of signet-ring cell carcinomas and a higher proportion of tumours located in the left side of the colon or in the rectum in the youngest age group (15, 19). In addition, we found that sporadic EOCRC patients <40 years of age had more often lymph nodes metastases. Another study using the SEER 9 Registries concluded that EOCRC were more often found at an advanced stage and were more often mucinous carcinomas (20). However, in this study they were unable to exclude LS patients which may have biased the results.

A consistent finding is that the incidence of rectal cancer in EOCRC patients increased over time. In a previous study, it was shown that the incidence of rectal cancer in patients <40 years of age over two time periods (1992-1996 and 2010-2014) increased from 2.7 per 100 000 to 4.4 per 100 000 patients (21). The incidence rates, however, of carcinoid carcinomas located in the rectum increased more steeply than adenocarcinomas. This may partly explain the rapid rise of rectal carcinomas, especially for those studies that did not assess cancers by histological subtypes (22).

We found that a higher proportion of CRCs were diagnosed in women aged 20-29 years old in more recent years. A true increase in incidence could however not be calculated because of the missing population numbers of women per time period. It is known that men are at greater risk for late-onset CRC, but recent studies revealed that men also have a higher risk for EOCRC (10, 23). These studies however did not stratify by age or ethnicity. An

American study for example found that rural Non-Hispanic black women had the highest incidence rate ratios, which was primarily driven by colon cancers (24). Differences may possibly explained by differences in genetic make-up and lifestyle factors, such as obesity and red meat consumption, but does not fully explain the gender difference in EOCRC (25). More research is required, stratifying groups by age, ethnicity and tumour site (colon vs rectal cancer) to elucidate explanations that may better clarify gender differences in EOCRC. Furthermore, a remarkable finding was the decline of poorly differentiated EOCRC over time, while more positive lymph nodes were found over time. The latter could be explained by the fact that the evaluation of lymph nodes became a quality measure for colon cancer care, since the number of lymph nodes examined is positively associated with the survival of patients (26). Another explanation for the higher proportion of patients with positive lymph nodes could be the improved techniques to harvest lymph nodes, such as fat clearance (27).

Our study included data on KRAS, NRAS and BRAF genes. KRAS is a common gene in CRC patients and has the ability to promote tumour proliferation and suppress differentiation. As biomarker, KRAS predicts response to anti-EGFR therapies (28, 29). NRAS is less prevalent in CRC patients and are able to suppress apoptosis (28). BRAF genes are found in 7% of the tumours and is considered as a driver in the serrated pathway (30). Previous literature showed conflicting results regarding the prevalence of KRAS, NRAS and BRAF genes in EOCRC patients. A review from Italy included 46 articles, of which ten studies reported on prevalence of KRAS genes in EOCRC (14). Seven studies reported a lower prevalence of KRAS genes in EOCRC compared to older CRC patients, two studies showed a similar prevalence and one study had a higher prevalence. The prevalence of BRAF genes was reported to be similar among EOCRC compared to older patients (14). NRAS mutation prevalence in EOCRC patients was only reported in one study with a small patient population, they reported three NRAS mutations in 69 patients (31). Our results showed no difference in KRAS, NRAS and BRAF genes between the different EOCRC age groups.

There is controversy around the prognosis of patients with sporadic EOCRC, varying from worse to better outcome compared to late-onset CRC patients (20, 32-35). The latter might be explained by the mixture with LS-CRC patients in these studies. Although OS increased over time, our study observed no difference in OS between the age groups in EOCRC. The increased OS over time may be explained by improved diagnostic modalities and treatment options (36). But also more early diagnosis of CRC in time may have contributed to the increased survival. Unfortunately, we were not able to analyse the CRC specific mortality due to the retrospective design of this study.

One could theorise that the low survival rate of EOCRC patients is the result of a patient- or doctor delay in diagnosing CRC, whereas for patients known with a hereditary disease

awareness of CRC occurrence exists. Young patients seek medical attention at a later stage because they neglect their symptoms or delay seeking medical attention. Doctors may attribute the alarm symptoms of young patients with CRC to benign causes without further examination. However, some characteristics of sporadic EOCRC could not be subjected to patient or doctor delay, like gender, location of the tumour and type of histology. Therefore, it is reasonable that differences in tumour features suggestive of differences in tumourigenesis may play a role in clinical outcome. The question what is causing the histopathological changes is still unanswered.

Previous studies on EOCRC have pooled the data of all CRC patients under the age of 40 or 50 years (37, 38). This study provides a more in-depth clinical and histopathological characterisation of young adults with sporadic CRC aged 20-29 years, 30-39 years and 40-49 years. We found that poor prognosis features of EOCRC were more prevalent in 20- to 29-year-old adults, followed by 30- to 39-year-old and less prevalent in 40- to 49-year-old adults. This makes a period effect resulting from external factors that equally affect all age groups at a particular time period less likely. In literature, it is hypothesised that the increased trend of EOCRC follows the pattern of a cohort effect where the youngest generation is more susceptible for the development of a different, more aggressive type of CRC. While CRC detected in adults aged 40-49 years are more comparable to the CRC found in the general population with comparable clinical and pathological features. The cause of the cohort effect is still unknown. Possible risk factors may be the increasing prevalence of obese individuals in the last decades or alterations in gut microbiota due to a more frequent use of antibiotics (39). But also germline variants of multiple genes could be associated with increased EOCRC risk. One study revealed that EOCRC patients have unique molecular features, with less BRAF V600 mutations compared to patients with late-onset CRC, and the presence of more subtypes of CMS1 and CMS2 (19). Another study showed a high prevalence (16%) of germline mutations in patients with EOCRC (40). Both studies however included LS patients. A recent published study showed that EOCRC exhibits a different genetic risk compared to late-onset CRC due to low-penetrance common genetic polymorphisms, with a stronger association in patients without a CRC family history (41). Though genetic factors probably play a role in the increased risk of EOCRC, most likely multiple (risk) factors are involved.

Strength of this study was the large nationwide database covering all patients diagnosed with CRC below the age of 50 years over the past 30 years in the Netherlands on which molecular analyses were performed. This study also has several limitations. First, the retrospective design of the study. This could have led to information and selection bias or misclassification of data. To ensure that LS patients were not included, we excluded all patients in who no molecular diagnostics was performed. Comparing the MSI tested group with the non-tested group, significantly more women were molecularly tested for

LS. This may have been caused by the fact that women had more often features of LS. Although we identified significant differences between the tested and non-tested group, the clinical relevance of this selection bias is less clear than including all patients, including unidentified LS patients. Ideally, one would like to follow a cohort of young adults over a long period of time. Although prospective studies should be initiated, it takes time before conclusions can be drawn and recommendations are given. With the increase in EOCRC incidence in different parts of the world, it is important to gather information at this moment in order to understand this trend and attempt to reverse it. This large retrospective study will help to contribute to the understanding of EOCRC. Second, because of the retrospective design of this study, we had no access to data regarding risk factors (e.g. smoking status, obesity, use of antibiotics). Also, no information was available regarding family history and ethnicity. Third, no linear analyses overtime were possible due to the small sample size in the youngest age groups.

To conclude, this study revealed clinicopathological differences within the groups defined as EOCRC in the last 30 years. The proportion of rectal cancer increased from the age of 30 years in more recent years, while in patients below the age of 30 years a higher proportion of CRC was found in females and characterised by a more frequent presence of signet-ring cells and poor histological features. Clinicians should be aware of these differences in clinicopathological characteristics to optimise (early) detection and eventually targeted CRC treatment.

Acknowledgements

The authors thank the registration team of the Netherlands Comprehensive Cancer Organization (IKNL) for the collection of data for the Netherlands Cancer Registry as well as IKNL staff for scientific advice. We also thank the Dutch pathology registry (PALGA) for the collection of data and their scientific advice.

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Supplementary material

Supplementary table 1. Baseline characteristics of MSI tested versus no MSI tested patients. MSI = microsatellite instability, SD = standard deviation

	MSI tested n = 7951	No MSI tested n = 7619	P-value
Age, mean (SD)	43.5 (5.9)	42.7 (5.8)	<0.01
Gender			<0.01
Male	4016 (50.5)	4078 (53.5)	
Female	3935 (49.5)	3541 (46.5)	
Location			0.06
Colon	4978 (64.1)	4759 (65.6)	
Rectum	2787 (35.9)	2500 (34.4)	
Lymphatic invasion			0.35
Absent	610 (77.9)	74 (82.2)	
Present	173 (22.1)	16 (17.8)	
Angioinvasion			0.22
Absent	436 (74.4)	49 (81.7)	
Present	150 (25.6)	11 (18.3)	
Number of positive lymph nodes			<0.01
<7 positive lymph nodes	5562 (91.9)	3272 (94.1)	
>7 positive lymph nodes	488 (8.1)	206 (5.9)	
Differentiation grade			<0.01
Well/moderate	4942 (80.1)	4663 (78.1)	
Poor	1230 (19.9)	1309 (21.9)	
Signet-ring cell differentiation			0.08
Absent	7790 (98.0)	7433 (97.6)	
Present	161 (2.0)	186 (2.4)	
TNM stage			<0.01
I	1040 (31.5)	1239 (21.3)	
II	551 (16.7)	1439 (24.7)	
III	654 (19.8)	1366 (23.5)	
IV	1056 (32.0)	1778 (30.5)	

Supplementary Table 2. Absolute numbers (percentages) of patients with sporadic EOCRC between 1989-2004 and 2005-2018 divided over three age groups. *Fisher's exact test

	20-29 years old N=201			30-39 years old N=1200			40-49 years old N=5025		
Year	≤ 2004	≥ 2005	P-value	≤ 2004	≥ 2005	P-value	≤ 2004	≥2005	P-value
Gender			<0.01			0.86			0.19
Male	38 (65.5)	65 (45.1)		187 (47.2)	382 (47.8)		620 (48.0)	1850 (50.1)	
Female	20 (34.5)	79 (54.9)		209 (52.8)	418 (52.3)		673 (52.0)	1846 (49.9)	
Location			0.64			0.01			<0.01
Colon	37 (66.1)	96 (69.6)		257 (66.2)	457 (58.4)		835 (65.7)	2142 (59.3)	
Rectum	19 (33.9)	42 (30.4)		131 (33.8)	325 (41.6)		435 (34.3)	1470 (40.7)	
Signet-ring cell carcinoma			0.73*			0.07			0.16
Absent	56 (96.6)	135 (93.8)		387 (97.7)	765 (95.6)		1280 (99.0)	3839 (98.5)	
Present	2 (3.4)	9 (6.3)		9 (2.3)	35 (4.4)		13 (1.0)	57 (1.5)	
Differentiation grade			0.80			<0.01			<0.01
Well/moderate	35 (72.9)	73 (70.9)		260 (74.9)	461 (82.6)		900 (79.7)	2306 (85.0)	
Poor	13 (27.1)	30 29.1)		87 (25.1)	97 (17.4)		229 (20.3)	407 (15.0)	
Number of positive lymph nodes			0.05*			0.04			0.06
<7 positive lymph nodes	28 (96.6)	101 (80.8)		198 (94.3)	618 (89.6)		590 (94.9)	3009 (91.6)	
>7 positive lymph nodes	1 (3.4)	24 (19.2)		12 (5.7)	72 (10.4)		32 (5.1)	275 (8.4)	

CHAPTER 10

Colon capsule endoscopy in colorectal cancer screening: a systematic review

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Endoscopy, August 2021

Abstract

Introduction

Primary colonoscopy and faecal immunochemical test (FIT) are the most commonly used colorectal cancer (CRC) screening modalities. Colon capsule endoscopy (CCE) might be an alternative. Data on the performance of CCE as a CRC screening tool in a screening population remain scarce. This is the first systematic review to provide an overview of the applicability of CCE as a CRC screening tool.

Methods

A systematic search was conducted of literature published up to September 2020. Studies reporting on CRC screening by second-generation CCE in an average-risk screening population were included.

Results

582 studies were identified and 13 were included, comprising 2485 patients. Eight studies used CCE as a filter test after a positive FIT result and five studies used CCE for primary screening. The polyp detection rate of CCE was 24%–74%. For polyps >6mm, sensitivity of CCE was 79%–96% and specificity was 66%–97%. For polyps ≥10mm, sensitivity of CCE was 84%–97%, which was superior to computed tomographic colonography (CTC). The CRC detection rate for completed CCEs was 93% (25/27). Bowel preparation was adequate in 70%–92% of examinations, and completion rates varied from 57% to 92%, depending on the booster used. No CCE-related complications were described.

Conclusion

CCE appeared to be a safe and effective tool for the detection of CRC and polyps in a screening setting. Accuracy was comparable to colonoscopy and superior to CTC, making CCE a good alternative to colonoscopy in CRC screening programs, although completion rates require improvement.

Introduction

Colorectal cancer (CRC) screening programs have been implemented in many countries to reduce CRC incidence and mortality by early detection of CRC and endoscopic removal of adenomas before their potential progression to adenocarcinomas. Several effective screening modalities are available (1). Most European countries use a faecal immunochemical test (FIT) followed by colonoscopy in individuals with a positive FIT result (2). However, the performance of this screening strategy seems to be hampered by low participation rates for colonoscopy (3). This could be due to the fact that colonoscopy is perceived as an invasive and painful procedure and the fact that it requires some form of sedation (4). Therefore, alternative strategies for CRC screening that result in higher participation rates would be desirable. To date, many CRC screening programs use computed tomographic colonography (CTC) as the primary alternative to colonoscopy. However, another promising alternative to colonoscopy is colon capsule endoscopy (CCE).

CCE provides a clear overview of the complete colon and has several advantages over colonoscopy: it is a noninvasive test, it carries minimal risks, no sedation is needed, and it can be performed at home. The performance of CCE was comparable to the gold standard (colonoscopy) in several trials (5). Sensitivity for the detection of polyps >6mm and >10mm increased markedly between the first-generation (CCE I) and second-generation (CCE II) colon capsules (6). The European Society for Gastrointestinal Endoscopy guidelines has already recommended CCE II as an option for average-risk CRC screening, and the US Food and Drug Administration has approved CCE II in patients with a previous incomplete colonoscopy and as a diagnostic tool in patients with suspected lower gastrointestinal bleeding (7, 8).

Even though the overall accuracy of CCE has been described in several trials, information on the performance of CCE in a screening population remains scarce. This is the first systematic review to provide an overview of the applicability of CCE as a CRC screening tool in an average-risk screening population, including information on participation, diagnostic value, bowel preparation, and completion rates.

Methods

We conducted a systematic search of published trials and abstracts following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (see **Table1s** in the online-only supplementary material). In collaboration with the Medical School Library of the Erasmus University in Rotterdam, The Netherlands, a systematic search was conducted of literature published up to 20 September 2020 to retrieve studies that reported on the use of CCE in a CRC screening program. Embase, Web

of Science, Ovid MEDLINE, and Cochrane CENTRAL were used as potential sources. The search was conducted using controlled vocabulary supplemented with several key words (see supplement).

Two independent reviewers (F.E.R.V. and S.A.V.N.) screened the selected studies by title and abstract. Studies that focused on the use of CCE in patients participating in a CRC screening program were included in the review. Studies using CCE I were excluded because of low sensitivity for detection of polyps compared with CCE II. Studies including first-degree relatives of patients with CRC were also excluded. The full texts of the selected publications were examined by the same authors. The reference lists from the included studies were hand-searched to identify potentially relevant studies that were not retrieved in the original search. Study authors were contacted when additional information was needed.

The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of CCE were calculated using the gold standard colonoscopy results as reference. Lesions included in the analyses were CRC and polyps of any size. Significant lesions were defined in this study as ≥3 polyps or one polyp >10mm. Non-significant lesions were defined as all remaining abnormalities and were not included in the analysis. Lesions observed by CCE but not seen at colonoscopy were defined as false-positive lesions. The polyp detection rate (PDR) was defined as the number of patients with ≥1 polyp detected by CCE. A meta-analysis could not be performed owing to the heterogeneity of the study designs.

Assessment of methodologic quality

Methodologic quality and risk of bias were assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 assessment tool (9). The two main categories evaluated were risk of bias and applicability. Two reviewers (F.E.R.V. and S.A.V.N.) independently assessed the methodologic quality.

Results

Literature search

After removal of duplicates, retrieved records were screened for eligibility based on their title and/or abstract. In total, 582 records were assessed for eligibility, after which 547 were excluded (**Figure1**). The full text of the 35 remaining studies was reviewed, after which 23 were excluded for various reasons. A total of 13 studies were included in the review, including one additional study, which was presented during Digestive Disease Week (18–21 May 2019, San Diego, California, USA) (10). Two of the included studies used

the same study cohort but with different study aims (11, 12). Eight investigators were contacted to obtain further information on their studies.

Study characteristics

Baseline characteristics of the included studies are shown in **Table1**. A total of 2485 patients were included. Eleven studies were performed in Europe and two were conducted in the USA. Ten studies were full papers. All studies were performed within a CRC screening setting in an average-risk population. Eight studies used CCE as a filter test after a positive FIT result and five studies used CCE as the primary screening tool. The design of the studies differed: in eight studies both CCE and colonoscopy were performed to assess the diagnostic accuracy of CCE for CRC and polyps (11-18); in one study CTC or CCE was offered to FIT-positive patients who refused colonoscopy (19); in one study the diagnostic accuracy of both CCE and CTC was compared with colonoscopy (20); in two studies the diagnostic yield was evaluated in patients who were randomized to undergo CCE or CTC before colonoscopy (10, 21); and in one study CCE was offered to study the effect of a new examination method on the uptake of CRC screening (22).

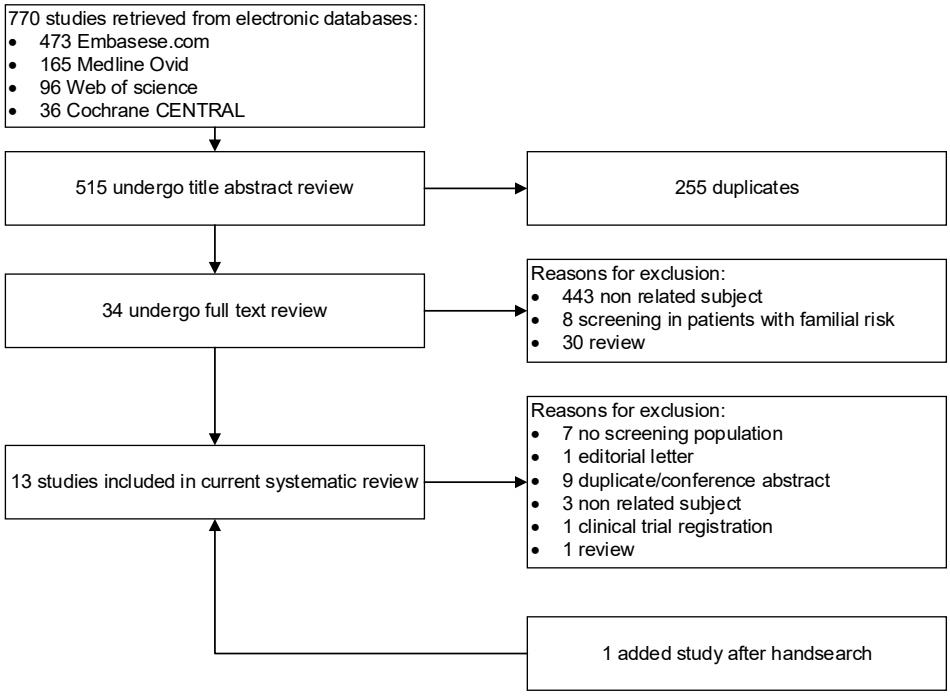

Figure 1. Flow chart of study selection. **Two studies used the same study cohort.*

Table1. Characteristics of the 13 included studies. RCT, randomized controlled trial.

Study	Year of publication	Type of article	Type of study	Centers	Patients enrolled, n	Patients included, n	Male sex, %	Mean age, y
Groth[18] Germany	2012	Full text	Cohort	Single center	154	90	64	62.7
Holleran[9] Ireland	2014	Full text	Cohort	Single center	62	62	55	62.5
Suchanek[26] Czech Republic	2014	Abstract	Cohort	Multicenter	225	225	-	59
Rondonotti[27] Italy	2014	Full text	Cohort	Single center	50	50	58	59.2
Romero[12] Spain	2015	Abstract	Cohort	Single center	67	53	58	61.3
Rex[11] US and Israel	2015	Full text	Cohort	Multicenter	884	695	44	57
Suarez[17] Spain	2016	Abstract	RCT	Single center	-	88	-	-
Kobaek-Larsen[10]* Denmark	2017	Full text	Cohort	Single center	306	253	58	64
Hassan[8] Italy, Spain	2018	Abstract	Cohort	Multicenter	222	203		
Voska[19] Czech Republic	2018	abstract	Cohort	Multicenter	200	105		
Pioche[15] France	2018	Full text	RCT	Multicentre	97	19	-	-
Thygesen[14]* Denmark	2019	Full text	Cohort	Single center	-	239	-	-
Cash US	2019	Abstract	RCT	Multicenter	320	286	42.3	55.7
Total						**2485**		

* Both studies used the same Danish cohort–no information was available.

Quality of studies

The quality of included studies and risk of bias using the QUADAS-2 tool are presented in **Table 2**. Three studies did not assess the diagnostic accuracy of CCE compared with colonoscopy and therefore most domains were not applicable (12, 19, 22). None of the studies included had a high risk of bias.

Table 2. Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) analysis for the risk of bias in included studies

	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Groth (22)	-	N/A	N/A	N/A	N/A	N/A	N/A
Holleran (15)	-	?	-	-	-	-	-
Suchanek (14)	-	?	?	?	?	-	-
Rondonotti (20)	-	-	-	-	-	-	-
Romero (13)	-	-	+	-	-	-	-
Rex (16)	-	-	-	-	-	-	-
Gonzalez-Suarez (21)	-	-	-	-	-	-	-
Kobaek-Larsen (11)	-	?	-	-	-	-	-
Pecere (17)	-	-	-	-	-	-	-
Voska (18)	-	-	-	-	-	-	-
Pioche (19)	-	N/A	N/A	N/A	N/A	N/A	N/A
Thygesen (12)	-	N/A	N/A	N/A	N/A	N/A	N/A
Cash (10)	-	-	-	-	-	-	-

– = low risk of bias; + = high risk of bias; ? = insufficient data; N/A, not applicable

Participation rate

Only two studies reported the participation rate of CCE. CCE was used as the primary screening modality in one study and as a filter test in the other. The lowest participation rate of 4.2% was reported in a German opportunistic screening study where CCE was offered as an alternative to primary colonoscopy screening (22). The average screening uptake in that area was 1%, so offering CCE actually resulted in a fourfold increase in screening uptake. In another study, CCE was offered to patients who were unwilling to undergo colonoscopy after a positive FIT result, with a participation rate of 5% (19).

Three other studies reported on the enrollment rate of participants for their study. An enrollment rate of 8.2% was found in an Italian study in which FIT-positive patients were invited to undergo both CCE and CTC in addition to colonoscopy (20). In this study, patients had to take bowel preparation twice. A Danish study showed an enrollment rate of 17.4% in FIT-positive patients who were invited to undergo CCE in addition to colonoscopy (11). An enrollment rate of 52.7% was found in a Spanish study in which FIT-positive patients were randomized to either CCE or CTC in addition to colonoscopy (21).

Patient preferences

One study assessed patients' experiences of CCE at home compared with colonoscopy in an outpatient clinic in screening participants using the same bowel preparation. Nearly 90% of the patients undergoing colonoscopy experienced a medium to high degree of discomfort compared with only 10% of patients undergoing CCE. The advantages of CCE mentioned were no pain, no embarrassment, and a less invasive procedure. Disadvantages were the waiting time for results, extended duration of the CCE procedure if the capsule had a long transit time, and the need for an additional colonoscopy when significant lesions were found. Advantages of colonoscopy were the immediate availability of results and the possibility to remove tissue during the same procedure. Disadvantages were more pain, more embarrassment, and a more invasive procedure (12). The previously mentioned German study showed that the main reason for a final choice of CCE over colonoscopy was the fear of colonoscopy-related discomfort and complications (22). With regard to patient preferences, one study showed that more participants preferred colonoscopy as the primary screening tool (53%) compared with CCE (47%) (18).

Furthermore, it was shown that 78% of patients preferred to undergo CCE over CTC. In all cases this was due to the bloating and mild pain perceived during CTC (20). When CTC or colonoscopy was preferred over CCE, the main limitation for CCE seemed to be the need for rigorous bowel preparation (20).

Diagnostic yield

Detection rate of CRC

The CRC detection rate by CCE was reported in 9 out of 13 studies and varied from 64% to 100%. The CRC detection rate for completed CCEs was 93% (25/27). The lowest detection rate of 64% was caused by a low completion rate of 57%. In this study, CCE missed four CRCs, which were all located in the left colon, because the battery life expired before excretion of the capsule (11). In another study, one CRC was missed by CCE. Unblinded review of the capsule video determined that the cancer was photographed by the capsule in multiple frames, but overlooked by the reviewer (16). In one study, CRC was misjudged as a 5-mm polyp instead of a 10-mm malignant polyp (17). The detection rate of CRC in the remaining six studies was 100% (13-15,18, 19, 21).

Detection rate of polyps

Four CCE studies provided the PDR, two of which compared the PDR of CCE with that of colonoscopy. The CCE detection rates for polyps ranged between 24% and 74% (**Table 3**, **Figure 2**). In one study, CCE detected any type of polyp in 69% of participants compared with 58% for colonoscopy (15). When only significant lesions (defined in this study as ≥3 polyps or one polyp >10mm) were included, CCE found 18 polyps (detection rate of 29%),

which was equal to the findings of colonoscopy. Another study also showed that the PDR of CCE was significantly higher than the PDR of colonoscopy (74% vs. 64%, respectively) (11). The same study performed repeat colonoscopies to determine an explanation for the difference in PDR of CCE compared with colonoscopy. An additional 82 polyps were found during repeat colonoscopy, after which the PDR of colonoscopy increased to 85%. This suggests that the discrepancy between PDR of CCE and colonoscopy might be explained by a colonoscopy miss rate (11).

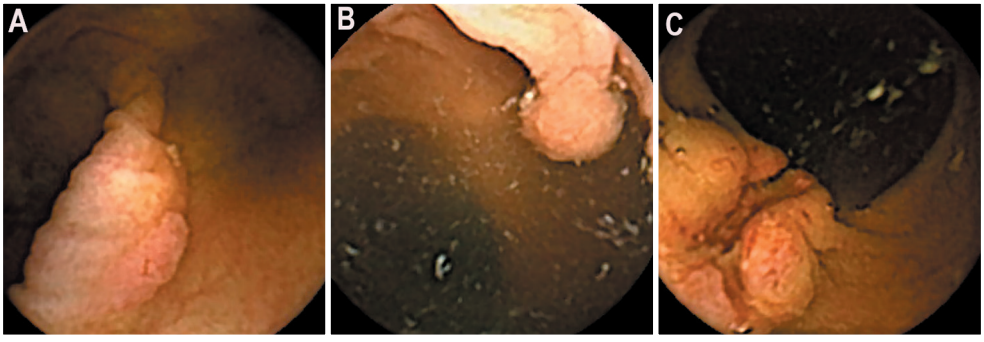

Figure 2. Lesions found during colon capsule endoscopy. a Sessile polyp. b Pedunculated polyp. c Colorectal cancer.

Table3. Overview of 13 studies reporting on diagnostic accuracy of colon capsule endoscopy and colonoscopy in a colorectal cancer screening population.

				CCE	Colonoscopy	CRC	Colono-scopy		Sensitivity	Specificity	PPV	NPV	
Groth [22]	Opportunistic, primary colonoscopy	90 (4.2)	82	–	–	–	–		–	–	–	–	–
Holleran [15]	FIT-based screening	62	73	69	58	100	100	Any polyp Sign. lesion, ≥3 polyps or 1 polyp >10 mm	95 89[1]	65 96[1]	79 89	90 96	92
Suchanek [14]	Opportunistic, primary colonoscopy or FIT	225	–	–	51	100	100	Polyp, 1 polyp ≥6 mm Polyp, 1 polyp ≥10 mm AN, 1 polyp ≥10 mm	79 (62–91) 88 (62–98)[1] 100 (72–100)	97 (94–99) 99 (97–100)[1] –	–	–	90
Rondonotti [20]	FIT-based screening	50	90	–	–	–	–	Polyp, 1 polyp ≥6 mm Polyp, 1 polyp ≥10 mm	88 (62–98) 93 (64–100)[2]	88 (78–99) 92 (76–98)[2]	–	–	70
Romero [13]	FIT-based screening	53	81	–	82	100	100	Polyp, 1 polyp >6 mm Polyp, 1 polyp >9 mm	87 88[2]	88 94[2]	–	94	–
Rex [16]	Opportunistic, primary colonoscopy	695	92	–	–	75	100	Polyp, 1 polyp ≥6 mm Polyp, 1 polyp ≥10 mm	87 (82–90) 85 (77–92)[1]	94 (92–96) 97 (96–99)[1]	–	–	80
Gonzalez-Suarez [21]	FIT-based screening	349	81		–	100	100	Polyp, polyp of any size Polyp, 1 polyp ≥6 mm Polyp, 1 polyp ≥10 mm	98 (94–99)[1] 96 (91–100) 97 (91–100)	77 (69–83)[1] 88 (80–95) 95 (91–99)	94 (88–97) 90 (84–96) 88 (77–97)	92 (86–95) 95 (89–100 99 (97–100	82
Kobaek-Larsen [11][3]	FIT-based screening	253	57	74 (69–79)	64 (58-70)	64	100	Polyp, 1 polyp >9 mm	87 (83–91)[2]	92 (89–95)[2]	–	–	85 (81–89)
Pecere [17]	FIT-based screening	178	88	–	70	91	100	AN, 1 polyp >6 mm AN, 1 polyp >9 mm	90 (79–96) 77 (67–86)[2]	66 (57–74) 91 (84–95)[2]	57 (47–68) 81 (68–90)	93 (85–97) 88 (81–93)	88
Voska [18]	Opportunistic, primary FIT	225	90	–	51	100	100	Polyp, 1 polyp >6 mm Polyp, 1 polyp >10 mm	79 88[1]	97 99[1]	–		90
Pioche [19]	FIT-based screening	19 (5.0)	68	63	–	100	100		–	–	–	–	74
Thygesen [12][3]	FIT-based screening	239	–	–	–	–	–		–	–	–	–	–
Cash [10]	Opportunistic, primary colonoscopy	286	84	24	–	–	–	Polyp, 1 polyp >6 mm Polyp, 1 polyp >10 mm	84 84[2]	93 97[2]	–	–	84

AN, advanced neoplasia, CCE, colon capsule endoscopy; CRC, colorectal cancer, PDR, polyp detection rate; PPV, positive predictive value; NPV, negative predictive value; FIT, faecal immunochemical test; Sign. lesion, significant lesion (defined as ≥3 polyps or one polyp >10mm).; –, Information not available. 1 Per-polyp sensitivity/specificity. 2 Per-patient sensitivity/specificity. 3 Both studies use the same (Danish) cohort.

Diagnostic accuracy of CCE vs. colonoscopy

Sensitivity and specificity

Sensitivity and specificity of CCE are shown in **Table 3**. Sensitivity of CCE ranged between 79% and 96% for polyps >6mm and between 77% and 97% for polyps >9mm. Specificity of CCE varied between 66% and 97% for polyps >6mm and between 91% and 99% for polyps >9mm. Data from the study by Holleran et al. showed that specificity increased when only significant lesions were included. The authors reported a specificity of 65% for all polyps; however, when looking at significant lesions only, specificity increased to 96% (15).

PPV and NPV

The PPV of CCE varied between 57% for polyps >6mm and 94% for any polyp (17, 21). The NPV varied between 88% for polyps >10mm and 99% (17, 21).

Diagnostic accuracy of CCE vs. CTC

Four studies compared the diagnostic accuracy of CCE with that of CTC. In general, the detection rate and sensitivity of polyps were higher for CCE than for CTC and the specificity was comparable.

In a randomized controlled trial, patients who were unwilling to undergo colonoscopy after a positive FIT result were randomized to CCE or CTC. Although more patients consented to participate in the CTC group than in the CCE group (7.4% vs 5.0%, respectively), the detection rate of polyps in the CCE group was 60% vs. 28.6% in the CTC group (19).

Another study comparing CCE with CTC in 50 FIT-positive patients reported a high accuracy of both CTC (sensitivity 88.2%, specificity 84.8%) and CCE (sensitivity 88.2%, specificity 87.8%) for polyps >6mm. When only polyps ≥10mm were included, a higher sensitivity for CCE (sensitivity 92.8%, specificity 91.6%) was found compared with CTC (sensitivity 78.6%, specificity 91.7%) (20). Gonzalez-Suarez et al. randomized between CTC and CCE in FIT-positive patients and found a higher sensitivity for neoplastic lesions ≥6mm and neoplastic lesion ≥10mm for CCE vs. CTC (96.1% and 97.3 vs. 79.3 and 90.0%, respectively). Specificity for neoplastic lesions ≥6mm and neoplastic lesions ≥10mm was lower for CCE compared with CTC (88.2% and 95.3% vs. 96.3% and 99%, respectively). CCE was superior to CTC (100% vs. 93.1%) for the detection of advanced adenomas and for the detection of any neoplastic lesion (CCE 100% vs. CTC 81%) (21). The study by Cash et al. showed a higher detection rate for CCE (32% for polyps >6mm and 14% for polyps >10mm) compared with CTC (9% for polyps >6mm and 6% for polyps >10mm). Sensitivity of CCE for polyps >6mm (84%) and polyps >10mm (84%) was higher than that for CTC (32% for polyps >6mm and 53% for polyps >10mm). Specificity was higher for CTC vs. CCE (99% vs. 93%, respectively) for polyps >6mm and comparable for polyps >10mm (99% vs. 97%, respectively) (10).

Quality scores

Bowel preparation

In this review, 10 studies reported adequate bowel preparation scores for CCE examinations (**Table 3**). One study (20) used a split-dose macrogol regimen of 2L, which resulted in the lowest adequate bowel preparation score of 70% (**Table 2s**). Three studies used a split-dose polyethylene glycol regimen of 4L, which resulted in the highest scores, between 88% and 92% (15, 17, 18). The bubbles effect scale was not reported in any of the studies.

Completion rate

One study used sulphate solution as a booster, which resulted in a completion rate of 92% (16). Sodium phosphate was used in five studies and was associated with completion rates of 68%–90% (17-20, 22). Two studies used polyethylene glycol as a booster, which resulted in the lowest completion rates of 57%–73% (11, 15).

Safety

No CCE-related adverse events occurred in any of the included studies. Furthermore, use of bowel preparation – especially the use of sodium phosphate – did not cause a serious adverse event in any of the studies. There was only one serious adverse event, which occurred after colonoscopy. This was a post-polypectomy bleed that required blood transfusion and colonoscopy to clip the visible vessel at the polypectomy base (15).

Experience of colon capsule readers

In 10 studies, the level of expertise of the CCE readers was provided. In seven studies, one or more gastroenterologists or endoscopists were trained in reading CCE videos (15-22). Two studies only mentioned that the videos were reviewed by centers that specialized in capsule endoscopy (14, 19). One study used the services of Corporate Health, a company of nurses and physicians trained in CCE reading (11). The remaining three studies did not mention the expertise of the viewers (10, 12, 13).

Discussion

This is the first review to provide an overview of the literature on the use of CCE as a CRC screening tool. Most of the studies included in this review investigated the use of CCE as a filter test after a positive FIT result in a CRC screening setting. CCE appeared to be a safe and effective method for finding polyps and CRC, with an accuracy comparable to that of colonoscopy and superior to that of CTC in a CRC screening setting. Its high yield and patient preference make it a suitable screening tool as an alternative to colonoscopy in CRC screening programs, although completion rates require improvement.

In a previous meta-analysis, the accuracy of the first- and second-generation colon capsules was evaluated (6). The analysis showed a sensitivity of 86% for polyps >6mm and 87% for polyps >10mm, with a specificity of 88.1% and 95.3%, respectively. These results are comparable to those in our study and confirm the good performance of CCE. However, this previous study did not focus on the performance of CCE as a screening tool in a screening population. Participation rate is one of the key performance indicators in a population-based screening program (1, 3). The overall participation in 21 European countries was 49.5% in countries using FIT-based screening, while the desirable uptake according to the European guidelines is >65% (1). The German study by Groth et al. was the only trial that offered CCE as a primary screening method in an opportunistic screening setting and this study showed a fourfold increase in screening uptake (22). The participation rate in the French study by Pioche et al. was very low (5.0%) because the study population consisted only of FIT-positive patients who were unwilling to undergo colonoscopy; therefore, this study population was biased and does not reflect a real-life situation (19). Other studies included in the review showed the enrollment rate, which does not reflect the participation rate, as those studies offered CCE in addition to colonoscopy instead of offering CCE alone. However, the extensive bowel preparation required for CCE and the possibility that bowel preparation would need to be repeated if the CCE was positive could have a negative effect on the participation rate. However, when reviewing the questionnaires, patients still preferred CCE over colonoscopy and CTC.

The CRC detection rate by CCE was 100% in almost all studies, which is an important condition for using CCE in a CRC screening program. Low completion rate is the main cause for missing CRC. Eight included studies showed a completion rate below the threshold for colonoscopy screening (90% cecal intubation rate) (23). Completion rates were highly dependent on the type of booster that was used. With the use of sodium phosphate, completion rates of up to 90% were reached. As sodium phosphate draws plasma water into the bowel, significant volume and electrolyte shifts may occur. Therefore, in older patients with renal insufficiency, cardiovascular disease, and electrolyte imbalance, the use of sodium phosphate is contraindicated (8, 24).

Although the bubbles effect scale is an important grading scale for CCE bowel preparation, it was not reported in any of the included studies. Bubbles may affect the visualization of the colon and they are important because they represent a different problem from debris and require a different solution (25).

This systematic review provides the first overview of CCE performance in a CRC screening setting; however, it has some limitations. First, because of the heterogeneity of the studies, no meta-analysis could be performed. Second, sensitivity and specificity of CCE could not be compared directly between the different studies because some studies performed per-

patient analyses and others performed per-polyp analyses. Third, no clear difference could be determined between the diagnostic accuracy of CCE as a primary screening tool and CCE as a filter test because of the limited number of studies using CCE as a primary screening tool. Fourth, most videos from studies included in this systematic review were analyzed by experienced readers. It is known that diagnostic accuracy for small-bowel endoscopy increases with experience of the reader (26). Fifth, information about the variation of size, type, and location of polyps detected by CCE vs. colonoscopy was often lacking.

At this stage, the good diagnostic accuracy of CCE ensures that CCE could be used as a screening tool. This review shows that CCE is a noninvasive method, with almost no risk of adverse events. However, some questions remain unanswered. Information on the participation rate of CCE in a screening setting is scarce. The uptake of CCE vs. colonoscopy was studied in first-degree relatives with CRC and found that the uptake was similar between the groups (55.8% CCE vs. 52.2% colonoscopy), but the crossover rate was higher from the CCE group (57.4%) than from the colonoscopy group (30.2%). Unwillingness to undergo bowel preparation twice was the main reason that participants assigned to the CCE group crossed over to colonoscopy (27). However, first-degree relatives with CRC might have an increased risk of developing advanced neoplasia compared with the average-risk population and therefore their choice in screening modality might be biased. Furthermore, the completion rate is moderate in several studies, especially if sodium phosphate is not used. As the use of sodium phosphate should be avoided in patients with an increased risk of sodium phosphate toxicity, and is prohibited in several countries, alternatives are needed. With these moderate completion rates for CCE, it is expected that additional sigmoidoscopies would be performed to review the sigmoid and rectum. This will have a negative impact on patient preference, workload of gastroenterologists, and costs. Without a completion rate of ≥90% it will be difficult for CCE to match colonoscopy. Finally, the time required to review the colon is extensive and more studies should investigate the use of artificial intelligence for the recognition of polyps and CRC.

In conclusion, despite its good diagnostic accuracy and noninvasiveness, and despite the fact that patients often prefer CCE over colonoscopy and CTC, CCE is still not used as a standard screening method. Further larger trials are needed to determine the role of CCE in population-based screening programs. Based on our review of the currently available literature, we believe CCE is a suitable screening tool as an alternative to colonoscopy and CTC in CRC screening programs, although the completion rate requires improvement.

Acknowledgments

The authors of this systematic review would like to acknowledge the contribution of Wichor Bramer and Maarten Engel, biomedical information specialists of the Erasmus University Medical Center, for developing and updating the search strategies.

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Supplementary material

Supplementary material 1

Embase

('colon capsule endoscopy'/de OR 'capsule colonoscopy'/de OR (('capsule endoscopy'/de OR 'capsule endoscope'/de OR microcapsule/de) AND ('colorectal cancer'/de OR colonoscopy/de OR colonoscope/de OR colon/exp)) OR ((colo* NEAR/6 (capsule* OR microcapsule*) NEAR/3 endoscop*) OR ((capsule* OR microcapsule*) NEAR/3 colonoscop*) OR PillCam*):ab,ti,kw) AND ('screening'/de OR 'cancer screening'/de OR 'early cancer diagnosis'/de OR 'screening test'/de OR (screening OR (positive NEAR/6 (fit OR Fecal-Immunochem*)) OR (early NEAR/3 cancer NEAR/3 (diagnos* OR detect*))):ab,ti,kw) AND [english]/lim NOT ([animals]/lim NOT [humans]/lim)

Medline Ovid

(((Capsule Endoscopy/ OR Capsule Endoscopes/ OR Capsules/) AND (exp Colorectal Neoplasms/ OR Colonoscopy/ OR Colonoscopes/ OR exp Colon/)) OR ((colo* ADJ6 (capsule* OR microcapsule*) ADJ3 endoscop*) OR ((capsule* OR microcapsule*) ADJ3 colonoscop*) OR PillCam*).ab,ti,kf.) AND (Mass Screening/ OR Early Detection of Cancer/ OR (screening OR (positive ADJ6 (fit OR Fecal-Immunochem*)) OR (early ADJ3 cancer ADJ3 (diagnos* OR detect*))).ab,ti,kf.) AND english.la. NOT (exp animals/ NOT humans/)

Web of science

TS=((((colo* NEAR/5 (capsule* OR microcapsule*) NEAR/2 endoscop*) OR ((capsule* OR microcapsule*) NEAR/2 colonoscop*) OR PillCam*)) AND ((screening OR (positive NEAR/5 (fit OR Fecal-Immunochem*))OR (early NEAR/2 cancer NEAR/2 (diagnos* OR detect*)))) NOT ((animal* OR rat OR rats OR mouse OR mice OR murine OR dog OR dogs OR canine OR cat OR cats OR feline OR rabbit OR cow OR cows OR bovine OR rodent* OR sheep OR ovine OR pig OR swine OR porcine OR veterinar* OR chick* OR zebrafish* OR baboon* OR nonhuman* OR primate* OR cattle* OR goose OR geese OR duck OR macaque* OR avian* OR bird* OR fish*) NOT (human* OR patient* OR women OR woman OR men OR man))) AND DT=(Article OR Review OR Letter OR Early Access) AND LA=(english)

Cochrane CENTRAL

(((colo* NEAR/6 (capsule* OR microcapsule*) NEAR/3 endoscop*) OR ((capsule* OR microcapsule*) NEAR/3 colonoscop*) OR PillCam*):ab,ti,kw) AND ((screening OR (positive NEAR/6 (fit OR Fecal NEXT Immunochem*)) OR (early NEAR/3 cancer NEAR/3 (diagnos* OR detect*))):ab,ti,kw)

Supplementary material 2

Table 2s: Overview of the bowel preparationand booster regimen, adequate bowel preparation score and completion rate of 9 out of the 13studies included.

Study	Bowel preparation and booster regimen		Colon cleanliness	Completion rate
Holleran(1)	Day -2	4 senna tablets 10 glasses of water	92%	73%
	Day -1	Liquid diet 4:00 pm: 2L PEG		
	Day 0	8:00 am: 2L PEG 8:45 am: Swallow capsule Small bowel detection: 250 ml bowel preparation 3 hours later: 250 ml bowel preparation 10:00 pm: if capsule nog passed: rectal bisacodyl suppository		
Kobaek-Larsen(2)	Day -2	Morning: 1000mg oral magnesium-oxide and 2L water Evening: 1000mg oral magnesium-oxide	85%	57%
	Day -1	Clear fluids diet Evening: 1L moviprep and 2L water		
	Day 0	8:00 am: 1L moviprep and 1L water 08:45 am: Swallow capsule + 20 mg oral domperidon Small bowel detection: 0.75L moviprep and 1L water 3 hours later: 0.25L moviprep and 0.25L water and 10 mg rectal bisacodyl		
Pecere(3)	Day -2	At least 10 glasses of water Bedtime: 4 senna tablets	88%	88%
	Day -1	Clear liquid diet 07:00-09:00 pm: 2L PEG		
	Day 0	05:00-07:00 am: 2L PEG 8-9am: capsule ingestion Small bowel detection: 40ml NaP* & 1L water and 50ml of gastrografin 3 hours later: 20ml NaP & 0.5L water and 30ml of gastrografin 2hrs after 2nd boost: 10 mg bisacodyl suppository		
Rodonotti(4)	Day -3	Low fibre diet	70%	90%
	Day -2	Low fibre diet		
	Day -1:	Clear liquid diet 5:00pm: macrogol 3350, 100 g + ascorbid acid 10.6g in 1L water + 1L water		
	Day 0	7 am: 10:00 pm: bisacodyl 5mgl; 4 tablets macrogol 3350, 100g + ascorbid acid 10.6 g in 1L water + 1L water 8:45 am: capsule ingestion + metoclopramide 10 mg + saline 100ml iv in 30 min Small bowel detection: Booster of Nap 30 ml + 1L water 90 min after small bowel detection: NaP 15ml + 500ml of water 1:00pm: light lunch		
Groth(5)	Day -2	Low-residue diet	-	82%
	Day -1	Clear liquids only 19:00-21:00: 2L PEG		
	Day 0	07:00-08:00: 1L PEG 08:15 am: 6mg Tegaserod 08:30 am: capsule ingestion 10.30 am: 30ml NaP + 1L water 13:00 pm: 6 mg Tegaserod 14:00 pm: 15ml NaP + 0.5L water 16:30 pm: bisacodyl rectal suppository		

Rex(6)	Day -2	Bedtime: 4 senna tablets	80	92
	Day -1	Clear liquids only 19:00-21:00: 2L PEG-ELS		
	Day 0	07:00-09:00 am: 2L PEG-ELS morning: capsule ingestion Small bowel detection: 0.5L sulfate solution + 1L water 3 hours later: 0.25L sulfate solution + 0.5L water 2 hours later: 10 mg bisacodyl suppository		
Pioche(7)	Day -2	10 glasses of water 4L PEG	74	68
	Day -1	Liquid diet 3L PEG		
	Day 0	Morning: 1L PEG Swallow capsule + 20 mg domperidon Booster 1: 30ml NaP + 1L water Booster 2: 25ml NaP + 0.5L water 1 bisacodyl suppository		
Gonzalez-Suarez (8)	Day -2	Pursenid 4 tablets (senosids A+B)	82	81
	Day -1	Clear liquid diet		
		7-9 pm: 1 L PEG based solution		
	Day 0	7-8 am: 1 L PEG based solution		
		9:30 am: Metoclopramide 10 mg		
		9:45 am: capsule ingestion (water + simethicone 80 mg)		
		1st Booster: 500 mL PEG based solution + Gastrografin (50 mL)		
		2nd Booster (3 h after 1st booster): 500 mL PEG based solution + Gastrografin (25 mL)		
		5 h after 1st booster: Bisacodyl suppository		
Voska(9)	Day -2	Low-residue diet Abundant liquids	90	90
	Day -1	All day: clear liquids 07:00-09:00 pm: 3L PEG		
	Day 0	07:00-08:30 am: 1L PEG 9:30 am: swallow capsule If capsule in the stomach > 1hour: 10 mg metoclopramide Booster 1: 30ml NaP + 1L water Booster 2: 25ml NaP + 0.5L water Suppository: Gycerin suppository 2g		

CHAPTER 11

Effect of anticoagulants and NSAIDs on accuracy of faecal immunochemical tests (FITs) in colorectal cancer screening: a systematic review and meta-analysis

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Gut, May 2019

Abstract

Introduction

Most colorectal cancer (CRC) screening programmes are nowadays based on faecal immunochemical testing (FIT). Eligible subjects often use oral anticoagulants (OACs) or non-steroidal anti-inflammatory drugs (NSAIDs), which could possibly stimulate bleeding from both benign and premalignant lesions in the colon. The aim of this meta-analysis was to study the effect of OACs and NSAIDs use on FIT performance.

Methods

A systematic search was conducted until June 2017 to retrieve studies from PubMed, Embase, MEDLINE, Web of science, Cochrane Central and Google Scholar. Studies were included when reporting on FIT results in users versus non-users of OACs and/or NSAIDs in average risk CRC screening populations. Primary outcome was positive predictive value for advanced neoplasia (PPV_{AN}) of FIT in relation to OACs/NSAIDs use. Values were obtained by conducting random-effect forest plots.

Results

Our literature search identified 2022 records, of which 8 studies were included. A total of 3563 participants with a positive FIT were included. Use of OACs was associated with a PPV_{AN} of 37.6% (95% CI 33.9 to 41.4) compared with 40.3% (95% CI 38.5 to 42.1) for non-users (p=0.75). Pooled PPV_{AN} in aspirin/NSAID users was 38.2% (95% CI 33.8 to 42.9) compared with 39.4% (95% CI 37.5 to 41.3) for non-users (p=0.59).

Conclusion

FIT accuracy is not affected by OACs and aspirin/NSAIDs use. Based on the current literature, withdrawal of OACs or NSAIDs before FIT screening is not recommended. Future studies should focus on duration of use, dosage and classes of drugs in association with accuracy of FIT to conduct more specific guideline recommendations.

Introduction

Worldwide, most colorectal cancer (CRC) screening programmes are now based on faecal immunochemical testing (FIT) (1). In the European Union, FIT-based CRC screening programmes have an average FIT positivity rate (PR) around 6.2% and a positive predictive value for advanced neoplasia (PPV_{AN}) between 35% and 55% and are thereby more accurate than those for older, guaiac-based faecal occult. blood tests (gFOBT) (2–5). PPV of FIT depends on AN, gender, FIT cut-off and participation in previous screening rounds. It is affected by false-positive results from bleeding sources other than colorectal neoplasia (6, 7). Several studies suggest the use of oral anticoagulants (OACs) or non-steroidal anti-inflammatory drugs (NSAIDs) as a possible contributor to the false-PR of faecal blood tests. These studies hypothesise that OACs/NSAIDs could stimulate other, benign lesions to bleed and thereby decrease PPV_{AN} (8–10). In contrast, these drugs may in theory also increase the tendency of neoplastic lesions to bleed and thus increase PPV_{AN} (11, 12). Results of a previous meta-analysis and systematic review were inconclusive (13, 14). However, most studies at that time were performed with gFOBT and not with the currently practised FIT (1). Until today, clinicians lack clear recommendations. This is remarkable given the widespread use of CRC screening tests and the frequent use of OACs and NSAIDs in the target population of subjects aged 50 years and above (15, 16). Moreover, discontinuation of anticoagulant therapy is not without risk in terms of (re) occurrence of cardiovascular events, and discontinuation should thus be considered with care (17). Therefore, this meta-analysis aimed to evaluate the PPV_{AN} and positive predictive value for CRC (PPV_{CRC}) in OACs and NSAIDs users compared with non-users in an average risk FIT-based CRC screening population. Second, we assessed PRs, sensitivity/ specificity and negative predictive values (NPVs) when possible. Subgroup analyses were performed with respect to patient and drug characteristics when possible.

Method

Search strategy

We conducted a systematic review and meta-analysis of published trials and abstracts following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (18). Additionally, the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) checklist was used, containing specifications for the reporting of a meta-analysis of observational studies in epidemiology (19).

Data sources

In collaboration with the Medical School Library of the Erasmus University in Rotterdam, the Netherlands, a systematic search was conducted until June 2017 to retrieve studies that reported on FIT performance in OACs or NSAIDs users versus controls. PubMed,

Embase, MEDLINE, Web of science, Cochrane Central and Google Scholar were used as potential sources. The search was conducted using controlled vocabulary supplemented with key words (online **supplementary S1**). First, two independent reviewers (SAVN and FERV) screened the selected studies by title and abstract. Studies were excluded if they did not correspond with the inclusion and/or exclusion criteria that are stated below. Furthermore, full text of the selected publications were examined by the same authors. Discrepancies were discussed with a third party (MCWS). References of the retrieved studies were manually searched to locate any additional studies.

Study selection

Studies were included if they met the following criteria: (1) population-based one-sample FIT screening in an average risk population (>40 years old), (2) subjects were screened with FIT, while taking an OAC or NSAID, with subsequent colonoscopy in case of a positive faecal occult blood test; and (3) control group included patients who were screened by means of FIT, not taking OAC or NSAID, and also undergoing colonoscopy in case of a positive faecal occult blood test. The following studies were excluded: (1) those that used gFOBT instead of FIT; (2) systematic reviews and meta-analyses; and (3) editorials/letters.

Outcome parameters

Primary outcome was the pooled positive predictive value (PPV) of FIT for detecting advanced neoplasia (PPV_{AN}) in patients using any OACs and for aspirin/NSAIDs alone compared with non-users. Secondary outcomes were the pooled PR of FIT, the pooled NPV and sensitivity and specificity of FIT for advanced neoplasia (AN) and CRC during OACs/NSAIDs use versus no use.

Definitions

Advanced adenomas (AAs) were defined as adenomas >10 mm, or with villous histology, or high-grade dysplasia. CRC was considered to be the case when malignant cells were observed beyond the muscularis mucosa. AN comprised AA and CRC. Pooled OACs included use of vitamin K antagonists, platelet aggregation inhibitors and novel OACs. NSAIDs were not further specified. We converted units for FIT positivity cut-off into micrograms (μg) of haemoglobin (Hb) per gram of stool for each study when other units were practised.

Data extraction

Data were extracted by the same authors (SAVN and FERV) according to previously stated variables (online **supplementary S2**). When data in the published studies were not conclusive for our analyses, authors were contacted by mail and/or telephone for additional data.

Data analyses

The sensitivity, specificity, PPV, NPV and PR with corresponding 95% CI were calculated for each study in case data were available. Pooled relative risks (RRs) were obtained by a random-effect forest plot using an inverse-variance estimator, in which an RR smaller than 1 reflects a higher PPV in users versus non-users. An RR greater than 1 implies a lower PPV in users versus non-users (20). Heterogeneity among studies was measured by calculating the inconsistency index (I^2). Heterogeneity levels can range from 0% to 100% (maximum heterogeneity), with greater than 25%, 50% and 75% being low, moderate and high heterogeneity, respectively (21).

Study quality

Publication bias was assessed by constructing funnel plots. Assessment of methodological quality of observational cohort studies and case–control studies was carried out using the Ottawa-Newcastle Scale (22). This scale scores quality of design, content and ease of use directed to the task of performing and interpreting meta-analyses results. A star system has been developed in which a study is judged on (1) selection of study groups, (2) comparability of groups and (3) the ascertainment of either the exposure for case–control studies or the outcome of interest for observational studies. The outcome ranges from 0 (low) to 9 (high) stars. Assessment of quality of evidence was carried out using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) (23). Two authors (SAVN and FERV) independently assessed study quality. Review Manager V.5.3 was used for all analyses. Forest plots were conducted in R V.3.4.2.

Results

Literature search

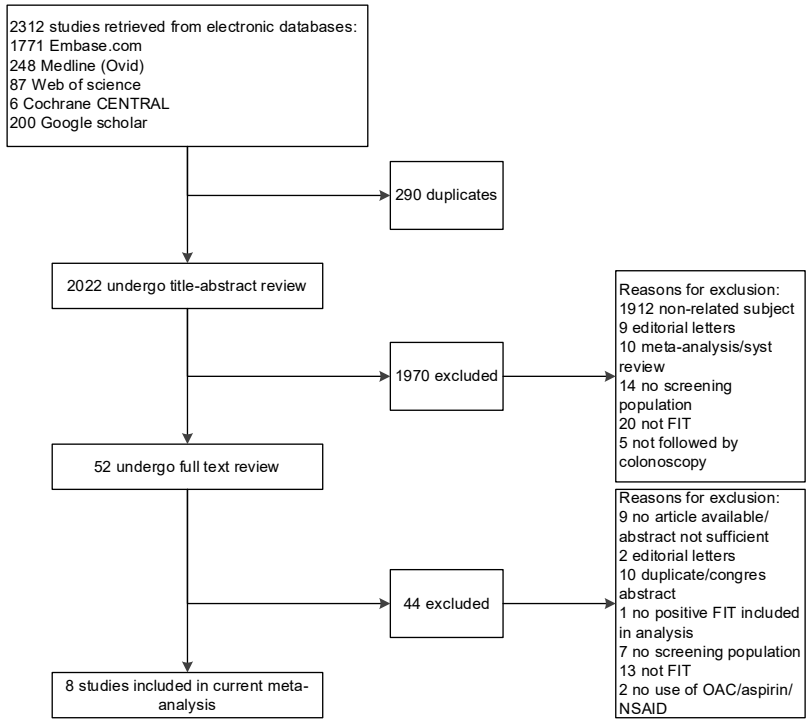

Figure 1. Flow chart: selection of studies for inclusion. FIT, faecal immunochemical testing; NSAID, non-steroidal anti-inflammatory drug; OAC, oral anticoagulant.

After removal of duplicates, we identified 2.022 studies through the electronic database search (**figure 1**). We excluded 1.970 studies after screening titles and abstracts. Of the remaining, 52 were examined by full-text review. Forty-four studies were excluded. We included six studies in full and two published abstracts in our meta-analysis (24–31).

Study characteristics

Baseline characteristics of the included studies are shown in **table 1**. Eight observational cohort studies and one case–control study were included. Seven studies were performed in Europe and one in Asia. The cut-off for a positive FIT ranged between 2 µg and 50 µg Hb/g faeces. Pooled analyses of different types of OACs were applied in the included studies (24, 27–29). Addition-ally, separate analyses were made for aspirin (24–26, 29–31). One study provided data on NSAIDs, and these users were pooled with aspirin users (31). All studies contained data to calculate PPV_{AN}. Two studies additionally included data on sensitivity, specificity and NPV (30, 31). Another two studies contained data on PR of FIT (26, 27). Two studies comprised the same screening cohort, yet subgroups for medication

use were defined differently in both studies (26, 27). For our analyses on pooled OACs, we used the most recent published data (27). For separate analysis for aspirin/NSAID use, we used the published data on the aspirin group (26). A summary of primary and secondary outcomes per study are presented in **table 2**. On methodological quality, studies scored between six and eight stars (out of a maximum of nine) according to the Newcastle-Ottawa Scale (online **supplementary S3**). According to the GRADE guidelines, quality of evidence for our analyses scored 'low' (online **supplementary S4**). Heterogeneity between studies for pooled OAC analysis was scored as 'low'. Separate analysis on aspirin/NSAIDs scored 'moderate' (**figures 2** and **3**). No publication bias was found when funnel plots were conducted (online **supplementary S5**).

Primary outcomes

Pooled OAC use versus no use

Positive predictive value for advanced neoplasia

Our meta-analysis composed pooled data on 633 OAC users and 2930 non-users, all FIT-positive patients. Users provided a PPV_{AN} of 37.6% (95% CI 33.9 to 41.4) compared with a PPVAN of 40.3% (95% CI 38.5 to 42.1) for non-users. The forest plot shown in **figure 2** showed no significant difference (p=0.75).

Positive predictive value for CRC

Two studies provided data on CRC with pooled OAC use comprising 336 users and 802 non-users (24, 29). Pooled OAC users provided a PPV_{CRC} of 5.7% (95% CI 3.7 to 8.7) compared with 6.2% (95% CI 4.8 to 8.1) for non-users.

Pooled data for aspirin/NSAID use identified 463 users and 2438 non-users in FIT-positive patients. Users yielded a pooled PPV_{AN} of 38.2% (95% CI 33.8 to 42.9) compared with 39.4% (95% CI 37.5 to 41.3) for non-users. The forest plot shown in **figure 3** revealed no significant difference (p=0.59).

Secondary outcomes

Positivity rate

The PR of FIT was calculated in one cohort (27). An overall PR of 6.3% was observed. When acenocoumarol was used, PR of FIT was 9.3% versus 6.2% for non-users.

Subanalysis of aspirin alone was associated with a PR of 7.3%, compared with PR of 7.1% for non-aspirin antiplatelet agents (26). In patients undergoing dual antiplatelet therapy (DAPT), PR of FIT was 22.2% compared with 6.3% for non-users (OR 3.5; 95% CI 1.7 to 7.3). Also, the number of AN found in the DAPT subgroup was higher than in non-users (OR 2.8; 95% CI 1.1 to 7.2).

Table 1. Baseline characteristics of included studies.

Study	Type of article	Type of study	Country	Age interval (years)	Time period	Eligible participants (N)	FIT cut-off (µg Hb/g feces)	Type of FIT	Negative FIT + colonoscopy	Medication use
Wauters, 2017 [24]	Abstract	screening cohort	Belgium	55-75	2015	463	15	OC-sensor	0	OAC: 111 Aspirin: 75
Botteri, 2016 [25]	Full text	screening cohort	Italy	50-69	2007-2009	743	20	HM-Jack	0	Aspirin < 5yr: 49 Aspirin > 5 yr:52
Wong, 2015 [31]	Full text	screening cohort	Hongkong	50-70	2008-2012	505	50	Hemosure	4834	Aspirin / NSAID: 40
Bujanda, 2014 [27]	Full text	screening cohort	Spain	50-69	2008-2011	386	15	OC-sensor	0	OAC: 21
Bujanda, 2013 [26]	Full text	screening cohort	Spain	50-69	2008-2011	365	15	OC-sensor	0	Aspirin: 28
Denters, 2011 [28]	Abstract	screening cohort	Nether-lands	50-75	2006-2008	510	10	OC-sensor	0	OAC: 88
Mandelli, 2011 [29]	Full text	screening case-control	Italy	50-69	2007-2009	675	20	OC-sensor	0	OAC: 225 Aspirin: 172
Brenner, 2010 [30]	Full text	screening cohort	Germany	> 55	2005-2009	281	2	RIDA-SCREEN Hb	1698	Aspirin: 47
Total	-		-	-	-	**3928**	-	-	**6532**	**Pooled OAC: 445** **Aspirin/NSAID: 463**

OAC, oral anticoagulants; *FIT*, faecal immunochemical test

Table 2. Summary of pooled data of oral anticoagulants users and non-users

Study		PR_{FIT} % [95%CI]	PPV_{AN} % [95%CI]	$Sensitivity_{AN}$ % [95%CI]	$Specificity_{AN}$ % [95%CI]
Wauters, 2017 [24]	Users	/	49.5 [40.0-59.1]	/	/
	Non-users	/	42.4 [37.1-47.7]	/	/
Botteri, 2016 [25]	Users	/	49.5 [39.5-59.6]*	/	/
	Non-users	/	54.2 [50.3-58.1]*	/	/
Wong, 2015 [31]	Users	/	7.5 [2.0-2.1]	15.8 [3.4-39.6]	89.1 [85.3-92.2]*
	Non-users	/	20.0 [16.5-24.0]	34.3 [28.7-40.3]	92.1 [91.3-92.3]*
Bujanda, 2014 [27]	Users	9.3 [6.0-14.2]	47.6 [26.4-69.7]	/	/
	Non-users	6.2 [5.7-6.9]	50.4 [45.2-55.6]	/	/
Denters, 2011 [28]	Users	/	43.2 [32.8-54.2]	/	/
	Non-users	/	46.9 [42.1-51.8]	/	/
Mandelli, 2011 [29]	Users	/	28.9 [23.2-35.4]	/	/
	Non-users	/	32.0 [27.8-36.6]	/	/
Brenner, 2010 [30]	Users	/	36.2 [23.1-51.5]	70.8 [48.9-87.4]*	85.7 [80.2-90.1]*
	Non-users	/	27.8 [22.2-34.1]	35.9 [28.9-43.4]*	89.2 [87.6-90.7]*

PR, positivity rate; *CI*, confidence interval; *PPV*, positive predictive value; *AN*, advanced neoplasia; *FIT*, faecal immunochemical test
* showed a significant result

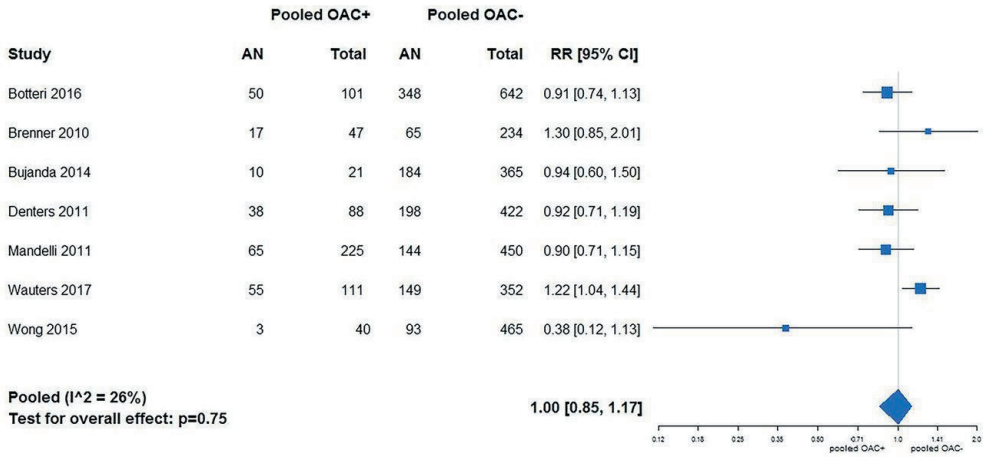

Figure 2. Forest plot on positive predictive value for advanced neoplasia (PPV_{AN}) of faecal immunochemical test (FIT) obtained with pooled oral anticoagulants (OAC) use versus no use. AN, advanced neoplasia; RR, relative risk.

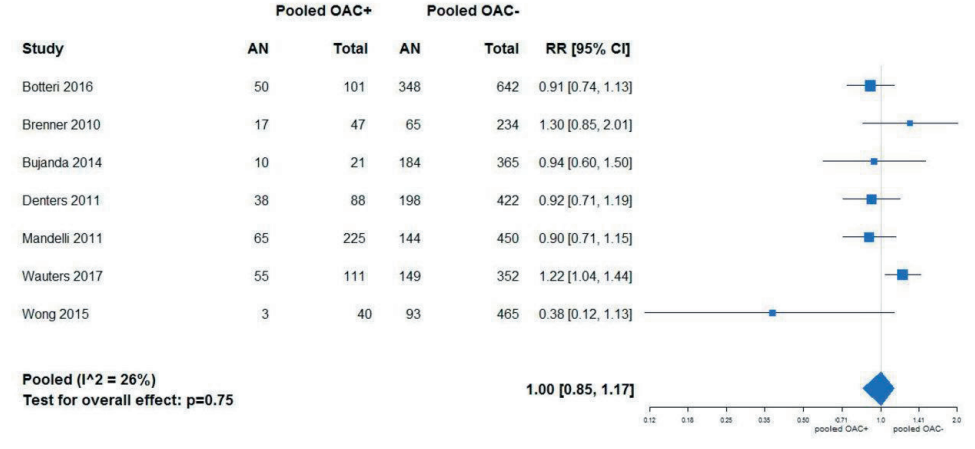

Figure 3. Forest plot on positive predictive value for advanced neoplasia (PPV_{AN}) of faecal immunochemical test (FIT) obtained with aspirin/non-steroidal anti-inflammatory drugs (NSAID) use versus no use. AN, advanced neoplasia; RR, relative risk.

Sensitivity and specificity

No data were available on sensitivity and specificity of FIT in pooled OAC users.

One study assessed sensitivity and specificity in aspirin/NSAID users (31). Sensitivity for AN was 15.8% for users, compared with 34.2% for non-users (p=0.097). Specificity for AN was significantly lower for aspirin/NSAID users; 89.1% compared with 92.1% for non-users (p=0.049). NPV showed no significant difference; 95.0% for users, compared with 96.1% for non-users (p=0.338).

Another study showed a sensitivity of 70.8% for aspirin users alone, compared with 35.9% for non-users (p=0.001). Specificity was 85.7% for aspirin users compared with 89.2% for non-users (p=0.13). NPV was 96.2% for aspirin users, compared with 92.3% for non-users (p=0.05) (30).

Subgroup analyses

Duration of drug use

One study made a distinction based on the median duration of aspirin use (25). Two categories were formed: a median use of ≤5 years and ≥5 years. A total of 49 patients using aspirin ≤5 years provided a PPV_{AN} of 61.2% (95% CI 47.2 to 73.6) compared with 52 aspirin users ≥5 years providing a PPV_{AN} of 38.5% (95% CI 26.5 to 52.0) (p=0.03) (25).

Type of FIT used

Seven studies used a quantitative FIT (24–30). One study used a qualitative FIT (31). When the study with a qualitative FIT was excluded, no changes in pooled results were seen (pooled PPV_{AN} in users of OAC: 39.6% vs 44.1% in non-users, RR: 0.99 (95% CI 0.89 to 1.11, p=0.44). Furthermore, five out of the eight studies included used the OC-sensor (24, 26–29). After excluding the three studies that used another FIT brand, no alterations in pooled results were seen (pooled PPV_{AN} in users of OAC: 37.8% vs 42.4% in non-users, RR: 1.00 (95% CI 0.87 to 1.14), p=0.99) (25, 30, 31).

FIT cut-off used

Different cut-offs were used; most studies vary between a cut-off level of 10–20 µg Hb/g faeces (24–29). Two studies used a cut-off of, respectively, 2 µg and 50 µg Hb/g faeces (30, 31). If these two outlier cut-offs were left out, no alterations in pooled results were seen (pooled PPV in users of OAC: 39.9% vs 45.8% in non-users, AN RR: 0.97 (95% CI 0.87 to 1.09), p=0.64).

Discussion

This is the first systematic review and meta-analysis to determine the PPV_{AN} of FIT in relation to OACs or NSAIDs use. Our results show that the use of OACs or aspirin/NSAIDs do not affect the PPV_{AN} in FIT CRC screening. The PPV_{AN} of pooled OAC users was 37.6% versus 40.3% in non-users. For separate analyses on aspirin/NSAID users, the PPV_{AN} was 38.2%, whereas PPV_{AN} of non-users was 39.4%. Based on current literature, the withdrawal of OACs or aspirin/NSAIDs during FIT screening is not recommended. Our data are supported by previous work that pooled data on warfarin use during faecal occult blood test screening. Results showed no alterations in PPV of colorectal AN (13). However, included studies were performed on gFOBT and not on FIT. Another meta-analysis compared accuracy of FIT and gFOBT screening if OACs or NSAIDs were used (32). They showed a decrease in PPV_{AN} in gFOBT screening and no significant difference in PPV of FIT. Hence, only one study on FIT screening was included in this meta-analysis (29). FIT and gFOBT differ in their interaction with Hb. Guaiac-based tests interact with the haem part of Hb, and immunochemical tests detect the globin portion of Hb. The latter does not survive passage through the upper gastrointestinal tract, and therefore, FIT has a proven superior accuracy for colon or rectum bleeding compared with gFOBT (2, 3). For this reason, it is to assume that effects of OACs and NSAIDs could act differently in both tests. Growing literature on FIT screening helped to perform the current meta-analysis based on the today's practised FIT. Our results support the previous suggestion that OACs and aspirin/NSAIDs do not affect PPV_{AN} of FIT. Only one cohort provided data on PR of FIT in which a higher PR was seen in users compared with non-users (26, 27). As already hypothetically stated, this could be due to possible stimulation of bleeding from lesions in the colon (both benign and (pre) malignant). More so, the use of DAPT showed an even more strong effect on increased PR, supporting the literature on DAPT and its stimulating effect on lower gastrointestinal bleedings (33). Bearing in mind the similar PPV for users and non-users (or even a greater PPV in the case of DAPT users), this could presume the stimulation of premalignant lesions to bleed and causing a beneficial effect of OAC and aspirin/NSAID use by having more true FIT positives in users. One study used a qualitative test (ie, providing a positive or negative result without specific blood count) (Hemosure test kit) and calculated a PPV_{AN} of 20.0% for aspirin/NSAID users, compared with 7.5% for non-users (31). In our meta-analysis, these results act as an outlier compared with other study outcomes. When left out of our analysis, no evident effects on pooled PPV_{AN} of users versus non-users were seen. In our meta-analysis, all included studies applied a one-sample FIT. There is one study evaluating FIT performance and the use of antithrombotics in a two-sample FIT screening showing also that OAC use do not affect FIT performance (34). Globally, CRC screening guidelines focus mostly on age range of screening, time intervals, multiple test options and follow-up diagnostics. Although specific subgroups are discussed (eg, different ethnicities and individuals with a family history of CRC), OAC/NSAID users are left out (35, 36). Given the

significant proportion of subjects using these drugs and the renewing scientific evidence on this topic, guideline adjustments should be considered. Although this has been an ongoing discussion (37), still no recommendations were made in the latest update of the US Multi-Society Task Force CRC screening guidelines (35).

Certain limitations have to be addressed in order to add specific recommendations. First, cut-off points of FIT were varying and overall relatively low. The use of different cut-off points of FIT affects accuracy of FIT. An increase in faecal Hb concentration cut-off is associated with higher PPV (6). Second, no subgroup analyses on age, gender, type of drugs or duration of drug use could be performed since the number of studies was too low. It was already pointed out that separate analysis on duration of drug use could play an important part in FIT performance (25).

In conclusion, OACs and aspirin/NSAID use do not affect the PPV of FIT in CRC screening. Based on current literature, withdrawal of OACs and/or NSAIDs before FIT sampling is not recommended. However, subgroup analyses on subject and drug characteristics should be performed in order to conduct specific guideline recommendations, and PR of FIT in relation to the PPV should be taken into account.

Acknowledgements

The authors of this systematic review and meta-analysis would like to acknowledge the contribution of Wichor Bramer, biomedical information specialist of the Erasmus University Medical Center, for performing the systematic literature search.

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Supplementary material

S1 Search strategy

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('acetylsalicylic acid'/de OR 'anticoagulant agent'/exp OR 'anticoagulant therapy'/de OR 'anticoagulation'/de OR 'thrombocyte aggregation inhibition'/exp OR 'nonsteroid antiinflammatory agent'/exp OR (aspirin* OR (acetylsalicylic NEAR/3 acid*) OR acetylsalicylate* OR anticoagul* OR anti-coagul* OR antithromb* OR anti-thromb* OR (clotting NEAR/3 inhibitor*) OR heparin OR antifibrinolyt* OR anti-fibrinolyt* OR antiplatelet* OR anti-platelet* OR ((platelet* OR fibrinoly* OR vitamin-K OR Factor-Xa OR Factor-X OR thrombin OR thrombocyte*) NEAR/3 (inhibit* OR antagon* OR anti OR antiaggregat*)) OR warfarin* OR coumarin* OR aspirin* OR (acetylsalicylic NEAR/3 acid*) OR acetylsalicylate* OR ((nonsteroid* OR non-steroid*) NEAR/3 (antiinflamm* OR anti-inflamm*)) OR nsaid* OR ibuprofen*):ab,ti) AND ('occult blood'/exp OR 'feces analysis'/exp OR (('feces'/de OR defecation/de) AND ('immunochemistry'/exp)) OR (((faecal OR fecal OR faeces OR feces OR stool OR defecat*) NEAR/3 (immunohistochem* OR immunochem* OR fit)) OR ifobt OR fobt OR ifobts OR fobts OR (fit NEAR/3 (test*))):ab,ti) NOT ([animals]/lim NOT [humans]/lim) AND [english]/lim

Medline (Ovid)

("acetylsalicylic acid"/ OR exp "anticoagulants"/ OR exp Anti-Inflammatory Agents, Non-Steroidal/ OR (aspirin* OR (acetylsalicylic ADJ3 acid*) OR acetylsalicylate* OR anticoagul* OR anti-coagul* OR antithromb* OR anti-thromb* OR (clotting ADJ3 inhibitor*) OR heparin OR antifibrinolyt* OR anti-fibrinolyt* OR antiplatelet* OR anti-platelet* OR ((platelet* OR fibrinoly* OR vitamin-K OR Factor-Xa OR Factor-X OR thrombin OR thrombocyte*) ADJ3 (inhibit* OR antagon* OR anti OR antiaggregat*)) OR warfarin* OR coumarin* OR aspirin* OR (acetylsalicylic ADJ3 acid*) OR acetylsalicylate* OR ((nonsteroid* OR non-steroid*) ADJ3 (antiinflamm* OR anti-inflamm*)) OR nsaid* OR ibuprofen*).ab,ti.) AND ("occult blood"/ OR (("feces"/ OR defecation/) AND (exp "immunochemistry"/)) OR (((faecal OR fecal OR faeces OR feces OR stool OR defecat*) ADJ3 (immunohistochem* OR immunochem* OR fit)) OR ifobt OR fobt OR ifobts OR fobts OR (fit ADJ3 (test*))).ab,ti.) NOT (exp animals/ NOT humans/) AND english.la.

Cochrane CENTRAL

((aspirin* OR (acetylsalicylic NEAR/3 acid*) OR acetylsalicylate* OR anticoagul* OR anti-coagul* OR antithromb* OR anti-thromb* OR (clotting NEAR/3 inhibitor*) OR heparin OR antifibrinolyt* OR anti-fibrinolyt* OR antiplatelet* OR anti-platelet* OR ((platelet* OR fibrinoly* OR vitamin-K OR Factor-Xa OR Factor-X OR thrombin OR thrombocyte*) NEAR/3 (inhibit* OR antagon* OR anti OR antiaggregat*)) OR warfarin* OR coumarin* OR aspirin* OR (acetylsalicylic NEAR/3 acid*) OR acetylsalicylate* OR ((nonsteroid* OR non-steroid*)

NEAR/3 (antiinflamm* OR anti-inflamm*)) OR nsaid* OR ibuprofen*):ab,ti) AND ((((faecal OR fecal OR faeces OR feces OR stool OR defecat*) NEAR/3 (immunohistochem* OR immunochem* OR fit)) OR ifobt OR fobt OR ifobts OR fobts OR (fit NEAR/3 (test*))):ab,ti)

Web of science

TS=(((aspirin* OR (acetylsalicylic NEAR/2 acid*) OR acetylsalicylate* OR anticoagul* OR anti-coagul* OR antithromb* OR anti-thromb* OR (clotting NEAR/2 inhibitor*) OR heparin OR antifibrinolyt* OR anti-fibrinolyt* OR antiplatelet* OR anti-platelet* OR ((platelet* OR fibrinoly* OR vitamin-K OR Factor-Xa OR Factor-X OR thrombin OR thrombocyte*) NEAR/2 (inhibit* OR antagon* OR anti OR antiaggregat*)) OR warfarin* OR coumarin* OR aspirin* OR (acetylsalicylic NEAR/2 acid*) OR acetylsalicylate* OR ((nonsteroid* OR non-steroid*) NEAR/2 (antiinflamm* OR anti-inflamm*)) OR nsaid* OR ibuprofen*)) AND ((((faecal OR fecal OR faeces OR feces OR stool OR defecat*) NEAR/2 (immunohistochem* OR immunochem* OR fit)) OR ifobt OR fobt OR ifobts OR fobts OR (fit NEAR/2(test*))))) AND LA=(english)

Google scholar

anticoagulants|anticoagulation|"clotting inhibitor"|heparin|antifibrinolytics|antiplatelet "faecal|fecal blood|bleeding|analysis|test|immunochemical|sample"|"occult blood"|ifobt|-fobt|gfobt|ifobts|fobts|gfobts

S2 Variables for data extraction

The following data was extracted when possible: (I) Study characteristics - first author, journal, year of publication, type of article, country of screening population, time period of patient inclusion; (II) FIT characteristics - number of samples per stool, FIT cut-off value, type of FIT; (III) Study cohort characteristics – total number of participants, total participants with a positive test or a negative test that underwent colonoscopy; (IV) Medication use – total number of participants on any OAC, total number of participants on any NSAID (incl. aspirin); (V) Advanced neoplasia characteristics – total number of AN/CRC after positive FIT in OAC and NSAID users and nonusers, total number of AN/CRC after negative FIT in OAC and NSAID users and nonusers.

S3. Newcastle-Ottawa Scale

	Selection (max. 4)	Comparability (max. 2)	Outcome (max. 3)	Total (max. 9)
Wauters, 2017	***	*	**	******
Botteri, 2016	***	*	**	******
Wong, 2015	***	*	***	*******
Bujanda, 2014	***	*	**	******
Bujanda, 2013	***	*	**	******
Denters, 2011	***	*	**	******
Mandelli, 2011	****	*	***	********
Brenner, 2010	***	*	**	******

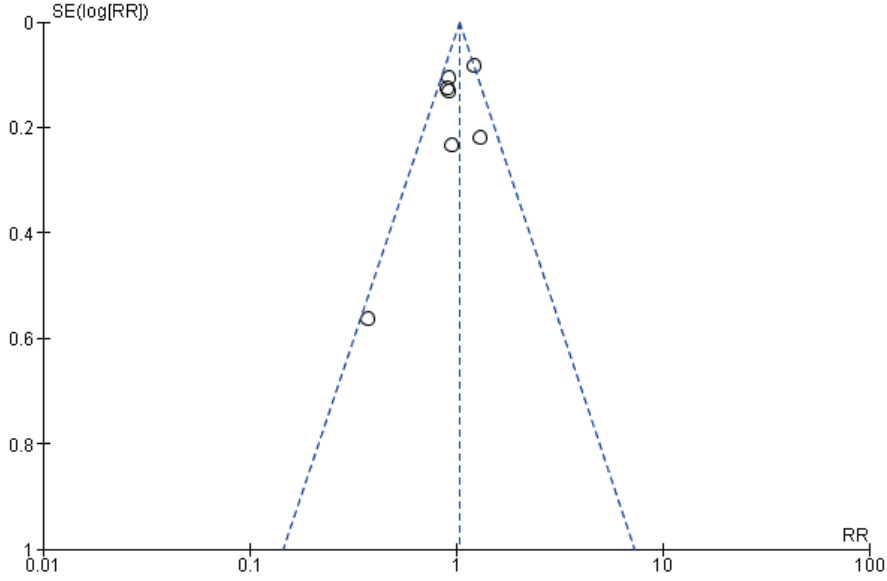
S4. GRADE score

Study design	Quality of evidence	Lower if	Higher if
RCT	High (4 points)	Risk of bias: -1 serious -2 very serious	Large effect: +1 large +2 very large
	Moderate (3 points)	Inconsistency: -1 serious -2 very serious	Dose response: +1 evidence of gradient
Observational	Low (2 points)	Indirectness: -1 serious -2 very serious	All plausible confounding: +1 would reduce demonstrated effect +2 Would suggest spurious effect when results show no effect
	Very low (1 point)	Imprecision: -1 serious -2 very serious	
		Publication bias: -1 serious -2 very serious	

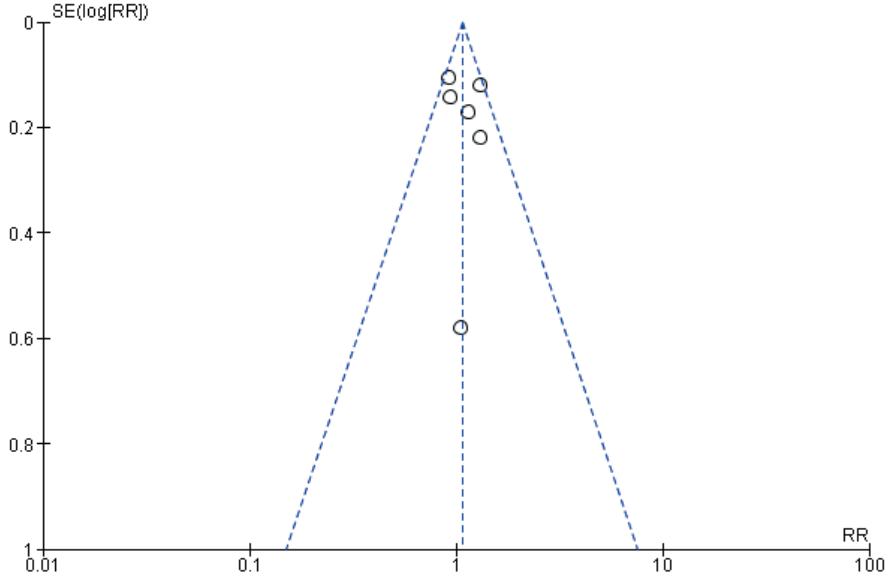
Comparison	Pooled PPV_{AN} RR (95% CI)	Quality of evidence	Lower	Higher	GRADE score
Pooled OAC Use vs no use	1.00 (0.85-1.17)	2 points	-	-	Low
Aspirin / NSAID Use vs no use	1.05 (0.87-1.27)	2 points	-	-	Low

S5. Funnel plots

S.5.1 Funnel plot for pooled oral anticoagulants (OAC) use and positive predictive value of advanced neoplasia (PPV_{AN}) of a fecal immunochemical test (FIT)



S5.2 Funnel plot for aspirin / NSAID use and positive predictive value of advanced neoplasia (PPV_{AN}) of a fecal immunochemical test (FIT)



PART IV

General Discussion

Chapter 12
General Summary and Discussion

CHAPTER 12

General Summary and Discussion

General Summary and Discussion

This thesis contains two main topics. First, premalignant gastric lesions and its surveillance strategies were evaluated. Second, prevalence rates of gastrointestinal abnormalities including colorectal cancer were discussed, together with its possible implications on CRC screening. This final part summarizes the main findings and implications obtained from our research projects and directions for future research.

Premalignant lesions of the stomach and surveillance

European surveillance guidelines for premalignant gastric lesions in low endemic regions for gastric cancer were first set up in 2012 (1). An updated version was published in 2019 with added risk factors, to name: having a family member with gastric cancer, a persistent H. pylori infection, incomplete intestinal metaplasia, or auto- immune gastritis (2). Also, in 2019 the British Society of Gastroenterology (BSG) published a surveillance guideline (3). As already stated earlier in this thesis, early detection of gastric cancer improves the 5-year survival to over 90% compared to overall survival of 25% (4). The global prevalence of gastric premalignant lesions is estimated around 35% of which a small proportion will progress to gastric cancer (5). No surveillance programme will perfectly identify only those who will progress to cancer and at the same time circumvent possible burdens due to surveillance. It is therefore that worldwide there is no consensus on how and if surveillance should be performed. In Part II of this thesis we evaluated the yield of existing surveillance programmes and studied several possible options to optimise surveillance.

Chapter 3 evaluated the yield of the surveillance guidelines of MAPS 2012, 2019 and BSG. This study showed that when these guidelines did not recommend surveillance due to low progression risk, 32.6% of the cases however, revealed progression of disease for which surveillance was indicated at the subsequent endoscopy. These cases contained four of the in total seven cases with high grade dysplasia or gastric cancer found in this study cohort. These cases would have been missed if guidelines was followed. Both when the more recent BSG and updated MAPS guideline of 2019 was followed, the yield of the surveillance programme improved slightly; three out of the seven gastric cancer/high grade dysplasia cases would have been missed. One additional follow up endoscopy would have identified these high risk- or malignant lesions. However, before pleating for performing extra endoscopies in all patients with premalignant gastric lesions - with the burdens that come with that for patients, doctors and health care – a few other possible solutions need further discussion.

Proper risk stratification to identify patients at risk for disease progression would improve the yield of surveillance strategies. It is therefore that chapter 4 studied several risk factors that might be related to the progression of precursor lesions of gastric cancer.

Smoking and having a family member with gastric cancer (first or second degree) showed a trend towards an association with the progression of precursor lesions. Further, single nucleotide polymorphisms (SNPs) were studied that were previously associated with the occurrence of gastric cancer or H. pylori infection. A significant inverse association was found between a SNP located on TLR4 (rs11536889) and the progression of intestinal metaplasia. This implies that presence of this SNP might have a protective effect on disease development, and that genetic findings might play a role in the (prediction of) course of disease. Future studies should focus on in-depth analyses on the physiological processes behind these associations.

Another way to improve surveillance strategies is by optimising the endoscopy itself. Chapter 5 contains a study protocol which compares the use of white light endoscopy (WLE) and a random biopsy scheme with the use of advanced imaging by narrow band imaging (NBI) and taking targeted biopsies. At the time of writing, this prospective study is halfway through. The results of this study will provide us the evidence for a more endoscopy-led risk stratification of patients at risk for gastric adenocarcinoma.

The last chapter of this part of the thesis contains a study which aimed to provide an easy-to-use noninvasive test for the detection of H. pylori colonization, the most important risk factor for the development of a gastric premalignant lesion. Multiple noninvasive tests are already available (i.e. urea breath test, serology and faeces testing) all with different pros and cons. This study proved that the faecal immunochemical test (FIT) used within colorectal cancer screening can also be used to detect H. pylori antigen just as accurate as the already available faecal tests, but with the highest rated user friendliness. This might be the steppingstone towards combined upper and lower gastrointestinal screening for malignancies. Future studies should focus on the feasibility of this purpose especially in high endemic regions.

Pre- and malignant lesions of the colon and screening

The efficacy of CRC screening is more established compared to gastric (pre-) malignancy surveillance programmes. Most countries have implemented a CRC screening programme (6). In the Netherlands this has now been active for several years (since 2014). This has provided us with a remarkable diagnostic yield of (advanced) neoplastic lesions that could be treated timely (7, 8).

On occasion lesions are found by coincidence of which we do not know the prevalence rate of in a healthy population - such as fundic glands, diverticula or mucosal erosions. Because of the invasive character of endoscopies, healthy participants usually would not undergo these diagnostic modalities. However, in order to assess the aetiology, contributing factors and burden of a certain condition, a frame of reference within a healthy population

is essential. Multigenerational prospective cohort studies with healthy participants are therefore becoming more and more the core of medical research nowadays (9, 10).

The Rotterdam study is a prospective cohort study including healthy individuals 45 years of age and older that are followed throughout their lives (11). Chapter 7 of this thesis is embedded within this cohort study. The entire GI tract was mapped in 451 healthy participants aged between 50-75 years using the Colon Capsule Endoscopy (CCE). The CCE is a video capsule containing a camera on each side making 4-35 frames per second and providing a 360 degree view. This study showed that the prevalence of any lesion found throughout the GI tract is very common in healthy individuals. In 56% of the participants colonic polyps were found, in 81.6% diverticula, in 18.1% fundic glands in the stomach, and in 8.3% a Barrett's oesophagus was seen. In 12% of all cases a significant lesion was found for which a subsequent endoscopy was needed (Barrett segment > 3 cm, severe ulceration, polyp >10 mm, > 3 polyps in small intestine and/or colon, cancer). This study provides a frame of reference for GI diseases in a general, healthy population and can be used to better inform patients on the prevalence of their condition and possible factors of influence.

This thesis further zooms in on colorectal cancer. Chapter 8 focused on the age related CRC incidence of 20 European countries over the past 25 years. On average, CRC incidence showed an increase from 2004 until 2016 of 7.9% per year in individuals aged 20-29. For individuals aged 30-39 years this increase was 4.9% per year, and for individuals aged 40-49 1.6% per year. We concluded that the most prominent increase was seen in young adults.

A subsequent question is if these CRCs found in the younger age groups are the same type of tumour as CRCs arising at an older age. This is discussed in chapter 9. In over 15,000 subjects who were diagnosed with CRC between 1990 and 2018 and below the age of 50 years, data was collected on tumour characteristics. The same age categories were made as for the previous study: 20-29 years, 30-39 years and 40-49 years. We concluded that tumours that arose at a younger age were more often of the signet cell type, more often poorly differentiated, with more often positive lymph nodes. Although these are all poor prognostic factors, overall mortality rates between the younger and older age groups did not differ. It should be said that data on CRC related mortality was unfortunately not available.

European guidelines advise CRC screening between the age of 50 and 75 years (12, 13). The American Guideline Society even lowered the age limit to 45 years of age (14). In the Netherlands a biannual FIT is offered to individuals aged between 55 and 75 years. A main barrier for most European countries is to provide sufficient capacity to properly

screen between 50-75 years of age. Within this scope, also alternative methods next to colonoscopy are being looked into. Chapter 10 contains a systematic review which evaluates safety and accuracy of the video capsule in detecting (pre-) malignant lesions of the colon. In this review we have shown that the video capsule appeared to be non-inferior to colonoscopy in terms of detection of (pre-) malignant colonic lesions. When the video capsule was compared with CT-colonography, capsule performance appeared to be better. Especially in cases where a colonoscopy would be too invasive (due to comorbidities or medication use) the video capsule might be a good alternative.

Besides evaluating target groups for screening, other elements can also affect the efficacy of a screening programme. FIT is based on finding occult blood in faeces. This might originate from a malignant source as well as a benign source, such as haemorrhoids or fissures. The use of oral anticoagulants might influence bleeding risk of such lesions. This could influence the accuracy of the FIT, both positive as negative (in case of stimulation of bleeding of malignant or benign lesions, respectively). For this reason, a meta-analysis was performed in chapter 11 in which eight studies were included comprising over 3,500 subjects in an average screening population that underwent FIT. Users and non-users of oral anticoagulants were compared. The positive predictive value for the detection of advanced neoplasia of FIT was not different for users versus non-users (37.6% vs. 40.3%). Based on the current data, there is no reason to seize the use of anticoagulants prior to FIT sampling.

In general, it might be stated that the CRC screening programme has shown to be effective over the years. Future challenges should focus on investigating alternatives next to colonoscopy, in order to be able to also screen participants with considerable comorbidities (or fear of colonoscopy) or to further increase participation rate. A trial already has been set up (the OCEAN trial). The aim of this prospective cohort study is to evaluate the applicability of CCE in CRC screening in participants with a positive FIT who are unwilling or unable to undergo colonoscopy.

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APPENDICES

Nederlandse Samenvatting

Het maagdarmkanaal is na het ademwegkanaal het grootste slijmvlies oppervlak binnen het menselijk lichaam, vergelijkbaar met een half badmintonveld (30 m^2). Daarnaast staat het in continu contact met de buitenwereld. Hierdoor wordt het blootgesteld aan onder andere verschillende temperaturen, medicatie, toxische en carcinogene substanties en allerlei micro-organismen. Om deze reden is het maagdarmkanaal steeds onderhevig aan verandering om deze dynamiek op te kunnen vangen. Mede hierdoor betreffen aandoeningen van het maagdarmkanaal een breed scala aan verschillende laesies, zoals bijvoorbeeld erosies, bloedingen en ontsteking.

Daarnaast is het maagdarmkanaal een belangrijke bron voor het ontstaan van maligniteiten. Jaarlijks overlijden wereldwijd 9.6 miljoen personen aan kanker. Van al deze kankers betreft het in 1/3 van de gevallen het maagdarmkanaal. De mortaliteitscijfers van darmkanker en maagkanker zijn hierbij het hoogst, zij nemen respectievelijk de vierde en vijfde plek in wereldwijd. Voor beide kankers geldt dat zij vaak een cascade aan voorloperafwijkingen volgen en dat vroege opsporing kan leiden tot een rigoureuze verbetering van de (vijfjaars-)overleving. Verschillende landen hebben daarom screening- en/of surveillance programma's opgezet met als doel de incidentie en de sterfte van darmkanker en maagkanker te verlagen.

Het tweede en derde deel van dit proefschrift beschrijft en verdiept zich in het vóórkomen van (voorstadia van) maagkanker en darmkanker en daarnaast de evaluatie en optimalisatie van zowel surveillance programma's voor maagkanker als screeningsprogramma's voor darmkanker.

Voorloperafwijkingen van maagkanker en surveillance
Maagkanker van het intestinale type wordt vaak voorafgegaan door een Helicobacter pylori (H. pylori) kolonisatie. Hierdoor kan (non-)atrofische gastritis ontstaan, wat verder kan ontwikkelen naar intestinale metaplasie, dysplasie, en uiteindelijk maagkanker. Door maagkanker in een vroeg stadium te vangen kan de vijfjaarsoverleving verbeteren van 25% naar 90%. Om deze reden zijn er in 2012 surveillance richtlijnen opgezet om (voorstadia van) maagkanker vroeg te ontdekken. Patiënten bekend met een voorloperafwijking van maagkanker wordt endoscopische surveillance aangeboden met verschillende intervallen. Deze zijn afhankelijk van de uitgebreidheid van de afwijking en de eventuele aanwezigheid van risicofactoren welke zijn toegevoegd in een richtlijn update in 2019 (eerstegraads familielid met maagkanker, auto-immuun gastritis, persistente H. pylori infectie, of de aanwezigheid van incomplete intestinale metaplasie). Geen surveillance programma zal perfect individuen kunnen identificeren die maagkanker zullen ontwikkelen en tegelijkertijd alle lasten voor patiënt, dokter en gezondheidszorg kunnen

vermijden. Om deze reden bestaat er wereldwijd dan ook geen consensus over óf en hóe voorstadia van maagkanker vervolgd moeten worden.

Hoofdstuk 3 evalueert de opbrengst van de surveillance richtlijnen opgezet in 2012, de update van 2019 en de Britse richtlijn. Uit dit onderzoek bleek dat wanneer de richtlijn géén surveillance adviseerde, maar in het kader van deze studie tóch een follow up endoscopie werd uitgevoerd, 32.6% op deze volgende endoscopie toch aanwijzingen bleek te hebben voor progressie van ziekte waarvoor surveillance opnieuw geïndiceerd is. Hiertussen zaten vier van de in totaal zeven gevallen van maagkanker of hooggradige dysplasie die in dit cohort gedetecteerd zijn. Deze zouden gemist zijn als de richtlijn was gevolgd. Het volgen van de richtlijn update uit 2019 waarbij extra risicofactoren in acht werden genomen, verbetert dit iets: drie gevallen van maagkanker of hooggradige dysplasie zouden dan gemist zijn. Voordat wij hieruit concluderen dat patiënten een extra gastroscopie moeten ondergaan, zijn er nog een aantal andere mogelijke opties voor optimalisatie van surveillance.

Hoofdstuk 4 onderzoekt of personen beter gestratificeerd kunnen worden op hun risico op progressie van ziekte. Verschillende factoren werden meegenomen, zoals leefstijl (roken, alcohol, BMI), een familielid met maagkanker, een H. pylori infectie in de voorgeschiedenis, maar ook serologische markers voor atrofische gastritis, zoals pepsinogeen I en II en gastrine-17 en potentiële genetische modificaties. Roken en het hebben van een familielid met maagkanker (eerste- of tweedegraads) lieten een trend zien naar een associatie met progressie van voorloperafwijkingen van maagkanker. Daarnaast is er een significante beschermde functie gevonden tussen de progressie van voorloperafwijkingen en een SNP (single nucleotide polymorfisme) op TLR4 (rs11536889).

Een andere manier om surveillance richtlijnen te optimaliseren, is het optimaliseren van de endoscopie zelf. Hoofdstuk 5 bevat een studieprotocol waarbij de huidige werkwijze van endoscopische surveillance wordt vergeleken met een meer geavanceerde endoscopietechniek waarbij gerichte biopten in plaats van willekeurige biopten worden afgenomen. Op het moment van schrijven is deze studie halverwege de inclusiefase.

Het laatste hoofdstuk van dit deel van het proefschrift onderzoekt of de ontlastingstest welke gebruikt wordt in het Bevolkingsonderzoek Darmkanker; de FIT (faecal immunochemical test), ook gebruikt kan worden voor de detectie van de H. pylori bacterie, de belangrijkste risicofactor voor de ontwikkeling van maagkanker. Deze studie laat zien dat deze test net zo accuraat is voor het aantonen van H. pylori in vergelijking met de reeds bestaande non-invasieve tests, met als extra voordeel dat de FIT werd ervaren als het makkelijkst in gebruik. Deze studie is een eerste stap naar gecombineerde screening voor zowel darm- als (voorlopers van) maagkanker.

Voorloperafwijkingen van darmkanker en screening

Ook darmkanker volgt een cascade aan voorloperafwijkingen voordat uiteindelijk darmkanker ontstaat. Dit begint bij een poliep, wat kan omvormen tot een adenoom, een advanced adenoom, en uiteindelijk darmkanker. De vijfjaarsoverleving van darmkanker wat in een laat stadium wordt ontdekt is 19%. De vijfjaarsoverleving van darmkanker in een vroeg stadium is 97%. Sinds 2014 bestaat er daarom in Nederland een bevolkingsonderzoek om darmkanker in een vroeg stadium op te kunnen sporen. Personen tussen de 55 en 75 jaar ontvangen tweejaarlijks een ontlastingstest (faecal immunochemical test; FIT). Indien deze afwijkend is wordt een colonoscopie uitgevoerd. Vele landen hebben inmiddels een Bevolkingsonderzoek Darmkanker geïmplementeerd. We weten dat in Nederland na de eerste ronde reeds bijna 2.500 kankers zijn gedetecteerd en 12.000 voorstadia. De screeningsrondes die daarop volgenden lieten een consistente opbrengst en deelnamegraad zien.

Daarnaast worden er echter ook geregeld toevalsbevindingen gevonden, zoals bijvoorbeeld divertikels, goedaardige poliepen of klieren, en erosies van het slijmvlies. Deze hoeven niet altijd tot klachten te leiden waarvoor (diagnostische) beeldvorming nodig is. Precieze prevalentiecijfers zijn daarom niet bekend. Regelmatig worden er toevalsbevindingen tijdens endoscopie gevonden, waarbij men niet weet hoe vaak deze voorkomen in een asymptomatische populatie. Echter, deze informatie kan wel belangrijk zijn voor de voorlichting naar de patiënt, zodat meer informatie gegeven kan worden over de gevonden afwijking. Daarnaast is voor het kunnen beoordelen van (de etiologie) van een ziekte of afwijking de wetenschap over het gezonde lichaam net zo belangrijk.

De Rotterdam Studie is een groot, prospectief cohort waarbij gezonde individuen van 45 jaar en ouder worden gevolgd in het leven. Hoofdstuk 7 is een studie binnen de Rotterdam Studie, waarbij met behulp van een colon videocapsule wordt aangetoond dat bepaalde bevindingen in het maagdarmkanaal veelvoorkomend zijn in een algemene, gezonde populatie. Zo werd bij 56% van de deelnemers poliepen in de dikke darm gevonden, bij 81.6% divertikels, bij 18.1% fundic glands in de maag, en bij 8.3% werd een Barrett slokdarm gezien. In 12% van de gevallen was er sprake van een significante afwijking (Barrett segment > 3 cm, ernstige ulceraties, poliepen > 10 mm, > 3 poliepen in dunne en/of dikke darm, kanker) waarbij verder beeldvormend onderzoek geïndiceerd werd. Dit biedt een referentiekader in de spreekkamer van dokter en patiënt bij de voorlichting van gevonden afwijkingen tijdens scopie.

Dit proefschrift concentreert zich verder op darmkanker. In hoofdstuk 8 van dit proefschrift is voor de afgelopen 25 jaar voor 20 Europese landen de trend in incidentie van darmkanker geanalyseerd voor verschillende leeftijdsgroepen. Gemiddeld steeg de incidentie van darmkanker in 2004 tot 2016 met 7.9% per jaar in 20-29 jarigen. Voor 30-

39 jarigen was dit 4.9% per jaar, en voor 40-49 jarigen 1.6% per jaar. De grootste stijging wordt dus gezien in de jongvolwassenen.

Daarna rijst de vraag of de darmkanker die op jongere leeftijd wordt gezien van een ander type is dan die op oudere leeftijd ontstaat. In hoofdstuk 9 is van ruim 15,000 personen die gediagnosticeerd werden met darmkanker onder de 50 jaar tussen 1990 en 2018 informatie over pathologische tumorkarakteristieken verzameld. Wanneer personen weer werden ingedeeld op basis van leeftijd: 20-29 jarigen, 30-39 jarigen en 40-49 jarigen, werd met name gezien dat de darmkankers die op jonge leeftijd ontstaan slechtere prognostische factoren bevatten in vergelijking met darmkankers ontstaan op oudere leeftijd.

De Europese richtlijn voor darmkanker screening adviseert screening tussen de leeftijden van 50 en 75 jaar. De Amerikaanse richtlijnen commissie heeft deze leeftijdsgrens zelfs verlaagd naar 45 jaar. In Nederland screenen we momenteel tussen de 55 jaar en 75 jaar. Een van de voornaamste obstakels om de leeftijdsgrens te verlagen draait om de (colonoscopie) capaciteit.

Om deze extra last op de colonoscopie capaciteit op te vangen is het belangrijk om te kijken naar andere opties. Hoofdstuk 10 zet daarom alle literatuur op een rij middels een systematisch review, waarin wordt geëvalueerd of het gebruik van een videocapsule een veilig en accuraat diagnosticum is voor de inzet binnen een Bevolkingsonderzoek Darmkanker. Hieruit blijkt dat de videocapsule een veilige en effectieve tool is. In vergelijking met de colonoscopie blijkt de videocapsule daarnaast niet inferieur te zijn in de detectie van (voorstadia van) darmkanker en superieur in vergelijking met CT-colografie. Zeker voor personen bij wie het ondergaan van een colonoscopie te invasief is (vanwege comorbiditeiten of bepaald medicatiegebruik) zou dit non-invasieve onderzoek een geschikt alternatief kunnen betekenen in de toekomst.

Buiten het evalueren van de targetgroep voor screening, zijn er andere elementen die de effectiviteit van een dergelijk programma kunnen beïnvloeden. De ontlastingstest is gebaseerd op het vinden van occult bloed in de ontlasting. Het gebruik van antistollende medicatie zou invloed kunnen hebben op een toename van bloeding van zowel benigne als maligne afwijkingen en de effectiviteit hiermee zowel positief als negatief kunnen beïnvloeden. In de meta-analyse van hoofdstuk 11, waarbij 8 studies zijn meegenomen met ruim 3,500 deelnemers, bleek dat de positief voorspellende waarde van FIT voor de detectie van voorloperafwijkingen van darmkanker niet beïnvloed wordt door het gebruik van antistolling (37.6% in gebruikers vs. 40.3% in niet-gebruikers).

Samengevat kunnen we concluderen dat het Bevolkingsonderzoek Darmkanker in meerdere landen zijn effectiviteit heeft bewezen. Voor de toekomst is het belangrijk om te zoeken naar alternatieven naast de colonoscopie. Dit is belangrijk om de deelnamegraad te verhogen onder individuen die geen colonoscopie willen of kunnen ondergaan (door bijvoorbeeld angst of ziekte). Er is reeds een prospectieve studie opgezet (de OCEAN trial). Het doel van deze studie is het evalueren van de toepasbaarheid van het videocapsule onderzoek in darmkankerscreening onder deelnemers met een afwijkende ontlastingstest en die geen colonoscopie kunnen of willen ondergaan.

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Courses in didactics and research	Year	Workload
Teach the teacher – 1, Erasmus MC, Rotterdam	2017	24 hours
BROK cursus, Erasmus MC, Rotterdam	2017	24 hours
Integrity in scientific research, Erasmus MC, Rotterdam	2017	16 hours
Omgaan met groepen, Erasmus MC, Rotterdam	2018	6 hours
Individuele begeleiding, Erasmus MC, Rotterdam	2018	6 hours
Tentamenvragen maken, Erasmus MC, Rotterdam	2018	6 hours
Research management, Molmed, Rotterdam	2018	6 hours
Writing a succesful grant proposal, RDO, Rotterdam	2018	6 hours
Basis kwalificatie onderwijs (bko) full certificate, Erasmus MC, Rotterdam	2019	60 hours

Courses in methodology and statistics	Year	Workload
EndNote workshop, Erasmus MC library, Rotterdam	2014	6 hours
Pubmed workshop, Erasmus MC library, Rotterdam	2014	6 hours
Basic Introduction on SPSS, Molmed, Rotterdam	2017	28 hours
Basic Introduction on Excel, Molmed, Rotterdam	2017	6 hours
Basic Introduction on R, Molmed, Rotterdam	2017	50 hours
Open Clinica, Erasmus MC, Rotterdam	2017	6 hours
Biostatistical Methods I, NIHES, Rotterdam	2018	56 hours

Educational activities and lecturing	Year	Workload
Coaching bachelor medical students, Erasmus MC, Rotterdam	2017-2020	50 hours
Tutoring first year medical students, Erasmus MC, Rotterdam	2017-2019	120 hours
Emergency and ic nurses in training, GI bleedings, Erasmus Zorgacademie	2017-2019	50 hours
Lecture first year medical students, colorectal cancer, Erasmus MC, Rotterdam	2018	10 hours
Supervising graduation project master medical student, Erasmus MC, Rotterdam	2019	50 hours

Awarded grants and prizes	Year
Digestive disease foundation grant - OCEAN trial	2018
Digestive disease foundation grant - HELI trial	2018
Poster of distinction, Washington D.C., United States	2018
Travel grant, UEG Week, Vienna, Austria	2018
Early career GI award, San Diego, United States	2019
Travel grant, ESGE, Prague, Tsjech Republic	2019
Travel grant, UEG Week, Barcelona, Spain	2019

Oral presentations	Year	Workload
Digestive disease days, Veldhoven	2014	12 hours
Digestive disease days, Veldhoven	2019	12 hours
Digestive disease days, Veldhoven	2019	12 hours
European society of gastrointestinal endoscopy, Prague, Tsjech republic	2019	12 hours
Digestive disease week, San Diego, United States	2019	12 hours
United European Gastroenterology Week, Barcelona, Spain	2019	12 hours

Poster presentations	Year	Workload
Digestive disease week, Washington D.C., United States	2018	12 hours
United European gastroenterology week, Vienna, Austria	2018	12 hours

Attended seminars	Year	Workload
Erasmus liver day, Rotterdam	2016	8 hours
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